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Cognitive deficits in subjects at risk for psychosis, first-episode and chronic schizophrenia patients

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ABSTRACT

Background: Identifying the types and characteristics of cognitive deficits before the onset of schizophrenia and during its subsequent course could improve early detection and contribute to our understanding of the evolution of the core behavioral deficits underlying this disorder. Methods: This study used the Measurement and Treatment Research to Improve Cognition In Schizophrenia (MATRICS) battery to identify cognitive deficits and their progression during the course of schizophrenia from genetic high risk (HRF) subjects, subjects with prodromal symptoms (prodromal), and patients with first episode (FSCZ) and multi-episode (CSCZ) schizophrenia, compared to controls, in a Chinese Han population of 267 subjects. Results: There were statistically significant cognitive deficits which first appeared in prodromal subjects which were also present in FSCZ and CSCZ. There were no statistically significant differences between controls and HRF on any cognitive measure. Deficits in Visual Learning, Speed of Processing, and Overall Cognition were significantly correlated with some symptom measures on PANSS or SIPS. There were no statistically significant differences in cognitive deficits between FSCZ and CSCZ, and on most measures the patients with schizophrenia did not show a progression to more severe cognitive deficits than the prodromal subjects. Conclusions: In this sample of Chinese subjects, prodromal subjects showed significant cognitive deficits which were similar in most domains to those found in patients with schizophrenia. Whether the pattern of cognitive deficits on the MATRICS battery found in prodromal subjects will help predict conversion to diagnosed schizophrenia or other psychotic disorders would help determine how useful this profile of cognitive deficits is as a potential endophenotype for schizophrenia.

1. Introduction

Impairment in cognitive function has been established as an important primary pathological manifestation in schizophrenia. These cognitive deficits persist even after other primary symptoms, such as hallucinations and delusions, are reduced or resolved with treatment,

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and they have been shown to be related to poor functional outcome (Bowie and Harvey, 2006; Green, 2006). Cognitive deficits have been identified in a wide variety of areas including verbal and visual learning and memory, working memory, attention, executive function, speed of processing and other areas (Braff et al., 1991; Heaton et al., 1994; Palmer et al., 2009). Over the past 20 years research has also identified some of these deficits in patients at risk for schizophrenia with sub-threshold variable symptoms (prodromal subjects) and also in healthy siblings and close relatives of patients diagnosed with schizophrenia (Bora et al., 2014; Bora and Murray, 2014; Corigliano et al., 2014; Niendam et al., 2006; Simon et al., 2007; Sitskoorn et al., 2004). Some studies have reported a progression of more severe cognitive deficits as the disease develops from the prodromal phase though first-episode and multi-episode chronic schizophrenia, while others have reported that deficits in prodromal patients are more similar to those with schizophrenia and that these cognitive deficits do not show significant further deterioration during the course of schizophrenia (Bora and Murray, 2014; Corigliano et al., 2014; Heaton et al., 2001; Hoff et al., 2005; Pukrop et al., 2006). Some studies have shown that the severity of cognitive deficits in subjects with prodromal symptoms or in subjects at genetic risk may be one of the factors capable of predicting conversion from subjects with variable degrees of sub-threshold symptoms to actual psychosis (Addington et al., 2017; Bora et al., 2014; Brewer et al., 2005).

Previous studies comparing cognitive deficits over the whole range of risk states and diagnosed schizophrenia have used a variety of different neuropsychological tests to examine cognitive deficits during the development of schizophrenia. Few have utilized the Measurement and Treatment Research to Improve Cognition In Schizophrenia (MATRICS) consensus battery, which was specifically developed to assess cognitive function in schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008). The MATRICS battery has been translated and adapted into a Chinese version, and this version has now been normed for age, sex and education T scores in the Chinese Han population (Shi et al., 2015). To our knowledge, there is no published study which used the MATRICS battery to assess differences in the extent of cognitive deficits over the whole range of symptomatic presentation from genetic family risk though prodromal and first episode and chronic schizophrenia in a Chinese Han sample. The current study utilized the MATRCIS battery test to investigate cognitive deficits in a large sample of subjects ranging from healthy controls (controls), subjects with genetic family risk (HRF) but no current symptoms, subjects with prodromal symptoms who did not meet criteria for schizophrenia or other psychotic disorders (prodromal), patients with first-episode schizophrenia (FSCZ) and patients with multi-episode chronic schizophrenia (CSCZ). We hypothesized that all other subject groups would show cognitive deficits relative to healthy controls on both the MATRICS Overall Composite and 7 Domain scores, and that there would be a relatively linear progression in severity of cognitive deficits from family risk though chronic schizophrenia.

2. Methods

2.1. Subjects

The study recruited 288 subjects in five groups: controls, HRF, prodromals, FSCZ, CSCZ. Subjects were part of a larger study investigating epigenetic-related mRNA measures in lymphocytes of these same 5 groups. All subjects were recruited from the Institute of Mental Health of the Second Xiangya Hospital, Central South University, Hunan province and its cooperation sites including Guangzhou, Nanjing, Zhengzhou, Xinxiang, Ji'ning, Wuhan, Qingdao and Shanghai. The inclusion criteria for subjects included is this report is as follows: 1) males and females with an age range of 18–40 years in each group; 2) HRF were non-affected offspring or siblings with at least one first-degree relative diagnosed with schizophrenia; 3) prodromal subjects met the criteria for prodromal syndrome (COPS) based on the Structured Interview for Prodromal Syndrome (SIPS); 4) controls were subjects in the community who did not meet criteria for the prodromal syndrome, HRF, or any DSM-IV disorder specified in the exclusion criteria below; 5) FSCZ subjects met the DSM-IV criteria for schizophrenia, with first-episode onset; 6) CSCZ were subjects who met the DSM-IV criteria for schizophrenia with several episodes, with years of illness not less than 3 years. The exclusion criteria were as follows: 1) For the schizophrenia group: a) subjects who in the past met DSM-IV criteria for any other psychotic disorder, dementia or intellectual developmental disabilities (IQ < 80) before their schizophrenia diagnosis, b) clinically significant somatic disease, c) substance abuse except cigarettes in the past 3 months, d) recent treatment with valproate or subjects who were currently high cigarette smokers (> 1 pack/day) or on regular nicotine patch or gum, because of its effects on some epigenetic markers (Guidotti et al., 2011; Satta et al., 2008; Smith et al., 2010). 2) The exclusion criteria for the other groups were the following: a) subjects who currently met or in the past met DSM-IV criteria for the following conditions: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar disorder, delirium, dementia, amnesia or other severe cognitive impairment, b) intellectual developmental disabilities (IQ < 80), mental disorders due to somatic disease, c) recent substance abuse except cigarettes in the last year; d) subjects with a documented history of brain injury, epilepsy, or other known organic disease of the central nervous system; e) subjects taking antipsychotics, antidepressants, stimulants, valproate acid or mood stabilizers in the past 3 months. The study was approved by the institutional IRB at the Second Xiangya Hospital, Central South University in Changsha, China and IRBs of other participating sites where this was deemed necessary. All the participants gave written informed consent.

2.2. General psychiatric and cognitive assessments

All subjects were evaluated with a demographic questionnaire, a questionnaire for the patient or relative about pregnancy, developmental history, physical illness, and family history of mental illness. All prodromal subjects were assessed with the SIPS that includes the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003), the Presence of Psychotic Symptoms (POPS), and schizoid -personality disorder diagnostic criteria. Prodromal subjects met criteria for one or more of 3 prodromal syndromes: (1) attenuated psychotic symptoms (Attenuated Positive Symptom Syndrome); (2) transient psychotic symptoms (Brief Intermittent Psychotic Syndrome); (3) a substantial drop in social/role functioning in conjunction with schizotypal personality disorder diagnosis or in the presence of a psychotic disorder in first-degree relative (Genetic Risk & Deterioration Syndrome). FSCZ and CSCZ was confirmed by DSM-IV criteria with chart review and Mini-SCID. Absence of mental illness in controls was assessed by mini-SCID interview. Additionally, FSCZ and CSCZ were evaluated with the Positive and Negative Syndrome Scale (PANSS).

All subjects received a baseline cognitive evaluation using the MATRICS Consensus Cognitive Battery (MCCB). The final sample excluded several subjects because of missing data on the MCCB. Twenty-one of the total 288 cases were deleted because of greater than 50% missing data on MCCB. The remaining 267 cases had almost completed data on all MCCB variables, except for 10% of subjects missing data on selected tests.

2.3. MATRICS training and study quality control

The Chinese MATRICS was developed and adopted by investigators at the Mental Health Institute at Peking University working together with colleagues at the University of California, San Diego (UCSD) and at MCCB Inc. from the University of California, Los Angeles (UCLA). The team published the original Chinese MATRICS Normative study in China (Shi et al., 2015). The MATRICS assessments in this study were

carried out by trained and certified neuropsychological examiners at each study site. The neuropsychological examiners from each site were trained by staff at the Mental Health Institute at Peking University who were involved in the creation of the Chinese MATRICS Norm study. The training course included an introduction to the individual tests of the MATRICS battery and demonstrations of how to administer the test, along with live subject assessment. After the training course, examiners were observed administering the MATRICS battery on their own to a patient in order to ensure they could correctly run the test before they were approved to do so for the study.

To monitor and ensure the quality and integrity of the study across all sites, we set up routine phone conferences and e-mail communications among the study leaders in the US and China to discuss the study's progress, data transformation to English spreadsheets and any issues arising from data collection. The US team (JMD, RS and HJ) included a bilingual psychiatrist (HJ) who received medical training in both the US and China; the US team also visited China twice a year for the duration of the study to verify source documents, such as study consent forms, clinical assessments, and lab reports, to ensure data was collected and recorded correctly. Additionally, a bilingual U.S. medical student (JM) was awarded a grant under the Fulbright U.S. Student Program to assist with the study; he helped visit individual sites, verify source documents, and contact study subjects to further ensure the integrity and quality of the study.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 19 and 25. SPSS general linear model was used for analysis of variance. Significance level was set at $p < 0.05$. Protected comparison levels used Dunnett's T for comparison of other groups with controls and Benjamini-Hochberg (BH) protected significance level (at $\alpha = 0.05$) (Benjamini and Hochberg, 1995; Hsueh et al., 2003) for comparison among the 5 subject groups for a specific test or variable or comparisons among the 7 MATRICS domain and composite scores. If distribution on a variable was very skewed, additional tests were done with non-parametric statistics, Kruskal-Wallis one-way ANOVA and Mann-Whitney *U* tests. For the analysis of the MATRICS cognitive battery, raw scores were computed for each subtest. The MATRICS program was used to compute the T-scores for each test, the summary of the seven MATRICS Domain scores, and the Overall Composite score. The Chinese norms for age, gender, and education were used to generate T-scores corrected or standardized for differences in these subject characteristics. We primarily present comparative analysis of the Domain scores and Overall Composite scores among the 5 groups, but we also analyzed T-scores from specific tests in some supplementary analyses. The relationship between MATRICS scores and psychiatric symptoms was assessed by Pearson correlations. Results are presented with both traditional significance levels and BH corrected significance level results.

3. Results

3.1. Demographic and clinical characteristics

A total of 267 subjects had sufficient evaluable data for analysis. This data set included 72 controls, 44 HRF, 73 prodromal subjects, and 78 with schizophrenia (44 FSCZ and 34 CSCZ). Demographic characteristics on age, gender, years of education, symptom ratings, and medication status are presented in Table 1.

There were significant age differences among the groups; both parametric analysis (Table 1) and non-parametric analysis (see supplement) showed significant differences in age across the total sample, with significantly higher ages observed in the CSCZ group (BH corrected) compared to controls, prodromal, and FSCZ patients. Education was also significantly different among the 5 groups (Table 1). Patients with schizophrenia, HRF, and prodromal subjects all had significantly lower education than controls (BH corrected). CSCZ were also lower than prodromals. There were no significant differences in psychiatric symptoms (PANSS scores) nor portions of patients on antipsychotic treatment in the FSCZ group compared to the CSCZ group. In this sample, our CSCZ patients had been diagnosed with schizophrenia an average of 7.5 years.

3.2. MATRICS cognitive scores

3.2.1. Comparison to controls

We hypothesized that all the at-risk and schizophrenia groups would have MCCB cognitive scores which were significantly lower than healthy controls (Table 2). Our results showed prodromal, FSCZ and CSCZ subjects had significantly lower cognitive scores than controls on the MATRICS Overall Composite score and on the following domain scores: Speed of Processing, Visual Learning, Reasoning and Problem Solving, and Social Cognition. Prodromal subjects also showed a trend (defined as $p < 0.10$), of lower scores than controls in the Verbal Learning domain. In the Attention/Vigilance domain, only subjects diagnosed with schizophrenia showed significantly lower scores than controls, and on Spatial Working Memory only CSCZ showed significantly lower scores. In this sample HRF subjects did not significantly differ from controls on any cognitive measure. Although HRF had slightly lower mean scores in most domains, except Attention/Vigilance, these differences did not approach statistical significance, even at a trend level ($p < 0.10$). Because some previous research studies reported significant differences between siblings or relatives with family risk compared to controls, using specific cognitive tests, we conducted additional analysis on T-scores of some specific tests which were the same or similar to the ones used in the previous studies. These analyses included the Trail Making Test A, Welcher Memory Scale-Spatial Span, Hopkins Verbal Learning Test, and Brief Visuospatial Memory Test. In none of these analyses did the HRF means differ significantly from the controls, even at a trend level. Because the Spatial Working Memory and Visual Learning domain scores had two or more groups whose distribution deviated from normality (significant probability values on the Kolmogorov-Smirnov test), additional nonparametric analysis was conducted for these domains. Fairly similar results were obtained with non-parametric analysis for working memory and visual learning (see supplementary data).

3.2.2. Prodromal subjects

Prodromal subjects generally had a level of cognitive impairment which did not substantially differ from patients with schizophrenia on most measures (Table 3). Although the prodromal subjects had marginally higher mean scores than SCZ in all comparisons, only one comparison remained statistically significant after the BH correction. On the Attention/Vigilance domain, CSCZ showed significantly worse cognitive performance than prodromal subjects and there was a trend showing FSCZ had worse cognitive performance in this domain. On Attention/Vigilance, prodromal subjects did not differ from controls. On the Speed of Processing and Reasoning/Problem Solving domains prodromal subjects showed a small trend for better performance at traditional significance levels ($p < 0.06$) which did not survive BH correction. On Overall Composite Scores and other MATRICS domains, there were no significant differences between prodromal and FSCZ or CSCZ subjects.

3.2.3. First-episode and chronic schizophrenia

There were no significant differences between FSCZ and CSCZ on the Overall Composite Score or any MATRICS cognitive domain score. However, there were small negative correlations in the CSCZ group between years of illness and MATRICS scores and a significant negative correlation between Overall Composite Scores and years of illness ($r = -0.388$, $p = 0.034$).

Table 1
Demographic and clinical data of healthy control subjects, high-risk family subjects, prodromal subjects, first-episode schizophrenia and chronic schizophrenia patients.

Characteristics	CSCZ		FSCZ		PRS		HRF		CON		Statistic	*p*
	n	Mean(S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)		
Age	34	27.1(2.6)	44	23.5(4.4)[a]	73	23.3(4.5)[a]	44	25.6(4.7)	72	24.0(2.9)[a]	F = 7.22, DF = 4262,	0.000
Gender (M/F)	34	17/17	44	31/13	73	41/32	44	24/20	72	43/29	*chi-square* = 4.091	0.394
Years of education	34	10.6(3.0)[b]	44	11.9(3.2)[b]	73	12.6(3.3)[b]	44	12.6(3.4)[b]	72	16.0(2.3)	F = 24.61, DF = 4261	0.000
Years of illness	34	7.5(3.0)										
PANSS total	34	72.0(19.9)	44	70.4(21.1)							*T* = −0.338, DF = 75	0.736
PANSS positive	34	17.7(6.3)	44	17.7(5.8)							*T* = −0.061, DF = 75	0.951
PANSS negative	34	20.2(7.9)	44	18.4(7.9)							*T* = −1.033, DF = 75	0.305
PANSS general	34	34.0(9.2)	44	34.4(10.7)							*t* = 0.151, DF = 75	0.880
SIPS total					73	37.1(17.2)						
SIPS positive					73	8.4(3.5)						
SIPS negative					73	9.2(6.6)						
SIPS disorganized					73	5.0(3.2)						
SIPS general					73	5.9(3.9)						
Medication status at time of testing												
Antipsychotic	34		42									
Traditional (T)	2		5									
Atypical (A)	26		34									
Combined (T + A)	6		3									
Antidepressant	0		1									
Valproate	2		5									
Benzodiazepine	2		6									
Antiseizure	11		4									
Phenobarbital	1		0									
None medicated	0		2									

CSCZ, chronic schizophrenia patients; FSCZ, first-episode schizophrenia; PRS, prodromal subjects; HRF, high-risk family; CON, healthy controls; S.D., standard deviation.

[a] Significantly different from CSCZ at BH protected significance level ($\alpha = 0.05$).

[b] Significantly different from CON at BH protected significance level ($\alpha = 0.05$), BH, Benjamini-Hochberg.

3.3. Correlation analyses

In order to explore the relationship between cognitive deficits and clinical features, a correlation analysis was performed between cognitive impairments and PANSS scores in patients with schizophrenia, and cognitive deficits and SIPS scores in prodromal subjects (Table 4, Fig. 1). We found some significant correlation results after the BH correction. PANSS negative scores correlated with impairments on the Visual Learning domain. The significant correlations between SIPS and cognitive domains were as follows: SIPS negative scores correlated with impairments on the Speed of Processing domain and Overall Composite Scores; SIPS disorganized scores correlated with impairments on Overall Composite Scores and the Speed of Processing domain; SIPS total scores correlated with impairments on Verbal Learning, Speed of Processing, and Overall Composite Score. (See supplementary data for additional figures.)

4. Discussion

The results of this study showed that Han Chinese subjects with prodromal symptoms showed cognitive deficits with significantly lower cognitive scores than healthy controls as measured by the MCCB. In most cognitive domains, the levels of these cognitive deficits were similar to those of patients diagnosed with schizophrenia, except for the Attention/Vigilance domain. Comparisons across all diagnostic groups for the specific domains of speed of processing and reasoning/problem solving also showed a difference between prodomals and patients with either acute or chronic schizophrenia but not both groups (Table 2); these differences were not statistically significant when the comparison was made across all domains between prodromals and the patients with schizophrenia (Table 3). Furthermore, there were no statistically significant differences in the degree of cognitive deficits between FSCZ and CSCZ. Although HRF subjects, generally showed slightly lower mean scores on most cognitive measures than controls, none of these scores were significantly different from those found in controls. There were some significant differences in sex, age, or education between some of the study groups. However, the analyses presented in this paper were based on T-scores which were corrected or normalized for differences in sex, age, and education based on Chinese norms for patients 18 years and older (Shi et al., 2015). Therefore, we believe these differences did not substantially impact our results.

Our findings are consistent with other recent studies which showed cognitive deficits to be present in prodromal and high risk groups, and in patients with schizophrenia, but they differ in some important ways. Several groups have now reported significant neuropsychological deficits in prodromal subjects compared to controls (Bora et al., 2014; Niendam et al., 2006, 2007; Pukrop et al., 2006; Simon et al., 2007; Zhang et al., 2015), although one study in Shanghai only found a statistically significant difference between high risk/prodromal subjects and controls on Visual-Spatial Construction and not on other measures (Zhang et al., 2015). Some studies have reported significant associations between selected measures of cognitive functioning and later conversion to schizophrenia; these include Verbal Learning, Verbal Memory, Verbal Fluency and Speed of Processing (Addington et al., 2017; Brewer et al., 2005), and deficits of delayed memory on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) battery (Zhang et al., 2015). In a meta-analysis of ultra-high risk/prodromal studies Bora and associates (Bora et al., 2014) found significantly lower cognitive function in verbal memory, executive function, verbal working memory, attention, and verbal fluency in the ultra-high risk subjects who subsequently converted to psychosis vs those who did not convert. Most studies have not shown a consistent worsening in cognitive function scores over the course of schizophrenia, and suggest that cognitive deficits are already well established in the prodromal stage (Bora and Murray, 2014; Corigliano et al., 2014; Heaton et al., 2001). Furthermore, most studies have not shown progressive deterioration in cognitive function between first-episode and multiple episode or chronic schizophrenia or progression of cognitive deficits on multiple repeat testing of the same psychotic subjects over several years (Bora and Murray, 2014; Heaton et al., 2001; Hoff et al.,

Table 2
Scores on cognitive domains for control, high-risk family, prodromal, first episode schizophrenia, and chronic schizophrenia patients.

Domain score	Control (*N*'s = 68–71)	High-risk family (*N*'s = 34–44)	Prodromal (*N*'s = 61–73)	First episode schizophrenia (*N*'s = 37–44)	Chronic schizophrenia (*N*'s = 30–34)	Overall test GLM F, DF, *p*
Speed of processing	46.83 ± 6.47	45.33 ± 8.82	39.47 ± 9.95^{***,a}	35.86 ± 9.21^{***,a,b}	36.56 ± 9.77^{***,a}	F = 16.756, DF = 4, 261, $p < 0.001$
Attention/ vigilance	45.09 ± 8.73	44.74 ± 12.20	44.67 ± 11.78	39.64 ± 9.71*	36.19 ± 13.34^{***,a,b}	F = 5.372, DF = 4, 255, $p < 0.001$
Spatial working memory	42.72 ± 10.20	44.05 ± 11.24	39.30 ± 10.32	38.93 ± 10.79	36.47 ± 14.17^{*,a}	F = 3.410, DF = 4, 262, $p = 0.010$
Verbal learning	38.64 ± 11.18	37.66 ± 15.76	34.21 ± 13.38^{+}	29.89 ± 12.37^{***,a,b}	32.03 ± 12.33*	F = 4.109, DF = 4, 262, $p = 0.003$
Visual learning	48.41 ± 11.57	45.37 ± 12.49	40.77 ± 12.14^{***,a}	37.64 ± 11.62^{***,a}	38.21 ± 11.91^{***,a}	F = 8.330, DF = 4, 262, $p \leq 0.001$
Reasoning/Problem solving	49.50 ± 9.63	46.41 ± 10.31	41.19 ± 11.15^{***,a}	40.73 ± 11.20^{***,a}	36.29 ± 13.94^{***,a}	F = 11.198, DF = 4, 262, $p \leq 0.001$
Social cognition	52.97 ± 14.55	50.94 ± 16.98	46.47 ± 13.83*	45.34 ± 16.36*	45.85 ± 18.89^{+}	F = 2.530, DF = 4, 237, $p = 0.041$
Overall composite score	52.69 ± 5.47	50.96 ± 9.53	44.27 ± 8.73^{***,a}	43.90 ± 6.95^{***,a}	43.65 ± 9.23^{***,a}	F = 15.482, DF = 4, 235, $p \leq 0.001$

Each number presents Mean ± S.D. of Overall Composite or Domain T scores adjusted for age, sex, and education based on Chinese norms. Statistical significance of each group's difference from Control group for that component score by Dunnett's T (one sided, less than).

*** $p < 0.001$.

* $p < 0.05$.

$^{+}$ $p < 0.10$.

[a] Significance of each group's difference from High-Risk Family group remained statistically significant at $\alpha = 0.05$ after BH correction (BH = Benjamini-Hochberg) taking into account comparisons between each of 5 diagnostic groups.

[b] Significance of two schizophrenia groups' difference from Prodromal group remained statistically significant at $\alpha = 0.05$ after BH correction taking into account comparisons between each of 5 diagnostic groups.

2005). However, in cross-sectional studies, Corigliano and associates (Corigliano et al., 2014), using the MATRICS battery, reported significant differences in Working Memory between ultra-high risk/prodromal patients and FSCZ, and significant differences between prodromal subjects and CSCZ in the Speed of Processing, Attention/ Vigilance, Working Memory and Reasoning and Problem Solving domains. Another cross-sectional study (Pukrop et al., 2006) also reported differences on most neuropsychological test scores between high-risk patients and those with schizophrenia and differences between FSCZ and CSCZ on Verbal and Visual Memory. This research literature is generally consistent with our findings that there were significant differences between prodromal patients and those with schizophrenia on only one the MATRICS domains and not on Overall Composite Scores. Our findings would be generally consistent with a neurodevelopmental rather than a neurodegenerative approach to explaining the cognitive deficits in schizophrenia, since they are already present in the prodromal stage and our own results and the majority of prior studies do not show marked worsening of overall cognitive impairment during the course of further development or progression of schizophrenia. The few cross-sectional studies cited above (Corigliano et al., 2014; Pukrop et al., 2006) which showed differences in cognitive function at different stages of the disease, and others which show heterogeneity of cognitive defects in prodromal patients compared to first episode schizophrenia (Simon et al., 2007) may temper the general support for this conclusion. Since there were small negative correlations between lower MATRICS scores and duration of illness, it is possible that the relatively short length of illness in our chronic schizophrenia sample, a mean length of illness of 7.5 years, may have attenuated potential differences between our CSCZ and our FSCZ or prodromal subjects, and this also be a factor to consider in interpreting our findings.

The most striking difference between the results of this study and previous studies, is the lack of significant differences on any cognitive measures between HRF subjects and our controls. Our own research group previously reported significant cognitive deficits on several individual neuropsychological tests in non-affected siblings of patients with schizophrenia compared to controls (Hu et al., 2011). Furthermore, two meta analyses (Bora et al., 2014; Sitskoorn et al., 2004) both found strong evidence for statistically significant differences in cognitive deficits between HRF subjects and controls. Although these other studies did not use the MATRICS battery, they used some of the tests which were the same or very similar to those included in the MATRICS battery. When we did additional analysis of T-scores form these individual tests, we again did not find any significant differences between controls and HRF. There was no major difference in the mean age of subjects in the earlier Chinese study (Hu et al., 2011) ($n = 56$, control 21.89, family risk 21.58) and the current study ($n = 72$, controls 23.99, $n = 44$ family risk 25.59). We have no clear explanation for this difference in the results for this sample. However, the mean corrected score of our control group on several MATRICS Domains (Speed of Processing, Attention/Vigilance, Working Memory, Verbal and Visual Learning, Reasoning Problem-Solving) were slightly to substantially lower (mean scores 38–48) than the mean scores of the controls in a Chinese normative sample (mean score 50) (Shi et al., 2017), so our control group may be slightly biased to lower cognitive performance. This could have attenuated a difference between controls and HRF subjects who would be expected to show only mild cognitive deficits. A few studies have not shown strong differences between cognitive performance of high-risk subjects and controls or only significant differences in one cognitive area. For example, Bertisch and associates (Bertisch et al., 2008) found only differences on delayed visual memory and not other neuropsychological test areas in high risk subjects vs controls when they used Bonferroni corrected significance levels. Nam and associates (Nam et al., 2009) found that only a test of category fluency showed differences between siblings of schizophrenics and controls when Bonferroni corrections were applied, although a larger number of neuropsychological tests showed significant differences at

Table 3
T-test comparison of cognitive scores of prodromal versus first episode or chronic schizophrenia.

MATRICS Domain	Prodromal (N = 61–73)	First Episode Schizophrenia (N = 37–44)	Chronic Schizophrenia (N = 30–34)
Speed of Processing	39.47 ± 9.95	35.86 ± 9.21	36.56 ± 9.77
Attention/ Vigilance	44.67 ± 11.78	39.64 ± 9.71*	36.19 ± 13.34**,a
Spatial Working Memory	39.30 ± 10.32	38.93 ± 10.79	36.47 ± 14.17
Verbal Learning	34.21 ± 13.38	29.89 ± 12.37	32.03 ± 12.33
Visual Learning	40.77 ± 12.14	37.64 ± 11.62	38.21 ± 11.91
Reasoning / Problem Solving	41.19 ± 11.15	40.73 ± 11.20	36.29 ± 13.94
Social Cognition	46.47 ± 13.83	45.34 ± 16.36	45.85 ± 18.89
Overall Composite	44.27 ± 8.73	43.90 ± 6.95	43.65 ± 9.23

Each value is mean ± S.D. of domain score or overall composite score from Chinese version of MATRICS battery. Variable numbers are due to missing data on specific tests on some subjects. Statistical significance of T-test difference between prodromal and either first-episode or chronic schizophrenia.

* $p < 0.05$.

** $p < 0.01$.

[a] BH protected significance (at $\alpha = 0.05$) taking into account 8 MATRICS score comparisons.

uncorrected significance levels. However, in the sample in our current study the HRF did not show any significant differences from controls in any cognitive area whether we used either uncorrected or BH corrected significance levels.

Working memory deficits, or deficits in delayed memory, have consistently been one of the greatest deficits found in schizophrenia, and some studies show them worsening over the course of illness. The absence of significant differences in the Working Memory domain of the MATRCIS battery in this study is likely due to the fact that we only measured Spatial Working Memory and not Verbal Working Memory. The Chinese version of the MATRICS battery does not include the Letter-Number Span test (LNS) subtest for assessing Verbal Working Memory, because this is not feasible in the Chinese language. Future studies utilizing the MATRICS battery in China should include an additional verbal working memory test, such as the PASAT (paced auditory serial addition task) or another verbal working memory task to compensate for this deficiency. A recent report recommends a revised cognitive testing battery for studies of schizophrenia in China (Shi et al., 2017).

The modest negative correlations between greater psychiatric symptoms, as measured by the PANSS for schizophrenia patients, or SIPS for prodromal subjects, suggests that the degree of psychiatric symptoms may be associated with some of the cognitive deficits, although a significant correlation does not necessarily mean there is a causative relationship. Previous studies and reviews have shown a relatively stronger relationship between negative symptoms and cognitive deficits, but improvement in positive symptoms was reported to correlate best with improvement in cognition (Addington et al., 1991; Harvey et al., 2006). Moreover, Harvey and associates (Harvey et al., 2006) have proposed that negative symptoms and cognition may be two relatively independent dimensions contributing to functional outcome in schizophrenia, and pharmaceutical companies are testing drugs targeted at each of these dimensions. Our correlations indicate that a relatively small portion of cognitive deficits are explained by positive or negative psychiatric symptoms, since R^2 values were in the range of 0.04 to 0.16.

There are several potential limitations of this study. As noted above the lack of a test for measuring verbal working memory in the Chinese with the MATRICS makes it more problematic to assess deficits in working memory. We recruited stabilized patients with schizophrenia who may have had slight improvements in cognition or who may have been more cooperative on complex neuropsychological tests because of antipsychotic treatment, especially treatment with second generation antipsychotics. This might have reduced potential differences in the patients with schizophrenia from other groups, especially the prodromal or family risk groups. Although our MATRICS battery T-scores corrected for most of the potential confounding factors of age, sex, and education, other factors we did not control for, such as being raised in an urban vs rural environment in China, and differences in socio-economic status could potentially influence cognitive capacity or prior cognitive learning, and, therefore, could be additional confounding factors we did not control for.

Although studies have indicated that some measures of cognitive deficits may help predict conversion of prodromal or family risk subjects to schizophrenia psychosis or related illness, there is little evidence showing whether MATRICS Composite or Domain scores are

Table 4
Summary of the Correlations Between MATRICS scores and Clinical Scale Scores.

Clinical characteristic	Speed of processing	Attention/ Vigilance	Spatial working memory	Verbal learning	Visual learning	Reason/problem solving	Social cognition	Overall Composite
PANSS positive	−0.032	−0.129	−0.065	−0.199	−0.213	−0.063	0.216	−0.194
PANSS negative	−0.169	−0.232*	−0.106	−0.158	**−0.378***,a	−0.237*	−0.080	−0.162
PANSS Total	−0.096	−0.204	−0.051	−0.129	**−0.304****,a	−0.131	−0.130	−0.150
SIPS positive	−0.051	−0.052	−0.236*	−0.113	−0.031	−0.136	0.016	−0.262*
SIPS negative	**−0.302***,a	−0.237*	−0.006	−0.226	−0.152	−0.075	−0.237	**−0.333***,a
SIPS disorganized	**−0.293***,a	−0.197	−0.286*	−0.224	−0.087	−0.118	−0.288*	**−0.361***,a
SIPS general	−0.022	0.007	0.057	0.036	−0.120	0.134	−0.179	−0.207
SIPS Total	**−0.337****,a	−0.208	−0.196	**−0.360****,a	−0.142	−0.215	−0.138	**−0.306***,a

Correlations are Pearson correction coefficient. N's for correlation with PANSS scores = 67–77; N's for correlation with SIPS scores = 59–73. Levels of significance prior to BH correction.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

[a] Correlation remained statistically significant at $\alpha = 0.05$ after BH correction including correlation with 8 SIPS and PANSS scores. Correlations which survive BH correction are also highlighted in bold.

PANSS,the positive and negative syndrome scale; SIPS, the structured interview for prodromal syndrome.

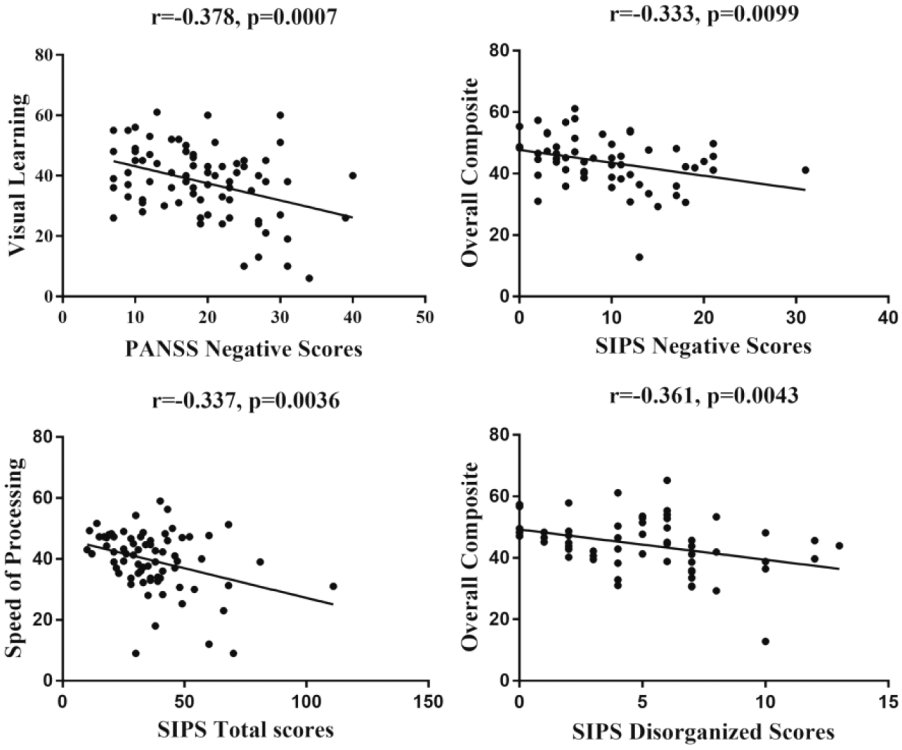

Fig. 1. Representative examples of correlations and linear regressions between MATRICS components and clinical scales which showed significant relationship between clinical scale and MATRICS scores.
The upper left graph shows the significant correlation between cognitive performances and PANSS Negative symptoms in patients with schizophrenia. The rest of the graphs show the significant correlations between cognitive performances and SIPS scores in prodromal subjects. The significance levels of the **r** are the original uncorrected significance levels. However, all correlations survived BH correction, see Table 4. PANSS = the positive and negative syndrome scale, SIPS = the structured interview for prodromal syndrome.

predictive in this regard. Although the results of this study are consistent with other research suggesting that the pattern of cognitive deficits in prodromal patients may be an endophenotype for schizophrenia-related disorders, the utility of the MATRICS Composite or Domain score for predicting later conversion to schizophrenia could be important in assessing the validity or usefulness of this conceptualization.

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Declaration of conflicts of interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.089.

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