



## Task-based functional connectivity as an indicator of genetic liability to schizophrenia



Andrew B. Poppe<sup>a</sup>, Cameron S. Carter<sup>b,c</sup>, Michael J. Minzenberg<sup>b,c</sup>, Angus W. MacDonald III<sup>a,d,\*</sup>

<sup>a</sup> Department of Psychology, University of Minnesota, 75 E River Rd, Minneapolis, MN 55455, United States

<sup>b</sup> Department of Psychology, University of California at Davis, 135 Young Hall, One Shields Ave., Davis, CA 95616, United States

<sup>c</sup> Department of Psychiatry, UC Davis Medical Center, 2230 Stockton Blvd., Sacramento, CA 95817, United States

<sup>d</sup> Department of Psychiatry, University of Minnesota School of Medicine, 2450 Riverside Ave. S., Minneapolis, MN 55454, United States

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### ABSTRACT

Impaired functional connectivity has been hypothesized as a potential source of the cognitive deficits routinely observed in patients with schizophrenia. Additionally, these deficits may be manifestations of the genetic liability to schizophrenia and present in the non-psychotic first-degree relatives of that group. However, no study has examined task-based functional connectivity in schizophrenia relatives using independent component analysis (ICA). We employed group ICA to test the hypothesis that the unexpressed genetic liability to schizophrenia is reflected in the functional connectivity between brain regions during a task measuring context processing. We compared 20 schizophrenia patients and 32 patients' first-degree relatives to 22 controls demographically matched to the patients and 28 controls' relatives, respectively. The group ICA showed differential connectivity between patients and controls in a task-related network constituting right middle frontal gyrus (MFG) and right posterior parietal lobe. A network constituting left MFG and left posterior parietal, which was also related to the context processing task, did not differ between groups. These findings demonstrate that connectivity abnormalities associated with the genetic liability to schizophrenia are most strongly expressed in a right lateralized executive fronto-parietal network, and that these abnormalities are linked to context processing impairments.

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### 1. Introduction

The liability to schizophrenia is highly heritable, and genetic epidemiology implicates complex, polygenic causes for this predisposition (Gottesman and Shields, 1972; Harrison and Weinberger, 2005). A growing literature suggests that this genetic liability may affect neural connectivity (see Tost et al., 2012 for review). To test this possibility, the current study examined task-based functional connectivity in schizophrenia patients and their non-psychotic first-degree relatives using group independent component analyses (ICA).

Functional connectivity measures may be particularly useful for understanding disorders that arise from dysconnectivity. Schizophrenia may be one such disorder, however studies report a great diversity of findings in functional connectivity at rest (Pettersson-Yeo et al., 2011). One possibility for such divergent findings in these studies is that resting state scans do not constrain the activities of subjects and thereby introduce state-related noise. Task-based functional connectivity may

provide an advantage in measuring certain functional connectivity differences, because subjects are engaged in tasks requiring functions that are disrupted in schizophrenia patients and their relatives.

One function that has been shown to be disrupted in schizophrenia patients and their non-psychotic relatives is context processing (Cohen and Servan-Schreiber, 1992), which is a putative endophenotype of schizophrenia (Gottesman and Gould, 2003). Context processing refers to the ability to represent and maintain goal-relevant information during the execution of a task, especially when the task requires inhibiting an automatic or over-learned response (Cohen and Servan-Schreiber). While a number of candidate endophenotypes are difficult to distinguish from generalized deficits (Dickinson et al., 2004; Snitz et al., 2006), the construct of context processing is specific and mechanistic (MacDonald et al., 2003). It has been shown that both schizophrenia patients (Servan-Schreiber et al., 1996; Jones et al., 2010) and their non-psychotic first-degree relatives (MacDonald et al., 2003) demonstrate deficits in their ability to perform tasks that require context processing abilities. Deficits in context processing ability as measured by AX continuous performance tasks demonstrated the highest effect sizes in studies of cognitive task performance between control subjects and the non-psychotic relatives of schizophrenia patients in a meta-analysis of putative endophenotypes of schizophrenia (Snitz et al., 2006). Furthermore, dysfunctional activation patterns have been observed in schizophrenia

\* Corresponding author at: Translational Research in Cognitive and Affective Mechanisms Laboratory, Department of Psychology, University of Minnesota, N426 Elliott Hall, 75 E. River Rd. Minneapolis, MN 55455, United States. Tel.: +1 612 624 3813; fax: +1 612 625 6668.

URL: <http://www.psych.umn.edu/research/tricam/> (A.W. MacDonald).

patients (Perlstein et al., 2003; MacDonald et al., 2005), and their non-psychotic relatives (MacDonald et al., 2006; Delawalla et al., 2008) during the performance of context processing tasks. The task used in the present study was the expectancy AX task, which will be discussed below.

One region of interest for studying the genetic liability to schizophrenia is the middle frontal gyrus (MFG). Functional connectivity between MFG and other brain regions is altered in schizophrenia patients (Yoon et al., 2008; Pettersson-Yeo et al., 2011). Degraded connectivity within functional networks that include MFG also has been demonstrated in the non-psychotic relatives of schizophrenia patients (Woodward et al., 2009), and evidence has shown this reduced MFG functional connectivity is present independent of differential activation (Rasetti et al., 2011). Despite this evidence, it remains to be seen what role impaired functional connectivity plays in the context processing deficits exhibited by schizophrenia patients and their non-psychotic relatives.

Group ICA was chosen as the analysis method in this study because it affords two primary benefits when compared with psychophysiological interaction analysis. First, it identifies a small number of components that can then be examined further, which reduces the number of comparisons and increases the power to detect subtle group differences. Second, because ICA extracts components without a model or spatial parameters, those components represent networks as they exist in the sample. This makes an improper characterization of a network less likely than if we were to define the network explicitly a priori.

Therefore, the first aim of the present study was to determine if functional connectivity networks that include MFG displayed differential task-relatedness in schizophrenia patients compared with healthy controls in response to demands on context processing. The second aim involved whether such connectivity differences fulfilled the familiarity criterion of an endophenotype (Gottesman and Gould, 2003) by examining these measures in the non-psychotic first-degree relatives of schizophrenia patients. Additionally, to our knowledge, no one has explored task-based functional connectivity using group ICA in the non-psychotic relatives of schizophrenia patients.

## 2. Methods

### 2.1. Participants

Schizophrenia patients were identified who had a DSM-IV chart diagnosis of schizophrenia or schizoaffective disorder with 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 patient was interviewed using the SCID IV (First et al., 2002). Patients' relatives, control subjects, and relatives' controls were screened for psychiatric disorders and substance abuse using the SCID IV and the Structured Interview for Schizotypy. Initially 155 subjects consented for the study. Of these, 30 were ineligible because of misdiagnosis or drug use, and 12 dropped out of the study prior to scanning. Eleven subjects were excluded from analyses because

their task performance was too poor (accuracy <10% on A–X, A–Y, or B–X trials, or accuracy <50% on B–Y trials). The Reading subtest of the WRAT-III (Wilkinson, 1993) was administered to rule-out mental retardation. No subjects needed to be removed due to poor performance on this test. An MRI safety screening was employed to exclude subjects for whom scanning would be unsafe. Analyses were thus performed on a total of 102 subjects. Demographic data for the final sample are presented in Table 1. Patients were only significantly different from controls on education. Patients' relatives were not significantly different from controls' relatives on any demographic variable.

### 2.2. Expectancy AX task

Subjects saw a series of letters and were instructed to respond only if an "A" cue was followed by an "X" probe. This created four unique trial types: A–X, A–Y, B–X, and B–Y, where "B" refers to any "non-A" cue and "Y" refers to any "non-X" probe. There were 70% A–X trials, 12.5% B–X trials, 10% A–Y trials, and 7.5% B–Y trials. Because the majority of all trials were valid A–X trials, 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 would be indicative of impaired context processing ability. Subjects are also prepared to respond "target," in the presence of an "A" cue, so A–Y trials serve as a difficulty control because they can be challenging even for those with intact context processing. Cues were presented for 1000 ms, and probes were presented for 500 ms. There was a 4000 ms ISI and an 1100 ms ITI. Subjects had 1500 ms to respond following the onset of each probe. For a detailed description of the expectancy AX task paradigm, see MacDonald (2008).

### 2.3. fMRI method

Subjects were administered the expectancy AX task in 4 blocks within the same study visit. 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 ms, a flip angle of 90°, a voxel size of 3.4 × 3.4 × 4 mm, a field of view of 22 cm, and 24 contiguous axial slices. T1 reference images were collected with the following parameters: voxel size was .86 × .86 × 1.5 mm thickness yielding dimensions of 256 × 256 × 124 voxels.

These data were then preprocessed in four steps using SPM 5 (<http://www.fil.ion.ucl.ac.uk/spm/>). The data were first slice-timing corrected. Next, realignment to the first volume in each time series 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 reslicing. 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<sup>3</sup> voxel size, and a trilinear interpolation. Finally,

**Table 1**  
Sample characteristics.

	Group				Patients vs. controls	Relatives vs. controls
	Patients	Patients' relatives	Controls	Controls' relatives		
N	19	33	22	28		
Mean age (yrs.)	26(7.7)	35(11.2)	29(7.6)	36(7.4)	$t(39) = 1.25$	$t(59) = 0.32$
% male	78.95	33.33	59.10	46.43	$\chi^2(1) = 0.28$	$\chi^2(1) = 0.84$
% Caucasian	47.37	63.64	50.00	60.71	$\chi^2(1) = 0.02$	$\chi^2(1) = 0.01$
% right handed	94.74	90.91	95.45	92.86	$\chi^2(1) = 0.48$	$\chi^2(1) = 0.07$
Education (yrs.)	13.50(2.9)	15.1(2.9)	15.6(2.0)	15.5(2.2)	$t(39) = 2.73^*$	$t(59) = 0.60$
Parental education (yrs)	15.0(2.3)	14.3(3.6)	15.1(1.6)	13.4(2.9)	$t(39) = 0.16$	$t(59) = -1.06$
Proportion of meds (atypical, other)	(.79, .21)	n/a	n/a	n/a		
BPRS	41.8	n/a	n/a	n/a		

Note: \* =  $p < .05$ ; parenthetical values following means represent standard deviations.

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