An Indian experience of neurocognitive endophenotypic markers in unaffected first-degree relatives of schizophrenia patients

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ABSTRACT

Context: Multiple vulnerability genes interact with environmental factors to develop a range of phenotypes in the schizophrenia spectrum. Endophenotypes can help characterize the impact of risk genes by providing genetically relevant traits that are more compliant than the behavioral symptoms that classify mental illness.

Aims: We aimed to investigate the neurocognitive endophenotypic markers for schizophrenia in Indian population.

Settings and Design: In a cross-sectional study, we assessed neurocognitive functioning in 40 unaffected first-degree relatives (FDR) of schizophrenia patients with an equal number of healthy controls.

Materials and Methods: FDR schizophrenia group was compared with the control group on measures of short-term memory, verbal working memory, auditory verbal memory on indices of immediate recall and recognition, visuospatial working memory, visual attention, and executive functions.

Results: The study found that FDR schizophrenia scored poorly on all tested measures of neurocognition except visual attention. On calculating composite score, we found that composite neurocognitive score better discriminated the FDR schizophrenia from the control group.

Conclusions: Neurocognitive measures of short-term memory, verbal working memory, auditory verbal memory, visuospatial working memory, and executive functions significantly differentiate FDR of patients with schizophrenia from controls and can be considered as endophenotypic markers of schizophrenia in non-Caucasian population. The exactitude of this approach can be increased by calculating a composite neurocognitive score which combines various neurocognitive measures.

Key words: Endophenotype, first degree relatives, neurocognition, schizophrenia

INTRODUCTION

Genetic factors are well-established etiological determinants for schizophrenia[1] as evidenced by heritability of 0.41–0.87.[2] Despite the irresistible evidence for heritability of schizophrenia,[2,3] the etiology and genetic underpinnings of this devastating disorder remains unclear. Endophenotypic vulnerability markers present during asymptomatic stage of illness can help characterize the impact of susceptibility genes by providing genetically reliable traits that are more compliant than the behavioral symptoms.[4] A marker can be considered endophenotype if it has a familial association, present with disease in the population, heritable, and can help differentiate at-risk individuals from healthy controls.

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state-independent, and demonstrates co-segregation. They are objectively measured, nonlocalizing abnormalities, unrelated to impairment of a specific brain region, state-independent, reflecting improper cortical-subcortical, and intercortical connection. Among the studied domains, neurocognitive functions are one of the important areas of research for determination of endophenotypes of schizophrenia. Several genetic studies have observed significant neurocognitive deficits in unaffected adult relatives that tended to be similar to those seen in schizophrenia patients. Neurocognitive deficits among schizophrenia patients have been consistently documented in research over the past three decades. Indeed, extensive reviews and meta-analysis have confirmed the presence of poorer performance in unaffected first-degree relatives (FDR) in several tasks encompassing attention, working memory, and executive functions, which may be congruent with the dysfunctions observed in non-affected relatives.

**Rationale for the present study**

The study of neurocognitive functioning in FDR of schizophrenia patients is particularly appealing. Although the endophenotypic approach enjoyed enough attention in the Western world, only few research programs have examined the credibility of approach in Indian context. Second, studies to date have evaluated individual domains independently but the nature of neurocognitive domains is complex and interrelated. It is proposed that combination of neurocognitive markers may address the issue of precision of endophenotypic approach. This study was an effort to bridge this gap to understand the neurocognitive endophenotypes in Indian population by comparing neurocognitive functioning in FDR of schizophrenia patients with healthy control group. We aimed to evaluate neurocognitive functioning as vulnerability markers in FDR of schizophrenia patients.

Based on the existing literature we formulated following hypothesis:

“For FDR of schizophrenia demonstrate deficits on measures of neurocognitive functions (i.e., short-term memory, auditory verbal memory, visual attention, psychomotor performance speed, working memory [verbal and visuospatial] and executive functions) and they differ significantly from controls.

To test the hypothesis following objectives were formulated:

- To evaluate neurocognitive functions in FDR of schizophrenia patients
- To compare neurocognitive functioning in FDR of schizophrenia with matched healthy controls
- To compare the composite neurocognitive score of FDR schizophrenia with the control group.

**MATERIALS AND METHODS**

**Study design**

We planned a cross-sectional study. The sample was drawn from the outpatient department of a major psychiatric hospital in India. Any two of the available consultant psychiatrist (RKS, YKS, SG, and PS) confirmed the diagnosis of schizophrenia independently before inviting accompanying FDR for the study. Similar to cases, healthy controls were selected from outpatients department and comprised any person satisfying inclusion and exclusion criteria of the study with the absence of first and second-degree relative with diagnosed psychiatric illness.

**Inclusion criteria for cases**

- Age 18–50 years
- Either sex
- Literate enough to read and understand the consent form and questionnaires in Hindi
- History of schizophrenia in at least one FDR diagnosed as per ICD-10 diagnostic criteria for research criteria.

**Exclusion criteria for cases**

- Unwilling subject
- A lifetime history of any psychiatric or medical illnesses that impair neurocognitive functions
- History of head injury with any documented cognitive sequel or loss of consciousness
- Mental retardation
- Substance abuse within past 6 months
- The presence of color blindness as per Ishihara’s isochromatic charts.

**Table 1: Studies on neurocognitive dysfunction in relatives of schizophrenia**

| Material and methods | Tests administered | Results |
|----------------------|--------------------|---------|
| Bhatia et al. 2009| TMT | Cases as well as their parents showed more cognitive impairment than controls on the TMT |
| Garg et al., 2013| WCST, CST, and SWMT | The siblings performed significantly poorly as compared to the controls on WCST, CPT, and SWMT |
| Solanki et al. 2012| Schizotypal Personality Questionnaire, digit span test, paired associate learning test, and visuospatial working memory matrix | First-degree relatives scored significantly worse on all neurocognitive measures (Cohen’s d = 1.27) |

TMT – Trail making test; WCST – Wisconsin Card Sorting Test; CST – Continuous Performance Test; SWMT – Spatial Working Memory Test
Forty consecutive FDR of schizophrenia patients and a similar number of controls satisfying inclusion and exclusion criteria were recruited in the study. Inclusion and exclusion criteria for controls were similar to cases except the absence of having first and degree relatives with a psychiatric disorder. Only individuals who attained 18 years of age were selected for study with the assumption that majority of vulnerable individuals to develop schizophrenia should have developed illness by this age.\textsuperscript{[19]} FDR above 50 years of age excluded from the study as degenerating process sets in many vulnerable individuals which could affect cognitive performance of participants. Every study participant was subjected to extensive history and physical examination to rule out major psychiatric illness affecting cognition not limited to schizophrenia, bipolar disorder, depression, and obsessive-compulsive disorder. The history and physical examination of cases, as well as controls, was performed independently by AK and any other consultant psychiatrist (RKS, YKS, PS, and SG). Any discrepancy in history and physical examination by authors, with regard to inclusion and exclusion criteria, resulted in the outright exclusion of individual from the study. History of substance abuse was probed thoroughly and any individual with a history of substance abuse, irrespective of amount, in past 6 months was excluded from the study. All neurocognitive tests were administered by AK, who was not aware of the group status of the participants in the study.

**Ethical consideration**

Study was approved by research review board and Ethical Committee of the institution. An informed consent was obtained from the subjects prior to participation in the study as per Helsinki declaration.\textsuperscript{[20]}

**Method/assessment**

To include in the study, invited subjects were screened with a specially designed screening proforma encompassing all the inclusion and exclusion criteria. Those subjects who satisfied the screening process were finally recruited in the study. Each participant’s sociodemographic data was recorded. After that, each participant in the study was subjected to neurocognitive assessment with use of digit span test forward and backward,\textsuperscript{[21]} test for verbal retention (paired associate learning),\textsuperscript{[21]} visuospatial working memory matrix\textsuperscript{[22]} and trail making test A and B.\textsuperscript{[23]}

We administered an extensive neuropsychological battery to cover several areas of cognitive functioning to enhance our ability to resolve illness heterogeneity or to more direct genetic determination of specific biological traits.

Tests were presented in the sequence in which they are mentioned to relax the subject in between tests (since performance tests cause less fatigue than speed tests),\textsuperscript{[24]} and if the subject felt fatigued after any test he was given 5 min relaxation time to ensure the best performance. On an average, each subject took approximately 1 h 30 min to complete the test battery.

**Instruments**

**Digit span test**

Digit span test is adapted from Wechsler adult intelligence scale.\textsuperscript{[25]} It has two parts - digit forward and digit backward test. In the digit forward test subject is asked to repeat the digits called by the examiner. The maximum number of digits correctly repeated is the score. It measures short-term memory, attention, and concentration.

In digit backward test, the subject is asked to repeat the digits read out by the examiner backward. The maximum number of digits repeated back and correctly is the score on this test. It measures verbal working memory. The test is well standardized in an Indian population with good test-retest reliability (0.87–0.98) and validity.\textsuperscript{[26]}

**Test for verbal retention (paired associate learning)**\textsuperscript{[21]}

This test is a sub-test of PGI memory scale. It is a paired associate learning test that assesses auditory verbal memory on indices of immediate recall and recognition. This is a cued recall test of verbal memory. The test consists of two series of associative pairs (five pair each). One is for the similar pair and another for the dissimilar pair.

In verbal retention of the similar pair, one mark is given for each correct reproduction of the associated word of the pair (maximum 5). For verbal retention of the dissimilar pair, one mark is given for each correctly reproduced word, separately for each trial. Summation of marks on three trials is the score in this test (maximum 15). Norms are available with respect to age and education.\textsuperscript{[27]}

**Visuospatial working memory matrix**\textsuperscript{[22]}

The test measures the capacity of a subject’s visuospatial working memory. Two different components are critical to this part of memory: Passive store and active imagery operation. The test consists of ten 4 × 4 matrices each printed on a different card in bright homogenous color. Two consecutive squares are yellow and another one is red on a given card. In the two-dimensional space of a card, these colored squares are situated at a different location in each card.

The subject is shown one card for 5 s and then hidden. Beforehand, the subject is asked to remember the spatial position of the all three squares on the card. Now from the guidance key the subject is given the stimulus pertaining to the particular card slowly, and according to these instructions he is asked to move red square’s position in his mind (yellow squares are stationary always). After completion of the stimulus, subject is asked to mark the final position of each square on a blank 4 × 4 matrix. This procedure is repeated with all 10 cards one by one.

Although norms were not available for Indian subjects but the test was used previously by other authors for a
similar assessment.\textsuperscript{[15]} Cronbach’s alpha coefficient for the verbal span working memory tasks was 0.85 suggesting an adequate degree of internal reliability.\textsuperscript{[22]}

\textit{Trail making test A and B}\textsuperscript{[23]}
This construct encompasses many neuropsychological abilities, such as visual attention, planning, and sequential behavior, initiating and choosing behaviors, and cognitive flexibility. Trails A has been used individually to effectively measure motor speed and visual attention.\textsuperscript{[20]}

Executive functioning was measured by trail B, which assesses the individual’s cognitive flexibility.\textsuperscript{[20]} Performance is indexed using the time to complete the task in comparison to a similar age, years of education, and gender comparison group. The performance of Indian population differed from other studied population.\textsuperscript{[20]}

\textbf{Statistical analysis}

The statistical analyses were performed using “SPSS (PASW) version 18.0 software (SPSS, Chicago [IL], US).”\textsuperscript{[31]} For computation of percentage, frequencies, means and standard deviations descriptive statistics were used and qualitative data were analyzed using Chi-square test. For comparison of neurocognitive performance, we compared the FDR schizophrenia group (n = 40) with the controls (n = 40) on each of the cognitive tests by means of “independent t-test.”

A composite neurocognitive index was calculated by the sum total of scores on different cognitive tests. After calculation subgroups of FDR schizophrenia were compared with controls on the individual neurocognitive function as well as composite neurocognitive score. The effect sizes for comparisons between the two groups were calculated by computing the Cohen d. Significance (P value) was set at \(P \leq 0.05\).

\textbf{RESULTS}

\textbf{Sociodemographic profile}

The mean age of FDR schizophrenia was 25.25 years which was comparable to control group (24.62). Both groups were statistically identical on different sociodemographic variables considered for the study [Table 2]. Majority of study participants consisted of married male population of rural background with no statistically significant difference between groups.

As depicted in Table 3, both groups were comparable regarding education, occupation and income. No statistically significant difference was found among groups. Over one-third of the subjects in both groups were unemployed, and a similar number of participants belonged to unskilled worker category. Majority of the participants belonged to lower socioeconomic status.

| Variable | FDR of SCZ (n=40) f (%) | Controls (n=40) f (%) | P |
|----------|------------------------|----------------------|---|
| Age (years) mean (SD) | 25.25 (4.16) | 24.62 (4.83) | 0.728 |
| Gender | | | | |
| Male | 31 (77.5) | 35 (87.5) | 0.149 |
| Female | 9 (22.5) | 5 (12.5) | |
| Marital status | | | | |
| Married | 17 (40) | 27 (67.5) | 0.154 |
| Unmarried | 23 (40) | 13 (32.5) | |
| Locality | | | | |
| Rural | 32 (80) | 30 (75) | 0.502 |
| Urban | 8 (20) | 10 (25) | |

As depicted in Table 4, performance on various neurocognitive tests was compared in unaffected relatives of patients of schizophrenia with the control group. FDR schizophrenia group performed poorly on measures of short-term memory (\(P = 0.001\)), auditory verbal memory (\(P = 0.001\)), and visuospatial working memory (\(P = 0.001\)) with medium to large effect size of 0.6, 0.93, and 0.71, respectively. FDR schizophrenia group also performed poorly on neurocognitive domains of verbal working memory (\(P = 0.001\)) and executive functions (\(P = 0.01\)). Composite neurocognitive score substantially differentiated case group from the control group with larger effect size (1.07).

On test of visual attention and psychomotor performance speed (trail making test A) unaffected relatives performed poorly compare to controls but differences does not reach statistical significance (\(P = 0.27\)).
Neurocognitive dysfunction as vulnerability marker among first-degree relatives schizophrenia patients

Compared to the controls, FDR schizophrenia group performed poorly on individual neurocognitive domains including short-term memory, auditory verbal memory on measures of immediate recall and recognition, visuospatial working memory, verbal working memory, and executive functions. On calculation of composite neurocognitive score the results have shown more robustness with larger effect size (Cohen’s $d = 1.07$) than individual cognitive domains, providing evidence in support of measuring a combined cognitive score for better differentiation on the basis of endophenotypic domains. Several studies[33,37] and meta-analyses[1,10,38] demonstrated similar cognitive deficits among relatives of patients with schizophrenia. Our results differed from other studies on the psychomotor speed while other domains yielded similar results.

Since attention and working memory deficits has been implicated in the pathophysiology of schizophrenia, its dysfunction in unaffected relatives indicates the presence of a substrate (probably genetically mediated) for future development of the disorder. A recent meta-analysis has demonstrated similar cognitive deficits among relatives of patients with schizophrenia.[10] Park et al.[39] have illustrated that healthy relatives of schizophrenia, show impaired performance (i.e., reduced accuracy, numerous uncorrected errors) on a spatial delayed response task when compared with normal controls. These observations indicate a genetically mediated dysfunction in spatial working memory which is consistent with linking of working memory deficit with genetic risk of schizophrenia. In a review, Brewer et al.[40] suggested that spatial working memory deficits is existent before the onset of illness and may be a more potent endophenotypic marker for psychosis than cognitively dense tasks such as verbal memory. Our study replicates this observation regarding visuospatial working memory with medium to large effect size (Cohen d = 0.71).

Toomey et al.[41] favored assessment of a combination of multiple cognitive risk indicators since it may help us in better identification of those relatives who carry the schizophrenia genotype. Our study supports the existing concept of composite neurocognitive score assessment which found to be a better indicator of endophenotypic approach usefulness.[46]

**Table 4: Neurocognitive performance among cases versus controls**

| Variable                  | FDR SCZ (n=40) (SD) | Controls (n=40) (SD) | $P$  | Cohen d |
|---------------------------|---------------------|---------------------|------|---------|
| Digit span test           |                     |                     |      |         |
| Forward                   | 5.55 (0.81)         | 5.97 (0.70)         | 0.0001 | 0.6     |
| Backward                  | 3.92 (0.57)         | 4.12 (0.56)         | 0.001 | 0.38    |
| Test for verbal retention |                     |                     |      |         |
| Similar                   | 4.55 (0.55)         | 4.62 (0.49)         | 0.542 | 0.14    |
| Dissimilar                | 11.57 (1.79)        | 13.15 (1.98)        | 0.0001 | 0.79    |
| Total                     | 16.10 (2.16)        | 17.75 (1.77)        | 0.0001 | 0.93    |
| WSWM matrix               | 4.57 (2.49)         | 7.85 (3.79)         | 0.0001 | 0.71    |
| TMT A                     | 35.10 (6.37)        | 32.67 (9.11)        | 0.141 | 0.27    |
| TMT B                     | 74.60 (18.06)       | 65.05 (10.78)       | 0.010 | 0.09    |
| Composite                 | −2.52 (2.80)        | 1.92 (4.15)         | 0.000 | 1.07    |

FDR – First-degree relatives; n – Sample size; SD – Standard deviation; TMT – Trail making test, WSWM – Visuospatial working memory; SCZ – Schizophrenia

**DISCUSSION**

Most of the existing studies from Indian subcontinent[14-16] have compared the neurocognitive performance of FDR schizophrenia subjects with healthy controls on individual domains and not taken account of the composite neurocognitive score.[14,15] For instance Bhatia et al.[14] administered the only trail making test in patients with schizophrenia, schizoaffective disorder, and controls. The administered test assessed only executive function, localized to prefrontal cortex leaving aside medial temporal lobe which is equally affected in patients with schizophrenia and their relatives. Similarly, study by Garg et al.[15] administered Wisconsin Card Sorting Test, Continuous Performance Test (CST) and Spatial Working Memory Test but did not calculate the composite score of various tested neurocognitive tests. In addition, cases were matched over education with controls which is a debatable issue.[10] Computerized tests were used which could have affected the performance of participants because of low education and largely computer illiterate participants.[15] In a previous study[16] we subjected 50 FDR of schizophrenia and 30 controls with Schizotypal Personality Questionnaire, the Cambridge neurological inventory, digit span test, paired associate learning test, and visuospatial working memory matrix. Results of the study demonstrated that composite neurocognitive score better differentiated FDR schizophrenia group from controls which encouraged us to conduct another study encompassing other cognitive tests for assessment of psychomotor performance speed and executive functions. We assumed that the comparative design of the study had a potential to provide better information regarding endophenotypes of schizophrenia. Therefore, we considered a need to evaluate multiple neurocognitive domains and calculate composite neurocognitive scores.

In our study, both groups were comparable on age, sex, and marital status. No significant differences were found on education, occupation, income, socioeconomic status, family type, religion, and locality. Although matching on education is a debatable issue, as noted in a meta-analysis[10] that if schizophrenia is a neurodevelopmental disorder, then matching patients and normal controls on education may cause mismatching of theoretically expected cognitive ability but in our study, it was found comparable by chance.

Since attention and working memory deficits has been implicated in the pathophysiology of schizophrenia, its dysfunction in unaffected relatives indicates the presence of a substrate (probably genetically mediated) for future development of the disorder. A recent meta-analysis has demonstrated similar cognitive deficits among relatives of patients with schizophrenia.[10] Park et al.[39] have illustrated that healthy relatives of schizophrenia, show impaired performance (i.e., reduced accuracy, numerous uncorrected errors) on a spatial delayed response task when compared with normal controls. These observations indicate a genetically mediated dysfunction in spatial working memory which is consistent with linking of working memory deficit with genetic risk of schizophrenia. In a review, Brewer et al.[40] suggested that spatial working memory deficits is existent before the onset of illness and may be a more potent endophenotypic marker for psychosis than cognitively dense tasks such as verbal memory. Our study replicates this observation regarding visuospatial working memory with medium to large effect size (Cohen d = 0.71).

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Cannon et al. found that deficits in frontal lobe gray matter and associated neurocognitive functions (spatial working memory, divided attention, intrusions during recall of a word list, and choice reaction time to visual targets) appear to be genetically mediated neuro-endophenotypic indicators. Neuroanatomical changes in the hippocampus, prefrontal cortex and white matter integrity, observed in relatives of patients with schizophrenia also lend support in favor of cognitive deficit observed in our study.

Shared and specific neurocognitive characteristics

To the best of our knowledge, this is the first study investigating FDR schizophrenia subjects on multiple cognitive domains with calculation and comparison of the composite neurocognitive score with healthy matched controls. We observed that the FDR schizophrenia group performed poorly on various neurocognitive measures which are found deficient in schizophrenia patients according to the available literature. This indicates that healthy relatives share the similar genetic risk for development of schizophrenia, and phenotypic expression of these genes can be utilized to quantify the genetic risk.

It is clear from the present study that neurocognitive measures such as short-term memory, verbal auditory memory, verbal working memory, visuospatial working memory, and executive functions significantly differentiate FDR of patients with schizophrenia from controls. Furthermore, the combination of all these measures is better at discrimination. The composite neurocognitive score had larger effect size (Cohen’s $d = 1.07$) than the individual cognitive domain, thus providing evidence in support of a combined cognitive index among high-risk individuals.

Despite our best efforts, the study had following limitations. Being a time bound study we were able to recruit a small sample, whose results cannot be generalized. The selection of large sample should have ensured representability of study sample. It is possible that unaffected relatives reacted defensively due to existing stigma leading to compromise over performance on neurocognitive functioning. We used extensive interview (unstructured) to rule out the presence of any psychiatric disorder, which could have been supplemented with the structured diagnostic interview. This may have missed patients with the subclinical psychiatric disorder, leading to poor performance on neurocognitive functioning. Furthermore, it is still difficult to have a definite interpretation of specific cognitive impairments in case group as well as control group since every test measured other domains of neurocognitive functioning. Having a cross-sectional study, we are unable to comment implications of neurocognitive functioning on the future development of schizophrenia.

The results of this study indicate the potential usefulness of endophenotypic approach for understanding genetic underpinnings of schizophrenia. To predict the development of schizophrenia in genetically vulnerable subjects’ longitudinal study with the large sample would be required. They will be also useful in early identification of individuals at high risk of developing the disease. In addition, further studies are needed to investigate whether the type of family history, homogeneous or mixed, of the affected parent, may affect the cognitive profile of the FDR’s. To determine the cognitive endophenotypic approach for schizophrenia, it seems more rational to conduct a comprehensive evaluation of neurocognitive domains in well-matched groups using sufficiently challenging tests to detect slight deficits. In addition, longitudinal studies with a larger sample size evaluating neurocognitive functions combined with genetic analysis may provide clues about explaining the genetic background of the disorder within the endophenotypes concept.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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