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Authors

Niendam, Tara A
Lesh, Tyler A
Yoon, Jong
et al.

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Impaired context processing as a potential marker of psychosis risk state

Tara A. Niendam[a], **Tyler A Lesh**[a], **Jong Yoon**[a], **Andrew J. Westphal**[a], **Natalie Hutchison**[a], **J. Daniel Ragland**[a], **Marjorie Solomon**[a,b], **Michael Minzenberg**[a], and **Cameron S. Carter**[a,c]

[a] Psychiatry & Behavioral Sciences, University of California, Davis, Sacramento, CA, USA

[b] MIND Institute, University of California, Davis, Sacramento, CA, USA

[c] Center for Neuroscience, University of California, Davis, CA, USA

Abstract

While structural abnormalities of the dorsolateral prefrontal cortex (DLPFC) may pre-date and predict psychosis onset, the relationships between functional deficits, cognitive and psychosocial impairments has yet to be explored in the at-risk period. An established measure of cognitive control (AXCPT) was administered to demographically matched clinical-high-risk (CHR; n=25), first-episode schizophrenia (FE; n=35), and healthy control (HC; n=35) participants during functional magnetic resonance imaging (fMRI) to investigate these relationships. CHR and FE individuals demonstrated impaired context processing and reduced DLPFC activation relative to HC individuals during increased cognitive control demands. FE and CHR individuals' ability to increase DLPFC activity in response to cognitive control demands was associated with better task performance. Task performance was also associated with severity of disorganization and poverty symptoms in FE participants. These findings support more extensive studies using fMRI to examine the clinical significance of prefrontal cortical functioning in the earliest stages of psychosis.

Keywords

Ultra high risk; clinical high risk; psychosis; cognition; prefrontal cortex; fMRI

1. Introduction

Cognitive dysfunction is a core deficit in schizophrenia, and has been consistently linked to poor daily functioning in affected individuals (Green, 1996; Green et al., 2000). Investigation of the "at risk" phase of illness may identify processes contributing to the

Corresponding Author: Tara A. Niendam, Ph.D. UC Davis Imaging Research Center 4701 X Street, Suite E Sacramento, CA 95817 tniendam@ucdavis.edu.

Contributors: Dr. Niendam designed the study, completed the analysis, and prepared the manuscript. Mr. Westphal participated in fMRI data collection, and he and Dr. Lesh assisted with data analysis and manuscript preparation. Ms. Hutchison coordinated clinical data collection. Drs. Yoon, Ragland, Solomon, Minzenberg and Carter assisted in conceptual development of the study, contributed to data collection and analysis, and helped to prepare and edit the manuscript for publication. All authors have contributed to and approved the final manuscript.

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onset of psychosis (Cannon et al., 2008; Fusar-Poli et al., 2012a; Yung et al., 2003) and clarify associated impairments in cognitive (Wood et al., 2008) and psychosocial functioning (Cornblatt et al., 2007; Niendam et al., 2006; Niendam et al., 2007). While clinical neuropsychological studies provided initial evidence for cognitive dysfunction as a predictor of outcome (for reviews, see Fusar-Poli et al., 2011b; Wood et al., 2008), neuropsychological tasks engage a wide range of cognitive and brain systems and hence are not optimal for use in studies that aim to identify specific cognitive and neural mechanisms underlying the at-risk state using fMRI (Carter et al., 2008). Behavioral and neuroimaging measures from cognitive neuroscience and functional neuroimaging methods hold greater promise in this respect (Cannon et al., 2008; Wood et al., 2008).

Cognitive neuroscience based imaging methods reveal replicable dorsolateral prefrontal cortex (DLPFC) deficits across phases of psychotic illness (Glahn et al., 2005; Minzenberg et al., 2009). The DLPFC plays a crucial role in "cognitive control," a set of higher-order cognitive mechanisms that coordinate thoughts and actions to produce goal-oriented behavior through synchronized activity of functional brain networks (Miller and Cohen, 2001), and reduced DLPFC activation is believed to underlie impairment in cognitive control in schizophrenia (Barch et al., 2001; Barch et al., 2003c; MacDonald and Carter, 2003; Yoon et al., 2008). DLPFC dysfunction in first episode schizophrenia individuals (FE) is accompanied by reduced frontoparietal functional connectivity reflecting a breakdown in coordinated brain activity necessary for cognitive control (Yoon et al., 2008).

Despite robust findings in schizophrenia individuals, neurobiological mechanisms underlying changes in clinical, cognitive and psychosocial functioning, associated with increased risk for psychosis onset, remain poorly understood. Clinical high risk (CHR) individuals show structural and functional abnormalities, including reduced gray matter density in frontal, temporal and subcortical brain regions (Borgwardt et al., 2007; Fusar-Poli et al., 2011a; Fusar-Poli et al., 2012b; Hurlemann et al., 2008; Phillips et al., 2002; Witthaus et al., 2008; Wood et al., 2005) and reduced N-acetylaspartate (NAA) in frontal regions (Jessen et al., 2006; Wood et al., 2003). Neuroimaging studies in CHR individuals have identified deficits in the cognitive control network (Allen et al., 2011; Broome et al., 2010; Broome et al., 2009; Fusar-Poli et al., 2010a; Fusar-Poli et al., 2010c; Morey et al., 2005) that are associated with clinical outcome (Fusar-Poli et al., 2011b). Links have also been established between poor psychosocial function and risk for psychosis (Cornblatt et al., 2007; Fusar-Poli et al., 2010b), and between cognition, clinical symptoms, and psychosocial functioning in CHR populations (Niendam et al., 2006; Niendam et al., 2007). These findings suggest that cognitive dysfunction may represent a clear risk marker for future deterioration in clinical and psychosocial domains.

The current fMRI study employs the AX version of the Continuous Performance Task (AXCPT; Cohen et al., 1999), an established measure of cognitive control widely studied in individuals with schizophrenia (Barch et al., 2001; Barch et al., 2003a; Barch et al., 2003b; MacDonald and Carter, 2003; Yoon et al., 2008), to examine CHR individuals and determine if cognitive control deficits are present in high risk individuals and if these deficits are associated with clinical symptoms and functional disability. We hypothesize that CHR individuals, relative to healthy controls, have cognitive control impairments accompanied by DLPFC dysfunction that are similar to FE individuals. Further, we hypothesize that reduced DLPFC activation in response to cognitive control demands is associated with poorer task performance and global functioning at baseline in FE and CHR individuals.

2. Methods

2.1 Participants

Thirty-two CHR and 92 FE participants were recruited from the UC Davis Early Diagnosis and Preventative Treatment (EDAPT) clinic (See Table 1). Ninety-five healthy controls (HC) were also recruited. Twenty participants (5 HC, 9 FE, 6 CHR) were excluded for excess movement, seven for poor behavioral performance (2 HC, 5 FE) based on published criteria (Henderson et al., 2012), three (2 FE, 1 CHR) for scanner related artifacts, and two FE for positive urine drug screens at the time of testing. The remaining HC and FE participants were excluded based on demographic variables to create a matched sample for the CHR participants comprised of 35 HC and 35 FE participants. All participants in this analysis were ages 12-25, fluent in English, had a WASI 2-subtest IQ estimate >70 (WASI; Wechsler, 1999), and had no neurological disorders, current DSM-IV substance abuse/dependence, or contraindications for MRI. CHR participants had no history of psychosis and met criteria for a Structured Interview for Prodromal Syndromes high risk state based on (SIPS; McGlashan, 2001); (1) attenuated psychotic symptoms (APS); (2) brief and self-limited psychotic symptoms (BIPS); (3) substantial drop in functioning over past year with schizotypal personality disorder or first-degree relative with psychotic disorder (GRD). Participants over 16 were assessed with the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR; First et al., 2002), while participants age 15 and under received the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1996). A revised Global Assessment of Functioning score (GAF; Hall, 1995), was also obtained. FE participants were ascertained one year or less from illness onset and diagnoses of schizophrenia, schizoaffective or schizophreniform disorder were confirmed 6 months after ascertainment. HC participants had no first-degree family history of psychosis, history of DSM-IV Axis I or II diagnosis, or significant attenuated symptoms (P score >2) on the SIPS. Fifteen FE and 9 HC participants were included in a previous publication by Yoon and colleagues (2008). All participants provided a negative urine drug screen at the time of testing. Participant groups were matched on age, gender, ethnicity, and highest level of parental education. Participants completed informed consent or assent for the study and were compensated for participating. Guardians provided informed consent for minors. Study protocol and informed consent procedures were approved by the University of California at Davis IRB.

2.2 Measures

2.2.1. Clinical Measures—FE participants' symptoms were rated on the 24-item Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Ratings were combined into 3 factors of Reality Distortion, Disorganization and Poverty Symptoms (similar to Liddle, 1987) and previously associated with impaired cognitive control in schizophrenia (Barch et al., 2003a; Cohen et al., 1999; Yoon et al., 2008).

CHR participants were rated on the Scale of Prodromal Symptoms (SOPS), embedded within SIPS. Similar to the approaches by Liddle (1987) and Klaassen and colleagues (2011), SOPS symptoms were combined into 3 factors comparable to those used for FE participants: 1) Reality Distortion: unusual thought content, suspiciousness, perceptual disturbances/hallucinations, and grandiosity; 2) Disorganization: disorganized communication, odd behavior and appearance, bizarre thinking, trouble with focus and attention, and personal hygiene; 3) Poverty Symptoms: social anhedonia/withdrawal, avolition, decreased expression of emotion, decreased experience of emotions and self, deterioration in role functioning, and decreased comprehension/abstraction.

AX Continuous Performance Task (AXCPT): Subjects were presented with a string of letters on a computer screen and made a target response to a probe X *only* when it followed an A (Cue A trials). All other stimuli require a non-target response, including trials in which X is preceded by any letter other than A (collectively referred to as "Cue B" trials). Trials with target (AX) cue-probe pairings occur with high frequency (70%), setting up the tendency to make a target response to the X probe (Cohen et al., 1999). Healthy subjects are better at engaging proactive cognitive control to inhibit BX errors and this is associated with increased DLPFC activity in response to Cue B trials during fMRI. Schizophrenia individuals, on the other hand, show attenuated activity during the Cue B trials with a concomitant increase in BX errors (MacDonald and Carter, 2003). Subjects completed 4 scanning runs of 40 trials each, for a total of 160 trials (See Figure 1 for details and timing).

2.3 AXCPT Behavioral Analysis

Error rates were normalized using the arcsine transformation (Neter et al., 1990). Reaction times were normalized using the inverse transformation (Ratcliff, 1993). A measure of sensitivity to context [d'-context = Z AX hits (% correct) − Z BX false alarms (% errors); (Servan-Schreiber et al., 1996)] was calculated to provide a specific index of participants' ability to correctly respond to the probe (X) based upon the context provided by the cue (A or B type). A correction was applied to cases with perfect hit rates (1.0) or false alarm rates (0.0) (Nuechterlein, 1991). Based on our hypotheses, we examined differences in behavioral performance (% error on each trial type, d' context) using planned between groups t-tests (CHR, FE, HC). Differences in reaction time across groups were examined using Greenhouse-Geisser corrected repeated measures ANOVA (RM-ANOVA) with a between-participant factor of Group (CHR, FE, HC) and within-participant factor of Trial Type (AX, AY, BX, BY), followed by post-hoc two sample t-tests. Analyses were two-tailed (unless otherwise noted) to test specific hypotheses with $p<0.05$.

2.4 Functional Neuroimaging

fMRI data were collected at the UC Davis Imaging Research Center using a 1.5T GE scanner. Prior to functional imaging, coplanar T1-weighted structural scans were obtained. Functional scans (T2-weighted echoplanar imaging: TR = 2,000-msec, echo time = 40-msec, flip angle = 90 degrees, field of view = 22 cm) were acquired with twenty-four contiguous 4.0-mm axial slices with 3.4 mm^2 in-plane resolution. Preprocessing was completed with Statistical Parametric Mapping-5 software (SPM5, http://www.fil.ion.ucl.ac.uk/spm5), using standard procedures for image reorientation, temporal realignment, spatial realignment, normalization to the Echoplanar Imaging (EPI) Montreal Neurological Institute (MNI) template using a nonlinear warping algorithm, and spatial smoothing using a Gaussian 8-mm full-width half-maximum kernel. Prior to analysis, individual blocks were excluded from the analysis if the participant had more than 4-mm of translational or 3 degrees of rotational movement for that block. Subjects were excluded from the analysis if they had fewer than 2 blocks with acceptable movement.

Using SPM-5 (http://www.fil.ion.ucl.ac.uk/spm), we performed a multiple regression in the general linear model, with regressors representing all cue and probe events. For all reported results, only correct trials were examined and incorrect trials were modeled as regressors of noninterest (Carter and Pine, 2006). In the first level analysis, regressors were convolved with SPM5's canonical hemodynamic response function, using the temporal derivative to account for inter-participant variability in BOLD signal time to peak (Barch et al., 2003b; Ford et al., 2005). Additionally, parameters used to correct for subject head movement in spatial realignment were included as nuisance covariates (Lund et al., 2005).

2.4.1 Whole brain analysis—To provide an exploratory examination of activation under high control conditions across the whole brain, we conducted a second-level random-effects comparison of the linear contrast between the Cue B (high control) and Cue A (low control) trials. We chose to focus on the cue phase of the AXCPT due to recent theories regarding the temporal dynamics of cognitive control processes (Braver et al., 2007) and analyses of proactive and reactive control processes in patients with schizophrenia (Lesh et al., 2013). Within- and between-group imaging maps reflect activations above a height threshold of $p<0.01$ and the determination of cluster-level significance followed the standard procedure with corrections for multiple comparisons at $p<0.05$ family-wise error (Friston et al., 1996).

2.4.2 ROI Analysis—To examine effects of cognitive control on DLPFC activation, we conducted an *a priori* region-of-interest (ROI) analysis with a functionally defined DLPFC ROI [Talairach coordinates Right: x=41, y=18, z=28, Left: x= −41, y=18, z=28, 36 voxels; (MacDonald et al., 2000)], previously shown to identify group differences under high cognitive control conditions in multiple FE studies (MacDonald and Carter, 2003; Snitz et al., 2005; Yoon et al., 2008). Beta weights for correct trials only were extracted from Cue A and Cue B contrast images separately. Output represents a mean Beta weight across voxels within the ROI, which is generated for each participant and used for statistical comparison. Paired sample t-tests examined within group change in DLPFC activation from low (Cue A) to high (Cue B) control conditions. Analysis of variance (ANOVA) examined between group differences in DLPFC activation for low versus high cognitive control contrasts (alpha set at $p<0.05$, two tailed).

2.4.3 Correlation with Clinical & Functional Status at Baseline—Bivariate correlations tested relationships between AXCPT performance (AY and BX Error rates, d' context), fMRI variables of interest (beta values in DLPFC ROI bilaterally), 3 clinical factors (Reality Distortion, Disorganization, Poverty Symptoms) and global functioning (GAF). Due to the exploratory nature of these analyses, alpha was set at $p<0.05$ uncorrected to permit identification of small effects.

3. Results

3.1 Sample Characteristics

HC, FE and CHR participants were matched on the demographic variables of age, gender and ethnicity (all $p>0.17$). HC individuals had higher estimated IQ scores than FE [$t(66) = 5.22$, $P<0.001$] and CHR participants [$t(57) = 2.30$, $P=0.029$].

3.2 AXCPT Behavioral Performance

Results supported our hypothesis that CHR individuals have a specific deficit on AXCPT trials requiring high levels of cognitive control (i.e. BX trials; Figure 2). Both CHR and FE participants demonstrated higher error rates on BX trials compared to controls [CHR versus HC, $t(58)= 1.77$, $p=0.025$, one tailed, Cohen's $d=0.50$; FE versus HC, $t(68)= 1.88$, $p=0.033$, one tailed, Cohen's $d=0.45$]. FE participants also had higher error rates than HC on BY trials [$t(68) = 2.08$, $p=0.04$]. HC and FE participants did not significantly differ on error rates for AX ($p=0.11$) or AY trials ($p=0.16$). CHR individuals had higher error rates on AX trials compared to HC participants [$t(58) = 2.59$, $p=0.02$], but no difference on AY ($p=0.89$) or BY trials ($p=0.25$). CHR and FE participants did not differ on any trial types (all $p>0.28$). Groups showed no differences in reaction time across trial types (all $p>0.09$). Groups also differed on d'-context. As shown in Figure 2, and similar to previously reported results in FE schizophrenia, planned comparisons revealed that CHR and FE participants were impaired in their ability to use context provided by the cue compared to controls [CHR versus HC, $t(58)= 2.33$, $p=0.013$, one tailed, Cohen's $d=0.63$; FE versus HC, $t(68)= 1.81$,

p=0.038, one tailed, Cohen's d=0.43]. CHR performance on d'-context was not different from FE participants [t(58)= 0.85, p=0.40].

Post-hoc t-tests examined the potential effect of atypical antipsychotic medication on behavioral performance in CHRs. Forty-eight percent of CHR participants were unmedicated at the time of testing. Use of atypical antipsychotic medication by CHR participants was not associated with significant differences in AXCPT performance (ANOVA of individual trial types and d' context, all p>0.24).

3.3 Functional Neuroimaging

3.3.1 Whole brain within-group analysis—Under conditions of high cognitive control (Cue B versus Cue A trials), HC participants engaged an extensive network of brain regions, including the bilateral middle frontal gyrus, left superior frontal gyrus, bilateral cuneus and bilateral superior parietal lobules, that survived FWE cluster correction (Table 2). Although FE and CHR participants engaged a similar network of cognitive control regions, no brain regions survived correction for multiple comparisons.

3.3.2 Whole brain between-group analysis—Compared to HCs, FE participants showed significantly reduced activation in the left inferior parietal lobule. CHR participants had significantly reduced activation in the left precentral gyrus, bilateral middle frontal gyrus, left inferior parietal lobule, medial frontal gyrus and medial cingulate gyrus when compared to HCs (see Table 2, Figure 3). No brain regions showed greater activity in FE or CHR participants compared to HCs, and no brain regions differed between FE and CHR participants.

3.3.3 ROI Analysis—HC participants showed increased activity in the DLPFC bilaterally in an a priori ROI under high (Cue B trials) versus low (Cue A trials) cognitive control demands [paired samples t-test – left: t(34)=3.88, p<0.001; right: t(34)=2.24, p=0.03] (Figure 4). In contrast, CHR participants did not increase DLPFC activity in response to increased control demands [paired samples t-test – left: p=0.90, right: p=0.22], and their level of activation on Cue B trials was lower than HC participants in the left [F(1,58)=4.25, p=0.04] and right DLPFC [F(1,58)=8.31, p=0.006]. FE participants also failed to increase DLPFC activity with increased control demands [paired samples t-test – left: p=0.62; right: p=0.39], and their level of Cue B activation in the left DLPFC was lower than HC participants [F(1,68)=4.99, p=0.03]. Further, in the Right DLPFC ROI, CHR individuals demonstrated significantly lower activation when compared to FE individuals [F(1,58)=5.32, p=0.025]. Use of atypical antipsychotic medications was not associated with significant differences in activation for CHR participants (all p>0.36).

3.4 Correlation with Clinical & Functional Status at Baseline

Similar to previous studies, AXCPT performance in FE participants (d' context) was associated with their ability to increase DLPFC activation within an a priori ROI in response to cognitive control demands (Cue B-Cue A mean Beta value: Left DLPFC ROI, r=0.35, p=0.04). FE participants' performance (d'context) also was inversely correlated with the severity of their Disorganization (r=−.53, p=0.002) and Poverty (r=−.36, p=0.04) symptoms, but was not significantly associated with global functioning (r=0.29, p=0.09). In contrast to previous findings (Yoon et al., 2008), FE participants' DLPFC functioning was not associated with symptom severity or global functioning (all p>0.32).

Consistent with hypotheses (Figure 5), CHR individuals' ability to increase DLPFC activity in response to cognitive control demands (Cue B-Cue A mean Beta value) was associated with better performance (d'-context, Right DLPFC ROI, r=0.47, p=0.02). Although CHR

individuals did not show a significant relationship between higher global functioning and DLPFC activation (GAF, Left DLPFC ROI, r=0.31, p=0.14), the direction of results was in accordance with previous findings (Yoon et al., 2008). No other significant relationships were observed between CHR individuals' clinical symptoms or global functioning and task performance (d'context) or DLPFC activation (all p>0.15).

4. Discussion

This investigation provides evidence that CHR individuals show a specific behavioral pattern of impaired cognitive control as well as failure to engage the DLPFC during high control conditions, relative to demographically matched healthy controls, in a manner that was similar to a sample of demographically matched FE individuals. These results are consistent with previous findings in individuals with both early and chronic schizophrenia (Barch et al., 2001; Barch et al., 2003c; MacDonald and Carter, 2003; Yoon et al., 2008). CHR individuals also demonstrated significantly lower right DLPFC activation under high control demands in comparison to FE participants. While previous findings related to behavioral measures of cognition typically show CHR impairments to fall intermediate between FE and HC individuals (see for example, Pukrop and Klosterkotter, 2010), there are few studies that directly compare CHR and FE brain activation during cognitive tasks and findings have not been consistent (Benetti et al., 2009; Brune et al., 2011). Moreover, within the CHR and FE individuals, disrupted DLPFC modulation was significantly associated with impaired task performance, consistent with other studies (Barch et al., 2001; Barch et al., 2003c; MacDonald and Carter, 2003; Yoon et al., 2008).

Although not reaching statistical significance, CHR individuals showed the predicted association between DLPFC activation and global psychosocial functioning, similar to previous work in FE individuals (Yoon et al., 2008). While significant associations between cognitive control performance and clinical symptom severity (ie. disorganization and poverty) were observed in the FE participants, no significant relationships were observed between cognitive control performance, DLPFC activation and clinical symptoms in the CHR sample. The relationship between reduced DLPFC activation and poor clinical and psychosocial functioning may be most apparent in those individuals at greatest risk for psychotic illness, and the clinical diversity inherent in CHR samples at ascertainment may have impacted our ability to detect a significant relationship. Further, the small CHR sample and lack of outcome data in the current analysis precluded our ability to examine this hypothesis further in a sample of CHR individuals who converted to psychosis. However, future investigations should continue to examine the potential role of specific cognitive markers and associated neural mechanisms that underlie clinical symptom severity and impaired psychosocial functioning in youth at risk for psychosis, as this could be critical in identifying targets for more effective early intervention efforts.

While these findings provide evidence of impaired PFC functioning in CHR youth, it is important to address potential factors that may influence the results. Poor performance on the AXCPT could be hypothesized to result from impaired sensory processing or generalized deficits. However, the inclusion of the AY control condition, in which any probe other than an X that follows an A, allows us to interpret performance differences in terms of a specific, rather than a generalized deficit (Chapman and Chapman, 1978) that would result from poor motivation, sedation or general inattention. Furthermore, Barch and colleagues (Barch et al., 1997) have demonstrated that increased cognitive control demands, rather than degradation of the AXCPT stimuli to affect sensory processing, impacted DLPFC activation and AXCPT performance in healthy individuals. Although the inclusion of FE and HC individuals who were demographically matched to the CHR participants represents a strength of this study, the age range of study participant (12-25 years old) spans a critical

period of prefrontal development (Luna et al., 2010) and the current sample size precluded examination of age-specific effects. Future studies should examine the role of age on prefrontal functioning associated with cognitive control to determine where in time neurodevelopmental processes may go awry for FE and CHR individuals.

Within this sample, both FE and CHR participants received routine psychiatric and psychological interventions through the UC Davis EDAPT Clinic. Although our own results and those of previous studies have shown no effect of antipsychotic medication on AXCPT performance (Barch et al., 2003a; MacDonald et al., 2005; Snitz et al., 2005), it is not clear how such interventions may have affected CHR performance or DLPFC activation. Future studies should seek to directly address the role of medication and psychosocial interventions on cognitive functioning in CHR youth.

Our data provide preliminary evidence for impaired DLPFC-related cognitive control mechanisms in CHR youth. Future investigations incorporating structural imaging, such as measures of cortical thickness, and genetic association analyses may provide additional insights into the neurobiological underpinnings of cognitive, clinical and functional outcome in CHR individuals.

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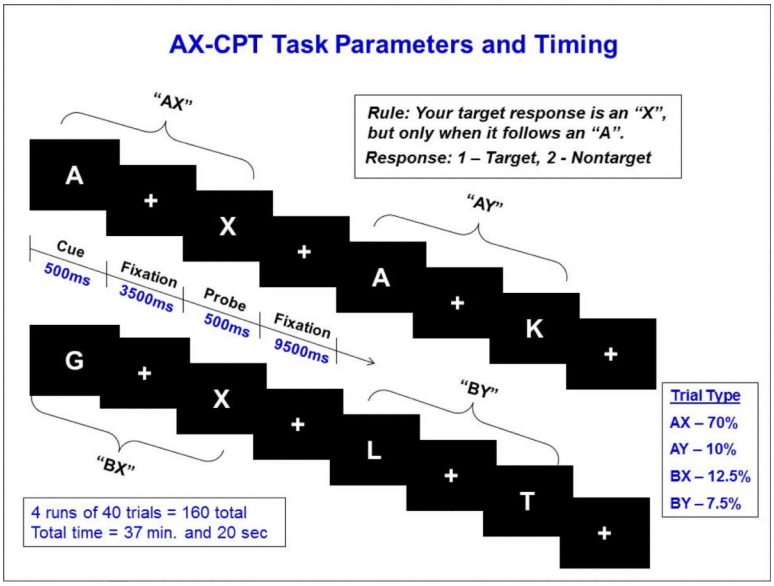

Figure 1.
AXCPT Task Parameters: Subjects make a target response to probe X, *only* when it follows the cue A. Non-target BX trials require increased cognitive control to prevent error.

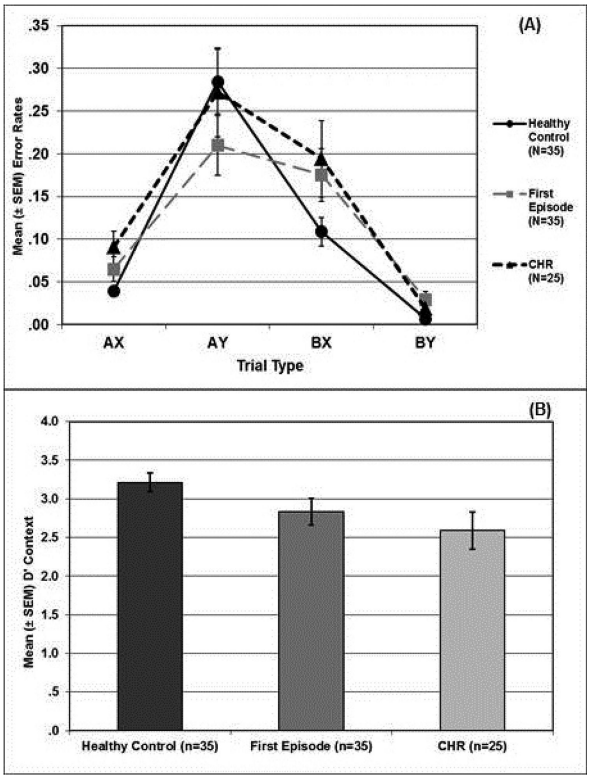

Figure 2.
CHR participants (n=25) show a specific deficit in cognitive control on the AXCPT, as indicated by higher BX errors (A) and lower d' context (B), when compared to HC individuals (n=35), in a manner that is similar to FE individuals (n=35)

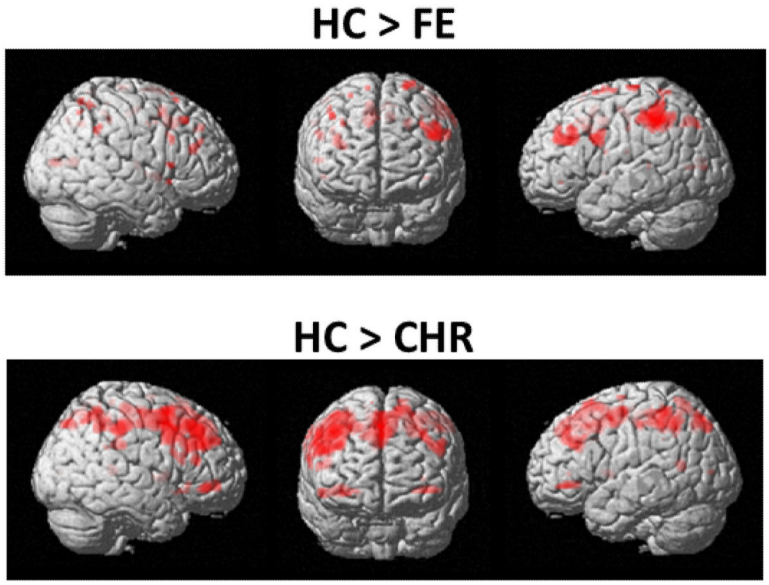

Figure 3.
Between-group activation maps contrasting HC participants to FE and CHR groups at an uncorrected threshold of $p<0.01$ for illustration purposes. Regions surviving FWE correction are outlined in Table 2.

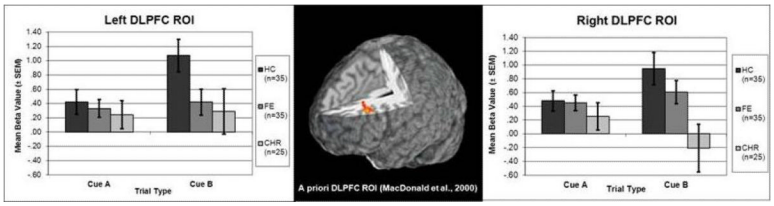

Figure 4.

HC participants (n=35) show increased DLPFC activation bilaterally during Cue B trials, which require higher levels of cognitive control, but CHR (n=25) and FE (n=35) participants do not.

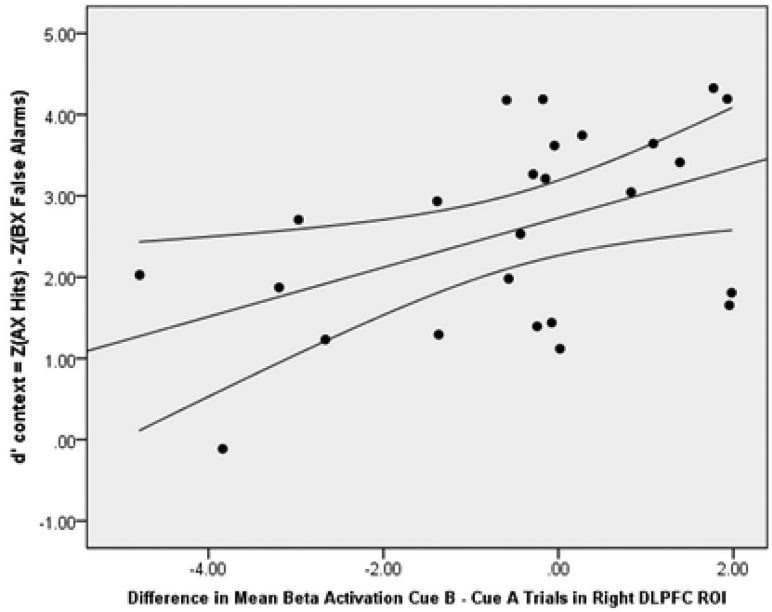

Figure 5.

In CHR individuals, the difference in activation (mean beta value) from Cue A to Cue B trials, which require higher levels of cognitive control, shows a pattern of association with improved ability to effectively process context on the AXCPT (d'-context, with 95% Confidence Intervals for the mean).

Table 1

Demographics, clinical characteristics and AXCPT performance across diagnostic groups

Characteristic	Healthy Control (HC, n=35)	First Episode (FE, n=35)	Clinical High Risk (CHR, n=25)
Age: mean ± SD	17.55 ± 3.16	18.27 ± 2.63	16.92 ± 3.85
Gender: % male	54%	74%	56%
Ethnicity: % Caucasian	49%	54%	52%
Parental Education: mean ± SD	15.53 ± 2.92	15.33 ± 2.88	14.91 ± 2.21
WASI IQ: mean ± SD	109.91 ± 7.67	95.79 ±12.86	101.25 ± 17.29
GAF: mean ± SD	-	46.03 ± 11.08	54.88 ± 9.75
Diagnosis: n (%)			
Schizophrenia	-	30 (86%)	-
Schizoaffective	-	3 (8%)	-
Schizophreniform	-	2 (6%)	-
Primary SIPS Syndrome			
% APS	-		23 (92%)
% BIPS	-		2 (8%)
Medication Use			
% Unmedicated	-	31%	48%
% Atypical	-	66%	20%
% Typical	-	0	0
% Antidepressant	-	3%	28%
% Missing			4%
Symptom Severity			
Reality Distortion	-	17.35±6.88	10.38±4.67
Disorganization	-	7.55±4.06	6.09±3.01
Poverty Symptoms	-	14.47±5.81	12.26±6.08
CHR Outcome			
Poor Outcome			9 (36%)
Convert to Psychosis (CHR+C)			4 (16%)
Persistent APS (CHR+P)			5 (20%)
Good Outcome			11 (44%)
Remission of APS (CHR-R)			11 (44%)
Follow up Data not Available			4 (16%)
Raw AX Error Rates: mean ± SD			
AX	0.04±0.04	0.07±0.09	0.09±0.09
AY	0.28±0.22	0.21±0.21	0.27±0.26
BX	0.11±0.10	0.18±0.18	0.19±0.22
BY	0.01±0.03	0.03±0.06	0.02±0.05
d’ context	3.21±.72	2.83±1.02	2.59±1.20

Characteristic	Healthy Control (HC, n=35)	First Episode (FE, n=35)	Clinical High Risk (CHR, n=25)
AX Reaction Time: mean ± SD			
AX	542.43±128.08	618.48±173.45	595.30±179.93
AY	711.65±145.61	756.51±157.13	721.51±171.34
BX	589.51±192.65	721.64±282.71	659.50±281.57
BY	559.29±158.96	636.91±203.08	616.56±192.80

Table 2

fMRI CueB-CueA Contrast, FWE-significant clusters in Whole Brain Analysis in CHR (N=25), First Episode (N=35) and Healthy Comparison Subjects (N=35)

		Statistics	
Brain Regions	**MNI Coordinates (x,y,z)**	**t**	**z**
WITHIN GROUP			
Within HC			
Left middle frontal gyrus	−48, 34, 28	6.03	4.94
Right middle frontal gyrus	50, 40, 28	5.94	4.88
Left superior parietal lobule	−22, −70, 50	5.72	4.76
Left superior frontal gyrus	−20, 12, 64	5.40	4.56
Bilateral cuneus	10, −80, 14	4.60	4.02
Right superior parietal lobule	32, −78, 48	4.52	3.97
Within FE*	None		
Within CHR*	None		
BETWEEN GROUP			
HC > FE			
Left inferior parietal lobule	−48, −40, 46	4.21	3.95
HC > CHR			
Right precentral gyrus	36, −4, 46	4.16	3.88
Right middle frontal gyrus	26, 10, 48	3.97	3.72
	48, 34, 32	3.44	3.27
Medial frontal gyrus	2, 40, 46	4.14	3.86
Medial cingulate gyrus	4, 22, 46	4.03	3.77
Left inferior parietal lobule	−56, −50, 48	3.62	3.42

*There were no brain regions that withstood correction for multiple comparisons in FE and CHR within-group analyses.