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Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia

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ABSTRACT

Background: The functional outcome of schizophrenia is affected by multiple factors such as cognitive function and clinical symptoms. The complex relationship among cognitive function (both neuro- and social-cognitions), clinical symptoms, and functional outcome remains unclear. The current study employed structural equation modeling (SEM) to examine whether clinical symptoms mediate the relationship between cognitive function and functional outcome in a large cohort of patients with schizophrenia.
Method: Three hundred and two Han-Chinese patients with chronically stable schizophrenia received evaluation of cognitive function (using the Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS] Consensus Cognitive Battery, including 7 domains covering neurocognition and social cognition), clinical symptoms (including positive, negative and depressive symptoms), and functional outcome as assessed by Global Assessment of Functioning Scale and Quality of Life Scale.
Results: SEM identified clinical symptoms as a mediator between cognitive function (including all 7 domains of MATRICS) and functional outcome in schizophrenia. The relationship between cognitive function and functional outcome was significant in the basic model. In the mediation model, the link between cognitive function and functional outcome was mediated by clinical symptoms, mainly negative symptoms.
Conclusion: This study suggests that clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. Future studies should explore the impact on other functional outcomes in different ethnicities and various illness phases.

1. Introduction

Schizophrenia is one of most disabling disorders worldwide that brings forth severe and persistent functional impairment. Identifying factors contributing to functional outcome becomes an important issue not only for drug development but also for psychiatric rehabilitation programming. Functional outcome, divided into domains of community outcome, social problem solving and psychosocial skill acquisition, is related to neurocognitive function (Green et al., 2000). Patients with schizophrenia are impaired in various cognitive functions, including both neuro- and social-cognitions which are associated with functional outcome (Green et al., 2000; Fett et al., 2011; Horan et al., 2012). In addition, clinical symptoms, particularly the negative symptoms, are linked to functional outcome (Milev et al., 2005). The relationships between symptomatic domains and cognitive domains are also strong. Negative symptoms are found to have the strongest relationship with neuro- and social-cognitions (Milev et al., 2005; Ventura et al., 2011); nevertheless, weak association is also noted between positive symptoms such as reality distortion (delusions and hallucinations) (Ventura et al., 2011) as well as depressive symptoms (Smith et al., 1999) with neuro- and social-cognitions.

The relationship among neuro- and social-cognitions, clinical symptoms and functional outcome is complex and it is important to take all these factors into account simultaneously while investigating their interactions. Moreover, the relationship between two factors may be mediated by another factor. For example, Ventura et al. (2009) addressed that negative symptoms at least partially mediate

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the relationship between neurocognition and functional outcome. Sergi et al. (2006) demonstrated that social perception mediates the influence of early visual processing on functional status. Schmidt et al. (2011) found that social cognition mediates an indirect relationship between neurocognition and functional outcome. Intrinsic motivation was also suggested to be a critical mechanism for explaining the relationship between neurocognition and psychosocial functioning (Nakagami et al., 2008). Traditional regression or correlation modeling may not be very satisfying in comparing the relative weights of each variable in an integral whole. A possible resolution is the structural equation model (SEM), which is powerful in testing a set of confirmatory factor analyses and regression equations simultaneously (Hoyle, 1995).

The MATRICS Consensus Cognitive Battery (MCCB) developed by the National Institute of Mental Health includes social cognition as one of the seven cognitive domains in schizophrenia (Green et al., 2004). MCCB, which serves as the standard measure for cognitive studies in schizophrenia, has excellent clinical relevance for real-world functioning and is more and more widely used by recent ongoing trials (Keefe et al., 2011). Although some researchers (van Hooren et al., 2008) have conceptualized social cognition as a construct separate from neurocognition, Vauth et al. (2004) used SEM to demonstrate that social cognition is closely correlated with neurocognition (correlation coefficient = 0.91) and neurocognition accounts for 83% of the variance in social cognition. However, it remains unclear when neuro- and social-cognitions, clinical symptoms and functional outcome are included in a single model: whether social cognition and neurocognition are better considered as a single construct or as distinct two?

Though the mediation models among neurocognition, social cognition, and functional outcome have been demonstrated by SEM (Sergi et al., 2006; Schmidt et al., 2011), one unanswered issue concerns the relationship between neuro- and social-cognitions and functional outcome when clinical symptoms are taken into account simultaneously. Furthermore, to date, SEM research using the MCCB for the assessment of neuro- and social-cognitions as well as comprehensive assessment of clinical symptoms is lacking. Albeit with limitation, the Global Assessment of Functioning (GAF) Scale of the DSM-IV was used as the sole assessment of functional outcome of schizophrenia in some studies (Schmidt et al., 2011). GAF, jointly with social and occupational functioning and quality of life, has been regarded as a valid tool for assessing functional outcome (Schennach-Wolff et al., 2009). In addition, quality of life as well as subjective wellbeing have also been recognized as an important measure of the outcome of schizophrenia patients (Narvaez et al., 2008; Schennach-Wolff et al., 2010), particularly when social cognition and clinical symptoms are among the predictive factors (Hofer et al., 2009). Patient satisfaction is related to their willingness to be engaged in treatment, subsequently related to symptomatic and functional outcome (Lambert and Naber, 2004). GAF scores are correlated with quality of life in schizophrenia patients (Woon et al., 2010). Subjective rating of quality of life and objective measure of global functioning has been used together for the assessment of longitudinal outcome of schizophrenia (Sim et al., 2006). Therefore, we used both GAF and quality of life to represent the functional outcome of schizophrenia in this study.

The present study aimed to use the SEM to test the relationship among neuro- and social-cognitions assessed by the MCCB, clinical symptoms composed of positive, negative and depressive symptoms, and functional outcome represented by both GAF and quality of life in a large sample of patients with schizophrenia who had been clinically stable for 3 months or longer. We hypothesized that the relationship between neuro- and social-cognitions and functional outcome would be mediated by clinical symptoms particularly the negative symptoms. We also tested whether a one-factor model that represents neurocognition and social cognition as a single construct or a two-factor model that represents the two domains as separate constructs would fit the overall data better.

2. Materials and method

This study was approved by the institutional review board of the China Medical University Hospital, a major medical center in Taiwan, and conducted in accordance with the Declaration of Helsinki.

2.1. Subjects

Unrelated patients with schizophrenia were recruited from inpatient and day-care units of the China Medical University Hospital and affiliated Taichung Chin-Ho Hospital. All were Han Chinese in Taiwan, with age between 18 and 65. The subjects gave their written informed consent for participating in this study after complete description and discussion. The patients were free from any Axis I or II psychiatric disorder including smoking, alcohol drinking or other substance abuse/dependence except schizophrenia, as determined by experienced research psychiatrists using the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). All patients had been clinically stable for at least three months. All were in good physical health, as determined by history taking, physical examination, electrocardiogram, and laboratory tests including fasting blood sugar, lipid profile, liver and renal function tests and electrolytes. The patients who were unable to accomplish the whole assessments of cognitive function, clinical symptoms, and functional outcome (see below) were excluded.

2.2. Measurements of cognitive function

Cognitive function was assessed using a battery of tests, which were the same as or the analogues of tests from the MATRICS Consensus Cognitive Battery (MCCB) recommended by the USA National Institute of Mental Health MATRICS committee, due to lack of Chinese versions of some tests (Green et al., 2004). This battery included 7 domains: 1) speed of processing, consisting of 3 tests: Category Fluency, Trail Making A (Reitan, 1958), and WAIS-III Digit Symbol—Coding (Wechsler, 1997a); 2) sustained attention by Continuous Performance Test (Chen et al., 1998); 3) working memory, verbal (backward digit span (Silver et al., 2003)) and nonverbal (WMS-III, Spatial Span (Wechsler, 1997b)); 4) verbal learning and memory (WMS-III, word listing); 5) visual learning and memory (WMS-III, visual reproduction); 6) reasoning and problem solving (WISC-III, Maze (Wechsler, 1991)), and 7) social cognition, measured by Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) V2.0 (Mayer et al., 2003). The MSCEIT includes eight tasks in four branches: perceiving emotions, facilitating emotions, understanding emotions and managing emotions (Mayer et al., 2003). Social cognition was assessed by the "managing emotions" branch, which has been recommended by the MATRICS committee as the most appropriate measure of social cognition (Green et al., 2005; Eack et al., 2010). The validity/reliability (Ma et al., 2010) and feasibility (Lo et al., 2010) of the Chinese version have been satisfactory. Each domain score was standardized to a T score with a mean of 50 and a standard deviation of 10 for making every domain more comparative. Similar methods have been reported previously with excellent test–retest reliability and validity (Keefe et al., 2011). For the domain with more than one test, a composite T score was calculated by standardizing the average of each T score.

2.3. Clinical assessments

The Positive and Negative Syndrome Scale (PANSS)-Positive subscale (Kay et al., 1987), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), and 17-item Hamilton Depression Rating Scale (HAMD17) (Hamilton, 1960) were used to assess positive, negative and depressive symptoms. Clinical ratings were done by research psychiatrists who were well-trained and experienced in the rating scales. Inter-rater reliability was analyzed using the analysis of variance (ANOVA) test. Only raters with an intraclass correlation coefficient of