Asian Journal of Psychiatry 6 (2013) 324–329

Contents lists available at SciVerse ScienceDirect

Asian Journal of Psychiatry

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

Schizophrenia patients experience substantial social cognition deficits across multiple domains in remission

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ARTICLE INFO

Article history:
Received 2 August 2012
Received in revised form 31 January 2013
Accepted 6 February 2013

Keywords:
Theory of mind
Attributional styles
Social perception
Emotion processing
Remission

ABSTRACT

Knowledge about SC (social cognition) during remission would inform us whether such deficits are trait- or state-markers of the disorder, as well as highlight its relevance for rehabilitation. We aimed to compare SC deficits and their relative independence from NC (neuro-cognition) deficits in remitted schizophrenia patients and matched health controls using comprehensive, culturally sensitive standardized tools. 60 schizophrenia patients meeting modified standardized criteria for remission and 60 age, gender and education matched healthy controls were compared on culturally validated tests of SC—Social Cognition Rating Tool in Indian Setting (SOCRATIS) & Tool for Recognition of Emotions in Neuropsychiatric Disorders (TRENDS) to assess theory of mind, attributional bias, social perception and emotion recognition and NC—(attention/vigilance, speed of processing, visual and verbal learning, working memory and executive functions). Patients had deficits in both SC and NC compared to healthy controls. Deficits in SC were largely independent of NC performance, and SC deficits persisted after adjusting for deficits in NC function. The effect sizes (Cohen's *d*) for SC deficits ranged from 0.37 to 2.23. All patients scored below a defined cut-off in at least one SC domain. SC deficits are likely to be state-independent in schizophrenia, as they are present in remission phase of the illness. This supports their status as a possible composite-endophenotype in schizophrenia.

1. Introduction

There is growing evidence for social cognition (SC) deficits in patients with schizophrenia and its importance in determining functional outcome. There is also an emergent neuro-anatomical (frontotemporal & frontoparietal circuits including mirror neurons) and physiological (interface between the neuropeptides oxytocin & vasopressin and dopaminergic reward circuits) understanding of a social brain neural network, which sheds light on the biological underpinnings of schizophrenia (Burns, 2006; Frith, 2007; Frith and Frith, 2007; Skuse and Gallagher, 2009). Their candidate status as endophenotypes (i.e. markers intermediate between phenotypic manifestations of the disease and the genotype) though posited (Bora et al., 2009b; Green, 2006; Meijer et al., 2012) has not been explored sufficiently. One of the criteria (Gottesman and Gould, 2003) to define endophenotypes is that the measured variable should primarily be state-independent (i.e., it should manifest in an individual whether or not illness is active). Thus, studying SC deficits in schizophrenia patients who have remitted from their symptoms would take us one step closer in establishing their endophenotype status.

Most literature on SC in schizophrenia comes from patients who are symptomatic, where active positive symptoms can interfere with test administration, comprehension and inference. While there are studies that have provided promising results indicating SC impairment in remitted schizophrenia, numerous key issues remain that preclude well-founded deductions from these findings. Remission status has not been defined using standardized criteria (Janssen et al., 2003; Mo et al., 2008). Matching control subjects for confounding factors like age, gender and education has been inadequate (Ba et al., 2008; Bediou et al., 2007). Studies have generally examined selected domains of SC—no previous study has studied diverse SC domains comprehensively in a single sample. Psychometric properties of tools used to assess SC were poor (Brune et al., 2007; Langdon et al., 2006). Sample sizes studied were small (Hall et al., 2004; Marjoram et al., 2005). Most

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http://dx.doi.org/10.1016/j.ajp.2013.02.001

importantly, none of these investigations have evaluated the independence of SC deficits relative to the well-replicated deficits in NC functioning. In this study, we examined if SC deficits are greater in remitted schizophrenia patients than in matched healthy controls using a comprehensive battery of tests for SC, which is standardized for use in India. We hypothesized that schizophrenia patients who are in remission would have greater deficits in all domains of SC, after controlling for NC performance.

2. Materials and methods

2.1. Patients

60 consenting schizophrenia ($n = 53$) or schizoaffective disorder ($n = 7$) 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 $\leq$3 on Positive and Negative Syndrome Scale 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, but not negative symptoms, 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 previous six months (except nicotine), presence of co-morbid neurological or medical disorder, clinically diagnosable or self-reported visual or auditory impairment, current pregnant or postpartum state and a score of $\leq$19 on the Hindi mental status examination (Ganguli et al., 1995) were excluded from the study. All patients were on stabilized doses of anti-psychotics with no change in pharmacotherapy four months prior to evaluation. The institute's ethics committee approved the study.

2.2. Controls

Healthy controls ($n = 60$) were selected from among acquaintances including hospital staff. They were matched for age, sex and education. They were screened to rule out Axis-1 psychiatric disorder using Mini-International Neuropsychiatric Interview—Screening (Sheehan et al., 1998). None of the controls had family history of psychotic disorder in first and second-degree relatives as assessed by clinical interview.

2.3. Assessments

2.3.1. Social cognition

Consistent with recommendations of the Measurement and Treatment Research to Improve Cognition in Schizophrenia New Approaches Conference (Green et al., 2005) and the National Institute of Mental Health (NIMH) sponsored meeting "Social Cognition in Schizophrenia: Basic Definitions, Methods of Assessment, and Research Opportunities" (Green et al., 2008), we selected 4 domains of SC, viz., theory of mind (ToM), emotion processing, social perception and knowledge, and attributional bias. We used social cognition rating tool in Indian setting (SOCRATIS) (Mehta et al., 2011b) and tool for recognition of emotions in Neuro-psychiatric disorders (TRENDS) (Behere et al., 2008) to assess these four domains. The former consists of tests to assess theory of mind (1st and 2nd order false belief picture stories, metaphor-irony stories and faux pas stories), social perception (true/false questions asked on social and non-social cues after showing the subjects four each of low and high emotion videos depicting a social interaction) and attributional styles (causal attributions made for positive and negative social events). The latter is a test of facial emotion recognition ability (static images and dynamic videos depicting 6 basic emotions). Both these test batteries have been validated in the Indian cultural setting with satisfactory psychometrics. Each test except the attributional biases provides an index of the respective test performance, which is equivalent to the score of an individual on the test divided by the maximum score possible (Mehta et al., 2011b). For attributional styles, external and personalizing bias scores were calculated according to (Kinderman and Bentall, 1996). The raw SC scores/indices were converted to Z-scores. Average of these Z-scores formed the SC composite score which was a global measure of SC performance.

2.3.2. Neuro-cognition

Consistent with recommendations of the measurement and treatment research to improve cognition in schizophrenia (MATRICS) initiative (Nuechterlein et al., 2008), subjects were assessed on neuro-cognitive domains of attention/vigilance (continuous performance test) (Cornblatt et al., 1988), speed of processing (digit symbol substitution test) (Wechsler, 1981) and (Color Trails A & B) (D'Elia et al., 1994), verbal learning/memory (auditory verbal learning test) (Rey, 1941), visual learning/memory (complex figure test) (Osterrieth, 1944), verbal (N-Back 1&2) (Kirchner, 1958) and visual (spatial span test) (Psychological Corporation, 1997) working memory and executive functions (cognitive flexibility, problem-solving and set-shifting abilities) (Wisconsin card sorting test) (Heaton et al., 1993). The raw NC scores were converted to Z-scores. Average of these Z-scores formed the NC composite score which was a global measure of NC performance. The Hindi mental status examination (HMSE) (Ganguli et al., 1995) was used to screen for significant cognitive deficits which could have interfered with social cognition test performance before recruitment of patients.

2.4. Statistical analyses

Analysis of covariance (ANCOVA) was used to assess differences between mean scores on seven social cognition indices/scores and SC composite score with group status (patients/controls) as fixed factor and the NC composite score as covariate. Effect sizes were calculated using Cohen's d (Cohen, 1988). For all domains except the 1st order ToM, we calculated the proportion of patients scoring below 1 SD of mean of controls. In the 1st order ToM, all healthy controls except 1 (98.33%) got the maximum score, i.e., 1. Hence, we chose 1 as the cut-off for this test. Proportion of patients scoring below the cut-off was calculated along with their 95% confidence intervals. All tests were two-tailed and results were regarded as significant at $<$0.007 level of probability after Bonferroni correction.

3. Results

3.1. Socio-demographic and clinical details

The patient and control group were matched and there was no significant difference on parameters of age, gender, socio-economic status, years of education of study subjects and years of education of their parents as shown in Table 1. Table 2 shows the clinical variables in patient group. Majority had paranoid schizophrenia and they were in remission for about 9 months (mean). Expectedly, they had moderately low scores on the PANSS negative syndrome (14.2 ± 4.1), low scores on positive syndrome sub-domain of PANSS (i.e. 8.5 ± 1.4) and low total PANSS scores (49.3 ± 9.3). We compared SC composite scores across patients with paranoid schizophrenia ($n = 44$) and other schizophrenias ($n = 16$); and found no significant differences ($t = 0.389$, $p = 0.698$). Similarly,