Neurocognitive Profile in Indian Individuals Genetically at Risk of Schizophrenia

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ABSTRACT

Background: Cognitive deficits have been noted in patients of schizophrenia in remission, as well as in first-degree relatives. This study aims to evaluate the neurocognitive performance in unaffected first-degree relatives of patients of schizophrenia in comparison with healthy controls, as well as patients of schizophrenia in remission. Methods: It was a 1-year case-control study by purposive sampling. Patients with a diagnosis of schizophrenia, first-degree relatives of patients of schizophrenia, and controls from non-genetic relatives of patients were recruited as per inclusion and exclusion criteria. Samples were matched for age and educational status. The General Health Questionnaire 28 (GHQ-28) screened them and they were checked for remission by Positive and Negative Syndrome Scale (PANSS) and then subjected to various instruments for assessment of neurocognition, standardized for the Indian population. To remove the effect of symptoms as confounding factors, PANSS score of <3 for each individual item was set as the criterion for remission. Intelligence quotient (IQ) was screened in all participants to exclude mental retardation. Statistical analysis used was the analysis of variance (ANOVA) with post hoc Fisher’s least significant difference (LSD). Results: Significant neurocognitive impairments were detected in the patients and first-degree relatives when compared with the control subjects. The most common impairment in the patient group was in speed of processing, and among unaffected first-degree relatives, it was in the working memory. Conclusion: Indian individuals genetically at risk of schizophrenia showed significant neurocognitive impairments in all domains compared with controls.

Key words: Cognitive impairment, executive function, first-degree relative, verbal memory, working memory

Key messages: Neurocognitive deficits occur in stable patients of schizophrenia. On assessment by instruments standardized for the Indian population, deficits were evident in all domains for individuals, asymptomatic but genetically susceptible. Hence, asymptomatic siblings of patients of schizophrenia may require screening.
Emil Kraepelin described dementia praecox or a group of schizophrenias as a disease with an early onset, a deteriorating course with hallucinations and delusions, and cognitive changes. Bleuler further explained that delusions and hallucinations were secondary to cognitive changes. Cognition is the sum total of mental processes that enable us to acquire knowledge and keep us aware of our surroundings, thereby enabling us to make appropriate judgments. The Division of Mental Disorders of the National Institute of Mental Health (NIMH), USA initiated and funded workshops known as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). The different domains of cognition impaired in schizophrenia, according to the NIMH-MATRICS are the speed of processing, attention or vigilance, working memory, verbal memory, visual memory, reasoning, problem-solving, and social cognition. Studies on cognition show that patients with schizophrenia perform at least one standard deviation (SD) below the normal population in global intellectual abilities, which places them in the lower 15 percentile of global intellectual ability. The importance of cognition extends beyond mental processes. Recently, it was noted that weight gain induced by antipsychotic therapy was affected not only by the body mass index (BMI) but also by cognitive performance.

Cognitive deficits in relatives of patients of schizophrenia

Genetic factors are a determinant in the etiology of schizophrenia. Schizophrenia heavily affects certain families. This tendency of genetic loading indicates a need to study relatives to better understand the genetic underpinning. Cognitive assessments performed as a part of routine assessment of asymptomatic people had shown deficits in people who developed schizophrenia years later. Relatives of patients with schizophrenia have been shown to have an increased reaction time, indicating a decreased speed of processing. In a recent ongoing study, known as the Pittsburgh Risk Evaluation Program (PREP), first- and second-degree relatives were shown to have neurocognitive impairments.

Although not diagnostic of a disease but certain symptoms are frequently found with the disease. They exhibit close inheritance with the candidate gene or the gene region. The study of these symptoms is an alternative experimental strategy and can increase our etiological understanding of the disorder. Evidence supports the fact that the same gene may be responsible for cognitive impairment as well as schizophrenia, while other genes may also affect cognition.

Research question

Most of the current literature focuses on the Caucasian race, with the Asian population being severely under-represented despite accounting for two-thirds of the world population. Substantial research since the beginning of this century has suggested genetic variation as the basis for differences in the phenotype and disease susceptibility across groups. A literature search for Indian studies on neurocognitive deficits of schizophrenic probands revealed only a few studies with highly inconsistent results [Table 1]. Domains of cognitive deficits, as prescribed by MATRICES, have rarely been examined. As mentioned by Solanki et al., the tests used in these studies were not standardized for the Indian population. Moreover, we could not

Table 1: Indian studies on neurocognition in schizophrenia

| Study | Tests Used | Domains Accessed | Groups Compared | Conclusion |
|-------|------------|------------------|----------------|-----------|
| Garg et al. | WCST, CPT, and SWMT | Planning (executive, performance, and concentration) | Siblings (n=36) and controls (n=36) | Global impairment in the cognition of siblings |
| Nehra et al.: Cognitive deficits in the unaffected sibling of patients with schizophrenia | WCST, Brief Visuospatial Memory Test-Revised, HVLT-R, and WAIS DST TMT | Planning (executive), memory, verbal learning performance, and concentration | Patients, siblings, and controls Each group (n=20) | Siblings had verbal learning impairment |
| Bhatia et al.: Executive functions and cognitive deficits in schizophrenia: Comparisons between probands, parents, and controls in India | DST, visuospatial working memory matrix, and TMT | Verbal retention, executive functioning, and working memory | Siblings (n=40) and controls (n=40) | Verbal, working memory and executive function deficits in siblings. |
| Solanki et al.: An Indian experience of neurocognitive endophenotypic markers in unaffected FDR | TMT, DST, and WMS Spatial span | Attention and executive function | High-risk patients, siblings (n=17), and controls (n=30) | Executive function task performance, attention, and working memory deficits in first-degree relatives. |
| Harave et al.: Schizophrenia risk and neurocognition | | | | |

WCST – Wisconsin Card Sorting Test, CPT – Continuous performance test, SWMT – Spatial working memory test, HVLT-R – Hopkins Verbal Learning Test-Revised, WAIS DST – Wechsler Adult Intelligence Scale Digit Symbol Test, TMT – Trail-making test, PALT – Paired associate learning test, WMS – Wechsler memory scale
obtain any findings on visual learning and visual memory. The domain of speed of processing also remains unexplored. Although executive function has been explored, the ability to innovate spontaneously has not. A test of design fluency, which has a distinct advantage in estimating executive function, might serve this purpose.\(^\text{[13]}\) The effect of intelligence quotient (IQ) as a confounding factor has also not been investigated.

We, therefore, decided to screen IQ before the cognitive assessment and exclude subjects with subnormal intelligence. Remission was ascertained for the participating patients. The tests used were standardized for the Indian population, and all domains of neurocognition, as mentioned by NIMH-MATRICES, were assessed using tests different from those already used, thus, enhancing reliability.

**SUBJECTS AND METHODS**

The study was conducted at a tertiary care center in India for a period of 1 year from January 1, 2011 to December 31, 2011. The institutional ethical committee provided ethical clearance. All patients of schizophrenia in remission (stable) attending the psychiatry outpatient department (OPD) and patients admitted in the psychiatry ward of the hospital were included in the study (Group 1). Eligible first-degree relatives of patients of schizophrenia attending the psychiatry OPD and patients admitted in the psychiatry ward of the hospital were identified (Group 2). The controls were non-genetic relatives of patients, who were neither suffering from a mental illness, attending psychiatry OPD nor admitted in the psychiatry ward of the hospital (Group 3). A cross-sectional analysis was carried out in this case-control study by purposive sampling.

The inclusion criteria were an age between 18 and 50 years, an English education up to at least the tenth grade, and consent to participate in the study. The exclusion criteria were having co-morbid conditions, such as drug abuse (except nicotine dependence); affective disorders; dementia; mental retardation; a history of head injury; or a seizure within 1 year. Subjects showing extrapyramidal symptoms were excluded. Mood symptoms were assessed and their presence was a criterion for exclusion.

A specially prepared pro forma was used to collect the patients’ sociodemographic data, history, and examination findings. The International Classification of Diseases 10 Diagnostic Criteria for Research (ICD-10 DCR) for Psychiatric Illnesses by the World Health Organization (WHO) were used to diagnose each patient.\(^\text{[16]}\) Mental retardation was ruled out by screening all subjects using Raven’s Colored Progressive Matrices (CPM), minimizing the effect of IQ as a confounding factor. All subjects were checked for remission using the Positive and Negative Syndrome Scale (PANSS). The accepted reported criterion for remissions was a PANSS score of <3 for each item in the last 6 months.\(^\text{[24]}\) The General Health Questionnaire 28 (GHQ-28) was used to check the presence of any psychiatric comorbidity. Subsequently, cognitive assessment tests were performed to estimate the extent and nature of cognitive dysfunctions. All these tests have been standardized and validated for the Indian population [Table 2].\(^\text{[21]}\) The speed of processing was tested by the Digit symbol substitution test (DSST), where the time taken to perform the task was the score. Verbal working memory was tested by the N-Back test, while Visual N-Back tested visual working memory. Correct identification was scored as a hit, while not identifying and misidentifying were scored as an error. The Verbal Paired Associates Test tested verbal learning.

| Domain                  | Test                     | Description                                                                 |
|-------------------------|--------------------------|-----------------------------------------------------------------------------|
| Speed of processing     | DSST\(^\text{[22]}\)     | Sheets with four rows each having 26 randomly arranged digits have to be     |
|                         |                          | substituted with symbols mentioned on top in a key                         |
| Working memory          | Verbal N-Back Test\(^\text{[22]}\)| A subject respond in N back-1 test whenever a consonant is repeated         |
|                         |                          | consecutively, and in N back-2 the subject responds when it is repeated    |
|                         |                          | after an intervening consonant                                              |
|                         | Visual N-Back Test\(^\text{[22]}\)| In Visual N-back 1, the subject is told to report if the positions of two   |
|                         |                          | dots coincide. In Visual N-back 2, the subject is told to report if the   |
|                         |                          | position of the dot coincides to the last but one card                     |
| Learning and memory     | Verbal Paired Associates | Five pairs of nouns are repeated one after the other. After this, the      |
|                         | Test\(^\text{[23]}\)       | subject is told the first noun and asked to repeat the other.              |
|                         | PG1- Visual Recognition  | First, a subject is shown a card containing ten pictures and asked to      |
|                         | Test\(^\text{[23]}\)       | memorize. Next, another card containing pictures from the first card, as   |
|                         |                          | well as other pictures, is shown, and the subject is asked to identify the  |
|                         |                          | pictures.                                                                  |
| Attention and vigilance | Digit Forward\(^\text{[24]}\) and Digit Backward\(^\text{[24]}\)| Digits are read at 1 digit per second and a gradually increasing number of |
|                         |                          | digits are presented. In digit forward, the subject has to reproduce the   |
|                         |                          | same order while backward it is to be reproduced in the reverse order.      |
|                         | Serial Subtraction\(^\text{[22]}\)| The subject has to subtract a number from another repeatedly and report the   |
| Executive function      | Animal Name Test\(^\text{[22]}\)| The subject is asked to generate from memory as many animal names as         |
|                         |                          | possible excluding birds, snakes, and fish.                                |
|                         | DF\(^\text{[25]}\)         | The subject has to draw novel designs.                                      |

\(^\text{DSST – Digit symbol substitution test, DF – Design fluency}\)
where the number of pairs correctly reproduced forms the score. Visual learning was tested by the PGI-visual recognition test, where a correct identification and naming of the object is given one mark, while a correct identification but wrong naming fetches $\frac{1}{2}$ mark. Attention and concentration were tested by digit forward, digit backward, and serial subtraction test. Animal name and design fluency (DF) tests were used for assessment of executive function, where the number of items generated is the score.

Cognitive assessment

Unaffected first-degree relatives showed significant impairments compared with controls in all domains except learning [Table 4]. Based on the norms for the Indian population, the most common impairment in the patients was in the speed of processing, while the most common impairment in the unaffected first-degree relatives was in working memory [Table 5].

DISCUSSION

We found neurocognitive impairments in unaffected first-degree relatives similar to those in patients of schizophrenia. Patients and first-degree relatives performed significantly worse than the controls in testing for speed of processing, which could be responsible for the slowness in performing various activities exhibited by the patients of schizophrenia.[25] Garg from India reported similar findings.[17] The bilateral parietal and temporal lobes and left middle frontal gyrus are involved in information processing and, probably, are the affected areas.[26]

Working memory includes verbal and visual memory. The patients and first-degree relatives performed significantly worse than the controls in this domain. From India, Harave and Solanki also reported similar findings. Patients also exhibit reduced blood flow in the inferior frontal gyrus, suggesting it as the area affected in working memory disturbance.[27]

Executive function deficits are known to be an integral part of schizophrenia. We found significantly higher executive function impairment even in unaffected first-degree relatives, compared with the controls. We used the animal name test and DF test for executive function assessment. The animal name test results showed that the control subjects performed better than patients of stable schizophrenia and unaffected

Table 3: Demographic Variables

| Variable       | Group 1 Patient (n=34) | Group 2 First-degree Relative (n=37) | Group 3 Control (n=47) | Chi-Square | F     | P     |
|----------------|------------------------|-------------------------------------|-----------------------|------------|-------|-------|
| Sex (Male)     | 22 (64%)               | 22 (59%)                            | 42 (89%)              | 10.98      | 0.01  |       |
| Age (years)    | 30.88±8.24             | 31.27±8.87                          | 29.26±7.91            | 0.70       | 0.50  |       |
| Education      |                        |                                     |                       |            |       |       |
| School         | 12 (35.5%)             | 8 (21.6%)                           | 11 (23.4%)            | 4.95       | 0.76  |       |
| High School    | 6 (17.6%)              | 5 (13.5%)                           | 10 (21.3%)            |            |       |       |
| Graduate       | 7 (20.6%)              | 9 (24.3%)                           | 10 (21.3%)            |            |       |       |
| Post Grad      | 2 (5.9%)               | 2 (5.4%)                            | 5 (10.6%)             |            |       |       |
| Professional   | 7 (20.6%)              | 13 (35.1%)                          | 11 (23.4%)            |            |       |       |
| GHQ Score      | 6.03±1.14              | 2.00±0.81                           | 1.87±0.74             | 254        | <0.001|       |

GHQ – General Health Questionnaire
first-degree relatives did. This set of tests assesses the ability to innovate and generate spontaneously, unlike the Trail-making Test (TMT), where the norm is to perform as instructed. In a recent study on the Indian population by Bhatia et al., the findings indicated significant impairments in first-degree relatives. Frontostriatal abnormalities are thought to explain these deficits.

A recent longitudinal cohort of more than 1,000 patients reported that patients had intellectual deterioration and poor academic performances much prior to the onset of the illness. In a cross-sectional study, cognitive deficits in first-episode psychosis were similar to those in patients of chronic, long-standing illness. Cognitive impairments in schizophrenia are stable and persistent, unlike the progressive deficits of dementia. On the other hand, they are not evident at birth as in patients of intellectual disabilities. We showed that there is a statistically significant difference from controls in the domains of neurocognition in unaffected first-degree relatives of patients of schizophrenia. Thus, cognitive deficits are certain inherited vulnerabilities that are present in genetically susceptible individuals.

**CONCLUSION**

To conclude, our findings suggest that neurocognitive impairments are present not only in patients of stable schizophrenia but also in the unaffected first-degree relatives of patients of schizophrenia. Neurocognitive impairments could also be screening criteria for those at risk. Our findings are in concurrence with studies from the West and suggest that Indian
patients of stable schizophrenia and unaffected first-degree relatives of patients of schizophrenia show similar cognitive deficits.

**Strengths**

1. Tests standardized for the Indian population were applied.
2. We screened out the confounding effect of IQ.
3. Groups were matched with respect to education and age, which affect cognition.
4. Noncomputerized tests were used as many are not well versed in computers.
5. Only patients in remission were assessed.
6. Conservative correction applied as multiple hypothesis testing was done.

**Limitations**

Our sample size was constrained as we used patients, similar to other Indian community studies.

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**Conflicts of interest**

There are no conflicts of interest.

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