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Persistence, diagnostic specificity and genetic liability for context-processing deficits in schizophrenia

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ABSTRACT

Context-processing deficits have been shown in schizophrenia during first-episode, medication-naïve status, that persist after short-term antipsychotic treatment and also in first-degree relatives of individuals with schizophrenia. To confirm longer term persistence of deficits, we examined schizophrenia patients (n = 63) during first-episode, medication-naïve status through to one-year follow-up, compared to healthy control (n = 83) and non-schizophrenia psychosis comparison (n = 47) groups, as well as unaffected first-degree relatives of individuals with schizophrenia (n = 31). Context-processing ability was assessed by performance on the AX-CPT (Continuous Performance Test) at baseline, 8 weeks, 6 months, and 1 year (relatives only at baseline). Reaction time, error rates and signal detection indices (d′-context) of context processing were analyzed. Linear discriminant analyses (LDA) on early timepoints (baseline, 8 weeks) were conducted to predict confirmatory diagnosis (schizophrenia vs. psychosis control) at 6 months. Schizophrenia patients showed evidence of impaired context-processing relative to both the healthy and psychosis comparator groups at baseline and continued through to 1 year. While context-processing impairments persisted in schizophrenia patients through one year, the impairments in psychosis controls, which were more modest at baseline, remitted at follow-up. First-degree relatives showed deficits that were intermediate between the schizophrenia and healthy control groups. LDA showed 67% classification rates for distinguishing schizophrenia from non-schizophrenia psychosis. The persistence, diagnostic specificity and association with genetic liability give support for context processing impairments serving as a cognitive endophenotype for schizophrenia and evaluation of context processing could contribute to diagnostic assessments.

1. Introduction

Cognitive deficits are a core feature of schizophrenia that predict functional outcomes (Niendam et al., 2007; Komlosi et al., 2008; Leung et al., 2008; Harvey et al., 2009). Context processing (Harvey et al., 2009), the ability to represent and maintain task-relevant information to inform subsequent responding, is impaired in schizophrenia compared to healthy subjects and psychiatric controls (Servan-Schreiber et al., 1996; Hawkins et al., 1997; Barch and Carter, 1998; Javitt et al., 2000; Stratta et al., 2000a,b; Barch et al., 2001; MacDonald et al., 2005; McClure et al., 2008; Barch, 2009). Context processing is closely related to the 'goal maintenance' component of working memory, which has been extensively investigated as a deficit in schizophrenia (Javitt et al., 2007; Forbes et al., 2009) and proposed to be one of the core cognitive deficits in schizophrenia (Bedwell et al., 2006; MacDonald, 2008).

Barch et al. (2003) examined context processing in medication-naïve patients with schizophrenia or non-schizophrenia psychosis at first episode and after short-term treatment. With similar deficits at baseline, psychosis controls improved by four-weeks while schizophrenia subjects did not, consistent with deficits in schizophrenia that are stable and diagnostically specific. Disorganization symptoms and context-processing deficits were also correlated among schizophrenia patients, consistent with previous research (Barch et al., 1999a,b; Cohen et al., 1999; Stratta et al., 2000a,b) but not among psychosis controls. The present study builds upon the study of Barch et al. (2003), with an expanded sample and extended follow-up period, as a more thorough evaluation of the persistence and specificity of context-processing deficits to schizophrenia.

Consistent with the strong heritability of schizophrenia, context-processing deficits are partially expressed in unaffected relatives (Pflueger et al., 2007; Wang et al., 2007). Previous research has found context-processing and working memory deficits in parents and siblings (Delawalla et al., 2008) that are milder than those of chronic medicated patients, consistent with partial expression in

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unaffected relatives (MacDonald et al., 2003; Barrantes-Vidal et al., 2007). In the present study, we also investigated unaffected first-degree relatives of medication-naïve first episode patients, thus avoiding the effects of active symptoms or medications.

The current study examined (1) diagnostic specificity of context-processing deficits in schizophrenia; (2) persistence of deficits over one year of treatment; and (3) comparison of first-degree patient relatives to healthy controls and first episode patients. We predicted that (1) context-processing deficits would be more severe in schizophrenia patients than psychotic controls and that these differences would help in discriminating between the two groups; (2) deficits would improve in psychotic controls but not in schizophrenia patients; and (3) first-degree relatives would display deficits intermediate to healthy controls and schizophrenia patients. To these ends, we assessed context processing in medication-naïve first episode psychosis patients, with follow-up at four/eight weeks, six months, and one year; first-degree relatives performed the task at a single timepoint.

2. Materials and methods

2.1. Participants

Patient subjects had first episode psychosis, were antipsychotic-naïve, with 6 month post-enrollment diagnostic confirmation using SCID-IV. Clinical ratings used the Brief Psychiatric Rating Scale (BPRS, $\alpha = .90$), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, $\alpha = .90$ and $\alpha = .77$ respectively), and the Global Assessment of Functioning Scale (GAS, $\alpha = .75$). Following Barch et al. (2003), patients' clinical state was summarized across the factors Reality Distortion, Disorganization and Poverty symptoms. Healthy controls were evaluated with SCID-NP IV. Relatives were unaffected first-degree relatives (parents, siblings, or offspring) of non-participant individuals with schizophrenia or schizoaffective disorder.

Exclusion criteria included mental retardation, substance dependence within 6 months or abuse within past month, head injury, neurological or medical illness, pregnancy/postpartum, and inability to provide informed consent. Relatives were excluded for lifetime history of schizophrenia spectrum or mood disorder with psychotic features, or mood disorder within three months.

Baseline assessments included 83 healthy controls (HC), 63 patients diagnosed with schizophrenia (48) or schizoaffective disorder (15), 47 psychotic controls (PC; 3 delusional disorder, 12 major depression with psychotic features, 20 psychotic disorder NOS, 2 schizophreniform disorder, 2 bipolar I disorder, and 2 bipolar disorder NOS), and 31 first-degree relatives. Of these participants, 53 HC, 50 schizophrenia patients (SZ) and 27 PC completed 4 or 8 week follow-up, 40 HC, 31 SZ and 19 PC completed the 6 month follow-up, 36 HC, 28 SZ and 14 PC completed the 1 year follow-up, and 25 HC, 23 SZ, and 8 PC completed all timepoints.

The groups did not differ in age, $F(3, 209) = 1.7$, $p > .16$, gender, $\chi^2(3, N = 224) = 7.6$, $p > .05$, or parental SES, $F(3, 183) = 2.5$, $p > .06$, but did in education, $F(3, 191) = 10.0$, $p < .001$ (Table 1). Participants who completed baseline only and participants who completed one year follow-up did not differ in age, $t(183) = -1.2$, $p > .21$, gender, $\chi^2(2, N = 184) = 1.11$, $p > .29$, parental SES, $t(172) = 1.3$, $p > .19$, or education, $t(171) = 1.43$, $p > .15$. All procedures were in accordance with the University of Pittsburgh Institutional Review Board.

2.2. Task

The AX-CPT required Target responses to AX trials (A followed by X) constituting 70% of trials, and Nontarget responses to the three other trial types (AY, A followed by non-X letter; BX, non-A letter followed by X; BY, non-A followed by non-X letter) each 10% of trials.

Table 1
Clinical and demographic characteristics.

	Healthy controls M (SD)	Schizophrenia patients M (SD)	Psychotic controls M (SD)	Relatives M (SD)
Age (years)	24.8 (7.3)	23.7 (7.5)	22.6 (8.4)	26.8 (11.4)
Parental SES	42.3 (8.8)	37.5 (14.4)	41.1 (11.2)	35.4 (9.9)
Years of education	14.6 (2.6)	12.2 (3.0)	12.2 (3.0)	12.5 (3.4)
Sex (% male)	51	73	72	50
GAS		35 (10)	40 (12)	
Disorganization		16 (4)	10 (4)	
Reality distortion		22 (5)	14 (5)	
Poverty		19 (5)	16 (5)	

Note. Clinical symptom scores are at the baseline assessment.

Stimuli were presented for 300 ms. Short-delay trials had 1 s cue-probe intervals and 5 s intertrial intervals while long-delay trials had 5 s cue-probe intervals and 1 s intertrial intervals. Participants practiced to 80% accuracy. PsyScope or E-prime controlled stimulus presentation and response recording.

2.3. General analysis approach

Dependent measures were error rates (ER), signal detection indices (d′-context; Barch et al., 2003), and correct reaction times (RT). Analyses were for all HC, SZ, and PC with baseline assessments, followed by analyses of subsets with 4/8 week, 6 month, and one-year follow-ups, respectively; and all four timepoints. Analyses used repeated measures ANOVAs (rmANOVAs) and Fisher's least significant difference for post-hoc contrasts to correct for multiple comparisons. Linear discriminant analysis (LDA) was used to conduct a multivariate test of discriminability between diagnostic groups based on a linear combination of the behavioral measures at baseline and 4/8 weeks, using cross-validation to avoid inflated discriminability estimates. A separate analysis compared relatives to other groups at baseline using rmANOVA and polynomial trend analysis to test for monotonic relationships between degree of genetic liability and cognitive impairment. Correlations between symptom scores and d′-context were calculated.

3. Results

Index assessment and 1 year follow-up data are presented here. For other results, see Supplemental Materials.

3.1. Index assessment

3.1.1. ERs

ANOVA with group (HC, SZ, PC) as a between-subjects factor, and delay (short, long) and trial type (AX, AY, BX, BY) as within-subjects factors, revealed main effects of group, $F(2, 190) = 10.1$, $p < .001$, and trial type, $F(3, 188) = 36.0$, $p < .001$, modified by a trial type × group interaction, $F(6, 378) = 3.9$, $p < .001$, and a delay × trial type interaction, $F(3, 570) = 49.3$, $p < .001$ (Fig. 1). Planned contrasts indicated that, as predicted, SZ made more BX errors than HC, $F(1, 190) = 10.0$, $p < .001$, but not more AY errors, $F(1, 190) = 1.5$, $p > .10$. PC also made more BX errors than HC, $F(1, 190) = 5.5$, $p < .05$. As predicted, SZ made more BX than AY errors, $F(1, 328) = 16.4$, $p < .001$. HC, $F(1, 328) = 8.6$, $p < .005$, and PC, $F(1, 328) = 4.7$, $p < .05$, also made more BX than AY errors; however, the difference between BX and AY errors was significantly higher for SZ as compared to HC, $F(1, 220) = 5.3$, $p < .05$.

3.1.2. d′-context

ANOVA at baseline (Fig. 2) with group as a between-subjects factor and delay as a within-subjects factor revealed main effects of group,