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The course of cognitive functioning over six months in individuals at clinical high risk for psychosis

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ABSTRACT

Cognitive impairment is common in psychosis and has recently been observed in individuals at clinical high risk (CHR) of developing psychosis. The purpose of this study was to characterize longitudinal change in cognition among CHR individuals, and compare cognition of CHR individuals who later convert to psychosis to that of CHR who do not convert. Participants were tested at baseline and followed-up after six months using a comprehensive cognitive test battery. Individuals who did not convert to psychosis either remained stable or significantly improved in their cognitive performance. At baseline participants who converted to psychosis compared to non-converters exhibited poorer performance in several cognitive tests, suggesting that some cognitive impairment is already present before conversion. Future longitudinal research should address if further decline takes place during the prodrome or after conversion to psychosis.

1. Introduction

There is a wealth of research demonstrating that compared to healthy controls individuals with schizophrenia have impaired cognition (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). The current interest in prospective research that examines individuals who appear to be putatively prodromal for developing psychosis, that is at clinical high risk of developing psychosis (CHR) (Addington and Heinssen, 2011) offers an excellent opportunity to examine cognitive functioning immediately prior to the onset of psychosis. Over the past 15 years numerous studies, often reporting contrasting results, have been published in this field. A systematic review (Brewer et al., 2006) highlighted a lack of consistency in the literature, but they did conclude that general cognitive ability appeared to remain intact and was a poor predictor of developing psychosis. Similar results have been reported by more recent reviews of the literature (Addington and Barbato, 2012). Two recent meta-analyses suggested impairment for those at CHR compared to healthy controls in IQ, language functioning, verbal and visual memory, attention, visual–spatial abilities, executive functioning and olfaction (Giuliano et al., 2012) and in tests measuring general intelligence, executive functioning, verbal and visual memory, attention and working memory (Fusar-Poli et al., 2012). Furthermore, as a group, the cognitive course of those at CHR tends to remain stable over time and in this way does not differ from healthy controls (Addington and Barbato, 2012). For those who go on to develop a full-blown psychotic illness compared to those who do not convert, there appeared to be baseline differences in general intelligence, verbal fluency, visual and verbal memory and working memory (Fusar-Poli et al., 2012). Additionally, over time the converters may show deterioration in certain cognitive abilities compared to the non-converters (Addington and Barbato, 2012).

The aim of the current study was to examine cognition in a large sample of young people at CHR of psychosis over a 6 month period and to determine if there were changes over time. Secondly to determine if those who later converted to psychosis had impaired cognition relative to those who did not convert.

2. Methods

This study, known as the PREDICT study, was a two-year longitudinal study to determine predictors of conversion in individuals at clinical high risk of developing psychosis, conducted at the Universities of Toronto, North Carolina, and Yale University.

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Table 1
Cognitive tests.

Domain	Test	Measure
Verbal fluency	Category instances (Benton and Hamsher, 1983)	Mean number of words
Processing speed	Trail Making Test A (Reitan and Wolfson, 1985)	Time to complete test
Motor function	Finger Oscillation Test (Reitan and Wolfson, 1985)	Average of dominant and non-dominant performance
Executive function	Wisconsin Card Sorting Test, 64-card computerized version (Kongs et al., 2000)	Mean of perseverative errors and categories
	Stroop Color–Word Test (Golden, 1978)	Number correct
	Trail Making Test B (Reitan and Wolfson, 1985)	Time to complete test
Verbal memory	Rey Auditory Verbal Learning Test (Rey, 1958)	Total number of words recalled in five trials
Spatial working memory	Computerized test of visuospatial working memory (Lyons-Warren et al., 2004)	Mean error distance of delay conditions minus no-delay error distance (sign reversed)
	N-back task (Kirchner, 1958)	Number correct for 1-back test; number correct for 2-back test.
Verbal working memory	Letter–Number Sequencing Test (Gold et al., 1997)	Number of correct sequences
Attention	Continuous Performance Test—identical pairs (Cornblatt and Keilp, 1994)	Mean response sensitivity (d-prime)
	Digit span distractibility (Oltmanns and Neale, 1975)	Total number correct with distraction
Olfaction	University of Pennsylvania Smell Identification Test (Doty et al., 1984)	Total correct responses
Intelligence	Wechsler Adult Intelligence Test/Wechsler Intelligence Scale for children-III block design, arithmetic, digit symbol/coding, vocabulary, information (Wechsler, 1974, 1981)	

2.1. Participants

The sample consisted of 151 CHR individuals (85 males, 66 females). All CHR participants met the Criteria of Prodromal Syndromes (COPS) diagnostic criteria for one of three Psychosis-risk Syndromes: the attenuated positive symptom syndrome (APS), the brief intermittent psychotic symptom syndrome (BIPS) or genetic risk and deterioration (GRD) (McGlashan et al., 2010). One hundred and forty-nine CHR participants met APS criteria and three met GRD criteria.

Participants were excluded if they met criteria for any current or lifetime axis I psychotic disorder, had a history or current use of antipsychotic medications, had an IQ of less than 70, or had past or current history of a clinically significant central nervous system disorder. Over our two year clinical follow-up we know that 25 of the 151 participants converted to psychosis. Six month cognitive data is available for 80 CHR. We compared the baseline cognitive scores of those who had 6 month data to those who did not ($n=71$). For most tests there was no significant difference between groups; the only exception being the finger oscillation test [$F(1,123)=4.17$, $p<0.05$] on which the group that dropped out performed slightly better.

2.2. Cognitive measures

Cognitive tests were chosen on the basis of their demonstrated reliability, ability to discriminate patients with schizophrenia from healthy participants, lack of ceiling and floor effects in a CHR population, and appropriateness for individuals as young as 14 years of age. The tests used are presented in Table 1.

2.3. Procedures

Clinical raters were experienced research clinicians who demonstrated adequate reliability on the SIPS at routine reliability checks. Gold standard post-training agreement on the distinction between high risk and psychotic levels of intensity was excellent (kappa=0.90). All cases were reviewed on weekly conference calls chaired by JA. Cognitive assessments were conducted by research assistants and pre- and post-doctoral neuropsychology fellows trained by JA, BC, KH, and RK. RK held monthly conference calls to review any concerns or issues related to cognitive testing. The study protocols and informed consents were reviewed and approved by the Institutional Review Boards of each site. All participants provided written, voluntary consent to participate.

2.4. Statistical analysis

Paired t-tests were used to compare baseline and 6 month cognitive scores. Due to the uneven sample sizes Mann–Whitney U tests were used to compare the baseline scores of the converters vs. non-converters. In order to reduce the data we used principal component factor analysis. The data were suitable for factor analysis, as Bartlett's test was significant, $p<0.0001$, and the Kaiser–Meyer–Olkin index=0.81.

3. Results

3.1. Demographic and clinical characteristics

Demographics and clinical characteristics of the sample are presented in Table 2. Twenty-five participants over the course of the PREDICT study developed psychosis, and 10 converted before the 6 month follow-up.

3.2. Cognition

Although the factor analysis yielded six factors with Eigenvalues greater than 1, the first factor accounted for most of the variance (32%). The only tests that did not primarily load on the first factor were the UPSIT and finger tapping. Examination of the scree plot suggested that only the first factor was worth retaining. Thus only a single factor was extracted.

Of the 25 participants who converted over the course of the PREDICT study, 10 converted before the 6 month follow-up; of the remaining 15, seven participants missed the 6 month assessment leaving only eight converters who had 6 month data. Therefore we only examined cognition over time in the non-converting CHR individuals who had 6 month data ($n=72$). There was significant improvement in measures of attention, processing speed, executive function, fine motor function and spatial working memory. Improvement was not observed on verbal memory, verbal fluency or olfaction. These results are presented in Table 3.

Baseline cognitive performance of those who converted was compared to that of those who did not convert during their time in the study. There were significant differences on the composite cognitive factor as well as for tests of attention, verbal explicit memory, verbal and spatial working memory, verbal fluency and executive function, with an advantage for the non-converters. See Table 4.

4. Discussion

This study examined cognition over a 6 month period in a large sample of CHR individuals. Over a 6-month period those individuals who did not develop psychosis during the two years of the study were either stable or improved on all tasks.

Table 2
Demographics and clinical characteristics of the sample.

Variable	Participants ($N=151$)
Sex, *n* (%)	
Male	85 (56.3%)
Female	66 (43.7%)
Race, *n* (%)	
Caucasian	120 (79.5%)
African American	13 (8.6%)
Asian	10 (6.6%)
Native Hawaiian or other Pacific Islander	1 (0.7%)
Mixed	7 (4.6%)
Current marital status, *n* (%)	
Common law or legal married	7 (4.6%)
Separated	2 (1.3%)
Never married	142 (94.0%)
Education, *n* (%)	
Did not complete High School	66 (43.7%)
GED/High School diploma	1 (0.7%)
Some college, did not graduate	14 (9.3%)
Community college or Technical School Degree	51 (33.8%)
College graduate	7 (4.6%)
College graduate and some Master's level courses	6 (4.0%)
Master's degree completed	4 (2.6%)
Advanced degree courses, not graduated	2 (1.3%)
Age *M* (S.D.), range	19.75 (4.7), 12–21
SOPS symptoms, *M* (S.D.), range	
Positive	10.97 (3.09), 4–20
Negative	8.58 (5.83), 0–22
Disorganized	4.09 (2.78), 0–13
General	6.87 (3.99), 0–18

Table 3
Change in cognition over time.

	Non-converters		
	Baseline Mean (S.D.)	6-M Mean (S.D.)	*t*-value
Verbal explicit memory			
RAVLT total of trials	53.56(9.41)	56.56(8.13)	−1.06
Verbal working memory			
Letter–Number sequencing	15.99(3.39)	16.21(3.67)	−0.84
Spatial working memory			
CTVWM no delay	1.94(2.57)	1.58(1.75)	0.99
CTVWM 5 s delay	18.87(10.59)	17.84(10.43)	0.82
CTVWM 15 s delay	20.87(13.21)	19.40(11.07)	0.89
N-back (1-back)	48.21(16.82)	51.97(13.95)	−1.93
N-back (2-back)	33.30(15.86)	37.59(15.82)	−2.92**
Executive function			
WCST categories	3.88(1.19)	4.09(1.07)	−1.56
WCST perseverative errors	7.35(4.57)	5.46(3.25)	3.42**
Stroop Color–Word	46.53(12.20)	48.15(13.41)	−1.75
Trail making B	66.25(29.17)	54.84(22.62)	4.38***
Verbal fluency			
Category instances	47.61(11.23)	47.04(11.50)	0.64
Attention			
CPT d′ 2 Digit	3.47(0.61)	3.61(0.61)	−2.10
CPT d′ 3 Digit	2.57(0.90)	2.86(0.91)	−3.26**
CPT d′ 4 Digit	6.86(41.89)	5.77(32.05)	0.16
Digit span distractibility			
Non-distraction	38.18(5.69)	38.42(4.84)	−0.46
Distraction	30.21(6.36)	31.42(5.06)	−2.88**
Processing speed			
Trail making A	27.80(12.08)	24.38(8.10)	2.28*
Fine motor function			
Finger oscillation—dominant	43.01(8.03)	45.10(7.89)	−2.86**
Finger oscillation—non-dominant	41.53(8.12)	43.05(7.50)	−1.75
Olfaction			
UPSIT right nostril	15.88(2.87)	16.05(2.19)	−0.51
UPSIT left nostril	16.26(2.66)	16.44(2.38)	−0.47

CHR=Clinical High Risk; RAVLT=Rey Auditory Verbal Learning Test; CTVWM=Computerized Test of Visuospatial Working Memory; WCST=Wisconsin Card Sorting Test; CPT=Continuous Performance Test; UPSIT=University of Pennsylvania Smell Identification Test.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Improvement was seen on attention, processing speed, executive function, fine motor function and spatial working memory. Interestingly scores on verbal memory and verbal fluency were stable. The observed improvement could be explained by practice effects (Goldberg et al., 2010). However, the stability of verbal fluency and verbal memory suggests that even though they do not go on to develop psychosis or at least not for the duration of this study, individuals at CHR of psychosis continue to have deficits on two of the tasks that are typically most impaired in schizophrenia (Bokat and Goldberg, 2003; Horan et al., 2008). They are also the measures that have been reported to differentiate between converters and non-converters (Fusar-Poli et al., 2012), a result which is also supported in our study.

Comparisons of baseline performance between converters and non-converters showed poorer performance for the converters in overall cognition based on the cognitive factor, and on some tasks of verbal explicit memory, verbal and spatial working memory, verbal fluency and executive function. The tasks in this study that differentiated the converters from the non-converters are most similar to those reported elsewhere (Fusar-Poli et al., 2012). Thus, it seems as if in a CHR group, that most likely has some impairment, there is a tendency for those who later develop a psychotic illness to have more impairment on a range of tasks. However, in the several studies that exist we are not seeing specific tasks or domains that are consistently impaired except perhaps for memory and fluency, similar to what is reported in the schizophrenia literature. Furthermore, those who appear to be at CHR and who have a reduced likelihood of conversion may possibly perform more poorly than healthy controls on tasks such as verbal memory and verbal fluency although not as poorly as those who go on to develop psychosis. One could speculate that there is an increase in severity of impairment as the risk of psychosis increases.

There were several limitations to this study. First, there was a loss of 40% of participants at the 6-month follow-up assessment. Secondly, although we had a conversion rate of 16.5% approximately half of our conversions occurred before the 6 month assessment and thus we were unable to determine if a decline occurs in cognition before conversion. Finally, we did not have a normal control group. However it is well established that CHR individuals are cognitively impaired compared to healthy controls (Fusar-Poli et al., 2012). The main strengths of our study are that we had a relatively large sample with a reasonable number of participants with 6 month follow-up data and used a comprehensive test battery. Our sample was antipsychotic naïve which avoids confounding, although we do not currently know the impact of antipsychotics on cognition in those at CHR.

Table 4
Comparisons of baseline performance between converters and non-converters.

	Mean rank		Mann–Whitney *U*
	Converters *N*=25	Non-converters *N*=126	
Cognitive factor	60.16	79.14	1179.00*
Intelligence			
IQ	56.40	63.67	918.00
Verbal explicit memory			
RAVLT total of trials	57.69	78.32	1084.50*
Verbal working memory			
Letter–Number sequencing	58.21	78.79	1097.00*
Spatial working memory			
CTVWM no delay	90.63	69.50	1029.00*
CTVWM 5 s delay	92.35	69.16	987.50*
CTVWM 15 s delay	80.58	71.50	1270.00
N-back (1-back)	67.57	75.19	1278.00
N-back (2-back)	62.33	75.01	1157.50
Executive function			
WCST categories	63.06	76.13	1213.50
WCST perseverative errors	90.52	70.78	1079.50*
Stroop Color–Word	71.63	76.24	1419.00
Trail making B	71.23	75.72	1409.50
Verbal fluency			
Category Instances	51.71	80.03	941.00**
Attention			
CPT d′ 2 Digit	72.79	73.64	1447.00
CPT d′ 3 Digit	62.29	75.70	1195.00
CPT d′ 4 Digit	64.44	75.28	1246.50
Digit span distractibility			
Non-distraction	63.40	76.65	1221.50
Distraction	58.13	77.67	1095.00*
Processing speed			
Trail making A	84.44	73.19	1273.50
Fine motor function			
Finger oscillation dominant	67.50	72.91	1320.00
Finger oscillation non-dominant	65.13	73.39	1263.00
Olfaction			
UPSIT right nostril	62.25	70.88	1116.50
UPSIT left nostril	64.66	70.42	1169.50

CHR=Clinical High Risk; RAVLT=Rey Auditory Verbal Learning Test; CTVWM=Computerized Test of Visuospatial Working Memory; WCST=Wisconsin Card Sorting Test; CPT=Continuous Performance Test; UPSIT=University of Pennsylvania Smell Identification Test.

* $p < 0.05$.
** $p < 0.01$.

In conclusion, our results support that CHR individuals who later convert to psychosis are cognitively impaired compared to those who do not convert (Fusar-Poli et al., 2012). However, we are not identifying specific cognitive functions that are consistent predictors of conversion. Furthermore, the issue of the point at which cognitive impairment really diverges from the norm in people who later develop psychosis has not been resolved in this study and is clearly a target for future research. It is possible that decline takes place within the first few months after conversion to psychosis, a period not currently captured by either CHR or first episode studies. Longitudinal studies that follow those who convert after conversion may prove useful in characterizing the cognitive decline that is presumed to take place in this population.

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