Organization of Cognitive Control Within the Lateral Prefrontal Cortex in Schizophrenia

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Context: Cognitive control is highly affected in schizophrenia, but its overall functional architecture remains poorly understood. A recent study demonstrated that, in healthy subjects, cognitive control is functionally organized within the lateral prefrontal cortex (LPFC) as a cascade of representations ranging from premotor to anterior LPFC regions according to stimuli, the present perceptual context, and the temporal episode in which stimuli occur.

Objective: To determine the functional hierarchical organization of cognitive control within the LPFC in patients with schizophrenia.

Design: Case-control study.

Setting: Hospital-based research units.

Participants: Fifteen schizophrenic patients and 14 controls.

Main Outcome Measures: Behavioral performance and regional brain activity as measured by functional magnetic resonance imaging during a task, varying the amount of information conveyed by episodic and contextual signals. **Results:** In patients and healthy controls, activity in caudal LPFC regions varied as episodic and contextual signals, whereas rostral LPFC regions only exhibited an episodic effect. However, patients made more errors than controls when information conveyed by contextual and episodic signals increased. These impairments were related to hypoactivation in caudal LPFC regions and hyperactivation in rostral LPFC regions, respectively. Activation in caudal LPFC regions negatively correlated with the disorganization syndrome score of patients.

Conclusions: In schizophrenic patients, the architecture of cognitive control follows the cascading organization from rostral LPFC regions to caudal LPFC and premotor regions depending on the temporal framing of action and events. We found, however, that immediate contextual signals insufficiently bias the caudal LPFC activity required to select the appropriate behavioral representation. This specific deficit could thus alter the internal consistency of schizophrenic patients' behavior. To compensate for this weakening of contextual influence, schizophrenic patients may inefficiently use temporal episodic information through higher activation in rostral LPFC regions.

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associated with schizophrenia and are thought to play a key role in patients' maladaptive and perseverative behaviors.^{1,2} The neural substrates of these deficits have been investigated by numerous studies that have focused on top-down attentional control,^{3,4} working memory,⁵ and episodic memory processes.⁶ In general, these studies reported consistent dysfunctions in various regions of the lateral prefrontal cortex (LPFC) related to impairments in the processing of immediate contextual information,^{7,8} manipulation of information within working memory,9-11 and information retrieval from episodic memory.¹²⁻¹⁴ Despite these notable advances, functional divisions of cognitive control within schizophrenic patients' LPFC remain poorly understood. In particular, researchers have failed to clearly describe (1) how the different temporal modules of cognitive control (particularly those related to episode and context) interact and are functionally organized within specialized LPFC subsystems and (2) how dysfunctions in those areas could be related to clinical symptoms.¹⁵

To investigate the overall organization of cognitive control within the LPFC in schizophrenia, we used a unified modular model proposed by Koechlin et al¹⁶ in which representations are distributed in the LPFC according to their temporal structure rather than their content or internal complexity. Specifically, Koechlin et al showed that the LPFC is organized as a cascade of executive processes (from

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Figure 1. The cascading architecture of cognitive control within the lateral prefrontal cortex (LPFC). The multistage organization of information processing includes a sensory control level involved in selecting the motor responses that are the most appropriate to specific stimuli. This control is subserved by the lateral premotor regions (typically, Brodmann area [BA] 6). The contextual control level is involved in selecting premotor representations (that is, stimulus-response associations) according to contextual signals that accompany the occurrence of stimuli. This control is subserved by the LPFC (typically, BA 9/44/45). The episodic control level is involved in selecting caudal LPFC representations (task sets or consistent sets of stimulus-response associations evoked in the same context) according to the temporal episode in which stimuli occur. This control is subserved by the rostral part of the LPFC (typically, BA 46/10). Reprinted with permission from the American Association for the Advancement of Science.¹⁶

premotor to anterior LPFC regions) that control behavior according to stimuli, the present perceptual context, and the temporal episode in which stimuli occur (**Figure 1**). Additionally, this model takes into account quantitative variations in the demands of these controls, using a mathematical framework that is based on information theory.^{16,17}

The cascading nature of this model is derived from the idea that each stage maintains active representations that are controlled by higher stages, which exert control on representations in lower stages, thus giving rise to a series of top-down, successive processes involved in controlling the appropriate stimulus-response association. This model offers an account of both top-down attentional and fractionation theories of LPFC function, consistent with findings from various domains within cognitive neuroscience, such as attentional control, working memory, and episodic memory retrieval.¹⁸ The cascade model is supported by a wide variety of evidence from neuroimaging studies in humans and lesion studies in nonhuman primates, including those referring to other hierarchical models of branching cognition.¹⁹⁻²⁴ We believe that the cascade model provides a useful holistic framework in which to investigate the temporal organization of cognitive control within the LPFC in schizophrenia. Using a protocol inspired by this model, Chambon and coworkers²⁵ previously showed that, in schizophrenic patients, a specific deficit occurred when the selection of an appropriate action was biased by immediate contextual cues. This defective contextual control was shown to account for significant variance in disorganization syndrome scores in patients. These results led to the hypothesis that caudal LPFC, the region of the prefrontal cortex that subserves contextual control, is dysfunctional in schizophrenia and that this dysfunction could be related to the disorganization syndrome.

To test this hypothesis, we used functional magnetic resonance imaging (fMRI) to evaluate LPFC activation in schizophrenic patients and matched healthy participants during a task that modeled contextual and episodic controls. This task was adapted from the experimental paradigm of Koechlin et al.¹⁶ In the healthy group, we first expected that the increasing demands of contextual and episodic controls would have additive cumulative effects on both behavioral reaction times and local brain activations that gradually add up from rostral to caudal LPFC and premotor regions.¹⁶ Second, as has been shown in previous studies, we expected that the increasing demand of both contextual and episodic controls would enhance error rates in schizophrenic patients.²⁵⁻²⁷ Third, as mentioned, we predicted that there would be insufficient modulation of activity in caudal LPFC regions relative to impaired control of contextual information and an association between caudal LPFC regions' dysfunction and the disorganization syndrome in the patient group. Finally, as patients' LPFC activation was shown to reflect a complex interaction between task difficulty and the subjects' motivation to perform the task,^{28,29} we also sought to determine the nature of any differences in regional brain activation when comparing patients and controls with equivalent behavioral accuracy.

METHODS

PARTICIPANTS

Fifteen schizophrenic patients and 15 healthy controls, who were all right-handed (Edinburgh Handedness Survey³⁰) and matched for age, sex, and years of education, were recruited to participate in the fMRI experiment (Table 1). These participants were different from those who had participated in Chambon and colleagues'25 previous study. 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 participation. 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.34 The clinical state of each patient was assessed using the Scale for the Assessment of Positive Symptoms³⁵ and the Scale for the Assessment of Negative Symptoms³⁶ on the day of testing. Symptoms were grouped into 3 syndromes: reality distortion, psychomotor poverty, and disorganization (Table 1). All patients were clinically stable and treated with only atypical antipsychotic medications. 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 (no patients were excluded).

TASK PARADIGM

Subjects had to respond as quickly and accurately as possible to a series of successive colored letters by pressing 1 of 2 re-

Table 1. Clinical and Demographic Characteristics of Schizophrenic Patients and Controls

	Mean		
Characteristic	Schizophrenic Patients (n=15)	Controls (n=14)	<i>P</i> Value
Male sex, No. (%)	8 (53)	8 (57)	.68
Age, y	35 (10.5)	36 (10.6)	.79
Education, y	11 (1.3)	11 (1.9)	.82
Right-handedness	0.86 (0.09)	0.84 (0.11)	.50
Duration of illness, y	10 (9)		
SANS score	43 (19)		
SAPS score	23 (21)		
Reality distortion score ^a	8 (10)		
Psychomotor poverty score ^b	34 (18)		
Disorganization score ^c	23 (13)		
Chlorpromazine equivalent, ^d mg/d	247 (190)		

Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

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

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

 $^{\rm C}Sum$ of the scores for formal thought disorder and bizarre behavior from the SAPS and the score for attention from the SANS. 31,32

^d Depot doses and daily oral atypical antipsychotic drugs 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 using guidelines described by Woods.³³ None of the patients received a concurrent typical antipsychotic, anticholinergic agent, sedative treatment, mood stabilizer, antidepressant, or other psychotropic agent.

sponse buttons (held in the right and left hands). The experimental design was administered using an 8×8 Latin square design consisting of 8 series of stimuli (scanning sessions), each presented in 8 separate blocks (behavioral episodes). A Latin square design was used to control for order of presentation of the blocks and transitions between the blocks. Each block included a series of 12 successive stimuli (duration, 500 milliseconds; onset asynchrony, 3500 milliseconds) preceded by an instruction cue (episodic signal) that lasted 4200 milliseconds. Participants learned the instructions before running the experiment to avoid possible biases due to learning effects during the test session. In each scanning session, the 8 blocks formed 4 distinct experimental conditions that crossed the demands of contextual and episodic controls varied by manipulating the contextual (I_{con}) and the episodic (I_{epi}) factors, respectively. The stimulations were delivered with the software Presentation (Neurobehavioral Systems, Albany, California).

Instruction cues varied from block to block and informed the subjects to make quick responses to colored letters or to withhold a response to a no-go stimulus. Contextual control was manipulated by requiring subjects to make either a lower-/ upper-case (task 1) or a consonant/vowel (task 2) letter judgment (using the left and right response buttons), the task being determined by the color of the letter (ie, the contextual signal within each block). Episodic control was manipulated by varying the contingencies that linked contextual signals and task sets (**Figure 2**).

In each block, sequences of contextual signals were pseudorandomized so that 33% of displayed letters were to be ignored. In dual task-set blocks, the ratio of task 1 to task 2 trials was 1. The proportions of 2 successive trials that included identical contextual signals were constant across blocks. Finally, letters were pseudorandomly chosen so that, in each block, the ratio of left- to right-button responses was 1 and the ratio of



Figure 2. Experimental design of the task paradigm. A, Rounded boxes represent behavioral episodes (1-8) with related stimuli (letters) and instructions. Episodes formed 4 distinct experimental conditions that crossed the episodic factor with the contextual factor. According to the color of the letter (contextual signal), subjects either ignored the letter or performed a vowel/consonant (T1) or lower-/upper-case (T2) discrimination task on the letters. For example, in block 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). When contextual control was low, the task remained the same across the entire block (T1 or T2, single task-set blocks, Icon=0 bits, blocks 1, 2, 5, and 6); in high-contextual control blocks, the task changed from trial to trial (T1 and T2, dual task-set blocks, I_{con} =1 bit, blocks 3, 4, 7, and 8). Episodic control was manipulated by varying the contingencies linking contextual signals and task sets. When the colors involved in the blocks were green, red, and white, the same colors always denoted the same tasks (in blocks 1, 2, 3, and 4, green always denoted T1, red always denoted T2, and white was always "no-go," Iepi=0 bits). However, when the colors were blue, purple, and yellow, the tasks demanded by each color varied on a block-by-block basis (in blocks 5, 6, 7, and 8, blue, purple, and yellow could all denote T1, T2, or no-go, I_{epl} > 0 bits). B, Typical episode. IC indicates instruction cues; I_{con} and I_{epi} , contextual and episodic factors.

congruent to incongruent letters (same vs different responses for task 1 and task 2) was 1. Accordingly, sensorimotor control was constant across the experiment.

MRI PROCEDURES AND PREPROCESSING

Images were collected using an 1.5-T MRI system. The fMRI blood oxygenation level–dependent signal was measured using a T2*-weighted echo-planar sequence (repetition time, 2500 milliseconds; echo time, 60 milliseconds; flip angle, 90°). Twenty-six axial slices (thickness, 4 mm; gap, 0.4 mm; field of view, 220 mm; matrix size, 64×64 ; in-plane resolution, 3.4×3.4 mm²) were acquired per volume. Following functional image acquisition, a high-resolution T1-weighted anatomical image (repetition time, 1970 milliseconds; echo time, 3.93 milliseconds; 256 × 256 matrix; resolution, $1 \times 1 \times 1$ mm³) was collected for each subject.

Image preprocessing was performed using SPM5 (Wellcome Department of Imaging Neuroscience, University College London, London, England). For each subject, each of the 8 scanning sessions contained 155 functional volumes after the first 5 scans were rejected to eliminate the nonequilibrium effects of magnetization. All functional volumes were realigned to the first volume to correct for interscan movement. Functional and structural images were coregistered and transformed³⁷ into a standardized, stereotaxic space (Montreal Neurological Institute template).³⁸ Functional data were then smoothed with a 10-mm full-width-at-half-maximum, isotro-

Table 2. Behavioral Performance in Each Group of Subjects and in Matched Performance Subgroups							
		Mean (SD)					
Condition	Measure	Controls	Schizophrenic Patients				
$I_{epi} = 0$ bits	Error rate, %	0.9 (1.6)	5.5 (4.3)				
$I_{con} = 0$ bits	Reaction time, ms	1005 (177)	1137 (310)				
$I_{epi} = 0 \text{ bits } $ $I_{con} = 1 \text{ bit } $	Error rate, %	2.0 (2.1)	9.5 (6.2)				
	Reaction time, ms	1369 (199)	1507 (278)				
$I_{epi} = 1 \text{ bit}$ $I_{con} = 1 \text{ bit}$ $I_{epi} = 2 \text{ bits}$ $I_{con} = 0 \text{ bits}$	Error rate, %	3.3 (2.8)	17.5 (13.6)				
	Reaction time, ms	1468 (186)	1608 (278)				
	Error rate, %	7.3 (5.7)	20.2 (12.5)				
	Reaction time, ms	1352 (194)	1538 (283)				

Abbreviations: I_{con} and I_{epi}, contextual and episodic factors.

pic gaussian kernel and temporally processed in a high-pass filter with a frequency cutoff of 128 seconds. 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 downweighted images with high noise variance.³⁹

STATISTICAL ANALYSIS

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. To conduct these analyses, we used the statistical software STATISTICA7 (StatSoft Inc, Tulsa, Oklahoma).

For the fMRI data, we first conducted voxelwise exploratory analyses of frontal regions subserving each level of cognitive control (context and episode) in both the schizophrenia and control groups. Using SPM5, statistical parametric t score maps 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.⁴ For all conditions, we defined the preparation phase as the interval between the instruction cue and the presentation of the first stimulus, and the execution phase as the period from the first stimulus until the end of the series of stimuli. In the current study, we analyzed the frontal regions that were engaged in cognitive control exertion during the execution phase. Specifically, regions that demonstrate a contextual effect are those that have higher activation in the dual $(I_{con}=1 \text{ bit})$ than in the single ($I_{con}=0$ bits) task-set episodes, with $I_{epi}=0$ bits. Regions that demonstrate an episodic effect are regions whose activation parametrically vary with Iepi. In a second level of analysis, contrasts were performed using a random-effect model. In each group, we identified regions that showed a contextual effect and regions that showed an effect of episode, but no contextual effect (computed by masking each region related to the episodic effect with the contextual effect, using an uncorrected voxelwise threshold P < .05). Montreal Neurological Institute coordinates were transformed to the standard space of Talairach and Tournoux⁴¹ 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,16,42,43 we restricted our analyses to the lateral frontal cortex by masking with WFU PickAtlas software.⁴⁴ A voxelwise significance threshold of P < .05 was chosen (corrected for the false discovery rate).

We then conducted hypothesis-driven functional regions of interest analyses in the different regions (rostral LPFC, caudal LPFC, and premotor regions) identified by the exploratory analyses in healthy subjects. Activations in the voxel that was the more significant in each of these regions (ie, the peak voxel) were 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 ($I_{evi}=0, 1, \text{ or } 2 \text{ bits}$) as a within-subject covariate, and group (patients vs controls) as a between-subject factor (when performing between-group analyses). When significant, interactions were further assessed using *t* tests. For schizophrenic patients, we also tested correlations between brain activity and the 3 symptom syndromes (reality distortion, psychomotor poverty, and disorganization) using the Pearson test. To conduct these analyses, we used STATISTICA7.

RESULTS

BEHAVIORAL ANALYSIS

Reaction Times

The analysis of covariance performed on reaction times showed significant effects of episode (F=100.16, P<.001) and context (F=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<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 (**Table 2** and **Figure 3**A and B).

Error Percentages

Participants' error percentages were found to significantly increase with the contextual (F=4.16, P<.05) and episodic (F = 66.23, P < .001) factors. Significant interactions between group and cognitive factors were observed in both the contextual (F=4.58, P<.05) and the episodic (F=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 (Table 2 and Figure 3C and D). Patients performed worse than controls for $I_{con}=0$ and 1 bit and for $I_{evi}=0$, 1, and 2 bits (all t > 3.50, P < .002). Finally, by comparing reaction times and error percentages in the first and second parts of episodes, we found that no effect significantly varied across the episodes (all interactions, F < 1.92, P > .05), indicating that cognitive control was recurrently exerted across episodes and that there was not a learning effect within the blocks for patients relative to controls.

fMRI ANALYSIS

Exploratory Voxelwise Contrasts

In controls, frontal regions that showed an effect of context were found bilaterally in the caudal LPFC (Brodmann area 9/44/45, inferior/middle frontal gyrus) and premotor cortex (Brodmann area 6, middle frontal gyrus). Frontal regions that exhibited an episodic, but not contextual, effect were found bilaterally in the rostral LPFC (Brodmann area 10/46, inferior/middle frontal gyrus) (**Figure 4**A and B and **Table 3**).

In patients, frontal regions that showed a contextual effect were found bilaterally in the caudal LPFC and in the left premotor cortex (however, these peaks were not significant, P=.09, false discovery rate–corrected). Frontal regions that exhibited an episodic, but not contextual, effect were found bilaterally in the rostral, caudal, and premotor regions (Figure 4A and B and Table 3).

Functional Region of Interest Analyses

To examine the group effects from the series of exploratory voxelwise contrasts, fMRI signal changes for each subject were extracted for each of the 3 LPFC regions identified in the healthy group (Table 3). In controls as in patients, activations in rostral LPFC regions linearly varied with the episodic factor only (F>5.4, P<.05), though in patients, this effect was only observed in the right hemisphere. In both groups, activations in these regions were independent of context (F<1.5, P>.05). Moreover, betweengroup analyses revealed a main group effect (F=7.1, P=.01), with patients activating these regions to a greater extent than controls (Figure 4D and E). There was no interaction between group and cognitive factors (F<1.2, P>.05).

In controls, activations in the caudal LPFC regions linearly varied with episode (F=10.6, P<.005) and context (F=19.3, P<.001). In patients, activations in these regions only varied with the episodic factor (F=5.0, P<.05), independent of context (F=0.8, P>.05). There was no interaction between episode and context in any group (F<0.2, P>.05). Moreover, between-group analyses showed a significant group × context interaction (F=9.8, P<.005) (Figure 4C, F, and G) but not a significant group × episode interaction or a main group effect (F<2.9, P>.05). Planned contrasts using t tests revealed that controls activated these regions to a greater extent in the dual task-set condition (I_{con} =1 bit) than in the single task-set condition (I_{con} =0 bits) (t=3.2, P<.005), whereas patients did not (t=0.5, P>.05).

One could argue that the hypoactivation in the patients' caudal LPFC could result from a bias of the analysis we used because we localized this region of interest from activations found in the healthy group alone. We therefore conducted a between-group analysis on the caudal LPFC activations whose localizations were different in each group. 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, false discovery rate-corrected). Then, these activations were entered into a new analysis of covariance, which still revealed a group \times contextual interaction (F=13.5, P < .001) but no main effect of group or an interaction between group and episode (F < 1.15, P > .05).



Figure 3. Behavioral results of the task paradigm. Reaction times (A and B) and error rates (C and D) (mean±standard error across participants) across experimental conditions.

Region of interest–based analysis performed on activations in premotor regions showed significant effects of episode (F=4.0, P<.05) and context (F=11.5, P=.001) in controls. In schizophrenic patients, we observed a significant episodic (F=5.3, P<.05) but not a contextual (F=1.7, P>.05) effect. There was no interaction between episodic and contextual factors in any group (F<0.1, P>.05). Between-group analyses revealed neither a significant group effect nor significant interactions between group and cognitive factors (F<3.0, P>.05) (Figure 4H and I).

Correlation analyses conducted between the 3 syndromes scores (reality distortion, disorganization, and psychomotor poverty) and fMRI signal change in these regions revealed a significant correlation in caudal LPFC regions for disorganization only (r=-0.59, P<.05). An increased disorganization score was associated with a decreased signal intensity change. Results from other correlation analyses between each of the 3 syndromes and signal intensity change in rostral LPFC and premotor regions were not significant.

It is noteworthy that schizophrenic patients as well as controls were found to complete some of the blocks by chance. If satisfactory blocks were defined as those completed with an accuracy greater than 65%,¹⁰ a mean of 0.75 blocks per run (standard deviation [SD], 1.06) were considered to be completed with chance in the patients, compared with a mean of 0.12 (SD, 0.32) in the control participants (P<.05). Such a difference in performance has been argued to constitute a so-called performance bias for the interpretation of the neuroimaging results. Indeed, in that case, differences in activations could be interpreted as resulting from patients' poor en-



Figure 4. Differences in prefrontal cortex activations between patients with schizophrenia and healthy controls. Topography of brain activation in healthy controls (A) and in patients with schizophrenia (B) (blue indicates regions exhibiting a contextual effect; yellow, regions showing an episodic but no contextual effect; 1, rostral lateral prefrontal cortex [LPFC]; 2, caudal LPFC; 3, premotor cortex). C, Brain regions demonstrating contextual effects that were significantly greater in healthy control participants than in participants with schizophrenia (2A indicates dorsocaudal LPFC; 2B, ventrocaudal LPFC). D-I, Peak-voxel activations (averaged regression coefficients ±standard errors across participants) in LPFC regions involved in cognitive control in healthy subjects are plotted against the episodic factor. Left and right activations are averaged together. fMRI indicates functional magnetic resonance imaging.

gagement in the task, rather than resulting from a specific cognitive deficit.

One way to control this bias is to remove blocks for which performance is unsatisfactory. When we reran the analysis considering only blocks for which the accuracy was acceptable (ie, accuracy >0.65), we found that there were no behavioral differences between the 2 groups regarding either episode or context (F < 0.21, P > .05). However, we still found a group effect in rostral LPFC regions (F = 6.97, P < .05), with patients activating this region more than controls. Likewise, caudal LPFC regions still demonstrated a group \times context interaction (F=3.76, P=.05), with patients showing no modulation of activation related to the contextual factor in these regions. Activation in the caudal LPFC was only found to correlate negatively with the disorganization score (Pearson r = -0.54, P < .05). Finally, there were no differences in fMRI signals in premotor regions between patients and controls.

Another way to address the potential confounding of task performance and group is to match subgroups of pa-

tients and controls based on performance.¹⁵ We therefore performed additional analyses with subgroups of subjects matched for behavioral accuracy (8 patients and 7 controls, t=1.72, P > .05) (**Figure 5**A-D). These analyses generally replicated those already described. In particular, even after selecting subjects with similar performance patterns, patients still underactivated the caudal LPFC regions compared with controls regarding the contextual factor (group × context interaction: F=5.2, P < .05) (Figure 5G and H). Additionally, patients matched for performance had higher activation levels than controls in rostral LPFC regions (main group effect: F=5.9, P < .05) (Figure 5E and F). No other effect involving group was significant in any of the 3 regions of interest (Figure 5).

COMMENT

We examined the hierarchical organization of cognitive control within the LPFC based on the temporal framing

Table 3. Within-Group Activation in Frontal Regions Displaying Episodic and Contextual Effects

		C	Coordinates ^a				
Lateral Frontal Cortex Region	Estimated BA	x	У	z	t Score ^b	Volume, mm ³	FDR-Corrected P Value
		Contr	ols				
Contextual effect							
Left middle frontal gyrus, caudal PFC	9	-42	39	36	6.27	37 084 ^c	.04
Left precentral gyrus, premotor cortex	6	-39	0	45	5.74	37 084 ^c	.04
Left inferior frontal gyrus, caudal PFC	44	-45	15	21	5.40	37 084 ^c	.04
Right middle frontal gyrus, caudal PFC	9	42	33	39	5.21	8277 ^d	.04
Right inferior frontal gyrus, caudal PFC	45	30	27	3	4.78	8277 ^d	.04
Right superior frontal gyrus, premotor cortex	6	27	-9	54	5.16	3422	.04
Episodic effect ^e							
Left superior frontal gyrus, rostral PFC	10	-27	54	-3	4.23	185	.04
Right middle frontal gyrus, rostral PFC	46	39	48	30	4.06	740	.04
Right middle frontal gyrus, rostral PFC	10	33	63	9	3.49	139	.04
	Sc	hizophren	ic Patients	;			
Contextual effect ^f							
Left middle frontal gyrus, caudal PFC	9	-33	42	12	4.92	2867	.09
Left precentral gyrus, premotor cortex	6	-57	-3	24	4.67	2081	.09
Right middle frontal gyrus, caudal PFC	9	33	36	27	4.41	786	.09
Left precentral gyrus, premotor cortex	6	-45	0	54	4.39	2127	.09
Left superior frontal gyrus, premotor cortex	6	-21	-6	57	4.35	1988	.09
Episodic effect ^e							
Right middle frontal gyrus, caudal PFC	9	42	42	33	5.52	23 814 ^g	.03
Right superior frontal gyrus, premotor cortex	6	30	-9	45	3.36	23 814 ^g	.03
Left middle frontal gyrus, caudal PFC	9	-42	21	33	5.09	14 843	.03
Right middle frontal gyrus, rostral cortex	10	27	51	0	4.77	8046	.03
Left middle frontal gyrus, rostral cortex	46	-36	48	9	4.02	1295	.03
Left superior frontal gyrus, premotor cortex	6	-33	-9	45	3.39	647	.03

Abbreviations: BA, Brodmann area; FDR, false discovery rate; PFC, prefrontal cortex. ^aFrom the stereotaxic atlas of Talairach and Tournoux.⁴¹

^bRegional peak activation representing blood oxygenation–level dependent signal change that reached a threshold of P<.05 (corrected for the FDR) in a random-effect analysis.

^cThese peaks belong to the same cluster of activation.

^dThese peaks belong to the same cluster of activation.

^eExcluding contextual effect.

^fThese peaks are nonsignificant but are reported because we wanted to show that the activations are not absent in schizophrenic patients regarding the contextual effect

^gThese peaks belong to the same cluster of activation.

of action and events in a sample of patients with schizophrenia and a group of matched healthy subjects. We first showed that, in healthy controls, the architecture of cognitive control is organized as a multistage, cascading organization of information processing along a rostrocaudal axis of the LPFC, which is consistent with previous results.^{16,25} In the comparison group, activity in the rostral LPFC only resulted from an effect of episode, whereas activity in the caudal LPFC resulted from effects of both context and episode.

In this cascading architecture, however, schizophrenic patients demonstrated dysfunctional recruitment of specialized areas involved in controlling episodic and contextual information to guide the selection of the appropriate action. Indeed, schizophrenic patients made more errors than controls when information conveyed by both contextual and episodic signals increased (consistent with our previous study25), which was associated with lower activation in the caudal LPFC and higher activation in the rostral LPFC, respectively. Finally, activation in the caudal LPFC—the region subserving contextual control—was associated, as expected, with the disorganization syndrome in the patients' group.

Two methodological issues have typical implications for interpreting specific cognitive functions thought to be impaired in schizophrenia. First, medications used to treat schizophrenia may influence behavioral performance and brain function. However, our findings of both reduced activation in caudal LPFC regions and enhanced activation in rostral LPFC regions in patients are consistent with findings of other studies that included schizophrenic patients who were not taking neuroleptic drugs.^{8,31,45} Therefore, the current pattern of results is likely not due to the treatment patients received.

A second common methodological problem in interpretation of fMRI data in schizophrenic patients is that poor performance may confound changes in functional brain activation.^{28,29} The specific patterns of patient-control differences in prefrontal cortex activation found in this study persisted, however, when compared with conditions in which patients' behavioral performances were matched with those of controls. Thus, the pattern of functional brain activation we observed is unlikely to result from a failure to engage in the task and rather expresses some inherent disturbances in schizophrenia.



Figure 5. Behavioral and neuroimaging differences between patients with schizophrenia and healthy controls matched for performance. A-D, Behavioral results (mean ± standard error across participants). E-J, Factorial analyses of regional activations. Peak-voxel activations (averaged regression coefficients ± standard errors across participants) in lateral prefrontal cortex (LPFC) regions involved in cognitive control in healthy subjects are plotted against the episodic factor. fMRI indicates functional magnetic resonance imaging.

It is worth noting that the box-car design of our study may at least partly confound additional cognitive processes that may have contributed to the differential effects observed between patients and controls.46 In particular, the single and dual task-set conditions do not only differ in the demands on contextual control but also in the working memory load during the corresponding task blocks. Indeed, dual task-set blocks require subjects to maintain twice as many stimulus-response mappings (4 vs 2) in mind for the response selection. However, if patients' impaired performances were the consequence of impaired maintenance of contextual signals within working memory, the increasing contextual demand $(I_{con}=0)$ bits to I_{con} = 1 bit) should have had a differential effect on reaction times or error percentages in patients compared with controls between the first and second parts of behavioral episodes, which was not the case.

Results from our study support numerous previous findings from top-down attentional theories of cognitive control,⁴ indicating an association between contextprocessing impairment, the disorganization syndrome, and dysfunction of caudal LPFC (though only its dorsal part was often found to be disturbed) in schizophrenia.^{7,8,31,45,47-49} Whereas researchers have provided convincing accounts for dysfunction in this area (eg, inappropriate dopaminergic modulation from subcortical systems),^{27,50} they have not clearly described the critical role this region plays in some of the major cognitive and clinical disturbances in schizophrenia.¹⁵ We believe that our study provides such clarification. Indeed, the cascade model considers that the caudal LPFC is functionally organized as a set of processes involved in control of the hierarchical structures of action plans (eg, lower-/ upper-case or consonant/vowel discrimination tasks) according to immediate contextual signals (eg, the color of the letter).^{16,51} Therefore, caudal LPFC dysfunction likely affects selection of the appropriate behavioral representation, which might complicate the planning and organization of contextually adapted behaviors. Consequently, this specific problem in the hierarchical monitoring of action could contribute to disharmonious behaviors (ie, maladaptive or perseverative behaviors), which is further corroborated by the negative correlation that we found between the disorganization syndrome score and patients' caudal LPFC activity.

A number of previous investigators have proposed other models for a better characterization of the physiopathologic substrates of impaired cognitive control in schizophrenia. One of those suggests that disturbances in the ability to detect conflict or errors in ongoing processing, which may be due to the function of the anterior cingulate cortex, may lead to deficits in selective attention, ie, the ability to enhance the processing of task-relevant information.^{45,52-55} Such abnormal selective attentional functioning in schizophrenia has been demonstrated by numerous studies using the Stroop task, in which the participant is required to name the color of a stimulus word while ignoring its meaning (eg, the word red printed in blue ink).⁵⁶ Interestingly, in the Stroop task, the color of the word could be assimilated to an immediate contextual signal as defined by the cascade model. Indeed, as an intrinsic dimension of the stimulus, the color

is thought to be involved in the control of lower-order, more automatic responses (ie, the meaning of the word). Impaired anterior cingulate conflict monitoring could therefore represent a potential cause for the weakening of contextual influences in schizophrenia,45 a hypothesis that should be further investigated in the future.

Another well-known paradigm that shows impaired cognitive control in schizophrenia uses the continuous performance task, in which subjects are presented with a sequence of letters and are instructed to respond to a prespecified probe (X) only if it follows a particular contextual cue (A).7,8,31,47,57 In this AX continuous performance task, context processing broadly refers to the ability to represent and maintain task-relevant information in working memory necessary to appropriately process the subsequent target. In this paradigm, contextual control mostly requires overcoming response interference on BX trials, which occur after a very high proportion of A cues. In both the AX continuous performance task and the cascade model, contextual control requires managing conflict between competing stimulus-response mappings but does not involve the maintenance and management of multiple task sets in memory, as is the case in the episodic condition of the present study. In the cascade model, context more closely refers to information associated with the immediate, physical features of the target itself (eg, letter's color), whereas more temporal processes (eg, task instructions) are devoted to episodic control.¹⁸ Based on the cascade model, our previous study revealed that impaired context processing in schizophrenia is specifically related to immediate task-relevant information, the more temporally distant information being adequately controlled in this illness.25

Investigations of LPFC functioning in schizophrenia related to the working memory model have often revealed impaired dorsal LPFC activity (eg, in relation to impaired context processing) but normal^{11,58} or enhanced^{9,10} ventral LPFC activity. In contrast, we showed an impaired recruitment of contextual control by the caudal LPFC in both dorsal and ventral sectors (Figure 4C). Although we cannot formally exclude the possibility that the rather long duration of illness in our patient sample did not contribute to decreases in their ventral LPFC activation,^{8,10} these differences may be justified by variations in the study tasks. Indeed, the cascade model makes no claims about the functional ventrodorsal segregation of the LPFC,18 whereas tasks that use the working memory paradigm can usually reveal such functional dissociation based on the modality or content of processed information (eg, representation of contextual cues in dorsal LPFC vs phonological storage in the ventral LPFC).^{59,60} Findings from studies that used the working memory model could thus bring into focus the functional organization of the posterior LPFC in schizophrenia. Within this region, which is globally ineffective at controlling immediate contextual signals, patients may have impaired specialization in the dorsal LPFC related to higherorder information processing, and they may try to compensate for this deficit through ventral LPFC activation.9

A possible alternative compensatory mechanism is suggested by the higher activation in rostral LPFC-the region subserving episodic control-observed in patients

with schizophrenia despite their impaired behavioral performances while controlling episodic signals. Higher activation in schizophrenic patients' LPFC in the context of normal or impaired performances has often been categorized as cortical inefficiency (graphically represented by an inverted U-shaped function shifted to the left), especially in rostral LPFC regions.^{29,61,62} However, the present results, together with others that have shown reduced dorsal LPFC but enhanced rostral and ventral LPFC activations, suggest an alternative account: cognitive compensation, rather than a mere shift on the inverted U curve.^{9,10,31} Indeed, while the cascade model claims that these regions are involved in selecting caudal LPFC representations, such hyperactivation could be interpreted as a consequence of the additional, though inefficient, effort that patients may expend to retrieve the poorly integrated contextual information.^{31,63,64} This interpretation is corroborated by a previous study from MacDonald et al³¹ that demonstrates that, instead of using context processing, schizophrenic patients may use an inefficient encoding and retrieval episodic strategy-related to enhanced activation in rostral LPFC. In this line of arguments, the disruption of episodic control observed in schizophrenic patients could be the result of an inappropriate binding process between temporal and more immediate aspects of information^{65,66} that may be due to a primary inefficient encoding strategy of contextual cues.

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