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Neurocognitive predictors of social cognition in remitted schizophrenia

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ABSTRACT

Knowledge of how specific neurocognition (NC) abilities predict social cognition (SC) in schizophrenia has potential to guide novel integrated cognitive-remediation therapies. The scope of studies conducted in this field is limited as they have not examined a comprehensive set of SC domains and they employ small sample sizes of heterogeneous patient groups. We studied a broad range of NC (sustained attention, processing speed, verbal/visual memory and visual processing/encoding, cognitive flexibility and planning) and SC [different levels of theory of mind (ToM)], attributional bias, emotion recognition and social perception] abilities in 170 remitted schizophrenia patients. Multivariate regression analyses revealed attention and planning as predictors of 1st order ToM. Memory encoding was the strongest predictor of 2nd order ToM. Faux-pas recognition, social perception and emotion recognition were influenced by a combination of cognitive flexibility and memory encoding abilities. Overall, NC predicted anywhere between ~4% and 40% of variance observed in specific SC sub-dimensions of attributional bias (4%), 1st order (19%) and 2nd order (12%) theory of mind, faux-pas recognition (28%), social perception (29%) and emotion recognition (39%). Individual SC abilities are predicted by distinctive as well as shared NC abilities. These findings have important implications for integrated cognitive remediation.

1. Introduction

Deficits in social functioning, including interacting with others, sustaining gainful employment and functioning in the community, are a defining feature of schizophrenia, making it a leading cause of disability worldwide (Murray and Lopez, 1997). Impairments across a range of cognitive abilities predict these deficits in social functioning. Neurocognition (NC) involves general information acquiring and processing abilities. Attention, processing speed, verbal and visual learning and memory, working memory and reasoning and problem solving are the neurocognitive functions impaired in schizophrenia (Green et al., 2004). Social cognition (SC) includes specific mental operations underlying social interactions. SC domains studied in schizophrenia include theory of mind (ToM), emotion processing, social perception and knowledge and attributional bias (Green et al., 2008). These processes involve an inter-subjective quality, requiring reflective (meta-cognitive) and social inferential abilities to infer thoughts and emotions of others, identify social roles, rules and contexts, as well as, make causal attributions of social events that have personal relevance.

Though NC and SC have been observed to exist as distinct cognitive constructs (Sergi et al., 2007; van Hooren et al., 2008; Mehta et al., 2013b), an average of about 10% of shared variance exists between these two constructs (Ventura et al., 2013). NC and SC together account for about a quarter of the variance in functional outcomes in schizophrenia (Fett et al., 2011). Specifically, social cognition mediates the influence of neurocognition on functional outcome (Schmidt et al., 2011). These findings have lead to the development of several cognitive remediation programs that target improvement in social and neurocognition, with the aim of translating this improvement to better functional outcomes (Medalia and Saperstein, 2013). Results of these interventions reveal benefits of small to moderate effect size in cognition and functional outcome (Wykes et al., 2011). Coordinated and integrated strategies that target enhancement of both neurocognition and social cognition have evolved over the years (Brenner et al., 1992; Hogarty et al., 2004).

In keeping with the findings that SC mediates the influence of NC on functional outcomes, emerging empirical evidence from longitudinal studies suggests that NC underlies, and is causally primary to SC (Hoe et al., 2012). Investigators have explored the relationship between NC and SC—a recent meta-analysis suggesting small to medium range non-specific correlations among

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different dimensions of these two constructs (Ventura et al., 2013). However, most of these studies report only correlation analyses without controlling for the confounding effects of multiple NC predictors. Nevertheless, it appears intuitive that basic NC abilities such as memory, executive functions and processing speed, among others, may underlie rapid interpretation of complex social stimuli to inform the moment-to-moment generation, refinement and selection of models for thoughts and emotions of others, which underlie diverse SC abilities.

Only a few studies have assessed specific neurocognitive predictors of social cognition, by controlling for influence of other cognitive predictors. A global neurocognitive index was found to influence 1st order ToM abilities in a group of 36 symptomatic schizophrenia patients (Bozikas et al., 2011). In a similar study on 43 clinically stable schizophrenia patients, none of the NC measures predicted 1st order ToM abilities, but executive functions from the WAIS-III had a significant influence on 2nd order ToM abilities (Fernandez-Gonzalo et al., 2013). Early visual processing, and not other cognitive abilities like attention and working memory was found to have a significant association with emotion recognition and social perception (Kee et al., 1998; Sergi et al., 2006) in schizophrenia. There are very few studies that have explored the influence of NC on attributional bias in schizophrenia. One such study found verbal IQ to be the only significant cognitive measure to predict externalizing bias (Donohoe et al., 2008).

Overall, these studies in patients with schizophrenia have provided results that are inconsistent and non-specific. Limitations of these studies include small sample sizes, limited measurement of SC and NC abilities, lack of controlling for multiple NC abilities and heterogeneous patient populations. Patients who have remitted from their positive symptoms may require cognitive remediation to overcome the subtle residual cognitive and negative symptoms, which influence their functional outcomes (Mehta et al., 2014). Interestingly, schizophrenia patients in remission also demonstrate substantial impairments across diverse dimensions of SC abilities (Bora et al., 2009; Mehta et al., 2013a), thus suggesting that SC deficits are likely trait-markers of schizophrenia.

We aimed to explore the general cognitive predictors of four social cognition dimensions (theory of mind, emotion processing, social perception and attributional bias) using multiple linear regression models in a homogeneous group of remitted schizophrenia patients.

2. Methods

Data for this analysis were obtained from a larger study to determine the clinical significance of SC ability in remitted schizophrenia patients (Mehta et al., 2013a), conducted at the National Institute of Mental Health and Neurosciences, Bangalore. The institute's ethics committee approved the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients provided written informed consent.

A total of 170 consenting schizophrenia patients diagnosed independently by two qualified psychiatrists according to DSM IV criteria, and confirmed using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) were recruited. They fulfilled operational criteria for remission (scoring ≤ 3 on Positive and Negative Syndrome Scale (PANSS) rated for previous 6 months) in psychotic (P1-delusions, P3-hallucinatory behavior and G9-unusual thought content) and disorganization (P2-conceptual disorganization and G5-mannerisms/posturing) dimensions according to the proposed multidimensional criteria for symptomatic remission by "The Remission in Schizophrenia Working Group" (Andreasen et al., 2005). Patients with substance dependence in the last six months (except nicotine), and those with co-morbid neurological or medical disorder or clinically diagnosable or self-reported visual or auditory impairment were excluded. Those with a score of ≤ 19 on the Hindi Mental Status Examination (Ganguli et al., 1995) were excluded. All patients were on stabilized doses of anti-psychotics 4 months prior to evaluation. 150 (88.2%) patients were on atypical antipsychotics, nine (5.3%) were on typical antipsychotics and the rest (6.5%) were on a combination of atypical and typical antipsychotic medications, with mean chlorpromazine equivalents of 398.76 ± 218.83 mg/day (Andreasen et al., 2010).

2.1. Assessments

Schizophrenia patients and healthy comparison subjects underwent assessments for SC performance. In addition, the patients were assessed for their neurocognitive performance and symptom status.

2.1.1. Social cognition

Consistent with recommendations of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) New Approaches Conference (Green et al., 2005) and the National Institute of Mental Health sponsored meeting "Social Cognition in Schizophrenia: Basic Definitions, Methods of Assessment, and Research Opportunities" (Green et al., 2008), we selected 4 domains of SC. Theory of Mind (ToM), social perception and attributional bias were assessed using the Social Cognition Rating Tools in Indian Setting (SOCRATIS) (Mehta et al., 2011). Emotion processing was assessed using the Tool for Recognition of Emotions in Neuropsychiatric Disorders (TRENDS) (Behere et al., 2008).

2.1.1.1. Theory of mind. Story-based tasks examined the ability, at different complexity levels, to 'meta-represent' mental states of others (e.g., Suresh thinks that Rani will go to the temple area to buy the ice-cream because she has not seen the ice-cream man go towards the school). The 1st, 2nd and higher order (faux pas) indices (see below) differentiated schizophrenia patients from healthy controls (-known groups validity) with effect sizes (Cohen's *d*) ranging from 1.1 to 2.3 (Mehta et al., 2011).

(a) *1st order ToM:* This assesses the subject's ability to infer mental states of another person (i.e., the capacity to infer "A believes that x"). Tasks included two false-belief stories [based on Sally–Anne (Wimmer and Perner, 1983) and Smarties (Perner et al., 1987) tasks], and two metaphor detection stories (Drury et al., 1998) since metaphor detection is considered to be a 1st order ToM function (Brüne, 2005; Mehta et al., 2013a).
(b) *2nd order ToM:* This assesses the subject's ability to infer what one person—other than the self infers about another person's mental states (i.e., the capacity to infer "A believes that B believes that x"). Tasks included two false belief picture stories [based on ice-cream van (Perner and Wimmer, 1985) and missing cookies (Stone et al., 1998) tasks], and two irony detection stories (Drury et al., 1998), since irony detection is considered to be a 2nd order ToM function (Brüne, 2005; Mehta et al., 2013a).
(c) *Higher order ToM:* Ten stories to identify unintended social blunders or faux pas (five stories) or non-faux pas control situations (five stories) were used [based on the faux pas recognition test (Stone et al., 1998)]. Faux pas recognition is described as a higher order ToM ability (Brüne, 2005). It involves the ability to understand a situation in which one person should have held information from another, but did not. In addition to mental state attribution (i.e., purely ToM), it taps affective processing (Freedman and Stuss, 2011) as well—for instance, some clarifying questions assess how a person in the story felt during the faux pas (Pijnenborg et al., 2013). In this background, faux pas scores were considered separately and were not combined with the 1st and 2nd order ToM scores for analyses.

2.1.1.2. Social perception. A set of 18 true/false questions were asked on social (e.g., Ali asked many questions about the movie because he was trying to impress Sunil) and non-social cues (e.g., Harish and Lakshmi were looking over a book together) after showing the subjects four each of low and high emotion videos depicting a social interaction. This test was adapted from the social cue recognition test (Corrigan and Green, 1993). Apart from satisfactory content and known groups validity, it had satisfactory internal consistency (Cronbach's alpha= 0.78 across the eight videos) and concurrent validity (Intra-class correlation or the total scores in English and modified versions > 0.7 for social cues) (Mehta et al., 2011).

2.1.1.3. Emotion processing. Facial emotion recognition ability was assessed using 52 static images and 28 dynamic videos portraying two different intensities (low and high) of six basic human emotions (happy, sad, fear, anger, surprise and disgust) depicted by four trained actors (one young male, one young female, one older male and one older female). The TRENDS had satisfactory inter-rater reliability and internal consistency (Cronbach's alpha 0.45 for dynamic videos and 0.67 for static images) (Behere et al., 2008).

2.1.1.4. Attributional bias. This was assessed using a 32-point questionnaire where subjects were required to make causal attributions for positive and negative social events, adapted from the Internal, Personal, and Situational Attributions Questionnaire (Kinderman and Bentall, 1996). Apart from satisfactory content and known