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Neurological soft signs and cognitive functions: Amongst euthymic bipolar I disorder cases, non-affected first degree relatives and healthy controls

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ABSTRACT

Both neurological soft signs (NSS) and cognitive deficits are present among euthymic bipolar patients. NSS could be related to neurocognitive performance, but this is not explored thoroughly. Healthy relatives of patients may also suffer from similar deficits.

This study compared NSS and cognitive functions in euthymic Bipolar I Disorder (BPI) cases to their non-affected first degree relatives and healthy controls. We also investigated the association between NSS and cognitive functions in these three groups. NSS were assessed in three groups using Neurological Evaluation Scale-revised (NES-r). Eight cognitive domains were assessed in 31 euthymic BPI cases, their 30 non-affected first degree relatives and 30 healthy controls using Computerized Neurocognitive Battery (CNB). Euthymic BPI patients had significantly more NSS than non-affected first degree relatives on 5/7 tests (p-value ranges from 0.042 to $p = 0.0001$) and healthy controls on all tests (p-value from 0.042 to <0.0001). Non-affected first degree relatives and controls did not have any significant difference. BPI participants performed worse than their non-affected first degree relatives on one neurocognitive domain of CNB (spatial memory accuracy, $p = 0.03$) and healthy controls on four domains (spatial memory accuracy ($p = 0.04$), abstraction and mental flexibility efficiency ($p = 0.04$), spatial memory efficiency ($p = 0.04$), and emotion efficiency ($p = 0.04$). Non-affected relatives and healthy controls were similar on neurocognitive domains. Accuracy and efficiency indices of some specific cognitive domains were negatively associated with AV rating and tap copying NSS ratings.

1. Introduction

Neurological soft signs (NSS) refer to subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts which cannot be precisely localized in the brain but an increased prevalence may suggest an underlying neurodevelopmental brain injury (Buchanan and Heinrichs, 1989; Griffiths et al., 1998). These signs possibly reflect role of genetic factors (Niethammer et al., 2000). Studies have reported the presence of NSS as commonly in Bipolar disorder as in schizophrenia (Nasrallah et al., 1983; Gureje, 1988; Dimitri Valente et al., 2012). About 9.5% and 14% of an affective disorder group were impaired on motor and sensory testing respectively compared to controls (Manschreck and Ames, 1984). Boks et al. (2004) reviewed 17 studies on first episode psychosis, bipolar patients and healthy controls comparing NSS and reported the conclusions as tentative mentioning small sample size of studies. Tobar and Hazem (2008) compared first degree relative of bipolar I disorder with normal controls and demonstrated significant difference on a subset of sensory integration tests (namely graphesthesia and rhythm-tapping).

Deficits in cognitive functioning among bipolar patients have been described as measures of illness progression or severity (Zubieta et al., 2001). Among remitted patients with bipolar I disorder (BPI) poorer performance has been reported on a range of cognitive tests, with deficits especially evident on tests of executive function, attention and memory (Malhi et al., 2007; Burdick et al., 2010). Euthymic BPI Chinese patients demonstrated marked cognitive impairments which correlated with illness parameters (Eric et al., 2013). Definite cognitive impairment and different patterns of cognitive style were reported in euthymic

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patients remitted from recent manic or depressive episode (Fakhry et al., 2013). Indian researchers have reported impairment of executive functions but not memory among first-degree relatives of patients with BPI (Goswami et al., 2006). Others have mentioned impairment in executive functioning and vigilance in first degree relatives of bipolar disorder (Trivedi et al., 2008; Pattanayak et al., 2012).

NSS and cognitive dysfunction in remitted state of bipolar disorder may represent trait deficits. A 6 year longitudinal study confirmed cognitive deficits in patients with bipolar disorder suggesting that these deficits persist even in the euthymic state of the disorder (Mora et al., 2013). The only Indian study correlating NSS with executive functions in euthymic bipolar disorder patients reported significant correlation (Goswami et al., 2006).

Mood and cognition share dynamic relationships with both state and trait dependent components. Because of their relatively static nature, study of the trait characteristics of cognition and neurological signs may provide insights into the etio-pathogenesis of mood disorders (Trivedi, 2006).

Most studies, that have been examined, used individual domains, while the underlying neurocognitive systems are inherently complex and interrelated. The relationship between NSS and neurocognitive performance in euthymic bipolar disorder patients in comparison with their first degree non-affected relatives has not been studied to date, to the best of our knowledge. The present study was conducted to fill this lacuna.

2. Methodology

2.1. Study population

This cross-sectional study was conducted at the Department of Psychiatry, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, India. Ethical permissions were taken in accordance with the Indian Council of Medical Guidelines for human research from the Institutional Ethics Committee. A consecutive, consenting sample of 18–60 years old BPI participants (euthymic for one month, and on steady dose of medications for previous 3 months) and their non-affected first degree relatives closest to their age, were recruited. Thirty consenting healthy controls (age range 18–60 years) were also recruited from comparable communities or friends of the patients (relatives were excluded). Participants suffering from any DSM-IV-TR Axis I or II disorder (except BPI disorder in patient group), neurological disorders or substance dependence were excluded.

2.2. Hypotheses

1. Cognitive functions are impaired more in euthymic BPI patients than non-affected first degree relatives and matched healthy controls.
2. Neurological soft signs are present more in euthymic BPI patients followed by their non-affected first degree relative and healthy controls.
3. Neurological soft signs are associated with cognitive impairment.

2.3. Assessment instruments

2.3.1. Young mania rating scale (YMRS)

It is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h (Young et al., 1978). A score of <12 is generally accepted to be within the normal range (or in clinical remission).

2.3.2. Hamilton depression rating scale (HAM-D)

It is a multiple choice questionnaire that clinicians may use to rate the severity of a patient's major depression (Hamilton, 1960). It consisted of 17 questions contributing to a total score. Each question has between 3 and 5 possible responses which increase in severity. A score of less than 7 is considered to be within normal range.

2.3.3. Diagnostic Interview of Genetic Studies (DIGS) – Hindi version

It is a structured interview schedule to record information regarding a subject's functioning and psychopathology with primary emphasis on information relevant to the study of the affective disorders and schizophrenia. The Hindi version has been validated in Indian population (Deshpande et al., 1998).

2.3.4. Simpson Angus scale (SAS)

It is a 10-item widely used instrument to assess extrapyramidal symptoms in clinical practice (Simpson and Angus, 1970). Rated for severity on a 0–4 scale, items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness.

2.3.5. Barnes akathisia rating scale (BARS)

The scale measures motor phenomena as well as systematically probe subjective aspects of akathisia, including the amount of discomfort and distress that might be reasonably attributed to the condition (Barnes, 1989).

2.3.6. Abnormal involuntary movement scale (AIMS)

This 12-item instrument assesses abnormal involuntary movements associated with antipsychotic drugs, such as tardive dystonia and chronic akathisia, as well as 'spontaneous' motor disturbance related to the illness itself (Guy, 1976).

2.3.7. Neurological Evaluation Scale-revised (NES-r)

A revised version of NES was administered (Sanders et al., 1998). This has 13 items with consistent inter rater reliability. NSS were scored as per the evaluation procedure by Buchanan and Heinrichs (1989) on four broad domains – sensory integration (audiovisual integration and graphesthesia), sequencing of complex motor acts (fist-ring, fist-palm and tap-copying tests), response inhibition (go-no-go test) and motor coordination (rapid alternating movement test).

2.3.8. Computerized neurocognitive battery (CNB)

This cognitive battery has ten cognitive domains of which eight performance domains were administered-abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotion (Gur et al., 2001). We did not evaluate verbal domains as they are currently available only in English, and most of our subjects did not speak English. For each domain, three summary functions were calculated: (1) accuracy, which reflects the number of correct responses; (2) speed, which reflects the median reaction time for correct responses; and (3) efficiency, which reflects both accuracy and speed by the formula: accuracy/log (speed) (Aliyu et al., 2006). CNB was administered in a quiet room, with minimal disturbance. Each test was preceded by a mock test to check the understanding and involvement of the subject. The battery was administered in a fixed order using clickable icons. The data was stored directly at University of Pennsylvania, USA and was downloaded in excel format. Mean and standard deviation were calculated.

2.4. Study design

The study was introduced to prospective BPI participants by their treating clinicians. Those who agreed to participate were