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Visual integration dysfunction in schizophrenia arises by the first psychotic episode and worsens with illness duration

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Abstract

Visual integration dysfunction characterizes schizophrenia, but prior studies have not yet established whether the problem arises by the first psychotic episode or worsens with illness duration. To investigate the issue, we compared chronic schizophrenia patients (SZs), first episode psychosis patients (FEs), and well-matched healthy controls on a brief but sensitive psychophysical task in which subjects attempted to locate an integrated shape embedded in noise. Task difficulty depended on the number of noise elements co-presented with the shape. For half of the experiment, the entire display was scaled down in size to produce a high spatial frequency (HSF) condition, which has been shown to worsen patient integration deficits. Catch trials—in which the circular target appeared without noise—were also added so as to confirm that subjects were paying adequate attention. We found that controls integrated contours under noisier conditions than FEs, who, in turn, integrated better than SZs. These differences, which were at times large in magnitude ($d=1.7$), clearly emerged only for HSF displays. Catch trial accuracy was above 95% for each group and could not explain the foregoing differences. Prolonged illness duration predicted poorer HSF integration across patients, but age had little effect on controls, indicating that the former factor was driving the effect in patients. Taken together, a brief psychophysical task efficiently demonstrates large visual integration impairments in schizophrenia. The deficit arises by the first psychotic episode, worsens with illness duration, and may therefore serve as a biomarker of illness progression.

Keywords

schizophrenia; contour integration; first episode psychosis; visual perception; biomarker

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None.

INTRODUCTION

Contour integration is a visual process that represents continuous contours or shapes from spatially separated edge elements. Numerous studies have shown that chronic schizophrenia patients are impaired at the process (Silverstein & Keane, 2011; Silverstein, Kovács, Corry, & Valone, 2000) but it remains unknown whether it worsens with illness chronicity or arises as early as the first psychotic episode. There are several reasons why the question is worth considering. One is that it would show that poor integration in older patients cannot solely be attributed to long-term medication use or other factors associated with illness chronicity (e.g., poor health, diet). Another is that it could help establish a new laboratory test that could in principle identify persons in the prodromal stage of the illness who are most at risk of converting to schizophrenia. Third, it would bear on the current debate as to whether schizophrenia deteriorates cognitive functioning over time or whether it instead is relatively static following the first psychotic episode (Kahn & Keefe, 2013; Zipursky, Reilly, & Murray, 2013). Finally, contour integration critically relies upon long-range horizontal excitatory connections between cells in V1 or V2, and top-down feedback from higher-level cortical areas such as V4 or lateral occipital complex (LOC) (Altmann, Bühlhoff, & Kourtzi, 2003; Chen et al., 2014). Any deficit found in first episode psychosis would naturally implicate these neural structures and the network activity between them, and would thereby motivate future follow-up neuroimaging work.

Two previous studies investigated contour integration in first episode and chronic schizophrenia but each was methodologically limited and unable to establish firm conclusions. In one study, subjects attempted to identify the shape of a segmented polygon embedded in a field of randomly oriented line segments (Parnas et al., 2001). Schizophrenia patients who recently underwent their first psychiatric hospitalization performed slightly better than chronic readmitted schizophrenia patients and slightly worse than healthy controls, but neither effect reached significance (Supplemental Figure S1). The null results might be attributable to the small number of trials ($t=15$) or scant number of subjects ($N=9$) in the first hospital admission group. In a later study, Feigenson and colleagues (2014) compared first-episode psychosis and chronic schizophrenia patients, once at admission to a short-term psychiatric hospital and once again at discharge; healthy controls were tested at corresponding time points. Notwithstanding a larger sample size (≥ 18 subjects per group) and more experimental trials ($t=336$), the results were qualitatively similar to before, with the first episode group performing non-significantly better than the chronic SZs and non-significantly worse than controls.

In the present investigation, we built on these past studies and hypothesized that integration deficits arise by the first episode and worsen over time but can only be detected with a more sensitive psychophysical task. To probe this idea, we used a recently developed contour integration variant in which subjects sought to identify the screen quadrant location of an integrated shape embedded in varying amounts of noise. The task has produced the largest effect sizes in chronic schizophrenia to date (Keane, Erlikhman, Kastner, Paterno, & Silverstein, 2014a) and therefore holds promise for unveiling smaller group differences with first episode patients.

Several features set this contour integration task apart from others. Rather than having a fixed number of trials at a pre-determined number of difficulty levels (the method of constant stimuli), ours implements a Bayesian adaptive staircase that efficiently determines an intermediate difficulty level (75% accuracy) for each subject and condition. Our task additionally has four response alternatives, which can generate an acceptable level of threshold uncertainty (i.e., 5%) with about half as many trials as when there are two response types (Jäkel & Wichmann, 2006). Finally, the tested paradigm incorporates high spatial frequency stimuli (scaled down in size), which—for reasons that are not fully understood—strongly exacerbate deficits in chronic patients (Keane et al., 2014a). Therefore, the current psychophysical procedure has methodological advantages over prior studies and has the potential to reveal differences that so far have gone undetected.

METHODS

Subjects

The subject sample comprised 24 participants with schizophrenia or schizoaffective disorder, 22 participants with first episode psychosis, and 25 healthy controls, which were well-matched group-wise on a variety of variables (Table 1). Controls without four-year college degrees were preferentially recruited to prevent exaggerated group differences in IQ or education. For all subjects, inclusion/exclusion criteria were (1) age 18–65; (2) no electroconvulsive therapy in the past 8 weeks; (3) no neurological or pervasive developmental disorders; (4) no substance dependence in the last six months as assessed with the Mini International Neuropsychiatric Interview 6.0 (MINI; Sheehan et al., 1998); (5) no brain injury due to injury or illness (e.g., stroke or brain tumor); (6) no amblyopia (as assessed by informal observation and self-report); (7) visual acuity of 20/32 or better (with corrective lenses if necessary); and (8) sufficient spoken English to complete testing. Additional criteria for chronic patients were having had at least two psychiatric hospitalizations, and a DSM IV-TR diagnosis of schizophrenia or schizoaffective disorder at the time of testing (the two diagnostic groups exhibit similar integration deficits; see Keane et al., 2014a). Additional criteria for controls were: no DSM-IV diagnosis of any psychotic or mood disorder, no current psychotropic- or cognition-enhancing medication, and no first-degree relative with schizophrenia or schizoaffective disorder. Additional criteria for first episode psychosis patients were: having had exactly one hospitalization for psychosis and having recently received a psychotic disorder diagnosis in most cases within one year of testing. The diagnoses of the first-episode group were: schizophrenia (N=6), schizoaffective disorder (N=4), schizophreniform disorder (N=5), and psychotic disorder NOS (N=7). The first episode status was confirmed by a review of medical records and a structured psychiatric interview (see below). All patients but one were on medication at the time of testing.

An experienced rater (DP) and the first-author (BK) had established reliability with each other and with raters in other ongoing studies ($ICC > .8$); they administered the clinical instruments and perceptual tasks. Psychiatric diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 2002) and was supplemented with electronic medical record information when the diagnosis was unclear.

Intellectual functioning of all subjects was assessed with a ten minute test (Shipley-2) that correlates highly ($r \sim 0.8$) with WAIS-III verbal and full-scale IQ (Shipley, Gruber, Martin, & Klein, 2009). Visual acuity was measured with a logarithmic visual acuity chart under fluorescent overhead lighting (viewing distance = 2 meters, lower limit = 20/10), and an in-house visual acuity correction kit was used for individuals without appropriate glasses or contacts. The Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) was administered within two weeks (most typically within 7 days) of the perceptual task and provided information about symptoms over the last two weeks. Medication effects were considered by first converting antipsychotic dosages to chlorpromazine equivalents based on published standards (Andreasen et al., 2010) and then correlating those values with task performance. The Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982) assessed social isolation, peer relationships, scholastic performance, school adaptation, and social-sexual aspects of life from 6 years of age to 1 year before illness onset. Illness onset was defined as when psychotic symptoms first became noticeable or concerning to the patient. Illness duration was defined as time elapsed between illness onset and task administration. The Multidimensional Scale of Independent Functioning (MSIF; Jaeger, Berns, & Czobor, 2003) evaluated how patients performed in work, education, and home life (in decreasing order of emphasis) within the month prior to the interview. Written informed consent was obtained from all subjects after explanation of the nature and possible consequences of participation. The study followed the tenets of the Declaration of Helsinki and was approved by the Rutgers Institutional Review Board. All participants received monetary compensation and were naïve to the study's objectives.

Stimuli & Procedure

Stimuli consisted of Gabor patches, which are oriented sinusoids multiplied by a circular Gaussian:

$$G(x, y, \theta) = c \sin(2\pi f(x \sin \theta + y \cos \theta)) \exp\left(-\frac{x^2 + y^2}{2\sigma^2}\right)$$

where (x, y) denotes the distance in degrees from the center of the element, θ is the element's orientation (in deg), f is the peak spatial frequency of the element, and c is the Michelson contrast. There were lower spatial frequency (LSF) and high spatial frequency (HSF) blocks of trials, which were counterbalanced across observers (Figure 1). The Gabors in the LSF block had a sine phase (to create a balanced luminance profile), a 95% contrast, a peak spatial frequency of 4 cycles/deg, and a Gaussian envelope SD (space constant) of 7.3 arcmin. The Gabors always appeared within a square region that subtended 19.81 on a side. The circular target (diameter = 7.37 deg) consisted of twelve equally spaced Gabors (inter-element spacing = 1.93 deg) and was positioned at a quadrant center with randomly added jitter (± 0.5 deg along each dimension). The target quadrant was randomly assigned on each trial and contained the same number of Gabors as at least two neighboring quadrants. Noise Gabors never overlapped with each other or with the target Gabors, and ranged in number from 36 to 464 depending on the staircase recommendation (see below). Stimuli in the HSF block were the same as the LSF block, except that the entire stimulus was scaled to one-third

the retinal size (e.g., so that Gabors had a peak SF of 12 c/d) similar to prior studies (Hess & Dakin, 1997). Scaling was achieved by shrinking the stimulus display area and increasing the viewing distance from 87.6 cm to 181.5 cm.

On each trial, an array of oriented Gabors appeared for 1000 ms after which subjects saw a homogeneous gray screen with numbers 1 through 4 centered in each quadrant. Subjects were given an unlimited amount of time to verbally identify the target quadrant number and did not receive feedback on response accuracy.

Within a block, there were three randomly interleaved Bayesian (“QUEST”) adaptive staircases—30 trials per staircase—and each determined the number of noise patches needed to yield 75% accuracy (Watson & Pelli, 1983). The three threshold estimates were averaged to produce one value per SF per subject. Fifteen catch trials (without noise) also appeared randomly in each block to ensure that all subjects were on task. At the start of the experiment, there were 20 practice trials. The mean duration including instructions and practice ranged from 13.3 to 15.2 minutes for the three subject groups.

Analysis

Psychophysical data were analyzed with a 2 (SF: lower, high) by 3 (group) mixed model analysis of variance (ANOVA)—once for the catch trials (percent correct) and once for the non-catch trials (threshold, which equals the number of noise Gabors needed for 75% accuracy). Follow-up comparisons were performed via one-way ANOVAs and, if significant, two-tailed post-hoc tests. Equal variances were assumed unless a significant Levene’s test dictated otherwise. Relationships between symptoms and CI performance were evaluated using Pearson correlations.

Results

Results are shown in Figure 2. Average catch trial accuracy for each group was at least 95%, indicating that each group was properly engaging in the task. A main effect of SF indicated that even for noise-free displays the smaller Gabor targets were harder to see than the larger ones ($F(1,68)=3.98$, $p=.05$, $\eta_p^2=.056$). There was a main effect of group ($F(2,68)=3.24$, $p=.045$, $\eta_p^2=.087$) that did not interact with spatial frequency ($F(2,68)=1.57$, n.s.), however, the magnitude of the group difference was small and never exceeded 3.1%.

For the non-catch trials, there was a main effect of spatial frequency ($F(1,68)=14.457$, $p<.001$, $\eta_p^2=.175$), a main effect of group ($F(2,68)=13.65$, $p=.00001$, $\eta_p^2=.286$) and an interaction ($F(2,68)=5.27$, $p<.01$, $\eta_p^2=.134$). A follow-up ANOVA for the LSF condition revealed group differences ($F(2,68)=4.98$, $p<.01$, $\eta^2=.128$), but planned comparisons showed only a difference between SZs and controls ($p<.01$). The ANOVA for the HSF condition also showed a group effect ($F(2,68)=12.65$, $p<.0001$, $\eta^2=.271$); planned comparisons here revealed that each group differed from every other, with the chronic SZ group performing worst and the healthy group best ($ps<=.02$).

Visual acuity (VA) is more often impaired among subjects who have or who go on to have schizophrenia (Schubert, Henriksson, & Mcneil, 2005; Viertiö et al., 2007); it also predicts contour integration performance in healthy subjects when all subjects have normal or corrected-to-normal VA (Keane, Kastner, Paterno, & Silverstein, 2014b). Despite enforcing a standard VA cut-off of 20/32 (e.g., Revheim et al., 2014), we took the unusual step of checking and ultimately finding an overall group difference ($F(2,67)=8.63$, $p<.001$, $\eta_p^2=.204$). Post-hoc tests revealed worse VA in the SZ group as compared to controls ($p<.001$) and FEs ($p<.05$). To consider whether acuity differences could explain our results, we removed seven SZ patients with worse-than-20/20 VA and one control with exceptional VA (20/10). With this more restricted sample ($N=17$ SZs, $N=24$ Ctrl, $N=22$ FEs), there was no longer an overall group difference in VA ($F(2,62)=2.9$, ns), there were no longer any VA group differences on post-hoc t-tests, and there were no longer any differences in the catch trial analysis. For the regular trials, however, there remained a main effect of group ($F(2,60)=9.53$, $p<.001$, $\eta_p^2=.241$), a main effect of SF ($F(1,60)=13.96$, $p<.001$, $\eta_p^2=.189$), and an interaction ($F(2,60)=4.29$, $p<.05$, $\eta_p^2=.125$). One-way follow-up ANOVAs revealed an effect at the high SF only ($F(2,60)=9.46$, $p<.001$, $\eta_p^2=.243$); follow-up t-tests demonstrated that integration was worst in SZs, intermediate in FEs, and best in controls (all $p<.05$). The difference between the SZ and control subjects was noteworthy in its magnitude ($d=1.72$). What makes these results more interesting is that having compromised visual acuity—which results from either less frequent optometric examinations or inability to improve beyond a given letter size—may be a risk factor for schizophrenia (Schubert et al., 2005) and so excluding these subjects may remove some of the variance associated with the illness itself.

The first episode psychosis patients in our sample included 7 psychotic disorder NOS patients and 5 schizophreniform disorder subjects, some of whom may not end up with a schizophrenia/schizoaffective diagnosis. To consider whether our results apply specifically to schizophrenia/schizoaffective disorder, the same analyses were run as above but with only the target diagnoses. The results were again similar to before. For the catch trials, there was a small but significant overall group difference ($F(2,56)=4.14$, $p<.05$, $\eta_p^2=.129$), however, FEs were within 2% of the other groups and did not significantly differ on post-hoc tests. For the non-catch trials, there was a main effect of group ($F(2,56)=17.58$, $p<.000001$, $\eta_p^2=.386$), a main effect of SF ($F(1,56)=7.64$, $p<.01$, $\eta_p^2=.120$) and an interaction ($F(2,56)=5.53$, $p<.01$, $\eta_p^2=.165$). Follow-up ANOVAs revealed contour integration differences at the LSF ($F(2,56)=5.75$, $p<.01$, $\eta_p^2=.170$) and HSF ($F(2,56)=15.47$, $p<.000001$, $\eta_p^2=.356$). The three groups could be statistically differentiated only in the HSF condition, with the caveat that the FE-SZ difference hovered at the level of significance ($p=.05$). The latter effect is credible, we believe, given that its direction matches what has been identified in the analyses above and in two prior studies (see Introduction).

Relationships between contour integration and demographic/clinical variables

Gender, race, age, education (self/parental), handedness and IQ did not correlate with performance at either SF for any of the three groups or across patients (see below for one exception with age). Medication dosage (CPZ equivalents) also did not bear any relationship to the threshold values within a group or across patients. The foregoing effects were all non-

significant *before* any statistical correction, underscoring their negligible role in explaining the data. Most central to the present study, longer illness duration predicted poorer integration across patients for both conditions (LSF: $r = -.35$, $p < .05$; HSF: $r = -.32$, $p < .05$). As a secondary analysis, it was also inquired whether performance varied across patients with PANSS symptoms (positive, negative, and general), current and premorbid levels of functioning (MSIF/PAS), age of onset, schizophrenia/schizoaffective diagnosis, or conceptual disorganization. Only a general symptom correlate was obtained ($r = -.31$; $p < .05$), but the effect (albeit in the right direction) would not survive multiple comparisons and must be replicated.

Across patients, advanced age predicted longer illness duration ($r = .88$, $p < .001$) and lower thresholds for each condition (LSF: $t = -41$, $p < .01$; HSF: $t = -.30$, $p < .05$). Might age rather than illness duration explain why chronic patients more poorly integrate? To better address the issue, we combined the current data set with that of a previous study (Keane et al., 2014a), which ran control and chronic subjects with the same task design and inclusion/exclusion criteria. The pooled sample comprised 50 controls and 64 patients matched group-wise on age and gender. Although multicollinearity prevented a simultaneous assessment of age and illness duration in a multiple regression model, results from the combined analysis revealed that—for controls—advanced age predicted worse performance for the LSF condition ($r = -.358$, $p = .01$) but not HSF condition ($r = -.25$), and that—for patients—longer illness duration predicted lower performance for each condition (LSF: $t = -.32$, $p < .01$; HSF: $t = -.38$, $p < .01$). The foregoing effects were robust and did not depend on specific assumptions of the analysis (whether visual acuity was added as a regressor, whether patients were restricted to confirmed cases of schizophrenia/schizoaffective disorder, see Supplemental Results). These results therefore suggest that, while age may help explain why chronically ill patients perform worse in the LSF condition, it does not do so for the HSF condition.

DISCUSSION

To better understand the trajectory of visual integration deficits in schizophrenia, we applied a recent variant of a contour integration task that is briefer and more sensitive than what has been used before. It was found that—when locating integrated contours embedded in arrays of randomly oriented noise elements—chronic schizophrenia patients tolerated less noise than first episode psychosis patients who in turn tolerated less noise than healthy controls. These effects were primarily apparent in the high spatial frequency portion of the experiment. Group differences could not be explained by generalized deficits (i.e., in visual acuity, or in attention or motivation as confirmed by catch trial performance) and were apparent even when the first-episode group was restricted to confirmed cases of schizophrenia or schizoaffective disorder. The integration deficits correlated with increased illness duration and PANSS General symptoms, although the latter was not specifically predicted. When data were pooled between the current study and one previously published, advanced age imposed little effect on high spatial frequency integration in controls even though illness duration exhibited a clear effect in patients. Together, these data suggest that i) schizophrenia patients poorly extract structure from fragmented visual arrays; ii) the deficit arises by the first psychotic episode; iii) it grows monotonically with illness duration;

iv) the deficit is clearest for stimuli composed of high spatial frequencies; and v) integration tasks, with certain improvements, can reveal group differences that have been hitherto undetected.

One intriguing finding was that even though the first episode patients integrated better than the chronic group, the groups did not differ on: medication, PANSS symptoms, or age of onset; current or premorbid levels of functioning; or scholastic, cognitive, or demographic factors other than age (see Table 1). Age differed between the two groups but could not reliably predict controls' performance in the critical HSF condition. Thus illness duration may impose a negative effect on integration independently of these other factors. These data support an at-times controversial hypothesis according to which schizophrenia is a progressive neurodevelopmental disorder (Kahn & Keefe, 2013; Zipursky et al., 2013) that manifests years before the onset of psychotic symptoms and that continues to deteriorate aspects of cognition even after the first psychotic episode (Kahn & Keefe, 2013). Our results go one step further and show that the deterioration very well may be happening in the visual cortex, though longitudinal behavioral and neuroimaging studies are needed to confirm this conclusion.

The presented data introduce new questions and lines of research. One issue is whether contour integration behavior can predict the final diagnosis in prodromal subjects since only some of these individuals go on to develop full-blown schizophrenia. This matter is important because psychotic disorders other than schizophrenia are highly unstable and provisional at first diagnosis (Heslin et al., 2015). If we could know in advance which individuals are at highest risk for developing schizophrenia, we could dedicate more support and resources to those individuals to optimize clinical outcomes. Another question is why our group effects became more apparent for high spatial frequency displays. One possibility—based on findings of reduced V1 volume and neuronal number in schizophrenia (Dorph-Petersen, Pierri, Wu, Sampson, & Lewis, 2007)—is that patients obtain fewer fine-grained samples from the visual field, making it harder to extract structure from small edge elements packed within close proximity to fixation. Regardless of whether this explanation is correct, future studies will have to parametrically vary the Gabor width (Gaussian envelope), target element spacing, and carrier wavelength to determine which aspects of the scaling elicit between-group effects.

Several limitations are worth noting. Patients were on medication at the time of testing. Despite CPZ equivalent dosages not differing between patient groups and not correlating with performance, research with never-medicated first-episode patients is still required. Next, our study was cross-sectional in nature and a longitudinal approach is needed to better confirm the effect of illness duration. Further, while the current sample size allowed detection of HSF integration differences, a larger number of subjects (or more trials per subject) may be needed for detecting smaller group differences at LSFs. Our paradigm was also limited in that it incorporated HSF stimuli on only half of the trials, thereby reducing the overall effect sizes. Note, however, that a significant SF by group interaction strengthened the case against generalized deficit confounds among patients. Nevertheless, future investigations may either replace LSF with HSF stimuli for a more sensitive task, or discard the LSF trials altogether to slash the testing duration to less than 8 minutes.

Taken together, the data show that schizophrenia patients poorly integrate contours especially in small, finely detailed displays, as revealed by a brief but sensitive psychometric task. The impairment emerges by the first psychotic episode, worsens with increased illness duration, cannot be explained by generalized deficits, and thus may represent a biomarker of illness progression and recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Contour integration stimuli and procedure

(A,B) Subjects observed a briefly presented array of oriented elements (Gabors) a subset of which formed a closed circular target. The task was to identify the quadrant in which the target appeared. (C) The entire display was scaled in size to produce a lower and high spatial frequency condition (4 and 12 cycles/deg, respectively).

Figure 2. Contour integration results for chronic schizophrenia/schizoaffective patients (SZ), first-episode psychosis patients (FE), and healthy controls (Ctrl)

Errors show $\pm$ SEM. * $p < .05$, ** $p < .01$, **** $p < .00001$

Table 1

Demographic and clinical characteristics of participants

Variable	SZ (N=24)		FE (N=22)		Ctrl (N=25)		Group comparison		Pairwise comparisons (uncorrected)
	Mean or Percent	SD	Mean or Percent	SD	Mean or Percent	SD	p		
Age (yrs)	41.4	11.1	25.6	6.4	29.5	11.1	<.001	SZ>FE*** SZ>Ctrl***	
Education, parental average (yrs)	12.7	3.2	12.8	2.4	14.3	2.5	.08		
Education, self (yrs)	12.8	1.8	13.8	2.2	14.4	2.0	.03	SZ<Ctrl**	
FSIQ (Shipley)	90	13	93	17	105	11	.001	SZ<Ctrl*** FE<Ctrl*	
Gender (% Male)	63		68		64		.92		
Handedness (% Right)	83		100		92		.06		
Antipsychotic Type: typical/atypical/both (%)	32/50/14		32/63/5				.51		
Chlorpromazine equiv. (mg/day)	499	343	342	235			.10		
Functioning, current (MSIF)	4.2	0.8	4.4	1.1			.52		
Functioning, premorbid (PAS)	0.34	0.19	0.31	0.17			.41		
Illness duration (yrs)	20.4	12.6	3.8	7.9			<.001		
Illness onset age (yrs)	19.2	6.9	22.1	5.2			.13		
PANSS, positive	13.9	5.7	11.3	6.1			.16		
PANSS, negative	16.1	5.3	17.0	3.5			.52		
PANSS, general	34.3	7.6	30.8	8.3			.15		

Note.

* <.05,

** <.01,

*** <.001