Prefrontal functioning during context processing in schizophrenia and major depression: An event-related fMRI study ☆

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Abstract

Patients with schizophrenia frequently demonstrate hypofrontality in tasks that require executive processing; however questions still remain as to whether prefrontal cortex dysfunctions are specific to schizophrenia, or a general feature of major psychopathology. Context processing is conceptualized as an executive function associated with attention and working memory processes. Impairment in the ability of patients with schizophrenia to represent and maintain context information has been previously reported in a number of studies. To examine the question of the specificity of a context processing deficit to schizophrenia, we used functional MRI and an expectancy AX continuous performance task designed to assess context processing in a group of healthy controls ($n=9$), depressed patient controls ($n=10$), and patients with schizophrenia ($n=7$). The behavioral performance was consistent with a context processing deficit in patients with schizophrenia, but not those with depression. The imaging data replicate previous results in showing abnormal activity in the right middle frontal gyrus (BA9) in schizophrenia patients related to context processing.
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1. Rationale

Schizophrenia patients' cognitive deficits, such as working memory impairments, are closely linked to patients' functional impairments (Green, 1996). Previous work suggests that some aspects of patients' working memory deficits can be attributed to a

specific deficit in context processing, and that these deficits are associated with the disorganization symptoms of schizophrenia (Cohen et al., 1999). Context processing is defined as the ability to represent and actively maintain information required to select and execute task-appropriate behavior (Cohen and Servan-Schreiber, 1992) and behavioral evidence suggests this processes may be selectively impaired in patients with schizophrenia (Brambilla et al., submitted for publication; Servan-Schreiber et al., 1996). Therefore, a better understanding of the psychological and neuroanatomical basis of impairments like context processing is an important step for improving treatment outcomes (Carter and Barch, 2000).

Several functional imaging studies have demonstrated the role for the prefrontal cortex in context processing (Barch et al., 1997; MacDonald et al., 2000). Further studies have shown the association between impaired context processing and decreases in activity in the prefrontal cortex of schizophrenia patients relative to control subjects (Barch et al., 2001; MacDonald and Carter, 2003; Perlstein et al., 2003). However, there is also a growing literature showing decreased prefrontal activation in depressed patients (Liotti and Mayberg, 2001; Mayberg et al., 1999). Thus, one possibility is that prefrontal dysfunctions are a general marker of severe psychiatric illness. To address this issue, several studies have begun to explore the specificity of prefrontal dysfunction to schizophrenia during executive processing tasks. Using the Wisconsin Card Sorting Test, one study found no differences between the prefrontal dysfunctions in patients with schizophrenia and bipolar illness (Morice, 1990), whereas another using the N-Back paradigm found a dissociation between patients with schizophrenia and major depression (Barch et al., 2003). Both the Wisconsin Card Sorting Test and the N-Back reliably engage the prefrontal cortex, but both are complex tasks that affect many processes in addition to context processing. It remains to be demonstrated that a context processing-related dysfunction in prefrontal cortex is specific to schizophrenia, or whether this is a characteristic of psychiatric disease more broadly. To this end, we conducted an fMRI study using a measure that is a specific indicator of context processing, the AX-CPT task (Servan-Schreiber et al., 1996).

The goals of the current study are:

1. Replicate the previous finding concerning a context processing deficit in schizophrenia, and that context processing dysfunction is related to an inability to activate the prefrontal cortex.
2. Demonstrate selectivity of behavioral and functional deficits associated with context processing to patients with schizophrenia relative to patients with major depression.

2. Methods

2.1. Participants

The study compared three groups, including a final sample of 7 patients with schizophrenia (3 medicated, 4 unmedicated), 10 depressed patient controls and 9 demographically similar healthy controls. Schizophrenia patients were recruited from the inpatient units of Western Psychiatric Institute and Clinic (WPIC) and the Schizophrenia Treatment and Research Center in Pittsburgh, Pennsylvania, as well as from a clinical trial during which inpatient subjects under medical supervision were withdrawn from all psychiatric medication. This medication withdrawal occurred 1 month prior to testing. All depressed patients were also being treated through WPIC either as inpatients or in the partial hospitalization program. For both patient groups, diagnoses were confirmed using the Structured Clinical Interviews for DSM-III-R (SCID, First et al., 1996). Control participants were recruited from the community through advertisements in local newspapers and notices, and reported no history of Axis I disorders according to the non-patient version of the SCID (Spitzer et al., 1990).

The exclusion criteria for all participants included in the study were (a) age greater than 40 or less than 14; (b) WAIS-R Full Scale IQ below 70; (c) non-English native language; (d) lifetime diagnosis of substance dependence or substance use disorder within six months of testing; (e) neurological disorders or family history of hereditary neurological disorder; (f) pregnancy; and (g) inability to perform the task in the scanner. Depressed and healthy control participants were excluded if they had a first-degree

relative with psychosis. In addition participants were excluded for head movement greater than two voxels from the reference scan in any direction (see Pre-processing). Participants provided informed consent in accordance with the University of Pittsburgh institutional review board.

All psychiatric participants were assessed clinically within 1 day of testing using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983a), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983b), and the Brief Psychiatric Rating Scale (BPRS) (Overall, 1974) (see Table 1). All diagnostic and clinical evaluations were performed by one of two clinical evaluators, both of whom had advanced degrees in clinically relevant areas and participated in bi-weekly calibration sessions in which the interrater reliability of diagnosis and clinical symptoms ratings were monitored.

As shown in Table 1, there were no significant differences between the analyzed participants in terms of most demographic characteristics (sex, age, handedness, and parental education). However, the three groups differed significantly on education ($F = 4.72$, $p = 0.02$). As expected the patients with schizophrenia differed significantly in their Reality Distortion ($p < 0.001$) scores from the depressed patient controls.

2.2. Cognitive task

After sufficient practice outside the scanner, participants were administered the expectancy AX task, a version of the AX-CPT (Servan-Schreiber et al., 1996) during functional scanning. In this task a sequence of large font letters were visually presented one at a time in a continuous fashion on a computer display. The participants were instructed to make a target response for every X probe following an A cue, and a non-target response to all other letters. The subjects completed a total of 16 blocks of 10 trials each, or 160 letter pairs presented in random order. In each block, 70% of the trials were valid AX cue-probe pairs, 10% were AY, 10% were BX, and 10% were BY pairs ("B" represents any non-A cue, and "Y" any non-X probe). The ability to maintain the expectation of an X following an A indicated good context processing. For that reason the AY condition was difficult for participants with good context processing who anticipated a valid X probe but then had to overcome their prepared response. The BX condition was difficult only if the context of the B cue was sufficiently degraded to lead to false alarms when presented with the generally valid X probe. This inability to represent and maintain the invalid cue indicated poor context processing. The BY condition was included to confirm that the participants understood the task.

Table 1
Demographic and clinical characteristics of sample

	Schizophrenia[a]	Depressed patient controls[b]	Controls	Test
N	7	10	9	–
Sex (% male)	86	70	56	$\chi^2 = 1.69$, $p = 0.43$
Age	39.00 (6.93)	32.00 (9.87)	34.33 (8.14)	$F = 1.38$, $p = 0.27$
Education	12.86 (1.46)	15.60 (1.84)	14.78 (2.05)	$F = 4.72$, $p = 0.02$
Parental education	12.00 (3.18)	15.22 (3.08)	12.72 (2.79)	$F = 2.64$, $p = 0.09$
Handedness (% right)	100	90	100	$\chi^2 = 1.56$, $p = 0.46$
Symptom dimensions				
Reality distortion[c]	17.00 (4.52)	5.2 (2.49)	–	$t = 6.81$, $p < 0.001$
Disorganization[d]	6.17 (2.79)	4.50 (2.37)	–	$t = 1.28$, $p = 0.22$
Poverty symptoms[e]	11.17 (3.25)	9.80 (3.08)	–	$t = 0.84$, $p = 0.41$

[a] Including unmedicated multi-episode inpatients, medicated multi-episode inpatients and medicated outpatients.

[b] Including major depressions.

[c] Including grandiosity, suspiciousness, hallucinations, and unusual thought content from the BPRS, hallucinations and delusions from the SAPS.

[d] Including conceptual disorganization, mannerisms and posturing from the BPRS, attention, positive formal thought disorder, bizarre behavior from the SAPS.

[e] Including emotional withdrawal, motor retardation and blunted affect from the BPRS, anhedonia/asociality, avolition/apathy, alogia and affective flattening from the SANS.

Half of the blocks had a short delay between the cue and probe (2000 ms) and half had a long delay (7000 ms). The intertrial interval was 2000 ms for the long delay blocks and 7000 ms for the short delay blocks to control for time on task. Stimulus durations were 500 ms. Thus each trial lasted 10 s. d'-context, a measure of sensitivity to context, was calculated as d'-context=z(AX hits)−z(BX false alarms) (Servan-Schreiber et al., 1996).

2.3. Neuroimaging methods

2.3.1. Acquisition

Functional scans were acquired in a 1.5-T G.E. Signa whole body scanner with a standard head coil. Structural (T1) and functional images were obtained in the same plane following a double oblique prescription. Functional scans, sensitive to BOLD contrast, were obtained beginning on the AC–PC line and consisted of 16 3.8-mm-thick axial slices with 3.75-mm^2 in-plane resolution. Functional scans were obtained with a 2-shot T2-weighted spiral scanning pulse sequence (TR=1250, TE=35 ms, FOV=24 cm, flip angle 60°), which allowed full image acquisition every 2.5 s. Four full sets of 16 slice fMRI scans were acquired during each 10-s trial.

2.3.2. Pre-processing

Functional images were reconstructed and movement was estimated and corrected using Automated Image Registration (Woods et al., 1992). The imaging data from each individual participant was motion corrected to their first functional time point. After applying a maximum movement criterion (less then 2 voxels measured in mm or degrees rotation) for inclusion, MANOVA results indicated no significant differences between groups (Wilks' Lambda=0.61, p=0.23). A 12 parameter automated algorithm (Woods et al., 1998) was used to estimate the transformations necessary to register each subjects' structural T1-weighted image to the same reference brain. These parameter estimates were then applied to the functional T2-weighted images to bring all subjects' data into the same brain space. These data were then smoothed in three dimensions using an 8-mm FWHM kernel to accommodate the individual differences in brain morphology.

2.3.3. Statistical analysis

The functional images were then analyzed using a general linear model implemented by AFNI (Cox, 1996). Beta maps for individual subjects were generated to reflect the extent to which voxels' activity correlated with a standard hemodynamic response function (HRF, Boynton et al., 1996; Dale and Buckner, 1997). This was done by coding five different independent variables to account for the predicted variance in the BOLD activity. They included the occurrence of any cue, any probe, non-A cue ("B cue"), long delay between cue and probe, and the co-occurrence of a B cue with the long delay. This scheme enabled us, for example, to examine variance associated with representing the B context over-and-above variance associated with any cue. The occurrence of each event was convolved with an HRF. These predictors were then entered simultaneously into a general linear model implemented using AFNI (Cox, 1996) to generate each participants' beta map. The functional data acquired during error and no response trials were excluded to control for on-task behavior. The resulting beta maps thus quantified the unique contribution of each variable for each participant.

The between-group differences were calculated by the use of a one-way ANOVA with beta values as the dependent variable. To correct for multiple comparisons, images were thresholded at a p-value of $p < 0.01$ with a contiguity criterion of 8 voxels (Barch et al., 2001; Forman et al., 1995). Between-group differences were derived from ANOVA's for each regressor with subject as a random variable, group as an independent variable and beta values as the dependent variable. Despite restricting our analyses to epochs of on-task behavior, there remained uncorrected individual and group differences in reaction times. Secondary linear regression analyses were conducted to control for the effects of reaction time on each groups' beta maps.

3. Results

3.1. In-scanner performance

The error rates for the expectancy AX task are summarized in Table 2. Table 2 also elaborates a 4×2×3 repeated-measures ANOVA conducted with trial-type (AX, AY, BX, BY) and delay (short, long)

Table 2
In-scanner performance: means (SDs) and effect sizes for expectancy AX task

Measure	Schizophrenia	Depressed patients	Controls
n	7	10	9
Errors (%)[a]			
AX short	0.05 (0.10)	0.02 (0.04)	0.01 (0.01)
AX long	0.22 (0.30)	0.05 (0.06)	0.04 (0.04)
AY short	0.22 (0.23)	0.14 (0.20)	0.00 (0.00)
AY long	0.05 (0.08)	0.15 (0.18)	0.06 (0.09)
BX short	0.17 (0.26)	0.08 (0.12)	0.18 (0.28)
BX long	0.23 (0.36)	0.06 (0.12)	0.06 (0.08)
BY short	0.05 (0.08)	0.01 (0.04)	0.00 (0.00)
BY long	0.02 (0.06)	0.01 (0.04)	0.00 (0.00)
d'-context			
Short	2.62 (0.81)	3.21 (0.64)	2.97 (0.88)
Long	1.34 (0.56)	2.95 (0.67)	3.06 (0.56)

RTs=reaction times. H–F=Huynh–Feldt degrees-of-freedom correction.

[a] Between group error analysis. Main-effects: group $F(2,23)=2.60$, $p=0.10$; trial-type H–F $F(2.03,46.60)=4.33$, $p=0.02$; delay $F(1,23)=0.12$, $p=0.73$. Two-way interactions: group × trial-type H–F $F(4.05,46.6)=1.10$, $p=0.37$; group × delay $F(2,23)=0.28$, $p=0.76$; trial-type × delay H–F $F(2.00,63.86)=2.79$, $p=0.05$. Three-way interaction: group × trial-type × delay H–F $F(5.55,63.86)=3.05$, $p=0.01$.

as within-subject variables, and group (schizophrenia, depressed patient, and control) as the between-subject variable. As expected there was a significant trial-type effect ($F(2.03,46.60)=4.33$, $p=0.02$) caused by an increase in AY and BX errors. There was also a trial-type by delay interaction ($F(2.00,63.86)=2.79$, $p=0.05$) of borderline significance generated by a slight increase in overall error rates for the long delay condition. There was also a three-way interaction between group, trial-type, and delay ($F(5.55,63.86)=3.05$, $p=0.01$). Contrast analyses showed this interaction was driven in part by a tendency for controls to show a more extreme pattern compared to depressed patients of making more errors in the long (vs. short) AY condition and the short (vs. long) BX conditions, whereas schizophrenia patients tended to make more errors in the short AY and long BX conditions relative to depressed patients. Among schizophrenia patients there was a non-significant tendency to commit a greater percentage of AX long delay compared to AX short delay errors ($t(8)=1.55$, $p=0.159$) and fewer AY long delay compared to AY short delay errors ($t(8)=-2.103$, $p=0.069$).

Table 3
Group differences in regional activity

Region of interest	BA	Coordinates			Vol.	F	Post-hoc
		x	y	z			
B-cue-related activity[a]							
r. mid./sup. frontal gyrus	9	39	42	39	1815	8.73	s<d,c
r. mid. frontal/precentral gyrus	9	44	23	40	1442	7.72	s<c
Delay-related activity							
l. inf./sup. pari. lobe/ang. gyrus/precuneus	7	−33	−70	49	5180	11.06	s<c<d
B-cue×delay-related activity							
r. sup./med. frontal gyrus	8	3	49	45	3044	8.36	d<c<s
r. mid./precentral gyrus	9	39	27	34	2617	8.59	c,d<s
l. ang./mid. temp. gyrus/precuneus	39	−37	−63	37	1442	7.40	d<s
r. sup. temp./post. central gyrus/inf. pari. lobe	40	64	−22	12	2136	12.42	c<s,d
l. sup. temp./post. central gyrus/inf. pari. lobe	40	−61	−22	19	1976	11.12	c<s,d
r. inf./mid. frontal gyrus	47	52	47	−12	1762	6.40	s<c<d

BA=Brodmann area; Coordinates of centroids are given according to Talairach and Tournoux (1988); vol.=#number contiguous active voxels × 53.4 mm^3 (3.75 × 3.75 × 3.8); F=average F-value of voxels; post-hoc=Newman–Keuls analysis ($p<0.01$), where c=healthy controls; d=depressed patient controls; s=schizophrenia patients; r.=right; l.=left; med.=medial; sup.=superior; mid.=middle; inf.=inferior; pari.=parietal; ang.=angular; temp.=temporal: post.=posterior.

[a] Illustrated in Fig. 1.

Analysis of d'-context showed significant effects of both group ($F(2,23)=4.55$, $p=0.02$), due to differences between patients with schizophrenia and controls, and delay ($F(1,23)=7.53$, $p=0.01$) due to differences between short and long. Additionally there was a significant interaction between group and delay ($F(2,23)=5.00$, $p=0.02$) due to schizophrenia patients' significantly reduced performance in the delay condition compared to both the depressed patients and controls. Thus, the error analysis generally confirmed the expectation that the patients with schizophrenia would be the most consistently impaired on the context processing sensitive BX trials, and that depressed patient controls would generally perform more like the healthy controls.

3.2. Functional neuroimaging

Regions with significant group differences in hemodynamic activity associated with the B cue, the long delay, and the B cue by delay interaction are summarized in Table 3. The B-cue-related activity
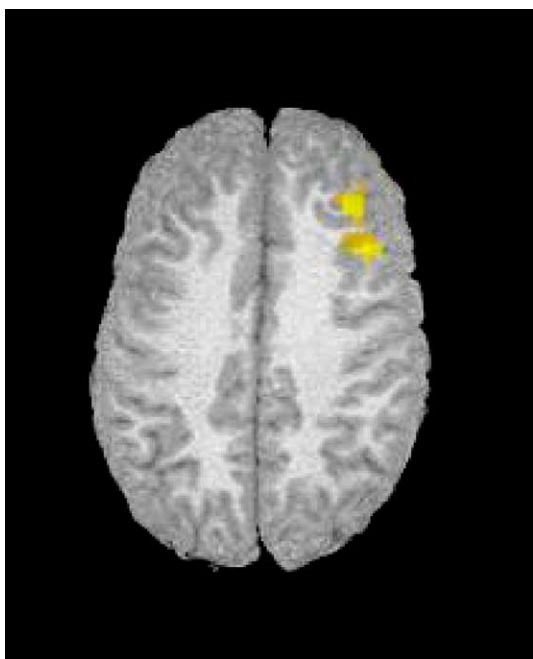

Fig. 1. Group Differences in B-cue-related activity in right middle frontal gyrus (BA 9). Note: activity in these regions showed a positive deflection in controls and a negative deflection in patients with schizophrenia.

corresponded with the regions associated with preparing to overcome a prepotent response collapsed across both short and long delay. As shown in Table 3, patients with schizophrenia showed less activity in BA 9 compared to both the depressed patient and the control groups during this condition (Fig. 1). After covarying out reaction times using linear regression analysis, there was still a significant difference in the group beta maps in this region ($F(2,24)=6.966$, $p=0.004$). The delay related activity shows the effect of increasing the temporal separation between the cue and the probe. In this contrast, depressed patients showed more activity than controls and patients with schizophrenia. The last covariate is the interaction between the cue type and the delay. In this final interaction, schizophrenia patients showed more activity in several prefrontal and parietal regions, including BA 9 and BA 8.

4. Discussion

This study utilized a version of the AX-CPT context processing task and fMRI to examine the differences between patients with schizophrenia, non-psychotic depressed patients, and demographically matched normal controls. Schizophrenia patients demonstrated an impairment in a behavioral measure of context processing, whereas the depressed patients performed more similarly to controls. In terms of brain activity, we replicated results from earlier studies which suggested that context processing demands from the B cue trials in general are associated with activity in middle frontal gyrus, BA 9 (Barch et al., 2001; MacDonald and Carter, 2003; MacDonald et al., 2005; Perlstein et al., 2003). We also replicated findings that patients with schizophrenia showed lower levels of activation in BA 9 on these types of trials relative to controls, even after controlling for reaction time differences. In addition to these predicted findings, we reported that in cases where the B cue had to be maintained over a delay, schizophrenia patients showed more activation in right middle and superior frontal gyri compared to depressed patients or controls (Table 3), which has also been previously observed (MacDonald et al., 2005).

One explanation for the reported hyperfrontality in right prefrontal cortex is that it is a statistical anomaly;

that is, depressed patients and controls activate these regions whether or not the B cue has to be maintained, and therefore variance associated with the B cue in the delay condition is better accounted for by the B cue alone for these groups. Thus, schizophrenia patients appear to be more active in this region simply because variance is differently allocated due to low activity on short B trials. This explanation alone is inadequate, however. The regions that show hyperfrontality in schizophrenia patients in the interaction analysis are physically larger than those that show hypofrontality associated with the B cue regressor.

Given that a statistical anomaly alone is unlikely to provide a compelling account of hyperfrontality, perhaps these results support the contention that this region functions less efficiently in schizophrenia patients (Callicott et al., 2003; Manoach, 2002). An alternative, or perhaps complementary account, suggests that hyperfrontality in some regions of prefrontal cortex reflects a shift in strategy to compensate for the dysfunctional region. From this perspective, hypo- and hyperfrontality may be inextricably connected as different manifestations of the same underlying behavioral dysfunction in which alternate areas of the frontal working memory network are recruited in supporting specific task demands (Quintana et al., 2003). According to this interpretation, the delay blocks of this context processing task may provide patients' time to recruit a qualitatively different, but generally less reliable, strategy.

Thus, the current study contributes to the on-going debate about the nature of prefrontal impairments in schizophrenia patients, and builds on previous findings by demonstrating the functional and behavioral specificity of the context processing deficits in schizophrenia. Although several studies have reported prefrontal deficits in depressed patients (see Ottowitz et al., 2002), such patients generally showed patterns of activation similar to controls in the current study. There were several exceptions, however, such as reduced activity in superior frontal gyrus (BA 8) when B cues had to be maintained, and increased activity in posterior regions, including parietal cortex. These differences in activity were not linked to context processing deficits, however. The current study cannot speak to prefrontal abnormalities in depressed patients that may occur in other cognitive or affective processes.

Unexpectedly, we found that controls made as many context related (BX) errors in the short condition as schizophrenia patients did, and nominally more than depressed patients did. Since the controls did not show elevated BX errors in the long condition or in the AX condition, which also has some context processing demands, this was unusual. The observation highlights that even when using a performance criterion for inclusion, behavioral results can be vulnerable to small sample sizes and procedural irregularities such as changes in performance from practice to scanner.

The current data does not address the relationship between these deficits and etiology, or how these deficits relate to functional outcomes. Instead, the current study combines a hypothesis driven cognitive task, a well-replicated impairment in schizophrenia, and control for on-task performance to provide an important perspective on the nature of the abnormalities of prefrontal cortical functioning in this debilitating mental disorder.

Acknowledgements

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