Schizophrenia Research 164 (2015) 40–46

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Neurocognitive functioning of subjects with putative pre-psychotic states and early psychosis

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ARTICLE INFO

Article history:
Received 27 August 2014
Received in revised form 11 February 2015
Accepted 6 March 2015
Available online 20 March 2015

Keywords:
At-risk mental state
Neurocognition
Pre-psychotic
Psychosis
Schizophrenia
Ultra-high risk

ABSTRACT

Background: The neurocognitive functioning of patients with schizophrenia is likely to decline at the early stage of the illness. More evidence is needed to determine whether deficits in certain domains of neurocognition precede the onset of illness and can predict the onset of psychosis.
Methods: Subjects were recruited from the SOPRES study in Taiwan. A neuropsychological battery including the continuous performance test, Wisconsin Card Sorting Test, Wechsler Adult Intelligence Scale-Third Edition, Trail Making Tests, Mandarin version of the Verbal Fluency Test, and Wechsler Memory Scale—Third Edition, was applied at baseline and 1-year follow-up. Neurocognitive profiles derived from these tests were categorized into 9 domains for comparisons among subjects with different levels of clinical severity.
Results: A total of 324 participants, including 49 with first episode psychosis (FEP), 53 with ultra-high risk (UHR), 42 with intermediate risk (IR), 43 with marginal risk (MR), and 137 normal controls completed a baseline assessment and 71% of the participants completed a 1-year follow-up assessment. The profiles of the UHR and IR groups were identical at baseline. Those who converted to FEP later on (UHR+) showed relatively poorer performance than non-converters (UHR−) at baseline. At follow-up the performance of UHR+ was compatible to that of FEP, while UHR− generally improved.
Conclusions: By including subjects with early putative pre-psychotic states, our study clarifies some inconsistencies about the timing and stability of changes in neurocognitive functioning that occur at the start of psychosis; it also raises questions regarding the feasibility of using neurocognitive deficits to predict the risks of transition to psychosis.

1. Introduction

Studies in chronic schizophrenia have demonstrated significant neurocognitive impairments at schizophrenia onset, with the impairments persisting yet non-progressive (Goldberg et al., 1993; Heaton et al., 1994), and other studies have re-iterated this presentation (Addington et al., 2005; Hoff et al., 2005; Albus et al., 2006; Lewandowski et al., 2011). Recent neurobiological studies revealed that the brain abnormalities in patients with schizophrenia precede or become apparent at around the time of transition to frank psychosis (Howes et al., 2009; Takahashi et al., 2009; Fusar-Poli et al., 2011, 2012b), thus suggesting that neurocognitive deficits resulting from such brain abnormalities should be evident during the prodrome and inception of psychosis.

The patterns of neurocognitive deficits during this critical period have been described previously (Keefe et al., 2006b; Lencz et al., 2006; Eastvold et al., 2007; Pukrop et al., 2007). The large scale North American Prodrome Longitudinal Study (NAPLS) suggested that individuals with high risk of psychosis already had significant neuropsychological difficulties, particularly in those who later became psychotic, although such impairments are generally less severe than in first-episode schizophrenia and did not add much information to the prediction of psychosis beyond clinical criteria (Seidman et al., 2010).

A recent meta-analysis summarized that neurocognitive deficits are relatively consistent in subjects at high risk for psychosis, yet the impairments indeed cover a wide range of cognitive domains, including general intelligence, executive function, verbal and visual memory, verbal fluency, attention and working memory, and social cognition (Fusar-Poli et al., 2012b). Specifically, deficits in verbal fluency and memory functioning may be associated with subsequent transition to psychosis and may serve as important indicators of risk of transition to psychosis (Fusar-Poli et al., 2012b). However, more evidence is needed to test the generalizability and applicability of these findings, as the emergence of

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http://dx.doi.org/10.1016/j.schres.2015.03.006
0920-9964/

the prodrome of psychosis can only be defined retrospectively; follow-up studies find that only 1 out of 3 patients convert from an ultra-high risk state (the putative prodrome) to frank psychosis; and the cohorts for such studies are usually quite small (Fusar-Poli et al., 2012a).

Genetic studies of families at high risk suggest that certain subtle cognitive impairments revealed by general neuropsychological testing might just be trait markers of high risk probands but not necessarily predictors of psychosis development (Byrne et al., 1999). Also, studies indicate that neurocognitive impairments, such as lower scores in verbal learning and memory tests, already exist in the ultra-high risk subjects, yet deterioration is not necessarily significant after first episode psychosis becomes apparent (Caspi et al., 2003; Becker et al., 2010). On the other hand, greater verbal memory and/or executive function difficulties are not evident until the first episode of psychosis occurs, implying that these functional changes are state markers (Cosway et al., 2000; Whyte et al., 2006). Moreover, changes in neurocognitive functioning before and after the transition period are intricate. Working memory and processing speed are observed to decline with progression of the illness (Niendam et al., 2006; Jahshan et al., 2010), while an improvement in general intelligence can be seen once psychotic symptoms stabilized in the early stages of the illness (Jahshan et al., 2010).

Not surprisingly, neurocognitive impairments are heterogeneous in this patient group and findings are inconclusive. Antipsychotic treatment in the early stage of psychosis can modify neurocognitive performance to a certain extent (Hill et al., 2004). A closer look at the early pre-psychotic state (characterized by the presence of basic symptoms) versus late pre-psychotic state (characterized by the presence of attenuated or brief psychotic symptoms), suggests linkage of different stages of the prodrome to different domains of neurocognitive impairment (Frommann et al., 2011). Thus, neurocognitive change prior to the onset of psychosis is complex and will need more exploration to understand the neurodevelopmental processes occurring during the development of psychosis.

In Taiwan, a study on the psychopathological progress of the putative pre-psychotic state (the SOPRES study) was initiated in 2006 to follow participants with different risk levels up to 2 years (Liu et al., 2010). In addition to including ultra-high-risk subjects who demonstrated a significantly higher probability of transition to first episode psychosis, we also recruited subjects with a gradient of clinical severities spanning from the normal state, early/broad at-risk state (E-BARS) (Keshavan et al., 2011), ultra-high risk state, to first episode psychosis. Thus the SOPRES data allowed us to explore the pathophysiological changes way ahead of and throughout the psychosis development. In this paper, we compared neurocognitive functioning across clinical severities and between baseline and follow-up to investigate 1) how neurocognitive impairments change after onset of first-episode psychosis; 2) if neurocognitive impairments are evident along a gradient of clinical severity; 3) if there is any neurocognitive deficit that can herald the risk of transition to psychosis; and 4) if non-transition to psychosis is accompanied by restoration of neurocognitive functioning.

2. Methods

2.1. Sample

Subjects were participants in the SOPRES study. The rationale and methodology for the SOPRES study have been described elsewhere (Liu et al., 2010, 2011). Briefly, individuals presenting with "non-specific Cognitive deficits, Affective symptoms, Social Isolation, and School failure" (CASIS) (Cornblatt et al., 2003) or newly developed subthreshold psychotic symptoms were referred for assessment. All adult participants voluntarily provided their written informed consent and minors gave written assent to participate with the informed consent of their parents. The protocol of this study was approved by the Research Ethics Committee of the study hospital.

Clinical participants were divided on the basis of 4 different risk levels, using the Thought/Perception Diagnostic Interview Schedule (TP-DIS) for clinical assessment. The first-episode psychosis (FEP) group included participants with schizophrenia, schizophreniform disorder, brief psychotic disorder, or schizoaffective disorder meeting the DSM-IV criteria in the preceding one year. The ultra-high-risk (UHR) group included participants with attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) (McGorry et al., 2003). The intermediate-risk (IR) group included participants presenting with odd thinking, feelings, speech, or perceptual experiences, yet not as severe as those presented by the UHR group, but meeting the symptom criteria of schizotypal disorder according to the 10th edition of the International Classification of Diseases (ICD-10) without the duration requirement of two years. The marginal-risk (MR) group included participants presenting with CASIS symptoms not meeting either the threshold for inclusion in the IR group or other diagnostic category. A group of age- and gender-matched healthy volunteers were recruited by public advertisement as normal controls.

Subjects with an IQ below 70, aged younger than 16 years, with a history of traumatic brain injury, a history of central nervous system illness, a prior psychotic episode lasting for more than one year, or current use of psychoactive stimulants were excluded.

All participants were invited to receive follow-up assessments annually for 2 years. As the attrition rates were high by the end of 2 years, only the baseline and 1-year follow-up results were analyzed. Some members of the UHR group who converted to first episode psychosis during the 2-year follow-up were designated UHR+, while non-converter members were designated UHR− at baseline.

2.2. Neurocognitive measurements

A battery of neuropsychological tests including the continuous performance test (CPT), Wisconsin Card Sorting Test (WCST), Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), Trail Making Tests, Mandarin version of the Verbal Fluency Test, and Wechsler Memory Scale—Third Edition (WMS-III) was given to all participants. Z-scores for all variables were computed based on the baseline mean and standard deviation of the control group and transformed such that higher scores indicate better performance. Many of these tests have been employed in our previous studies (Liu et al., 2006, 2012).

Individual subtests of the neurocognitive tests were re-categorized into constructs of eight cognitive functional domains which hypothetically reflect basic cognitive processes following Kremen's method (Kremen et al., 2004). Domain scores were calculated by averaging the z-scores of designated subtests in each domain, including verbal conception ability (VC: information and similarity in the WAIS-III), visual spatial ability (VS: block design in the WAIS-III), executive function (EF: number of perseverative errors and number of categories achieved in the WCST, Trail-Making Test Part-B), processing speed (PS: digit symbol substitution in the WAIS-III and Trail-Making Test Part-A), mental control (MC: arithmetic and digit span backward in the WAIS-III), attention (ATT: d′ in CPT, digit span forward in the WAIS-III), verbal memory (VM: immediate and delayed recalls in logic memory tests in the WMS-III), and visual memory (ViM: immediate and delayed visual reproduction tests in the WMS-III). In addition, verbal fluency (VF) is also examined as it is thought to be important for prediction of transition to psychosis (Fusar-Poli et al., 2012b).

2.3. Statistical analysis

For demographic characteristics, we used the Chi-square test and analyses of variance (ANOVAs) to compare categorical and continuous variables across different risk groups and normal controls, respectively. The differences in neurocognitive function across groups were tested by the Kruskal–Wallis one-way analysis of variance and post-hoc analyses