FMRI OF GENETIC LIABILITY TO SCHIZOPHRENIA: REGIONAL ACTIVITY AND
CONNECTIVITY DIFFERENCE PERSPECTIVES

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Abstract

Typically, fMRI analyses of schizophrenia patients' family members have employed the general linear model (GLM) to examine clusters of activation in the brain, which provides a region-by-region examination of brain activity. This study additionally examined a newer group independent component analysis (ICA) to test the hypothesis that the unexpressed genetic liability to schizophrenia is reflected in the functional connectivity between brain regions during a context processing task, the expectancy AX task. We compared 20 schizophrenia patients and 32 first-degree relatives to 22 controls and 28 control relatives. The subjects completed the expectancy AX task, a context processing measure, while being scanned in a 1.5T MR scanner. We then performed a group ICA on all participants' fMRI data in order to examine the functional networks that are active during the AX task. Next, a GLM analysis was performed. Groups' mean activations were contrasted with each other to obtain differential activation. The group ICA showed significantly different activations between patient probands and control probands in a network constituting dorsolateral prefrontal cortex and posterior parietal lobe. The relative groups differed in an anterior cingulate network. The GLM analysis showed differential functioning between patient and control relatives in the dorsolateral prefrontal cortex, but failed to show any differences between patient and control probands. These disparate findings suggest some potential advantages to functional connectivity relative to region-by-region approaches to understanding the neural basis of genetic liability to schizophrenia.

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Difference Perspectives

Schizophrenia is a psychotic illness characterized by a collection of diverse impairments in cognitive and affective functioning. The liability for the development of the disorder is highly heritable, yet genetic studies implicate complicated, polygenic causes for this liability (Harrison & Weinberger, 2005). This complex genetic basis for the predisposition to schizophrenia has led researchers to develop investigative methods aimed at teasing out these elusive underlying causes. One such method involves searching for biological mechanisms that result in schizophrenia liability instead of the disease itself. Taking such a tack has methodological as well as interpretive benefits. Investigating specific mechanisms as opposed to the global construct of schizophrenia allows researchers to both narrow their etiological searches and to design studies that would be difficult otherwise, such as creating animal models that reflect specific underlying mechanisms.

These points argue for the use of endophenotypes in schizophrenia research. These endophenotypes represent biomarkers for schizophrenia liability that exist in predisposed individuals regardless of whether the disease manifests and so provide a more reliable measure of liability than the disease entity itself (Gottesman & Gould, 2003). More specifically, because it is assumed that the healthy first-degree relatives of schizophrenia patients have nevertheless inherited a portion of the genetic liability to schizophrenia, it is

also assumed that the effects of this unexpressed liability will manifest in phenotypic traits that reflect this predisposition (Gottesman & Gould, 2003). Because first-degree relatives have not manifested schizophrenia, observed cognitive impairments that resemble those experienced by schizophrenia patients can be assumed to result from the genetic predisposition to the disease. When studying schizophrenia patients it is difficult to disentangle impairments or deficits in functioning that result from the genetic predisposition from those that result from the effects of antipsychotic medication and the disease entity itself. Additionally, an unknown proportion of control subjects, though without manifest psychosis, nevertheless possess a degree of schizophrenia proneness. These difficulties make studying endophenotypes a useful method.

      Although some studies have found that patients' healthy relatives typically have deficits in many cognitive domains, suggesting a generalized deficit (Dickinson, Goldberg, Gold, Elvevag, & Weinberger, 2010; Snitz, 2005; Snitz, MacDonald, & Carter, 2006), researchers have identified specific constructs that are potential endophenotypes for schizophrenia (Harvey, 1981; A. W. MacDonald, M. F. Pogue-Geile, M. K. Johnson, & C. S. Carter, 2003; Oltmanns & Neale, 1975). Specific deficits in functioning that reflect underlying dysfunctional mechanisms provide researchers with clues as to what causes liability to schizophrenia as well as ideas for how to investigate those clues. Generalized deficits in functioning are of less use when trying to identify the sources of schizophrenia liability, because they do not provide clues about what specific

mechanisms, neural pathways, or genes might be involved. With generalized deficits, the source of the deficit is elusive.

Impairments in executive functions such as context processing show promise as possible endophenotypes (MacDonald, Pogue-Geile, Johnson, & Carter, 2003), and may help to guide the search for the etiology of schizophrenia. Context processing refers to the ability to represent and maintain goal-relevant information during the execution of some task, especially when this task requires overcoming an automatic or over-learned response (Cohen & Servan-Schreiber, 1992). It has been shown that both schizophrenia patients (Jones, Sponheim, & MacDonald, 2010; Servan-Schreiber, Cohen, & Steingard, 1996) and their healthy first-degree relatives (MacDonald et al., 2003) demonstrate deficits in their ability to perform tasks which require context processing abilities.

Previous studies have examined brain functioning using functional magnetic resonance imaging (fMRI) in both patient samples (Barch et al., 2001; MacDonald et al., 2005) and healthy relatives (Macdonald, Becker, & Carter, 2006) while these groups performed context processing tasks. These studies have shown that areas of the prefrontal cortex (PFC), especially dorsolateral PFC (MacDonald & Carter, 2003), function differently between control subjects and both patients and their relatives. However, it is not known exactly how the functioning differs, and this uncertainty has implications for

the method with which fMRI data are analyzed. Some studies suggest that cognitive

impairment in schizophrenia patients may involve improper connectivity in neural

networks as opposed to localized pockets of differential activation (Camchong,

MacDonald, Bell, Mueller, & Lim, 2009).

Such findings suggest the typical method of analyzing fMRI data, which employs

the general linear model (GLM), may not be ideal for examining PFC dysfunction

corresponding with context processing deficits. This is because if neural dysfunction in

schizophrenia occurs not in clusters but in networks, GLM-based analyses may not be

sensitive to them. These GLM-based analyses require the researcher to specify the

expected response pattern of subjects. Independent component analysis (ICA), a blind

source separation technique, may be a more appropriate method as it can detect sources

of signal based on common "behavior" as opposed to the regional approach of the GLM

(Calhoun, Eichele, & Pearlson, 2009; Calhoun, Liu, & Adali, 2009). ICA approaches

then may be better able to detect dysfunctional neural networks because it does not rely

on localized clusters of differential activation.

ICA was developed as a means of separating individual, statistically independent

sources of signal variance within an intermingled set of data (Hyvarinen & Oja, 2000).

The requirement that source signals be statistically independent is a tighter restriction

than other methods like factor analysis and principal component analysis impose (e.g., uncorrelated sources). Applied to fMRI data, this technique assumes a certain number of spatially independent groups of voxels which share a temporal pattern of hemodynamic activity (Calhoun, Adali, Pearlson, & Pekar, 2001). These components thus can be thought of as temporally coherent networks (TCN), because they consist of groups of voxels with temporal similarity. This method has been used extensively with fMRI data acquired from individual subjects as a means of eliminating sources of "noise," but group ICA extends the utility of ICA to examine data from many subjects (Calhoun, Adali, & Pekar, 2004). However, this extension introduces potential problems in interpretation, which GLM analyses do not share. For instance, it is difficult to infer the meaning of TCMs if subjects do not share the same time course. Analyses involving the use of the GLM specify regressors for each subject, which allows for more obvious interpretation. Recent studies suggest that group ICA can be successfully applied to studies of schizophrenia patients (Kim et al., 2010). Some studies have compared GLM-based analyses with ICA-based analyses (Britz, Van De Ville, & Michel, 2010; Calhoun, Adali, Stevens, Kiehl, & Pekar, 2005), but, to the authors' knowledge, the present study represents the first such comparison using schizophrenia patients and their first-degree relatives.

Thus, the research questions of the present study involved three aims. The first two had to do with the substantive issues of whether context processing as measured by the

expectancy AX task is supported as an endophenotype for schizophrenia and, if so, what

brain areas (or networks) seem to function differently between control subjects and both

schizophrenia patients and their relatives. The last question involved the comparison of

GLM analyses and group ICA analyses with regard to fMRI studies between patients,

relatives, and control subjects. The hypotheses were 1) Schizophrenia patients would

perform worse on the expectancy AX task than control subjects and that the first-degree

relatives of schizophrenia patients would perform worse than the first-degree relatives of

control subjects on the same task; 2) Patients and their relatives would show differential

activation patterns as compared with control subjects and their relatives, respectively,

during key trials during the expectancy AX task; and 3) Group ICA analyses would

detect spatially broader areas of activation that differ between groups than the clusters

provided by GLM analyses.

Method

Participants

Schizophrenia probands were identified who had a DSM-IV chart diagnosis of

schizophrenia or schizoaffective disorder and who had siblings living nearby. When at

least one first-degree relative (biological parent, child, or full sibling) between the ages of

21 and 40 contacted the researchers or agreed to be contacted, the proband would be

interviewed using the Structured Clinical Interview for the DSM-IV Axis I Disorders,

Patient Edition (SCID IV) (First, Spitzer, & Williams, 2002). Healthy controls were

recruited from the general community through newspaper advertisements and fliers and must also have had at least one first-degree relative between the ages of 21 and 40 living nearby. Advertisements were placed in the newspapers known to serve the neighborhoods of the patients' relatives. Patients' relatives, control subjects, and control relatives were screened for psychiatric disorders and substance abuse using the SCID IV and the Structured Interview for Schizotypy– Revised (SIS-R) (Kendler, Lieberman, & Walsh, 1989; Vollema & Ormel, 2000).

Of the 155 subjects who consented for the study, 30 were ineligible due to misdiagnosis/misclassification or drug use, and 12 chose not to participate in scanning. Eleven subjects were removed for poor task performance (error rate > 90% on A-X, A-Y, and B-X trials, or error rate > 50% on B-Y trials. No subjects were removed due to poor performance on the WRAT-III Reading subtest (Wilkinson, 1993), which was administered as an estimate of full-scale IQ in order to rule out mental retardation. We conducted a standard MRI safety screening in order to exclude subjects who would be unsafe to scan. Thus analyses were performed on a total of 102 subjects. Demographic data for the final sample are presented in Table 1.

Table 1. Demographic Information of Proband/Relative Groups

	Group					
	Control Probands	Control Relatives	Patient Probands	Patient Relatives	Probands	Relatives
N	22	28	19	33		
Mean Age (Yrs.)	29	36	26	34	$t(39)=1.55$	$t(59)=0.32$
% Male	59.10	46.43	78.95	33.33	$\chi^2(1)=0.28$	$\chi^2(1)=0.84$
% Caucasian	50.00	60.71	47.37	63.64	$\chi^2(1)=0.02$	$\chi^2(1)=0.01$
% Right Handed	95.45	92.86	94.74	90.91	$\chi^2(1)=0.48$	$\chi^2(1)=0.07$
Mean Education (Yrs.)	15.57	15.50	13.50	15.11	$t(39)=3.05$ *	$t(59)=0.40$
Mean Parental Education (Yrs.)	15.14	13.30	15.21	14.24	$t(39)=-0.23$	$t(59)=-1.15$
Proportion of Meds (Atypical, Other)	n/a	n/a	(.79, 0, .21)	n/a		
BPRS	n/a	n/a	41.8	n/a		

* $= p < .05$

Expectancy AX task

The expectancy AX task is a variant of the classical AX continuous performance task (CPT) (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). Although the AX CPT originally was considered a measure of visual vigilance and attention (Mirsky, 1987), the expectancy AX task's increase in the ratio of A-X trials (described below) make it well-suited to measure the ability of subjects to overcome an overlearned, or prepotent, response by maintaining contextual clues (Servan-Schreiber et al., 1996). The stimuli consisted of a series of letters displayed on a computer screen one at a time and was programmed in E-Prime. The task presentation consisted of a cue letter followed by a probe letter. The letter "A" was designated as a valid cue, whereas all "non-A" letters

(e.g., "B") represented invalid cues. Likewise, the letter "X" represented a target probe, while any other letter (e.g., "Y") represented a non-target probe. Subjects were instructed to respond via button box only after a target trial consisting of an "A" cue followed by an "X" probe. Seventy percent of trials were valid A-X. A-Y trials constituted 10%, B-X trials made up 12.5%, and the remaining 7.5% were B-Y trials. Each cue was presented for 1000 milliseconds. After a 4000 ms interstimulus interval, probes were displayed for 500 milliseconds. Subjects then had 1500 milliseconds to respond. The time between probe discontinuation and cue onset was 1100 milliseconds. Subjects responded to stimulus materials using a button box.

The expectancy AX task is optimized for detecting specific deficits in context processing. Four unique trial types, A-X, A-Y, B-X, and B-Y, make up the expectancy AX task. Because 70% of all trials are valid A-X trials, subjects with intact context processing are "primed" to respond in the presence of an "A" cue. This means those subjects with intact context processing should make more false alarms on A-Y trials relative to subjects with deficits in context processing. Likewise, subjects with compromised context processing should make more false-alarm errors on B-X trials because of a failure to keep the "non-A" information in mind long enough to disregard the "X" probe. Therefore, a relatively high number of B-X errors is indicative of impaired context processing ability.

fMRI method

Subjects were administered the expectancy AX task in 4 blocks or sessions.

Functional scans were collected using a 1.5 Tesla GE Signa Scanner with the following

parameters: 280 scans with a repeat time (TR) of 2 s, an echo time (TE) of 40, a flip

angle of 90 degrees, a voxel size of 3.4 x 3.4 x 4 mm, a field of view of 22 cm, and 24

axial slices. T1 reference images were collected with the following parameters: voxel size

was .86 x .86 x 1.5 mm thickness yielding dimensions of 256 x 256 x 124 voxels.

These data were then preprocessed in four steps using SPM 5 (see

http://www.fil.ion.ucl.ac.uk/spm/). The data were first slice-timing corrected. Next,

realignment was performed according to the following parameters: a 5 mm full width at

half maximum (FWHM) Gaussian smoothing kernel, a 2nd degree B-spline interpolation

for movement correction and a 4th degree B-spline for re-slicing. Subsequently the data

were normalized by employing an affine regularization into ICBM space, a nonlinear

frequency cutoff of 25, 16 nonlinear iterations, a 4 mm^3 voxel size, and a trilinear

interpolation. Finally, the data were smoothed with an 8 mm FWHM Gaussian kernel.

Statistical Analyses

To analyze the behavioral data from the expectancy AX task, we first calculated d'

context scores , which uses correct responses on A-X trials and incorrect B-X trials

("false alarms") to arrive at a more specific measure of context processing. d' context

does not, however, correct for a generalized deficit. Therefore, a mixed-effects logistic

regression was performed to examine expectancy AX task results (Henderson et al., in

press). Because the mixed-effects logistic regression does not rely on the strict

parametric assumptions that repeated-measures analysis of variance does, it may be a

more appropriate tool for analyzing expectancy AX task data. Group status and trial type

were included in the regression model.

For purposes of comparison, functional data were subject to two analysis paths: one

using a mixed-model general linear model (GLM) and the second using group

independent components analysis (ICA). GLM analyses were conducted using the fMRI

Expert Analysis Tool (FEAT), which is included in the FMRIB Software Library (FSL,

see www.fmrib.ox.ac.uk/fsl/feat5/detail.html). This analysis consisted of three "levels"

of analysis: scan level, subject level, and group level. At the scan level of analysis, we

analyzed the subjects' data for each of the four scans including the following regressors

in the regression model: "A" Cues, "B" Cues, "X" Probes, "Y" Probes, Fixation, Cue

Error, and Probe Error. Cue regressors were defined as the time between the onset of the

cue stimulus and the onset of the probe stimulus only on trials in which the subject

responded correctly. Likewise, probe regressor times started at the onset of the probe

stimulus and ended when a correct response was made. Cue and probe error regressors

were defined by trials in which the subject responded incorrectly. Last, fixation was defined as the time between a response being recorded and the onset of the next trial's cue stimulus.

Thirteen contrasts were computed at the first level of analysis to determine the average areas of activity during each regressor time as well as to contrast regressors with each other. Only positive activations were recognized in this analysis. The contrast of interest determined areas where "B" Cue activation was greater than "A" Cue activation. Cluster-wise thresholding was employed at $z = 2.3$. At the subject level, we averaged each subject's data from the four sessions using the results from the session level analysis. At the group level, we averaged the data for each of the four groups. Before thresholding the final output, we masked the possible voxels to include only those areas that showed differential activation between controls and schizophrenia patients in an activation likelihood estimation (ALE) study of executive function studies (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). This ALE employed GingerALE meta-analysis software (Eickhoff et al., 2009).We also performed the group level analysis using instead a probabilistic mask of the middle frontal gyrus obtained from the Harvard-Oxford structural atlas included in FSL.

Group ICA was performed on all subjects' fMRI data using the Group ICA of fMRI Toolbox (GIFT, see http://icatb.sourceforge.net) to examine the functional networks that are active during the expectancy AX task. Data reduction was achieved prior to ICA by means of three consecutive principle component analyses (PCA) in order to create one data matrix. Minimum description length (MDL) criteria designated the number of components within the data. The infomax ICA algorithm (Bell & Sejnowski, 1995) extracted the individual and group component spatial maps and accompanying time courses.

Once the components had been identified, we determined which components activated differently between groups. To do this, we first compared the same two ALE maps that were used to mask the GLM analysis to the components' spatial maps using a multiple regression. This regression employed each component's spatial map for each subject as regressors. The components' timelines were then regressed onto the time course of all "B" trials of the expectancy AX task. We analyzed the beta coefficients of this step to determine if a given component was task-related as well as if subject groups differed with regard to how task-related a component was.

Results

Behavioral Results

To determine if participant groups differed with regard to context processing ability, d' context scores were computed for each participant, and independent samples t-tests were then performed to determine if groups differed on d' context. The results of behavioral analyses are illustrated in Figure 1. Schizophrenia probands (M = 2.34, SD = 1.00) had significantly lower d' context scores (Figure 1A) compared to control participants (M = 3.13, SD = 0.64), $t(40)$ = 3.01, p = .0025, one-tailed. Likewise, schizophrenia relatives (M = 2.75, SD = 0.88) had significantly lower d' context scores compared to control relatives (M = 3.13, SD = 0.57), $t(58)$ = 1.96, p = .0275, one-tailed. We also calculated BX-AY error rates to better demonstrate a specific context processing deficit. Patient probands (M = -0.05, SD = 0.27) did not differ from control probands (M = -0.15, SD = 0.24) on this measure, $t(40)$ = -1.33, p = .097, one-tailed. Likewise, patient relatives (M = -0.03, SD = 0.22) did not differ from control relatives (M = -0.03, SD = 0.12), t = -0.12, p = .453, one-tailed.
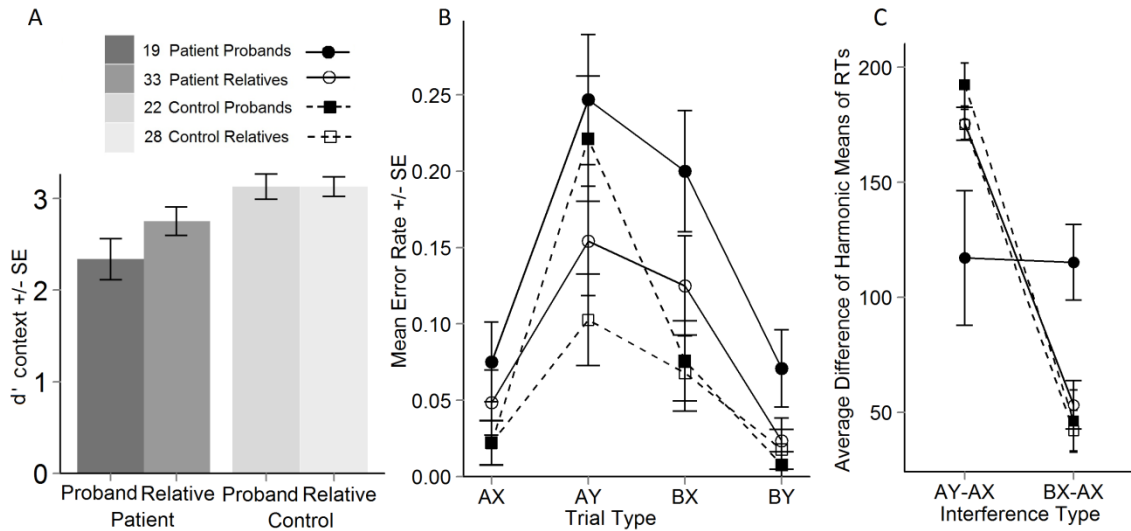
Figure 1. Expectancy AX task performance – A) d' context scores, B) error rates by trial type, and C) reaction time interference.

We also evaluated whether these deficits were more specific to a failure of goal maintenance by investigating the relative deficit of patients on B-X compared to A-Y trials (error rates are illustrated in Figure 1B). Overall, subjects were less likely to correctly respond to A-Y trials as compared with A-X and B-Y trials ($z=9.43$, $p < .001$ and $z=5.39$, $p<.001$) but were equally likely to respond correctly on B-X trials ($z=1.59$, $p=.11$). Patient probands performed worse than control probands across all trial types except A-Y trials ($z=.385$, $p=.70$). Relative to A-Y trials, patient probands performed worse than control probands on B-X trials ($z=3.41$, $p<.001$), as well as A-X ($z=4.43$, $p<.001$) and B-Y ($z=2.71$, $p<.001$) trials. Patient relatives did not differ from control relatives in any comparison. Overall, we found that patient probands showed specific context processing deficits on the Expectancy AX task compared with control probands.

We also found that patient relatives showed deficits on the Expectancy AX task compared with control relatives, but we could not demonstrate a specific context processing deficit in patient relatives compared with control relatives. Interestingly, patient relatives differed from control probands on A-Y trials ($z=-1.96$, $p=.05$) and, relative to A-Y trials, patient relatives performed worse than control probands on A-X($z=4.99$, $p<.001$) and B-X($z=3.56$, $p<.001$) trials.

Additionally, reaction times (RTs) were calculated for correct trials. The harmonic mean RT was computed due to non-normality of the distribution of RTs (Ratcliff, 1993). To compare groups, we subtracted participants' mean A-X RTs from their respective A-Y RTs and B-X RTs to determine to what extent A-X trials interfered with the other trials (Figure 1C). Pairwise t-tests were performed to compare A-Y interference RTs with B-X interference RTs within groups. Control probands, control relatives, and patient relatives all showed significantly longer RTs in the A-Y minus A-X condition compared with the B-X minus A-X condition. However, patient probands did not differ between these two conditions ($p = 0.27$). Independent sample t-tests were performed to determine differences between groups. There was a trend in the data indicating patient probands had longer A-Y interference RTs ($t(36.9) = -1.47$, $p = 0.08$), but all other comparisons were not significant. This means that A-X trials did not interfere with patient probands' performance on A-Y and B-X trials in the same way that they did for the other three groups.

GLM Results

With regard to the GLM analysis of these data, bilateral clusters of activation in the MFG were found that represent main effects of "B" trials compared with "A" trials, as illustrated in Figure 2A. The final group comparison between control probands and patient probands resulted in no significant clusters of activation masking for either the middle frontal gyrus mask or the cognitive control mask. However, in the final group comparison where control relatives' activation was significantly greater than patient relatives' activation, one cluster was found to be significant using the middle frontal gyrus map, and two clusters were found to be significant using the cognitive control map, as illustrated in Figure 2B. One of the two significant clusters found by masking using the cognitive control map was completely subsumed by the significant cluster revealed using the MFG mask.
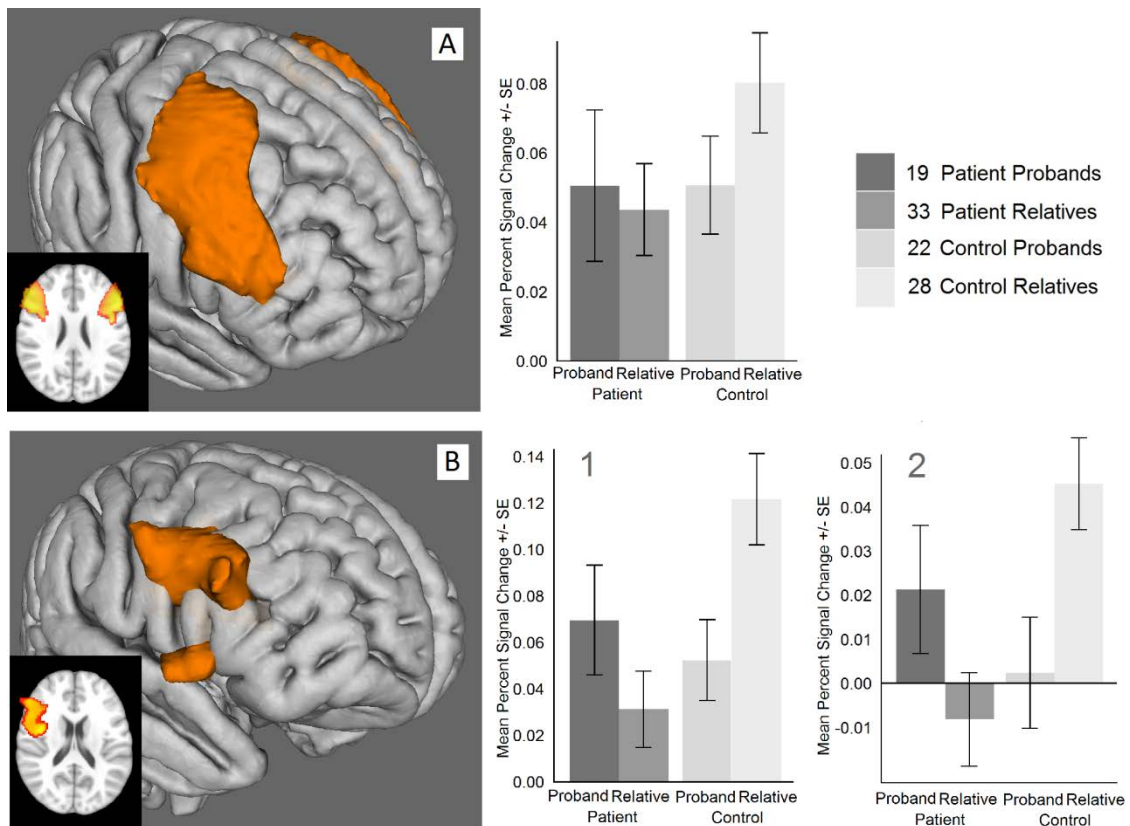
Figure 2. GLM analysis results – A) Spatial map and mean percent signal change in regions showing main effect of "B" cue greater than "A" cue on expectancy AX task, B) Spatial map and mean percent signal change of two clusters in which control relatives showed more activation than patient relatives on "B" cues relative to "A" cues of the expectancy AX task.

Subsequently, we created a binary mask of these significant clusters to determine the nature of the difference. We employed Featquery, a tool within FSL, to determine the average percent signal change of the voxels within that mask for each subject. We then

averaged these averaged percents of signal change for each group. Independent samples t-tests were performed to compare groups with regard to these means of percent signal change. Control relatives' mean percent signal change was significantly higher than patient relatives' change within this area ($t(59) = 3.60$, $p < .001$). Control probands did not differ from patient probands in this regard.

ICA Results

The group ICA on these data resulted in 23 components. These components were arbitrarily numbered 'C1' to 'C23'. The three components whose spatial maps were most closely related (in order of largest to smallest R^2 values) to the cognitive control mask based on a multiple regression were C10, C3, and C8. The R-squared values for these three components ranged from .002 to .001. The three components whose spatial maps were most closely related to the middle frontal gyrus mask were C5, C13, and C18. The R-squared values for these three components ranged from .137 to .106.

We then established how related to the "B" trials of the expectancy AX task timeline those six components were. We did this by performing one-sample t-tests on the beta weights of a multiple regression involving the participants' "B" trial expectancy AX task timeline and their individual component timelines. We performed these t-tests for all four groups combined. We used a p value of .008 ($p = .05/6$). It was found that three

components were significantly related to the "B" trials of the expectancy AX task (as illustrated in Figure 3): C8 ($t(101) = -3.80, p < .0001$), C13 ($t(101) = 2.71, p < .008$), and C18 ($t(101) = 7.46, p = 3.06*10^{-11}$).

Next, we determined if the extent to which these three components were related to task timeline differed between groups. We did this by performing independent samples t-tests on the same beta weights of the multiple regression involving the participants' "B" trial expectancy AX task timeline and their individual component timelines from the previous step. Between patient probands and control probands, the mean weights for those three components were as follows: C18 was not significantly different between patient probands and control probands C18 ($t(40) = 0.001, p = 0.500$, as illustrated in Figure 3A). C8 ($t(40) = 0.748, p = 0.229$) was also not significantly different between proband groups (illustrated in Figure 3B). C13 ($t(40) = 2.27, p = 0.014$) was significantly different between groups at an alpha level of .017 (Figure 3C). Control relatives differed significantly from patient relatives with regard to how closely C8 ($t(58) = -2.63, p = 0.005$) was related to their task timelines (Figure 3B). However these groups did not differ with regard to C13 ($t(59) = 1.23, p = 0.112$) and C18 ($t(59) = 0.139, p = 0.445$). Component 18, being significantly related to the expectancy AX task timeline but not differentially related between groups, represents a main effect of the expectancy AX task.
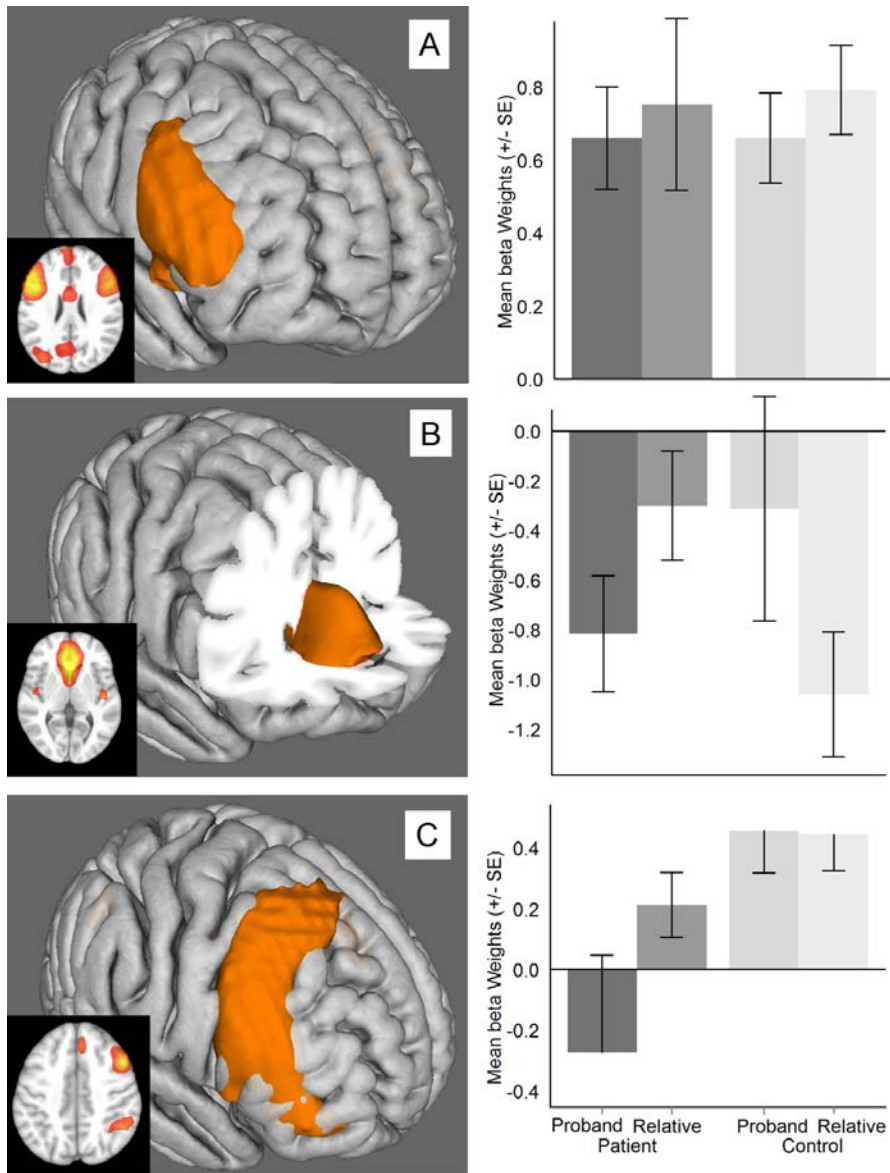
Figure 3. ICA analysis results – Spatial maps and mean temporal regression coefficients indicating relatedness with task for A) component 18, a MFG component which does not differ between groups and is analogous to the clusters in Figure 2A, B) component 8, a component centered on anterior cingulated cortex which differs between relative groups but not proband groups, and C) component 13, a MFG component significantly different between proband groups and showing a trend between relative groups.

Finally, we determined the percent of variance in participants' data each component

accounted for by back-reconstructing the group mean components onto the individual

subjects' data. We then performed Mann-Whitney Rank Sum tests to determine if groups

differed with regard to how much variance a given component accounted. When

comparing control probands with patient probands, the following components had a *p*

value below .05: C4, C11, C13, and C16. There were no significant differences between

patient relatives and control relatives. When probands and relatives were combined,

however, only component C13 remained below the .05 level.

Discussion

To test the hypothesis that schizophrenia patients and their first-degree relatives

have a specific deficit in context processing, 20 patient probands, 32 patient relatives, 22

control probands, and 28 control relatives completed the expectancy AX task in a 1.5T

fMRI scanner. Patient probands showed a specific deficit in context processing

compared with control probands. Patient relatives showed a mild deficit across

conditions compared with control relatives. With regard to neuroimaging results, the

findings largely supported our hypotheses. The results of the GLM analysis were

difficult to interpret, but the fact that no differences were found between patient probands

and control probands suggests any differences between relative groups are likely

spurious. The ICA results revealed three components which were both related to the

expectancy AX task timeline and correlated with regions of interest, and of these only the

component representing right PFC was differentially active between control probands and patient probands.

The behavioral finding that patient probands displayed a specific deficit in context processing on the expectancy AX task as compared with control probands supports previous research findings (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Dias, Butler, Hoptman, & Javitt, 2011; Javitt, Shelley, Silipo, & Lieberman, 2000). However, we failed to replicate previous research (Delawalla, Csernansky, & Barch, 2008; MacDonald et al., 2003) that showed a specific deficit of context processing in the healthy relatives of schizophrenia patients. However, this failure only emerged when comparing patient relatives with control relatives. It is clear that the control relatives performed abnormally on the expectancy AX task both compared with the control proband group and with controls in previous studies of context processing (see context processing studies cited above). It is not clear what the cause of the control relatives' error pattern on the expectancy AX task was, as pertinent demographic variables did not differ in that group compared with the other groups. When compared with control probands, patient relatives showed a specific deficit in context processing. These results support context processing as an endophenotype for schizophrenia.

Previous research has found that schizophrenia patients (MacDonald & Carter,

2003; Perlstein, Dixit, Carter, Noll, & Cohen, 2003) and their healthy first-degree

relatives (Becker, Kerns, Macdonald, & Carter, 2008; Delawalla et al., 2008) show

dysfunctional activation patterns in areas of the PFC, including dorsolateral PFC, during

cognitive control tasks as compared with healthy controls. The results of the GLM-based

analyses of functional imaging data do not support this prior research. Whole brain

comparisons between groups revealed no significant differences in BOLD response.

ROI comparisons revealed differences between relative groups but not proband groups.

Based on the performance of the control relative group and their average percent signal

change in the area identified in Figure 2B, it is likely some aspect of that group drove the

differences observed between the relative groups. The differences between the relative

groups are therefore likely the result of sampling error, although the nature of that error is

unknown due to the lack of demographic differences between the control relatives and

the control probands. It seems unlikely that a volunteer bias, which the control relatives

were intended to control for, could fully explain the differences in activation in this

group.

In contrast to the GLM, the ICA analyses did show components which were

temporally task-related and which were differentially task-related between groups. These

findings potentially support the notion that ICA is more sensitive to differences in neural

activity as measured with fMRI than GLM (Rombouts et al., 2009). Additionally, they

could lend support to the idea that brain connectivity differences, which would result in

dysfunctional networks as opposed to regional clusters, are underlying causes of

differential neural activity between schizophrenia patients and healthy controls (Kim et

al., 2009; Repovs, Csernansky, & Barch, 2010; Skudlarski et al., 2010). However, these

conclusions are tentative due to the failure of the GLM to find *any* differences between

patient probands and control probands. Additionally, although group ICA may be more

sensitive to dysfunctional networks of neural function that GLM-based analyses, the

components found in this study to be differentially task-related between groups did not

show characteristics of a distributed network. On the contrary, they appear to be

localized clusters of differential activation. It is possible that dysfunction inherent in

context processing deficits is actually a localized one in the dorsolateral PFC. Further

research is needed to determine the nature of this dysfunction.

Although previous studies of middle frontal dysfunction in the relatives of

schizophrenia patients have resulted in contradictory findings of both hyper- and

hypofrontality, a recent meta-analysis revealed that most such studies found a relative

decrease in activation in the middle frontal region in patient relatives during executive

tasks (Goghari, 2010). The results of the present GLM analysis of these data revealed less

activation in patient relatives compared with control relatives in the MFG. This result

agrees with the previous literature, but the results of the ICA analysis revealed a greater

activation in the anterior cingulate in patient relatives compared with control relatives.

The anterior cingulated has been hypothesized to be involved with error detection (Carter

et al., 1998), and so it is possible that this error monitoring played a role in the odd task performance of the control relative group.

The limitations of this study revolve around the control relative group. More information about the nature of the differences between that group and the control probands might explain why their performance and their neuroimaging data appear so different from the control probands and from previous research. Additionally, within-group differences in both performance on the expectancy AX task and in neuroimaging results could give clues as to the relationship between the two, but these differences were not examined in this study.

In conclusion, this study examined context processing in patients with schizophrenia and their unaffected first-degree relatives compared with healthy controls and their first-degree relatives using the expectancy AX task and functional magnetic resonance imaging. Additionally, it examined the relative merits of group ICA and GLM-based analyses in discovering dysfunctional brain regions and networks that underlie context processing impairments. It was shown that both patient probands and their first-degree relatives demonstrated specific context processing deficits as compared with healthy controls. Both the GLM-based analysis and the ICA found main effects of context processing in bilateral middle frontal gyrus. The GLM analysis of the functional

data failed to reveal areas of differential activation between patient probands and control probands but did show areas where control relatives showed significantly more activation than patient relatives in the right middle frontal gyrus. The ICA found differential activation in the anterior cingulated between relative groups and in the middle frontal gyrus between proband groups. These results replicate previous findings of specific context processing deficits in schizophrenia patients and their healthy first-degree relatives and also demonstrate a possible advantage of group ICA over GLM in detecting areas and networks that underlie the genetic predisposition to schizophrenia.

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