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Cognitive functioning in individuals at ultra-high risk for psychosis, first-degree relatives of patients with psychosis and patients with first-episode schizophrenia

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ABSTRACT

Objective: The aim of the present study was to investigate and compare cognitive functioning of first-degree relatives of people with schizophrenia who were also at ultra-high risk (UHR) for psychosis with patients with first-episode (FE) schizophrenia, first degree relatives of patients not fulfilling UHR criteria (FDR), and healthy control (HC) subjects.

Method: Forty subjects in each group were included, underwent a face-to-face interview and completed a neurocognitive test battery, including the Trail Making Test-A (TMT-A, psychomotor functions), Stroop Color Word Test (attention), Digit Symbol Coding Test (DST, processing speed and working memory) and Hopkins Verbal Leaning Test-Revised (HVLT-R, verbal memory).

Results: Functioning in all the cognitive test domains displayed a gradual decrease from the HC, FDR, UHR to FE groups. After controlling for covariates, there were still significant differences in TMT-A ($F_{(7160)} = 35.4$, $P < 0.001$), DST ($F_{(7160)} = 38.9$, $P < 0.001$), Stroop Color Word Test ($F_{(7160)} = 35.0$, $P < 0.001$), Stroop Word Test ($F_{(7160)} = 36.2$, $P < 0.001$), Stroop Color Test ($F_{(7160)} = 40.9$, $P < 0.001$) and HVLT-R ($F_{(7160)} = 62.5$, $P < 0.001$) between the four groups, indicating that the cognitive functioning in the UHR group was intermediate between the FE and FDR groups, while the FDR group had poorer performance than the HC group, and the FE group had the poorest cognitive functioning across all four examined domains.

Conclusion: The results indicate that impairments in processing speed, attention, working memory and verbal memory exist in both UHR and FDR subjects. In order to clarify the associations between cognitive functioning and UHR and schizophrenia, longitudinal studies are warranted.

1. Introduction

Cognitive dysfunction is one of the core features of schizophrenia (Bora et al., 2010). Decreased cognitive performance is evident in the first-episode of schizophrenia and seems to be stable across its different stages (Mesholam-Gately et al., 2009).

The ultra-high risk (UHR) state for schizophrenia is characterized by subjectively experienced impairment in perception and thinking, attenuated psychotic symptoms, which are distinct from typical psychotic symptoms due to intact reality testing and insight, or brief and self-limited psychotic episodes (Correll et al., 2010; Yung and Nelson, 2013; Ziermans et al., 2014). Cognitive impairments exist in UHR for schizophrenia (Dickson et al., 2012; Matheson et al., 2011), which has the potential to be a neurobiological maker for future schizophrenia (Bora et al., 2014).

Significant deficits in various cognitive domains, such as verbal memory, working memory, executive functions, attention and processing speed, have been reported in UHR individuals (Kelleher et al., 2013a, 2013b; Lencz et al., 2006; Pukrop et al., 2006; Seidman et al., 2010) and people at familial high risk for psychosis (Agnew-Blais and Seidman, 2013; Besnier et al., 2009; Breton et al., 2011; de la Serna et al., 2011; Maziade et al., 2011; Seidman et al., 2006, 2010; Torniainen et al., 2011; Woodberry et al., 2010).

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Increasing evidence suggests that UHR individuals perform more poorly than healthy controls in a range of neurocognitive domains, but having less severely impaired performance than schizophrenia patients (Eastvold et al., 2007; Giuliano et al., 2012; Keefe et al., 2006). In addition, most UHR individuals will not develop psychosis (Cannon et al., 2008; Fusar-Poli et al., 2012a; Yung et al., 2004). Therefore, reduced neurocognitive functioning may be either driven by a more severely impaired subgroup at true risk for psychosis or reflect generalized distress, psychopathology, or other psychiatric problems in UHR subjects (Velthorst et al., 2009), rather than impairment exclusively associated with emerging psychosis (Lin et al., 2013).

To date, only limited studies have directly compared cognitive performance between persons with a family history of schizophrenia and UHR individuals (Mukkala et al., 2011; Myles-Worsley et al., 2007; Seidman et al., 2010; Ucok et al., 2013), which have yielded conflicting results. For example, in one study UHR individuals exhibited greater impairment than those with a family history of schizophrenia in verbal memory (Seidman et al., 2010). In another study, however, cognitive impairments were similar between UHR, first-episode schizophrenia, and relatives of psychotic patients (Ucok et al., 2013).

Comparing cognitive functioning across several domains between individuals at different levels of the psychotic spectrum, such as UHR individuals, first-degree relatives of patients with schizophrenia, and patients with first-episode schizophrenia, would be helpful to understand the degree to which cognition may be a risk marker for psychosis (Keefe et al., 2006). In order to examine neurocognitive impairments as a potential endophenotype of schizophrenia, we assessed the neurocognitive performance of first episode (FE) patients, UHR, first-degree relatives of psychosis (FDR) and healthy controls (HC). Based on previous findings (Lin et al., 2013; Mukkala et al., 2011; Myles-Worsley et al., 2007; Seidman et al., 2010; Ucok et al., 2013; Yung and Nelson, 2013), we hypothesized that UHR individuals would have poorer neurocognitive performance than HC participants across all domains, but have also better neurocognitive performance than FE. We also hypothesized that FDR subjects would have better neurocognitive functioning than UHR individuals, but poorer performance than HC.

2. Methods

2.1. Subjects

Inpatients or outpatients who received treatment in Guangdong Mental Health Center and Luoding Psychiatric Hospital, Guangdong province, China, were included in the FE group (n = 40) if they had experienced a FE schizophrenia within the past year based on a review of medical records and confirmed in a clinical interview according to the International Statistical Classification of Diseases and Related Problems-10th Revision (ICD-10).

Inclusion criteria for the UHR group (n = 40) were based on the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003). Individuals who were selected from the first-degree relatives with schizophrenia and who met the clinical criteria defined in the Criteria of Prodromal Symptoms (Miller et al., 2003) were invited to participate in the study. The Criteria of Prodromal Symptoms demand individuals to meet at least one of the following three clinical criteria: (1) brief intermittent psychotic state (BIPS): emerging psychotic symptoms with spontaneous remission in <1 week; (2) attenuated positive symptoms state (APS): these include subthreshold delusional unusual thoughts and subthreshold hallucinatory perceptual abnormalities; or (3) genetic risk and deterioration state (GRDS): genetic risk for schizophrenia plus a functional decline in the past year equivalent to a drop in global assessment of function of 30% sustained for at least 1 month (Miller et al., 2003). The first-degree relatives (siblings, parents or offspring) of the FE patients were evaluated with the SIPS. If they met the criteria of SIPS, then they were included in the UHR group. Otherwise, they were in the FDR group (n = 40). All FDR and UHR subjects were antipsychotic-naive.

The HC group (n = 40) consisted of the volunteers without any psychiatric disorders and without a first-degree relative with a psychiatric disorder. They were recruited by advertisements in the community.

General inclusion criteria for all the groups included (1) being aged 15–45 years, (2) an ability to understand the survey instructions and contents, and (3) at least primary school education level. General exclusion criteria included a history of significant head injury, seizures, cerebrovascular disease, other neurological disease, impaired thyroid function, learning difficulties, and ICD-10 criteria of alcohol or substance abuse or dependence in the past year.

The study protocol was approved by the Clinical Research Ethics Committee of Guangdong General Hospital. Written informed consent was obtained from each adult subject after the study procedures were fully explained, and additionally from their parents if subjects were younger than 18 years. If subjects agreed to participate in the study, they received a face-face structured interview by one trained psychiatrist with more than three years of clinical and research experience.

2.2. Assessments

Basic socio-demographic and clinical characteristics were collected using a form designed for the study by two psychiatrists. The Chinese version of the positive and negative syndrome scale (PANSS) (He and Zhang, 1997; Kay et al., 1987) was used for the assessment of positive symptoms, negative symptoms and general psychopathology in the UHR, FDR and FE groups.

To date, there has been no agreement on selection of cognitive dimensions and measurements in UHR-related research. In this study, following the recommendation of the Chinese Society of Psychiatry we measured four neurocognitive domains described in the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" cognitive battery (MATRICS) (Nuechterlein et al., 2008). These MATRICS domains were also used in several meta-analyses of neurocognition in clinical high risk adults (De Herdt et al., 2013).

The comprehensive neuropsychological battery included the following measures:

1) The Trail Making Test Part A (TMT-A) was used to measure psychomotor speed (Pukrop and Klosterkotter, 2010). The TMT-A consists of 25 circles distributed over a sheet of paper with the circles numbered 1–25. Subjects need to draw lines to connect the numbers in ascending order as quickly as possible while still maintain accuracy (Corrigan and Hinkeldey, 1987). Results for TMT-A are reported as the number of seconds required to complete the task with a higher score indicating greater impairment (Corrigan and Hinkeldey, 1987).
2) The Stroop Color and Word Test (SCWT) (Chung et al., 2008; Hawkins et al., 2004) was used to assess the attention, as well as working memory functions. The SCWT consists of three parts each lasting 45 s, and each with five columns of 20 items. Part 1 involves reading a list of 100 words (e.g., the words "red", "green" or "blue") that are printed in black ink. Part 2 requires the participants to identify the color of the ink of a list of meaningless characters. The third task requires the participants to report the color of the ink in which the words "red", "green" and "blue" were printed; the content of each word conflicts with the color of the ink with which it is printed (Homack and Riccio, 2004).
3) The Digit Symbol Coding Test (DST) was used to measure cognitive processing speed and working memory functions (Pukrop and Klosterkotter, 2010). The DST involves a key consisting of the numbers 1–9; each paired with a unique, easy-to-draw symbol such as a "V", "+" or ">". Below the key are a series of the numbers in random order and repeated several times.

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