



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.

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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 \times group interaction, $F(6, 378) = 3.9$, $p < .001$, and a delay \times 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,

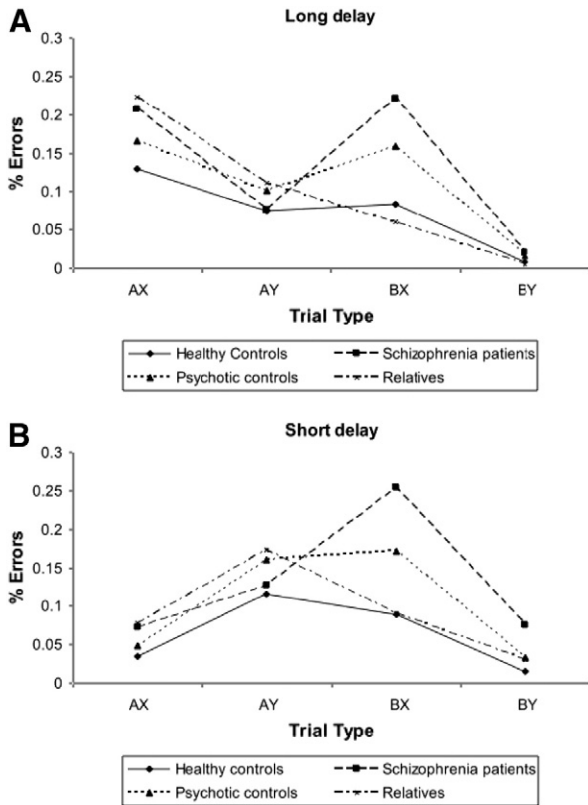


Fig. 1. Proportions of errors for all four groups at the baseline assessment of context processing using AX-CPT. A. Long-delay condition. B. Short-delay condition.

$F(2, 190) = 11.3$, $p < .001$, and delay, $F(1, 190) = 23.4$, $p < .001$. Contrasts indicated that, as expected, SZ had lower d' -context than HC at both long, $F(1, 190) = 22.4$, $p < .001$, and short delays, $F(1, 190) = 4.1$, $p < .001$, and lower d' -context than PC at long delay, $F(1, 190) = 5.1$, $p < .05$.

3.2. 1 year assessment

3.2.1. ERs

ANOVA with all subjects at both baseline and 1 year (Fig. 3) was conducted, with group as a between-subjects factor, and delay, trial

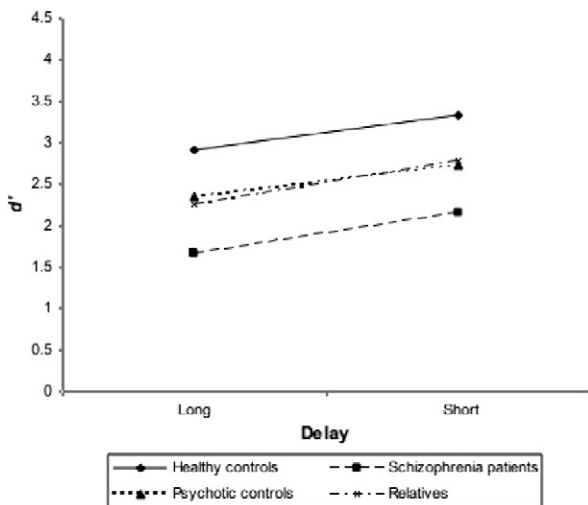


Fig. 2. Signal detection indices for all four groups using BX false alarms at the baseline assessment of context processing using AX-CPT.

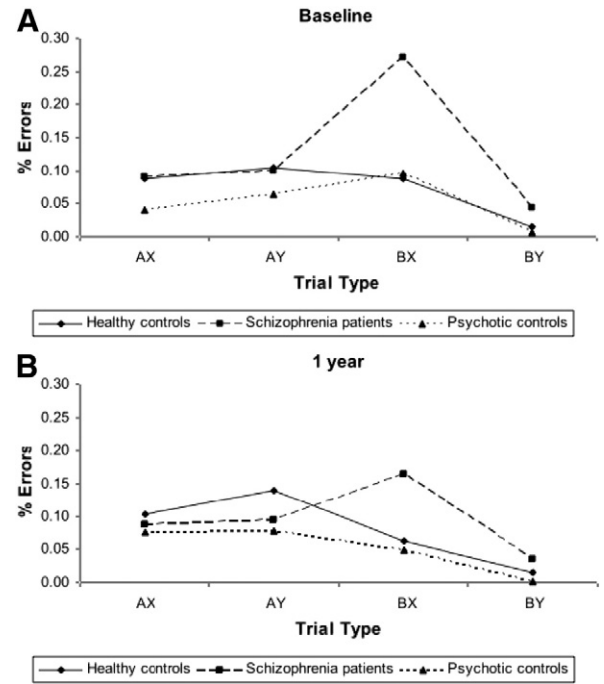


Fig. 3. Proportions of errors at the baseline and 1 year assessments of context processing for subjects who completed both assessments using AX-CPT. A. Baseline assessments. B. One-year follow-up assessments.

type, and visit as within-subjects factors, revealing main effects of group, $F(2, 88) = 4.0$, $p < .05$, delay, $F(1, 76) = 7.9$, $p < .01$, and trial type, $F(3, 74) = 12.2$, $p < .001$, modified by a trial type \times group interaction, $F(6, 150) = 4.6$, $p < .001$, a visit \times delay interaction, $F(1, 76) = 5.0$, $p < .05$, a visit \times trial type interaction, $F(3, 74) = 3.2$, $p < .05$, and a delay \times trial type interaction, $F(3, 74) = 13.2$, $p < .001$. Planned contrasts indicated that SZ made more BX errors than HC and PC at baseline and 1 year (all $ps < .05$). HC made more AY than BX errors at 1 year, $F(1, 144) = 7.1$, $p < .01$, while SZ made more BX than AY errors at baseline, $F(1, 108) = 12.4$, $p < .001$.

3.2.2. d' -context

ANOVA with all subjects at both baseline and 1 year (Fig. 4) with group as a between-subjects factor, and delay and visit as within-subjects factors, revealed main effects of group, $F(2, 75) = 5.9$, $p < .005$, visit, $F(1, 75) = 4.6$, $p < .05$, and delay, $F(1, 75) = 19.3$, $p < .001$. Planned contrasts indicated that SZ had lower d' -context than HC and PC at both delays at baseline (all $ps < .05$), and lower d' -context than HC at short delay at 1 year, $F(1, 76) = 7.2$, $p < .01$. T-tests between baseline and 1 year revealed improved d' -context at short delay for HCs, $t(36) = 2.21$, $p < .05$, and PCs, $t(14) = 2.29$, $p < .05$, and at long delay for SZs, $t(28) = 2.64$, $p < .01$, consistent with practice effects.

3.3. Relatives analysis

3.3.1. ERs

ANOVA for all subjects at baseline (Fig. 1) with group (HC, SZ, PC, relatives) as a between-subjects factor and delay and trial type as within-subjects factors, revealed main effects of group, $F(3, 220) = 7.0$, $p < .001$, and trial type, $F(3, 218) = 27.5$, $p < .001$, modified by a trial type \times group interaction, $F(9, 660) = 4.1$, $p < .001$, and a delay \times trial type interaction, $F(3, 220) = 59.2$, $p < .001$. Planned contrasts indicated that relatives trended toward fewer BX errors than SZ, $F(1, 220) = 3.6$, $p = .058$. There were no differences between relatives and PC or HC. Relatives' ERs on AY and BX trials were not significantly different, $F(1, 120) = .42$, $p = .52$.

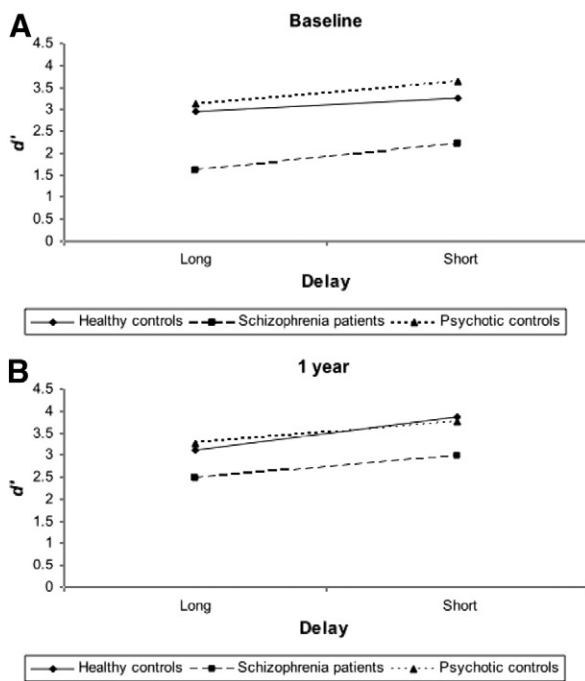


Fig. 4. Signal detection indices using BX false alarms at the baseline and 1 year assessments of context processing for subjects who completed both assessments using AX-CPT. A. Baseline assessments. B. One-year follow-up assessments.

3.3.2. d' -context

ANOVA with all subjects at baseline (Fig. 2) with group as a between-subjects factor, and delay as a within-subjects factor, revealed main effects of group, $F(3, 220) = 7.2$, $p < .001$, and delay, $F(1, 220) = 29.4$, $p < .001$. Contrasts indicated that relatives' d' -context scores trended toward being lower than HC at long, $F(1, 220) = 3.8$, $p = .052$, and short delays, $F(1, 220) = 2.3$, $p = .13$, and higher than SZ at long, $F(1, 220) = 2.7$, $p = .10$, and short delays, $F(1, 220) = 2.7$, $p = .10$. Polynomial trend analysis revealed that increasing degrees of genetic liability (i.e. $SZ > relatives > HC$) were associated with linear ($F(1220) = 3.8$, $p = 0.053$) and quadratic ($F(1220) = 6.3$, $p < 0.05$) decreases in d' -context at short delay, and linear ($F(1220) = 6.3$, $p < 0.05$) and quadratic decreases ($F(1220) = 6.1$, $p < 0.05$) at long delay.

3.4. Discriminant analysis

LDA of SZ and PC, using leave-one-out cross-validation using ERs and RTs on all trial types and d' -context at both delays, at baseline and the 4/8 week timepoint ($n = 75$), correctly classified 64% of patients, including 62% of SZ and 67% of PC ($\chi^2 = 16.1$, $df = 2$, $p < .001$). LDA of SZ vs. HC ($n = 100$), correctly classified 76% including 77% of HC and 74% of SZ ($\chi^2 = 44.5$, $df = 3$, $p < .001$). LDA of relatives vs. HC, using baseline only yielded 69% classification, including 77% of HC and 45% of relatives ($\chi^2 = 30.2$, $df = 18$, $p < .05$) indicating that while, as a group, relatives are discriminable from HC, many individuals with genetic liability for the illness are indistinguishable from HC by these measures.

3.5. Clinical symptoms

Patients' symptoms (Table 1) were evaluated for severity and relationship to context-processing deficits. SZ had higher reality distortion and lower GAS than PC at baseline, and higher reality, disorganization, and poverty and lower GAS scores at all follow-up timepoints, all $ps < .05$. At baseline, d' -context for SZ at baseline at both short and long delays was correlated with disorganization and

poverty, but for PC did not correlate with symptoms. Among SZ at one year, d' -context at both short and long delays correlated with disorganization at baseline, and at 1 year d' -context at short delay was correlated with reality and poverty symptoms, and trended toward significant correlation between long delay d' and disorganization ($p = .06$). Among PC, d' -context was not correlated with baseline symptoms, but at 1 year d' -context at short delay correlated with poverty. All symptoms for both groups improved from baseline to 1 year (all $ps < .01$).

4. Discussion

Our findings provide further support for the persistence and specificity of impaired context processing in schizophrenia. Differences in context processing among first episode, medication-naïve patients demonstrate diagnostic specificity of deficits, while a lack of correlation between context processing and symptoms among psychotic controls suggests that context-processing deficits are attributable to schizophrenia itself and not to state-dependent symptom severity. Furthermore, deficits remained stable over one year follow-up in schizophrenia. Comparisons of first-degree relatives to schizophrenia and healthy controls suggest that relatives display more modest context-processing deficits than patients, consistent with genetic liability to schizophrenia.

Performance in schizophrenia was consistent with context-processing deficits, with more BX than AY errors and more BX errors than healthy and psychotic controls; healthy and psychotic controls made more AY than BX errors and healthy controls were slower on AY than BX trials, consistent with intact context processing. Deficits in schizophrenia were present through one year, while psychotic controls had modest baseline deficits with intact context processing through one year, consistent with Barch et al. (2003).

LDA yielded 76% correct classification of healthy controls vs. schizophrenia, comparable to previous classification studies (Winterer et al., 2000; Jafri and Calhoun, 2006; Georgopoulos et al., 2007; Kawasaki et al., 2007; Shi et al., 2007; Demirci et al., 2008; Ince et al., 2009). LDA of schizophrenia and psychotic controls provided provisional support for diagnostic specificity, successfully classifying 64%. As little research has been done on diagnostic classification to distinguish first episode schizophrenia from non-schizophrenia psychosis (Gelber et al., 2004), our findings employing a simple behavioral paradigm could serve as a benchmark and may be useful in combination with other measures for early diagnosis.

Our results follow previous work showing relatives' context processing performance to be intermediate to healthy controls and schizophrenia. Relatives made fewer BX errors and had faster RTs than schizophrenia, and d' -context was intermediate to healthy controls and schizophrenia, with polynomial trend analysis indicating a monotonic relationship between degrees of genetic liability and context processing impairment.

In contrast to Barch et al. (2003), our findings indicated that psychotic controls had less impairment than schizophrenia at baseline, and that this difference did not change over time. Schizophrenia showed limited improvements in BX ERs and AY RTs. This could indicate that context processing improved over time; however, comparable improvements for schizophrenia and healthy subjects indicate a possible practice effect. Furthermore, schizophrenia patients' lower baseline GAS scores compared to psychotic controls indicate a more acute state of illness that could account for more severely impaired performance that improved somewhat upon treatment. Despite these improvements, schizophrenia continued to display impaired context processing through one year while psychotic controls did not.

Barch et al. (2003) suggested that impairments in schizophrenia reflected either a stable vulnerability indicator, a process that is equally impaired during psychotic episodes and clinical remission, or a mediating vulnerability factor, a process that is impaired during

clinical remission and even more so during psychotic episodes. Our findings appear consistent with a stable vulnerability factor. d'-context in schizophrenia was consistently worse than both healthy and psychotic controls at all timepoints. Furthermore, while there were significant correlations between symptoms and performance within timepoints, there was a lack of correlation between changes in symptoms and changes in d'-context over the 1 year follow-up (data not shown). This suggests that performance improvements were not merely a function of clinical improvement. For psychotic controls, baseline deficits were no longer apparent at 1 year, consistent with Barch et al. (2003) at 1-month follow-up, suggesting that deficits are an episodic indicator within this group. Furthermore, if deficits were a function of symptom severity then d'-context would be correlated with symptom scores for both groups. As this was not the case in our analysis, this further indicates that context-processing deficits are specific to schizophrenia.

There is also the question of the specificity of and the underlying mechanism for the association between context-processing deficits and disorganization symptoms. A potential neural basis for this association is offered by Yoon et al. (2008) who in an fMRI study of schizophrenia patients performing the AX-CPT found that disturbances in frontoparietal connectivity were correlated with disorganization. Thus, disorganization associated with deficits in processing of context may be due to disturbances of executive functions rather than a more generalized disturbance or one restricted to other processes (such as perceptual processing). Consistent with this, prior studies have found that context-processing deficits are most strongly associated with disorganization compared to reality distortion and poverty symptoms (e.g. Cohen et al., 1999; Barch et al., 2003; Snitz et al., 2005).

The primary limitation of the current study is relatively high attrition; however, no demographic differences were noted between participants who completed baseline only and participants who completed one year follow-up. Another limitation is that we did not explicitly ascertain genetic liability for context-processing deficits, which would require the study of monozygotic vs. dizygotic twins. While it seems unlikely that all findings in unaffected relatives would be due to environmental factors, explicit investigation is required to distinguish genetic from environmental influences on context-processing deficits.

The current study's findings of the persistence, diagnostic specificity and the presence in unaffected relatives of context-processing deficits in schizophrenia are consistent with such impairments being a cognitive endophenotype in the illness. Further research is needed to determine the source of the modest improvements in schizophrenia patients' performance after the baseline assessment. Furthermore, while AX-CPT performance has only modest predictive value in distinguishing between schizophrenia vs. non-schizophrenia psychosis, given the ease of administering such a test, future studies could evaluate the degree to which it could provide complementary information to other behavioral or biological measures to enhance their potential utility as instruments for early diagnosis.

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Conflict of interest

The authors declare they have no conflicts of interest.

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These data were presented, in part, at the 2010 Annual Meeting of the Society of Biological Psychiatry, New Orleans, LA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2013.02.020>.

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