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Relationship between diminished expression and cognitive impairment in first-episode schizophrenia: A prospective three-year follow-up study

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ABSTRACT

Background: Diminished expression (DE) is a core sub-domain of negative symptoms construct in schizophrenia. There is limited, yet inconsistent data regarding DE and its associations with cognition, particularly in the early illness course. This study aimed to examine cross-sectional and longitudinal relationships of DE with cognitive functions in first-episode schizophrenia utilizing a prospective design.
Method: Ninety-three Hong Kong Chinese aged 18 to 55 years presenting with first-episode schizophrenia-spectrum disorder were studied. Severity of DE was measured as sum of individual item scores indicative of affect flattening and alogia. Symptom evaluation was conducted at intake, after clinical stabilization of first psychotic episode, at 12, 24 and 36 months. Cognitive functions were evaluated at clinical stabilization, 12, 24 and 36 months.
Results: DE was significantly correlated with various cognitive functions in successive follow-up assessments. Regression analyses adjusting confounding effects of sex, pre-morbid adjustment, duration of untreated psychosis and chlorpromazine equivalents showed that DE was associated with performance on verbal fluency at 12 ($p < 0.01$) and 24 months ($p < 0.05$), visual reproduction at 24 ($p < 0.05$) and 36 months ($p < 0.01$), logical memory at 36 months ($p < 0.05$) and Modified Wisconsin Card Sorting test at 24 ($p < 0.05$) and 36 months ($p < 0.05$). Neither cross-lagged associations between DE and cognition nor significant correlations between changes in these two domains over three years were observed.
Conclusions: DE and cognitive functions were correlated concurrently but no longitudinal associations between these two domains could be demonstrated. Our findings indicated that DE and cognitive impairment represented relatively independent domains of the illness with potentially distinctive therapeutic implications.

1. Introduction

Negative symptoms and cognitive impairment are considered as the core features of schizophrenia. Substantial evidence indicated that these two symptom dimensions constitute an unmet therapeutic need, and are associated with poor functional outcome (Green et al., 2000; Bowie et al., 2006) and limited response to pharmacotherapy (Murphy et al., 2006; Goldberg et al., 2007). Numerous studies have therefore been conducted to examine whether negative symptoms and cognitive dysfunction are intrinsically related to each other or represent independent domains with distinguishable pathological processes (Harvey et al., 2006b).

Literature suggested that negative symptoms were significantly related to cognitive impairment (Dominguez et al., 2009). Negative symptoms were found to be correlated with generalized cognitive deficit (Bilder et al., 2000; Heydebrand et al., 2004), or specific cognitive domains including executive function (Donohoe et al., 2006), memory (Villalta-Gil et al., 2006) and processing speed (Leeson et al., 2010). However, previous research consistently demonstrated only modest associations between negative symptoms and cognition with limited explained variance (Green and Neuchterlein, 1999; Harvey et al., 2006b). Furthermore, the majority of these studies was cross-sectional in design and focused mainly on patients with chronic illness. Thus far, few prospective studies have been conducted to investigate the longitudinal relationship between these two symptom dimensions. Even fewer have examined first-episode sample which, nonetheless, allows the trajectories of symptom manifestations and cognitive deficits to be better elucidated right from the onset of psychosis. In fact, inconsistent results were noted across studies regarding the longitudinal relationship between negative symptoms and cognitive impairment (Harvey et al., 2006b). Some investigators reported significant association between symptom improvement and cognitive change (Censits et al., 1997; Gold et al., 1999; Schuepbach et al., 2004; Leeson et al., 2010), while others failed to find a lawful relationship between these two

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symptoms dimensions over time (Hoff et al., 1991; Harvey et al., 1996; Friedman et al., 2002; Hughes et al., 2002; Bell and Mishara, 2006; Harvey et al., 2006a; Gonzalez-Blanch et al., 2008).

Of note, several methodological issues that may influence the magnitude of association between negative symptoms and cognitive impairment warrant consideration. First, inclusion of items that are in fact cognitive in nature in negative symptom assessment such as impaired attention and abstract thinking abnormality introduced overlap in definitions of cognitive dysfunction and negative symptoms, and may inflate correlation between these two symptom dimensions (Harvey et al., 2006b). Second, most, if not all, previous studies examined negative symptoms as a unitary construct. Yet, factor-analytic studies consistently showed that negative symptoms comprised two distinct sub-domains, namely diminished expression (DE) and avolition (Messinger et al., 2011). Measuring negative symptoms by single symptom score as adopted in most prior studies may therefore obscure potentially significant relationships between symptom sub-domains and cognitive functions. Third, evaluation of avolition relies primarily on reports of self-care and occupational performance which overlap substantially with functional outcome measure. As cognitive dysfunction is a key determinant of psychosocial functioning, it is thus plausible that observed correlations between negative symptoms and cognitive impairment may partly be attributable to significant associations of cognition with functional deficits (Harvey et al., 2006b). Conversely, DE is examined on the basis of observation of expressive deficits in gestures, speech and facial expression, and thereby minimizing confounding effects of functional deficits on the relationship between DE and cognition.

Recently, research investigating negative symptom sub-domains began to emerge and focused mainly on the relationship of avolition with cognitive and functional impairments (Faerden et al., 2009; Konstantakopoulos et al., 2011). Yet, despite being closely linked to poor illness outcome (Evensen et al., 2012), DE and its associations with cognitive functions have rarely been studied. As DE and AA represent separable symptom dimensions that may necessitate different interventions, investigating differential relationships of these two symptom sub-domains with cognitive dysfunction may therefore unravel potential therapeutic targets and shed light on their underlying neurobiological mechanisms (Liemburg et al., 2013; Strauss et al., 2013). Given the clinical and research significance of DE, along with a paucity of data regarding its relationship with cognitive impairment, particularly in the early course of the illness, we present a prospective three-year follow-up study in a representative cohort of Chinese patients having first-episode schizophrenia-spectrum disorder in Hong Kong with an aim to examine both the cross-sectional and longitudinal relationships between DE and cognitive impairment. The potential confounding effects of pre-morbid adjustment and duration of untreated psychosis (DUP) on cognitive and symptom measures were adjusted to enable better clarification of any independent associations between DE and cognitive domains.

2. Materials and methods

2.1. Subjects

One hundred and thirty-eight consecutive patients aged 18 to 55 years with first-episode schizophrenia, schizophreniform disorder or schizoaffective disorder were recruited from both outpatient and inpatient psychiatric units covering a defined catchment area in Hong Kong. Patients with known neurological disorder, learning disability or current substance abuse were excluded from the study. Of the initial cohort, 93 subjects completed the three-year follow-up, 40 defaulted, four committed suicide and one died of medical disease. There were no significant differences between completers and non-completers in socio-demographics, DUP, baseline symptom ratings and cognitive functions. The current study was part of a prospective three-year follow-up study in first-episode schizophrenia-spectrum disorder and findings regarding persistent negative symptoms and the influence of DUP on cognitive functioning have been reported elsewhere (Chang et al., 2011, 2013a). The study was approved by local institutional review board and all of the subjects gave written informed consent before participation.

2.2. Assessments

The three-year diagnosis of each subject was determined according to DSM-IV criteria (American Psychiatric Association, 1994) using all available information encompassing the whole follow-up period including Chinese-bilingual Structured Clinical Interview for DSM-IV (CB-SCID-I/P; So et al., 2003) administered at baseline and at 3 years, informant histories and medical records. Previous validation study showed that CB-SCID-I/P yielded reliable DSM-IV diagnoses in Chinese patients with psychotic disorders (So et al., 2003). Pre-morbid functioning was measured with the Pre-morbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982). We only included childhood ($\leq$11 years) and early adolescence (12–15 years) periods for assessment to avoid any possible confounding with early symptoms because the onset of prodrome and psychosis usually occur in late adolescence and early adulthood (Cassidy et al., 2010; Chang et al., 2013b). The PAS total score was calculated by summing the scores on all items encompassing both childhood and early adolescence periods and dividing by the total possible score (score range 0 to 1, higher score indicates lower functioning). Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Hafner et al., 1992) was used to assess DUP which was defined as the time interval between onset of positive psychotic symptoms and treatment initiation.

High Royds Evaluation of Negativity Scale (HEN; Mortimer et al., 1989) was employed to measure negative symptoms. It comprises six subscales and 18 items which are rated along an anchored five-point severity scale (range 0–4, higher score indicates more severe negative symptoms). ICCs for the subscales ranged from 0.74 to 0.85. Validation of HEN for use in Chinese schizophrenia patients has previously been reported (Chen et al., 1996). In this study, we focused on three of the six subscales, i.e., Affect, Behavior and Speech subscales. Our earlier study using principal component analysis revealed that items of these three subscales aggregated into a single factor which corresponded to DE, a core sub-domain in negative symptoms comprising affect flattening and alogia (Chen et al., 1996). In the current study, DE score was defined as sum of individual item scores of these three HEN subscales. A comprehensive battery of cognitive assessments was administered to all subjects, comprising logical memory test (Wechsler Memory Scale Revised, WMS-R-HK; Hong Kong Psychological Society, 1989a,b), visual reproduction test (WMS-R-HK), forward digit span (Wechsler Adult Intelligence Scale, WAIS-R-HK; Hong Kong Psychological Society, 1989a,b), category verbal fluency and Modified Wisconsin Card Sorting Test (MWCST).

Psychopathological evaluation was conducted at intake, after clinical stabilization of the first psychotic episode (based on clinical judgment of the treating psychiatrists with a mean of 42.6 days after initial assessment), at 12, 24 and 36 months. To maximize cooperation and to reduce state effects of acute psychosis, cognitive assessment undertaken when patients were clinically stabilized was regarded as baseline cognitive measure. Cognitive assessment was re-administered to each subject at 12, 24 and 36 months. A group of healthy controls, matched with age, sex and educational level, were recruited via advertisements and were evaluated with the same battery of cognitive assessments as patients at baseline only.

2.3. Statistical analysis

Differences between patients and controls on baseline cognitive functions were evaluated using independent *t*-test. A repeated-