



Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high risk

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ABSTRACT

Background: While deficits in cognitive functions are frequently reported in psychotic disorders, further longitudinal research is needed to confirm the specific risk factors for the development of psychosis. We examined longitudinally the social–cognitive and neurocognitive function of individuals at ultra-high risk for schizophrenia who developed psychosis later as predictive markers.

Method: The investigators studied 49 subjects at ultra-high risk (UHR) for psychosis and 45 healthy controls. The UHR subjects were followed for up 5.2 years (mean:2.8years) and 13 of these subjects developed psychosis. Theory of mind (ToM) tasks and neuropsychological tests were administered at baseline. Analyses compared the UHR patients who later developed psychosis, those who did not develop, and healthy controls. To examine the cognitive variables to predict transition to psychosis, Cox regression analyses were conducted. **Results:** At baseline, we found significant differences among the three groups in social cognition according to the False Belief and cartoon tasks and in neurocognition according to tasks measuring executive function, working memory, verbal memory, and visual memory. Our study showed that a model combining working memory, visual memory, executive function, and ToM tasks was significantly predictive of time to conversion to psychosis.

Conclusion: This study indicated that UHR patients who later converted to psychosis performed more poorly on tasks involving social cognition and neurocognition than did those who did not convert. We suggest that these deficits can serve as specific markers to predict the development of psychosis.

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1. Introduction

In the context of increasing interest in early intervention of illness, many researchers have attempted to identify specific markers for the development of psychosis (Cannon et al., 2007). To improve predictive accuracy, previous longitudinal studies have determined the risk of transition to psychosis and have evaluated a differential predictive model in a clinical high-risk sample (Cannon et al., 2008, Ruhrmann et al., 2010). A recent study on high-risk individuals reported that the rate at which psychosis developed decreased to 12% within one year and to 16% within two years; these results were attributed to early effective treatment or to the inclusion of “false positives” who were not at risk of psychosis (Yung et al., 2007). Hence,

we remain in need of reliable methods for precisely identifying those who will develop psychosis.

Recent prodromal studies investigated the role of neurocognitive impairment as a predictor of psychosis. A few prospective studies with individuals who later developed psychosis have suggested that neuropsychological deficits in visuospatial memory (Brewer et al., 2005), visual memory (Wood et al., 2007), speed processing, verbal memory (Brewer et al., 2005, Lencz et al., 2006, Pukrop et al., 2007), and attention (Keefe et al., 2006) occur early in the development of psychosis. Several studies demonstrated that predictions of the conversion could be improved by focusing on selected clinical symptoms in combination with neurocognitive deficits (Lencz et al., 2006, Riecher-Rossler et al., 2009). In addition, a recent review suggested that investigations of other specific variables including neurocognition, social cognition, and neuroanatomy are needed to identify the precise predictors of psychosis (Niendam et al., 2009).

Recently, a study on social dysfunction in schizophrenia suggested that measures of social cognition may also contribute to the prediction of functional outcomes in schizophrenia (Sergi et al., 2007). Many

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researchers have reported that patients with schizophrenia displayed impairments in such domains of social cognition as theory of mind (ToM) (Roncone et al., 2000, Greig et al., 2004). Several studies have focused on clinical subjects at high risk for schizophrenia according to ToM dysfunction, as proposed by Frith (1992). Couture et al. (2008) used the Eyes task as a measure of ToM, but were not able to find any significant differences within groups. Another study suggested that deficits in verbal ToM abilities characterize individuals at risk for schizophrenia (Chung et al., 2007). However, thus far, the ability of ToM impairment in the prodromal phase to predict progression to psychosis remains undetermined. Therefore, we need to investigate specific ToM deficits in efforts to predict which high-risk subjects subsequently convert to psychosis.

The aim of this study was to determine the usefulness of baseline ToM abilities and neurocognitive functions as predictors of psychosis. We hypothesized that those at ultra-high risk (UHR) who converted later (converters) would perform significantly more poorly than those who did not convert (nonconverters) on tasks involving social cognition and neurocognition at baseline. We further hypothesized that these primary deficits would be significantly predictive of the conversion.

2. Method

2.1. Participants

Based on the criteria contained in the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), we recruited the 49 participants in the ultra-high risk (UHR) group from the Seoul Youth Clinic between November 2004 and January 2009. After the baseline assessment, the UHR subjects received at least monthly follow-up assessments to detect the onset of acute psychotic symptoms. We followed the UHR subjects for up to 5.2 years (mean: 2.8 years, lowest: 1 year) to identify “true” prodromals. Forty-nine subjects met the criteria for UHR with regard to early transition to first-episode psychosis and membership in at least one of the following three subgroups at the time of intake: (1) attenuated psychotic symptoms ($n = 42$); (2) brief, limited intermittent psychotic symptoms ($n = 1$); and (3) trait-plus-state risk factors ($n = 10$). Four subjects met the intake criteria for both attenuated psychotic symptoms and trait-plus-state risk factors.

At baseline, all 49 subjects at UHR were between the ages of 15 and 35 years, and none had experienced a previous psychotic episode. Transition to psychosis was defined according to the PACE clinic criterion (Yung et al., 1998). These criteria require the presence of at least one of the following symptoms: suspiciousness, unusual thought content, hallucinations, or conceptual disorganization at least several times a week for longer than one week. The subjects were subsequently divided into two subgroups according to their psychotic status at the follow-up assessment (converters = 13, nonconverters = 36). Six individuals converted during the first 12 months after inclusion, whereas four of all transitions occurred after 12 but within 24 months. Only three subjects converted during the remainder of the study. Using Kaplan–Meier method, the cumulative prevalence rate \pm SE of conversion to psychosis was $12.5 \pm 4.7\%$ at 6 months, $14.3 \pm 5.2\%$ at 12 months, $20.1 \pm 6.0\%$ at 18 months, $23.9 \pm 6.8\%$ at 24 months, and $35.5 \pm 9.7\%$ at 30 months. The mean survival time was 2.78 ± 0.2 years (95% C.I., 2.30–3.26 years; median time, 3.09 ± 0.6 years). The DSM-IV diagnoses of the 13 UHR subjects who developed psychosis were determined by using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Nine were diagnosed with schizophrenia (six with paranoid type and three with undifferentiated type), and four were diagnosed with bipolar disorder with psychotic features.

We administered neurocognitive and social-cognitive tests every 12 months after baseline assessment unless the onset of psychosis occurred earlier. Those who transitioned to psychosis before one year

were assessed every 12 months after the evaluation that detected the onset of psychosis. At the initial assessment, three of the 49 subjects in the UHR group were receiving treatment with atypical antipsychotics: amisulpride, 400 mg ($n = 1$); quetiapine, 75 mg ($n = 1$); ziprasidone, 40 mg ($n = 1$).

Forty-five healthy controls, recruited from the community via newspaper advertisements and screened by the Structured Clinical Interview for DSM-IV, Non-Patient Version (SCID-NP), participated in the study. They were screened with the additional exclusion criterion of any first- or second-degree relatives with a history of a psychotic disorder.

Exclusion criteria for all subjects included any lifetime diagnosis of psychotic illness, substance dependence, or neurological disease; any illegal drug use or medication; a history of head injury or medical illness with documented cognitive sequelae; sensory impairment; or mental retardation. All participants were screened by using an additional exclusion criterion of any first- or second-degree biological relatives with a lifetime history of a psychotic disorder.

2.2. Measures

2.2.1. Entry assessments

At intake, psychotic symptoms were assessed by two experienced psychiatrists using the CAARMS, SIPS (Jung et al., 2010) and a modified 24-item version of the Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986). In addition, the severity of psychotic features was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Subjects were assessed in terms of GAF scores, parental socioeconomic status (SES) using the Hollingshead scale, the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967), and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). The family interview for genetic studies (Gershon and Guroff, 1984) was used to document any family history of psychotic disorders.

2.2.2. Theory of mind

ToM ability was evaluated using two verbal tasks, the False Belief (FB) and Strange Story tasks, and a nonverbal cartoon task. The FB task consisted of four short scenarios including first-order (Wimmer and Perner, 1983) and second-order tasks (Perner and Wimmer, 1985). The first-order FB task assesses the subject's understanding of a character's false belief about reality, and the second-order FB task measures the cognitive ability to imagine a third character's mental state. The Strange Story task (Happé et al., 1999) consisted of 16 short stories revised from those used in a study of ToM in autism (Happé, 1994). These stories were divided into eight ToM and eight Physical Story short stories. ToM stories were related to double bluffs, mistakes, persuasion, and white lies, and were presented prior to questions calling for inferences about characters' thoughts, feelings, or intentions. Subsequent Physical Story, non-ToM questions did not require inferences about characters' mental states. Verbal ToM tasks were translated into Korean under the direction of clinical psychologists and psychiatrists. A nonverbal ToM task, the cartoon task, comprised 30 comic strips. This task consisted of two strips that were revised from those included in Sarfati's Intention Inference Task (Sarfati et al., 1997) to reflect cultural differences. Response and reaction times for all trials were computerized.

2.2.3. Neurocognition

Measures of executive function included the Wisconsin Card Sorting Test (WCST), in which the number of perseverative responses was calculated; the Controlled Oral Word Association Test (COWAT); the Trail Making Test, Part B (TMT-B); and the Stroop Color–Word Test (Stroop C–W). Visual memory was evaluated with the Rey–Osterrieth Complex Figure test (ROCF), for which we calculated immediate and delayed scores. The Korean-California Verbal Learning Test (K-CVLT) (Kang and Kim, 1997), which addresses verbal memory and learning, provided measures of immediate and delayed recall. Measures of

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