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Guillaume Barbalat, Nicolas Franck

► To cite this version:

Guillaume Barbalat, Nicolas Franck. Dysfunctional connectivity in posterior brain regions involved in cognitive control in schizophrenia: A preliminary fMRI study. *Journal of Clinical Neuroscience*, 2020, 78, pp.317 - 322. <10.1016/j.jocn.2020.04.089>. <hal-03492333>

HAL Id: hal-03492333

<https://hal.science/hal-03492333v1>

Submitted on 22 Aug 2022

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TITLE PAGE

Title: Dysfunctional connectivity in posterior brain regions involved in cognitive control in schizophrenia: a preliminary fMRI study.

Running title: Fronto-posterior dysconnectivity in schizophrenia.

Authors: Guillaume BARBALAT, M.D., Ph.D.¹ & Nicolas FRANCK, M.D., Ph.D.¹

¹ Centre Ressource de Réhabilitation Psychosociale,
Centre Hospitalier le Vinatier & UMR 5229,
CNRS & Université Lyon 1,
France

Corresponding author:

Guillaume Barbalat
Centre Ressource de Réhabilitation Psychosociale,
Centre Hospitalier le Vinatier & UMR 5229,
CNRS & Université Lyon 1,
France
+33 7 57 51 22 05
guillaumebarbalat@gmail.com

Abstract word count: 240.

Word count: 4961 (inclusive of references, tables and figure legends).

ABSTRACT

Cognitive control, the ability to use goal-directed information to guide behaviour, is impaired in schizophrenia, and mainly related to dysfunctions within the fronto-posterior brain network. However, cognitive control is a broad cognitive function encompassing distinct sub-processes that, until now, studies have failed to separate and relate to specific brain regions. The goal of this preliminary fMRI study is to investigate the functional specialization of posterior brain regions, and their functional interaction with lateral prefrontal cortex (LPFC) regions, in schizophrenia. Fourteen healthy participants and 15 matched schizophrenic patients participated in this fMRI study. We used a task paradigm that differentiates two cognitive control sub-processes according to the temporal framing of information, namely the control of immediate context (present cues) vs. temporal episode (past instructions). We found that areas activated during contextual and episodic controls were in dorsal posterior regions and that activations did not significantly differ between schizophrenic patients and healthy participants. However, while processing contextual signals, patients with schizophrenia failed to show decreased connectivity between caudal LPFC and areas located in ventral posterior regions. The absence of group difference in the functional specialization of posterior regions is difficult to interpret due to our small sample size. One interpretation for our connectivity results is that patients present an inefficient extinction of posterior regions involved in attention shifting by prefrontal areas involved in the top-down control of contextual signals. Further studies with larger sample sizes will be needed to ascertain those observations.

Keywords: schizophrenia; cognitive control; fMRI; fronto-posterior network; functional specialization; functional connectivity.

MAIN TEXT

INTRODUCTION

Individuals with schizophrenia exhibit major cognitive deficits in a wide variety of domains, such as executive functions, working memory, episodic memory, attention, and inhibition¹. Some have argued that those cognitive impairments could all result from a disturbance in cognitive control, that is, the ability to represent and use goal-relevant information to guide the selection of an appropriate behavioural response^{2,3}. A vast amount of studies have related this deficit to impairments in the lateral prefrontal cortex (LPFC)⁴ and its interaction with other brain regions^{5–9}. However, cognitive control is a very broad cognitive function encompassing distinct sub-processes that need to be separately manipulated in order to better categorize these brain disturbances.

Cognitive control involves a higher level of processing than simple stimulus/response association (that we also refer to as “task-set”), where a stimulus is directly associated to a motor response (e.g. answering the phone if it rings). Indeed, in real life, the same stimulus can be associated to a different response given the specific context in which the person is acting. For instance, if the phone rings *while I am at home*, I will answer; *if I am in someone else's home*, I will let it ring. Here, contextual signals (e.g. being home vs. at someone else's) refer to any *immediate* cues that inform which specific response is appropriate for the situation. Such immediate contextual cues differ from past instructions, which refer to a *preceding episode* exposing the specific rules for the task at hand¹⁰. Still using the same analogy, even if I am not at home, I will answer the phone *if I am instructed to*, for instance by the owner of the house. We refer to these past instructions as *temporal episodic signals*.

Unfortunately, studies investigating cognitive control in schizophrenia do not

generally disentangle present contextual vs. temporal episodic cues, while such differentiation would be crucial to better specify cognitive control disturbances in this illness. To address this issue, we previously used a paradigm developed by Koechlin et al. (2003) where we were able to manipulate incoming signals according to the temporal framing of information, that is, the present context vs. the temporal episode in which the person is acting¹¹. In a series of studies investigating the organization of cognitive control within the LPFC in schizophrenia, we showed that the control of immediate contextual signals was specifically impaired in patients, and that this was related to dysfunctions of the caudal LPFC and to the disorganization syndrome^{12–14}. The scope of this analysis, however, did not extend to the contribution of posterior brain regions to cognitive control disturbances in patients.

Posterior brain regions have also been robustly incriminated in cognitive disturbances in schizophrenia. For instance, using task paradigms mainly related to working memory, studies have found either abnormal functional specialization or connectivity involving the posterior parietal cortex (PPC)^{15–22}. Various interpretations have been proposed such as deficits in central executive components of working memory (by opposition to domain-specific storage buffers) or compensatory processes to palliate defects in the LPFC^{15,17}. Dysfunctions in ventral posterior regions, and impaired connectivity from or to those regions, have also been incriminated in cognitive deficits in schizophrenia, especially related to cognitive components such as inhibition, auditory change detection (mismatch negativity), or attention^{23–26}. Such results are in line with the role usually devoted to ventral posterior regions in cognitive control, that is, to redirect attention to salient or incongruent events²⁷.

However, findings related to the participation of posterior regions in cognitive control disturbances in schizophrenia have remained elusive. To our knowledge, only one study

has found impaired activation in posterior regions during context processing in schizophrenia²⁸. Likewise, we only found two studies that have reported dysfunctional interaction between prefrontal and posterior regions related to context processing, where it was interpreted that the former failed to up-regulate the latter^{5,6}. Moreover, those studies mostly used the AX-Continuous Performance Test (AX-CPT), where context processing relates to a preceding letter informing how to process a subsequent letter. Therefore, the AX-CPT is a cognitive task where, as mentioned above, the present context and the temporal episode are not separately manipulated. This in turn jeopardizes any interpretations of dysactivations and dysconnectivity within posterior regions in schizophrenia.

In the current study, we aimed to better characterize the specific role played by posterior brain regions in cognitive control disturbances in schizophrenia. We used the paradigm of Koechlin et al. (2003) where present contextual vs. temporal episodic signals are manipulated separately and based our analysis on data collected in our previous study¹³. We were specifically interested in investigating whether schizophrenic patients would demonstrate any impaired functional segregation within posterior regions and/or impaired interaction between posterior and LPFC regions while processing immediate contextual and temporal episodic cues.

Finally, two important methodological matters are worth mentioning here. First, due to our small sample size ($n=15$ schizophrenic patients and $n=14$ healthy participants), any non-significant difference between patients and healthy participants would not necessarily mean a real absence of effect, but could simply be due to a lack of power. Likewise, with such small sample sizes, any significant difference would be difficult to generalize. Nonetheless, we aimed for this preliminary study to guide further investigations looking at unfolding the neural correlates of impaired cognitive control in schizophrenic patients'

posterior brain regions. Second, to prevent performance bias (the possibility that the differences in activations arise from patients' poor engagement in the task, rather than from a specific cognitive deficit)²⁹, we matched groups for accuracy by removing from the analysis blocks in which performance was unsatisfactory.

MATERIALS AND METHODS

Participants

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

Supplementary Material and Supplementary Table 1.

Training was done outside the scanner, in the three days preceding the scanning session, and lasted one to two hours. This procedure was critical to ensure that participants correctly understood the task and to prevent any learning effects in the scanner (which might have recruited extra brain regions).

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 (coloured letters) preceded by an instruction cue lasting 4200 ms. Each instruction informed participants 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. In each scanning session, the eight blocks formed four distinct experimental conditions crossing the demands of contextual and episodic controls (**Figure 1**).

The colour of the letter was the ***contextual*** signal within each block. According to

the contextual signal, participants had to perform one of three tasks: i) ignore the letters; ii) 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); iii) a lower/upper case discrimination task (T2: if the letter is upper case, press right; if the letter is lower case, press left). Where contextual control was low, the task remained the same across the entire block (T1 or T2, single-task-set blocks; blocks #1,2,5,6 in **Figure 1**). In high contextual control blocks, the task changed from trial to trial (T1 and T2, dual-task-sets blocks; blocks #3,4,7,8 in **Figure 1**).

The *episodic* signal was the instruction cue preceding each block. Episodic signals conveyed information about the contingencies linking contextual signals (i.e. the colour of the letter) and task-sets (i.e. T1 or T2) that occurred in the proceeding sequence of letters. For example, in block #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, using information theory, we computed different values for the episodic control demand, such that the more frequent the crosstemporal contingencies between contextual signals and tasks-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 #1,2,3,4 where green always denoted ‘T1’, red always ‘T2’ and white was always ‘no-go’, **Figure 1**), the demand of episodic control was low. By contrast, the decrease of this frequency ($f<1$, such as in blocks #5,6,7,8 where blue, purple and yellow could all denote ‘T1’, ‘T2’ or ‘no-go’, **Figure 1**) led to an increase in the episodic control demand. As the same crosstemporal contingencies were involved in blocks #7 and #8, these two blocks had a lower episodic control demand than that in

blocks #5 or #6, which contained different crosstemporal contingencies (**Figure 1**).

Variations in the episodic control demands were quantified according to the computational model from Koechlin et al. (2003)¹¹, based on Shannon's information theory³⁰ (from $I_{\text{epi}}=0$ bit for blocks with low episodic control demand to $I_{\text{epi}}=2$ bits for blocks with high episodic control demand).

Figure 1 about here

MRI procedures and preprocessing

The methods for MRI procedures and pre-processing are reported in **Supplementary Material**.

Statistical fMRI analysis

As in previous studies based on a similar paradigm, we designed the present study as a block-design experiment and followed identical analysis procedures^{11,13}. Using SPM5, we first conducted voxel-wise exploratory analysis of posterior regions subserving each level of cognitive control (context and episode) for each participant³¹. The context effect was computed as larger activations in the dual- than in the single-task-set blocks when the episodic control demand was low. The episode effect was computed as activations that parametrically varied with the episodic control demand (**Supplementary Material**).

In a second level analysis, we identified posterior regions that showed an episode and a context effects in each group, treating "subject" as a random factor. In addition, we looked at whether there were any between-group differences for each of those first level contrasts. All contrasts were thresholded at $p<0.001$ uncorrected at the voxel level and

$p < 0.05$ FWE (family-wise error)-whole brain corrected at the cluster level³², except otherwise specified.

To find any group differences that would have been unseen in the exploratory analysis (because of a use of a too stringent statistical threshold), we conducted regions of interest (ROI) analysis in the regions identified using the above exploratory analysis. Percent signal change from a sphere of 5 mm around the peak voxel at the group-level in those regions were separately entered into univariate repeated-measure analysis of covariance, with subject as a random factor, hemisphere (left vs. right) and context (single- vs. dual-task-sets) as within-subject factors, episode ($I_{epi}=0, 1$, or 2 bits) as a within-subject covariate, and group (patients vs. healthy participants) as a between-subject factor. This analysis was conducted with STATISTICA8.

Functional connectivity analysis (Supplementary Material)

Here, we tested whether frontal and posterior brain regions demonstrating an effect of context and episode (seed regions) influenced activity in other brain regions when each cognitive control demand (contextual and episodic) was high versus when it was low.

For each participant, we first created a PPI (psycho-physiological interaction) regressor that was mean-corrected and orthogonalized with regard to the main effect of task (i.e. contextual or episodic control: psychological regressor) and seed regions time series (i.e. frontal and posterior regions influences: physiological regressor).

Then, we aimed to determine which sites demonstrated context- and episode-related increased and decreased connectivity with the seed region. For both healthy participants and schizophrenic patients groups, subject-specific contrast images were entered into random effects within-group analysis. Finally, we tested whether there were any between-group differences in functional connectivity between the groups. We used a

significance threshold of $p < 0.001$ uncorrected at the voxel level and $p < 0.05$ FWE-whole brain corrected at the cluster level³².

RESULTS

Statistical fMRI analysis

In healthy participants, posterior brain regions that demonstrated an effect of episode were the inferior parietal lobule bilaterally (**Figure 2, Table 1**). Likewise, posterior brain regions that demonstrated a context effect were the inferior parietal lobule bilaterally (**Figure 2, Table 1**). In patients, only the right superior parietal lobule demonstrated an effect of episode at the chosen threshold ($p < 0.001$ uncorrected at the voxel level and $p < 0.05$ FWE corrected at the cluster level), while no regions outside the frontal cortex demonstrated an effect of context (**Figure 2, Table 1**). We therefore used a more liberal threshold of $p < 0.005$ uncorrected at the voxel level to find activations demonstrating an episode effect in the left hemisphere (found in the left superior parietal lobule) and bilateral activations demonstrating a context effect (found in the precuneus bilaterally, the left postcentral gyrus and the right inferior parietal lobule) in patients (**Figure 2, Table 1**).

No posterior brain regions demonstrated a significant difference in activity between schizophrenic patients and healthy participants. Likewise, between-group ROI analysis in the regions identified above did not demonstrate any significant group effects or any group x cognitive factor (context or episode) interaction effects (all $F < 2.1$, $p > 0.17$).

Figure 2 about here

Table 1 about here

Functional connectivity analysis

To investigate in more detail the information-flow from regions related to the control of contextual and episodic signals to functionally connected regions, we performed functional connectivity (PPI) analysis. Seed regions were bilateral LPFC (**Supplementary Table 2**) and PPC regions (**Table 1**). When healthy participants had to control information conveyed by contextual signals, PPI revealed a significant decrease in functional connectivity between the left caudal LPFC regions and a set of regions located in the right superior and middle temporal gyrus, the left posterior cingulate, the right precuneus, the right lingual gyrus, the postcentral gyrus bilaterally, and the right insula (**Supplementary Table 3**). Likewise, when healthy participants had to control information conveyed by contextual signals, the right caudal LPFC regions demonstrated a significant decrease in functional connectivity with the middle occipital gyrus bilaterally (**Supplementary Table 3**). Activity in the caudal LPFC regions was significantly less correlated with activity in those regions when the demand in contextual control was high (dual-task-sets condition) relative to when it was low (single-task-set condition). In healthy participants, no region demonstrated increased or decreased connectivity with any posterior regions involved in contextual control. No regions showed increased or decreased connectivity with any frontal or

posterior regions involved in contextual control in schizophrenic patients. Finally, in both groups, no regions demonstrated increased or decreased connectivity with any frontal or posterior regions involved in episodic control.

In a direct comparison between the groups, context-related decreased functional connectivity between left caudal LPFC regions and both the right middle temporal gyrus and the right superior temporal gyrus was greater in healthy participants than in schizophrenic patients (**Figure 3, Table 2**). Likewise, context-related decreased functional connectivity between right caudal LPFC regions and the right lingual gyrus was greater in healthy participants than in schizophrenic patients (**Figure 3, Table 2**). No other brain regions demonstrated any differences in functional connectivity with any other regions involved in cognitive control between healthy participants and schizophrenic patients.

Figure 3 about here

Table 2 about here

DISCUSSION

This preliminary fMRI study aimed at better categorizing cognitive control disturbances in schizophrenic patients' posterior brain regions, by using a task paradigm that differentiates two sub-processes according to the temporal framing of information, namely the control of immediate context (present cues) and temporal episode (past instructions)¹⁰. We were specifically interested in the functional specialization and integration of immediate

contextual vs. temporal episodic signals within schizophrenic patients' posterior brain regions.

First, when participants had to control information conveyed by contextual or episodic signals, they activated a set of regions within the PPC (superior and inferior parietal lobules – note that patients also activated regions located in the precuneus and the postcentral gyrus at a more liberal threshold). We did not find any impairment in the functional specialization of those regions in schizophrenic patients, even when using a more liberal statistical threshold (ROI analysis). However, in general the absence of group difference always raises the issue as to whether the findings are evidence of no effect (real equivalence) or no evidence of effect (lack of power). Clearly, with a sample size of $n=15$ in patients and $n=14$ in healthy participants, our study is too underpowered to draw meaningful conclusions regarding the absence of a statistical effect. Whether processes involved in cognitive control are adequately implemented in posterior regions in schizophrenia would need to be investigated in further studies with greater sample sizes.

Second, healthy participants showed greater decrease in functional connectivity than schizophrenic patients between caudal LPFC and a set of ventral posterior regions located in the superior temporal gyrus, the middle temporal gyrus and the lingual gyrus. In cognitive control tasks, such regions have been found to be involved in the shifting of attention in order to interrupt and reorient goal-directed behaviours^{27,33–36}. This “attention-breaker” function is thought to be under the control of prefrontal areas^{33,37,38} and is usually active in conditions where salient or unexpected signals announce the start, stop or switch of a task³⁶. Overall, the fact that ventral posterior brain regions were specifically extinguished by caudal LPFC in blocks with high demands of contextual control suggests a specific inhibition of this “attention-breaker” network by regions subserving contextual control to ensure continued performance across task trials. Indeed, in each

block, incoming stimuli were not meant to interrupt or redirect attention, but rather continuously conveyed contextual information important for the selection of task-sets. This was made possible by (1) the hourly training session where participants had learned all the contingencies linking contextual signals and task-sets; and (2) the 4.2 second instruction cue preceding each sequence and informing which of those contingencies were to be expected in the subsequent block.

As compared to healthy participants, schizophrenic patients did not show this decreased functional connectivity from caudal LPFC to ventral posterior brain regions. This result adds support to earlier findings of functional dysconnectivity between prefrontal and posterior regions in schizophrenia^{5–9,19–22}. Moreover, the impaired modulation of ventral posterior regions by caudal LPFC suggests an inefficient inhibition of regions involved in attention shifting by areas responsible for top-down contextual control. Without this inhibiting influence, contextual cues might be preferentially processed by areas involved in stimulus-driven control to capture attention away from the task at hand. This in turn would potentially disturb the continuity of the top-down selection of relevant task-sets by caudal LPFC during contextual control. This hypothesis fits well with an influential model of cognitive control disturbances in schizophrenia where it has been proposed that patients rely more on transient, stimulus-driven cognitive control (called reactive control) than sustained, contextual control (called proactive control) to guide decisions^{39–41}. Based on our results, we postulate that such a reliance on stimulus-driven, rather than top-down, control is mediated by a failure from caudal LPFC to inhibit ventral posterior regions, a hypothesis that future studies should clarify.

Limitations

The main limitation of the current study is our limited sample size, which prevents any

generalization of our findings to a broad population of schizophrenic patients. While our findings need to be interpreted with caution, the preliminary nature of this study demands confirmation with larger sample size.

Another limitation was that patients were not free from antipsychotic medications. The latter could have compensated low inherent activations in the posterior cortex and/or the functional interaction between prefrontal and posterior regions. Ideally, our results would be further explored in studies with patients free from antipsychotic medications.

In addition, in the present study, we only analysed data where performance levels were equated for schizophrenic patients and healthy participants. Such a method of analysis clearly improves the interpretation of activation differences, because those differences could not be attributed to any lack of motivation or inability to perform the task. However, when taking into account good as well as bad performance blocks, we did not retrieve any significant differences between patients and healthy participants in functional connectivity from caudal LPFC to posterior regions. Therefore, our results might be specific to high performing schizophrenic patients and would not be generalizable to other sub-populations.

Finally, given the nature of our functional connectivity analysis (PPI), we cannot determine the directionality of interaction between caudal LPFC and ventral posterior regions in a definitive manner. However, given that caudal LPFC, and not ventral posterior regions, were activated during contextual control, it is very unlikely that the latter underlies the altered pattern of connectivity between the two regions.

ACKNOWLEDGEMENTS: This work was supported by a grant from the Conseil Scientifique de la Recherche, Le Vinatier.

Dr Barbalat was supported by grant DEA20050904971 from the Fondation pour la Recherche Médicale.

DECLARATION OF INTEREST STATEMENT: The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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FIGURE LEGENDS

Figure 1. Experimental design.

A: rounded boxes represent blocks (numbered from #1 to #8) with related stimuli (letters) and instructions. Blocks formed 4 distinct experimental conditions crossing the episodic factor with the context factor. According to the colour 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. Dashed lines connect episodes involving congruent associations between contextual signals and task-sets. A complete description of the blocks is provided in **Supplementary Material**.

B: typical block.

Figure 2. PPC activations in patients with schizophrenia and healthy participants.

(A) Topography of brain activation in the PPC in healthy participants and in patients with schizophrenia. Red indicates regions showing an episode effect; blue indicates regions exhibiting a context effect. For display purpose, those regions are displayed with a threshold of $p < 0.005$ uncorrected voxel-wise.

Percent signal change in PPC regions involved in episodic (B) and contextual (C) controls in healthy participants and schizophrenic patients are plotted against the episodic factor. Left and right activations are averaged together. There was no differences in percent signal change between the groups in any of the activated PPC regions. Open and solid squares indicate single- and dual-task-sets episodes, respectively. The error bars represent the standard errors.

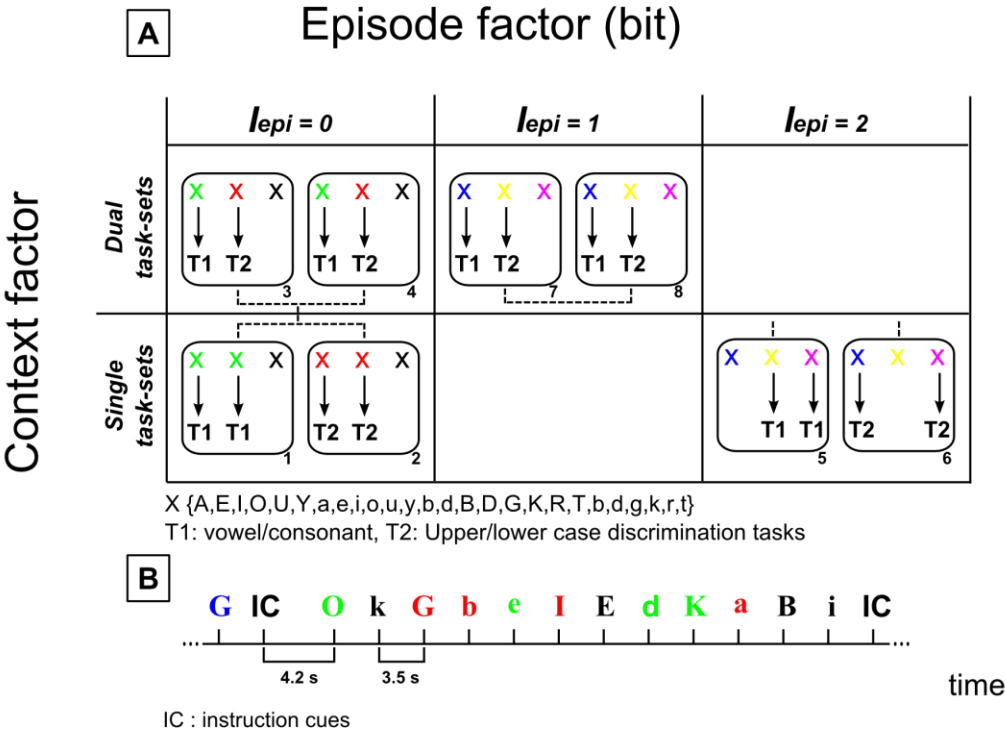
Figure 3. Regions that displayed decreased functional connectivity with left (A) and

right (B) caudal LPFC regions during contextual control for healthy participants relative to schizophrenic patients.

Threshold: $p < 0.001$ uncorrected voxel-wise and $p < 0.05$ FWE corrected cluster-wise.

(A) Regions were located in the right superior and middle temporal gyrus.

(B) Regions were located in the lingual gyrus.



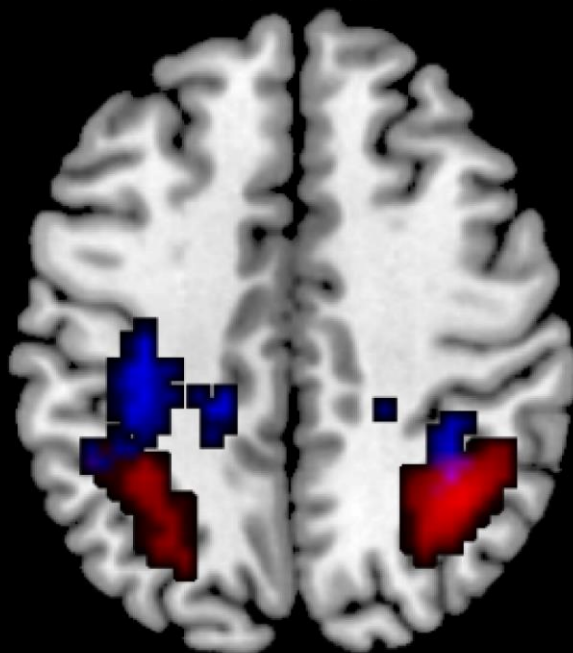
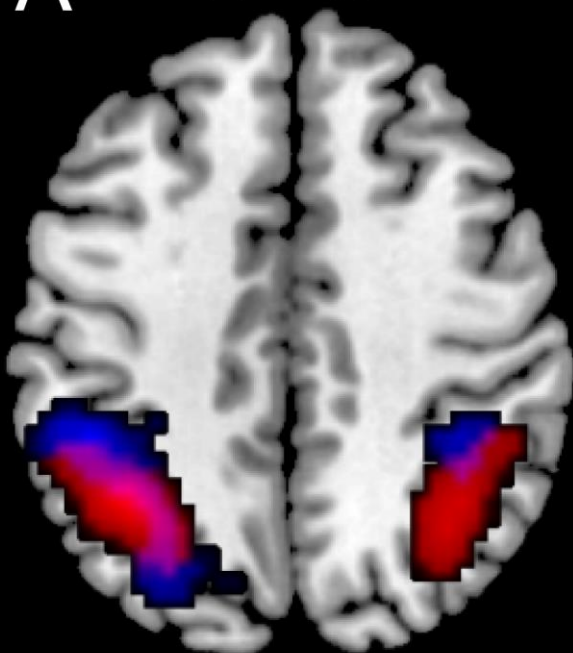
HEALTHY

SCZ PATIENTS

A

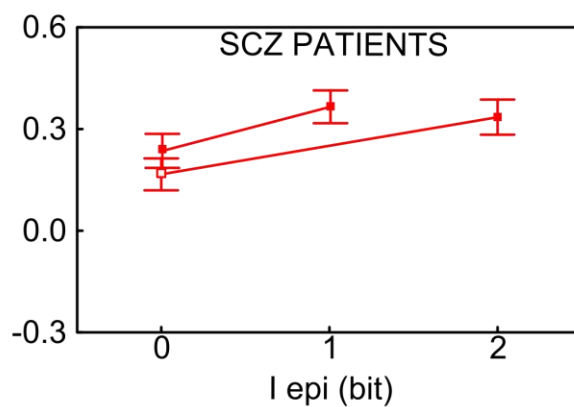
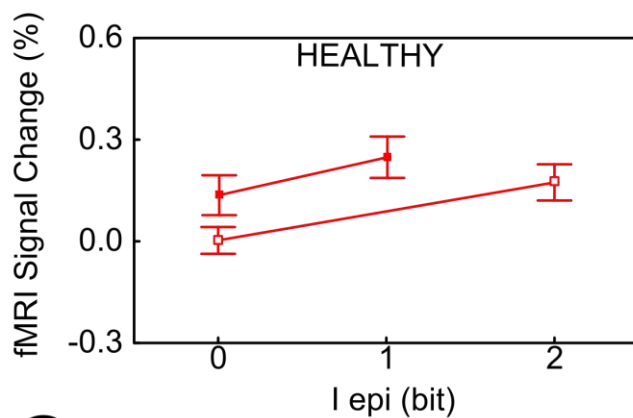
$z = 43$

$z = 43$

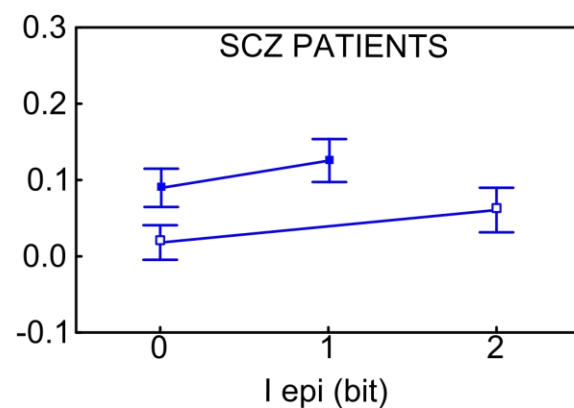
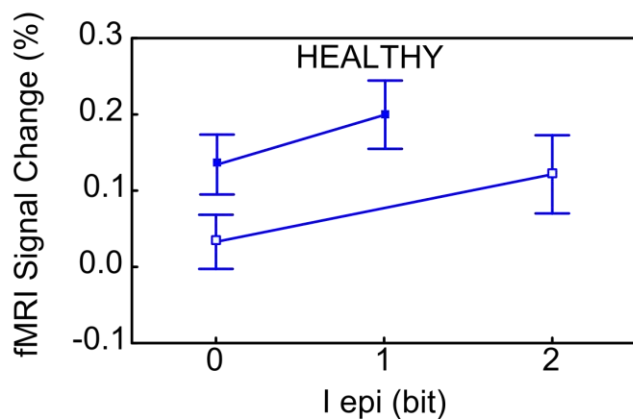


B

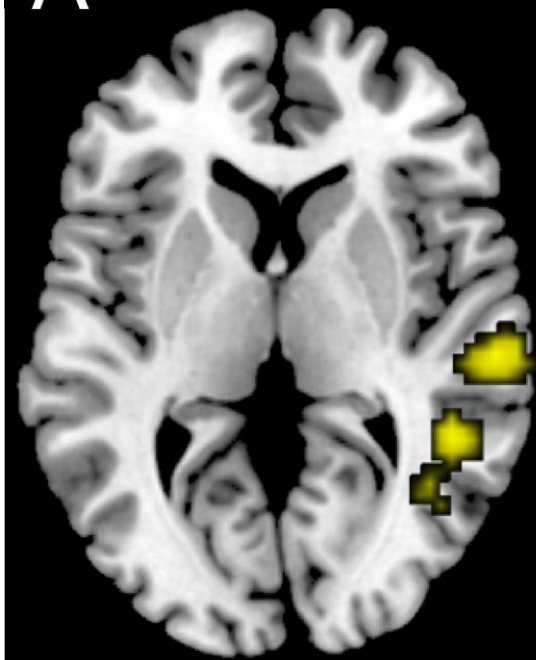
□ Single task-sets
■ Dual task-sets



C



A $z = 5$



B $z = -2$



Table 1. Coordinates of activations in regions showing an episode and context effects in the healthy participants and the schizophrenic patients groups.

Regions	Coordinates (x, y, z)	Volume (mm³)	FWE cluster corrected p value	T score	Z value
<u>Healthy Participants</u>					
Episode Effect					
Left Inferior Parietal Lobule	-36, -51, 42	1971	<0.001	5.35	4.35
Right Inferior Parietal Lobule	36, -60, 42	747	0.02	4.54	3.86
Context Effect					
Left Inferior Parietal Lobule	-45, -39, 42	2052	<0.001	6.40	4.23
Right Inferior Parietal Lobule	36, -42, 39	468	0.04	6.07	4.11
<u>Schizophrenic Patients</u>					
Episode Effect					
Right Superior Parietal Lobule	33, -54, 45	783	0.01	6.22	4.89
Left Superior Parietal Lobule	-30, -60, 48	180	0.46	4.13	3.62
Context Effect					
Left Precuneus	-15, -69, 39	1611	0.002	4.78	3.62
Left Postcentral Gyrus	-33, -30, 42	1017	0.02	4.45	3.46
Right Precuneus	21, -57, 24	171	0.97	4.27	3.36
Right Inferior Parietal Lobule	36, -45, 39	540	0.23	4.08	3.26

Table 2. Regions showing decreased functional connectivity with left and right caudal LPFC regions during contextual control for healthy participants relative to schizophrenic patients.

Regions	Coordinates (x, y, z)	Volume (mm³)	FWE cluster corrected p value	T score	Z value
Seed Region: left caudal LPFC					
Right Superior Temporal Gyrus	60, -21, 6	837	0.003	5.49	4.46
Right Middle Temporal Gyrus	48, -45, 3	729	0.007	5.45	4.44
Seed Region: right caudal LPFC					
Right Lingual Gyrus	6, -60, 3	837	0.02	4.63	3.94