Original Article

Neurocognitive Functioning in Schizophrenia, their Unaffected Siblings and Healthy Controls: A Comparison

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ABSTRACT

Aim: Neurocognitive functions are considered to be reliable endophenotypes for schizophrenia. This study aimed to study the neurocognitive functioning of unaffected siblings of patients with schizophrenia and compare the same with a group of patients with schizophrenia and a group of healthy controls. **Materials and Methods:** Three study groups, that is, unaffected siblings of patients with schizophrenia, patients of schizophrenia and healthy controls, each group comprising of 20 participants were evaluated on Wisconsin Card Sorting Test, Brief Visuospatial Memory Test-Revised, Hopkins Verbal Learning Test-Revised, Wechsler Adult Intelligence Scale and Digit Symbol Test. **Results:** Compared to healthy controls, unaffected siblings of patients with schizophrenia performed poorly on the tests of short-term verbal learning and memory, but no significant differences were seen between the two groups for executive functions, visual learning and psychomotor speed, concentration and graphomotor abilities. However, when compared with patients with schizophrenia, unaffected siblings performed poorly on the tests of executive functions, visual memory, verbal memory, psychomotor speed, concentration and graphomotor abilities. **Conclusion:** Cognitive markers like verbal memory deficits can distinguish unaffected siblings of schizophrenia from healthy controls and serve as an endophenotype for schizophrenia.

Key words: *Cognitive functions, endophenotype, schizophrenia, unaffected siblings*

INTRODUCTION

Over the years, one of the main goals of schizophrenia research is to evaluate the risk factors for development of schizophrenia. Out of the various attempts to understand the factors that make a person vulnerable to schizophrenia, one of the focus groups of multiple studies is unaffected relatives. The main advantage of studying this group is that they also possibly harbor the genetic vulnerability to develop schizophrenia. Further, this group has also been shown to have subthreshold clinical symptoms and neurocognitive deficits in the similar domains as seen in patients.[1]

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It is now well-understood that cognitive deficits are one of the core features and are important endophenotype of schizophrenia. Besides being seen during the symptomatic phase of illness, these are also present in the prodromal phase and during clinical remission and impair functional recovery from the disorder.[2]

Cross-sectional studies involving first-degree relatives (FDRs) of patients with schizophrenia show that compared to age and gender-matched healthy controls, FDRs have more deficits in the domains of sustained attention, executive functions, learning, episodic memory, and working memory.[1] However, these deficits have not been consistently replicated across all the studies. A recent review which included 28 studies published before May 2011, involving the FDRs of individuals with schizophrenia who had not passed through the peak age illness risk (<age 30) concluded that compared to the healthy controls, the FDRs had moderate level of deficits. Overall, largest effect sizes were seen for intelligence quotient (IQ), followed by that for vocabulary and single word reading tests. Findings of declarative memory, sustained attention, working memory and other cognitive domains had modest effect sizes. Further, this review also showed that cognitive deficits in the FDRs are lower than those seen among patients with schizophrenia. The authors also noted that there was heterogeneity in the tests used to assess various cognitive domains.[3] Another recent meta-analysis and systematic review of studies involving the 2113 familial-high risk or ultra-high risk and 1748 healthy controls showed that co-occurrence of genetic risk and attenuated symptoms was associated with more severe cognitive dysfunction. Further, it was seen that ultrahigh risk subjects, who later developed psychosis had more severe cognitive deficits in all domains except sustained attention. The authors also concluded that there was lot of heterogeneity in the studies.[4] Longitudinal studies involving siblings and offsprings of patients also suggest that over the follow-up period of 1-2 years, executive dysfunction do not improve in the high risk subjects, whereas, improvement is seen among healthy controls.[5]

Although many studies from India have evaluated cognitive deficits in patients with schizophrenia,[6-12] there is lack of data on the FDRs. One study evaluated the parents of patients with schizophrenia along with patients and healthy controls and reported that compared to the healthy controls, deficits in trail making B test in patients and their parents was more but there was no statistically significant difference between the patient and the parent groups.[10] However, it is important to note that this study was limited to the parents and did not include other FDRs.

Based on this brief review, it is evident that there is a need to expand the literature on the cognitive deficits in FDRs of patients with schizophrenia. Accordingly, this study aimed to assess and compare the cognitive deficits in FDRs of patients with schizophrenia with a healthy control group and the patient group.

MATERIALS AND METHODS

This study was conducted at a tertiary care hospital in North India. Institute Ethics Committee approved this study, and all the participants were recruited after obtaining proper written informed consent. A cross-sectional assessment was carried out and participants were selected by purposive sampling.

The study included three groups: Patients with a diagnosis of schizophrenia as per ICD-10 (Group-I), unaffected siblings of patients with schizophrenia (Group-II) and a healthy control group (Group-III). Each group comprised of 20 participants. Participants of all the three groups were included in the study if they were aged between 18 and 60 years, were able to read and write Hindi and/or English, and were free from any significant medical co-morbidity (involving the brain, raised blood pressure etc.) and did not have any auditory/visual impairment. Patients using auditory aids and not able to understand the instructions of the neurocognitive battery were excluded.

Patient of schizophrenia (Group-I) were required to fulfill the diagnosis of schizophrenia as per the DSM-IV criteria and were clinically stable, which was defined as no increase in drug dosage by more than 50% in the 3 months preceding the assessment and having a PANSS score of <52. Those with co-morbid psychiatric illness and substance dependence (except for nicotine) were excluded. Patients who received electroconvulsive therapy in the past 6 months were also excluded.

Group-II included FDRs of patients with schizophrenia, who were free from any psychiatric morbidity. The same was acertained by a qualified psychiatrist using a semi-structured interview. As in schizophrenia group those with alcohol and drug dependence (except for nicotine) were excluded.

Group-III (healthy controls) comprised of subjects who were not suffering from any psychiatric disorder apart from nicotine dependence. This was established on the basis of General Health Questionnaire-12[13] score of <2 and history provided by the participants and their relatives. Additionally they were required not to

have any first or second degree relative suffering from a psychiatric disorder.

All the patients with a clinical diagnosis of schizophrenia were eligible for the study. Patients fulfilling the selection criteria were recruited by purposive sampling. The sibling group was recruited from the family members of patients with schizophrenia attending the outpatient services as caregivers. The healthy control group was recruited from the nongenetically related caregivers of the patients attending the psychiatry outpatient services.

Following instruments were used for assessment of neurocognitive functions

- Wisconsin Card Sorting Test (WCST):[14] The 128 cards computerized version of the test was used for the study. WCST evaluates executive functions that require planning, use of feedback and cognitive set shifting.
- Brief Visuospatial Memory Test-Revised (BVMT-R):[15] This test evaluates immediate recall, delayed recall, learning and recognition for visuospatial information.
- Hopkins Verbal Learning Test-Revised (HVLT-R):[16] This test is used to evaluate short-term verbal learning and memory. This test involves three learning trials for a set of words each followed by a recall and then followed by a delayed recall after a delay of 20 min.
- Wechsler Adult Intelligence Scale Digit Symbol Test (WAIS DST):[17] This test evaluates psychomotor speed, concentration and graphomotor abilities. In this test, the participant is required to match symbols to numbers in the shortest possible duration using a visual reference. Scoring is done on the basis of number of symbols drawn in 120 s.

Statistical analysis

Data were analyzed using SPSS software version 14 (SPSS, Chicago, IL, US). Frequencies, percentages, means, and standard deviations (SDs) were calculated for descriptive data. Comparisons were done using Chi-square test and ANOVA. To account for the confounders, analysis of covariance was used for computation of corrected F scores. Effect sizes of the differences in neurocognitive performance were calculated using partial η^2 scores.

RESULTS

Sociodemographic and clinical profile

All the groups were matched on age, gender, level of education, religion, and locality [Table 1].

Clinical profile of the patient group

The mean duration of illness in patients with schizophrenia disorder was 103.5 (SD – 92.13) months with mean duration of treatment of 87.3 (SD – 78.7) months. The mean score on various domains of PANSS was as follows: Positive symptoms – 8.3 (SD – 1.75), negative symptoms – 9.0 (SD – 2.66), general psychopathology – 20.6 (SD – 3.48) and total score was 38.0 (SD – 6.20).

Comparison of cognitive functioning of the three groups

In general healthy controls performed better than the unaffected siblings and patients with schizophrenia on various neurocognitive tests, but significant differences were noted for some of the tests. As shown in Table 2, on WCST, there was no significant difference between the healthy controls and unaffected siblings. However, the performance of unaffected siblings was poor compared to healthy controls on HVLT. Patients with schizophrenia performed significantly worse than the healthy controls and also the unaffected siblings on some of the subtests of WCST, BVMT, HVLT, and WAIS DST.

DISCUSSION

Neurocognitive deficits are hallmark of schizophrenia and are considered as the central features of this

Table 1: Demographic profile of participants

Variables	Unaffected siblings (n = 20) (US)	Patients with schizophrenia (n = 20) (SP)	Healthy controls (n = 20) (HC)	χ^2/F (P)
Age				
Mean (SD)	36.6 (11.26)	34.7 (10.42)	40.9 (9.67)	1.81 (0.172)
Gender (%)				
Male/female	13 (65)/7 (35)	10 (50)/10 (50)	12 (60)/8 (40)	0.96 (0.619)
Education (%)				
Below 10th grade/above 10th grade	3 (15)/17 (85)	4 (20)/16 (80)	6 (30)/14 (70)	0.57 (0.447)
Religion (%)				
Hindu/others	12 (60)/8 (40)	12 (60)/8 (40)	15 (75)/5 (25)	1.31 (0.517)
Locality (%)				
Urban/rural	11 (55)/9 (45)	11 (55)/9 (45)	15 (75)/5 (25)	2.25 (0.324)

Table 2: Comparison of findings of cognitive functioning

Variables	Mean (CI)			*t*-test (P)			ANOVA *F* (*P*)	Effect size (partial η^2)	*Post-hoc* analysis@
	Group-I (US) Unaffected siblings (*n* = 20)	Group-II (SP) Patients with schizophrenia (*n* = 20)	Group-III (HC) Healthy controls (*n* = 20)	Comparison of Groups I and II	Comparison of Groups I and III	Comparison of Groups II and III			
WCST									
WCST total score	56.8 (48.2-65.4)	37.2 (31.5-42.8)	59.1 (51.6-67.0)	3.988 (0.003)	0.414 (0.681)	4.751 (<0.001)	11.412 (<0.001)	0.286	SP > US, SP > HC, SR=HC
WCST total errors	71.8 (62.8-80.8)	87.6 (80.0-95.1)	67.2 (57.7-76.6)	2.801 (0.008)	0.748 (0.459)	3.533 (0.001)	6.9620 (0.003)	0.188	SP > US, SP > HC, US=HC
WCST perseveratory responses	29.3 (23.0-35.5)	38.7 (26.3-51.1)	29.7 (23.2-36.2)	1.428 (0.162)	0.104 (0.918)	1.134 (0.186)	1.593 (0.212)	0.053	SP=US=HC
WCST perseveratory errors	24.8 (20.1-29.5)	34.1 (25.1-43.0)	26.1 (20.5-31.6)	1.910 (0.064)	0.358 (0.722)	1.588 (0.121)	2.477 (0.093)	0.080	SP=US=HC
WCST nonperseveratory errors	39.6 (29.5-49.6)	53.7 (43.6-63.7)	38.3(27.8-48.7)	2.071 (0.045)	0.188 (0.852)	2.224 (0.032)	3.076 (0.054)	0.097	SP > US, SP > HC, US=HC
WCST conceptual level responses	37.4 (26.2-48.5)	16.4 (9.6-23.1)	37.9 (27.2-48.5)	3.363 (0.002)	0.068 (0.946)	2.574 (0.001)	6.974 (0.002)	0.197	SP > US, SP > HC, US=HC
BVMT-R									
BVMT-R trial 1	3.5 (2.5-4.5)	2.1 (1.2-2.9)	3.9 (2.6-5.2)	2.243 (0.031)	0.497 (0.622)	2.416 (0.021)	3.443 (0.039)	0.108	SP > HC, SP=US, US=HC
BVMT-R trial 2	5.6 (4.2-6.9)	3.9 (2.7-5.1)	5.0 (3.5-6.4)	1.909 (0.064)	0.645 (0.523)	1.176 (0.247)	1.737 (0.185)	0.057	SP > HC, SP=US, US=HC
BVMT-R trial 3	7.0 (5.6-8.3)	5.5 (4.0-6.9)	7.4 (6.0-8.7)	1.598 (0.118)	0.431 (0.669)	2.015 (0.051)	2.289 (0.111)	0.074	SP > HC, SP=US, US=HC
BVMT-R total	16.1 (12.7-19.4)	11.5 (8.2-14.8)	15.8 (12.1-19.5)	2.021 (0.051)	0.103 (0.918)	1.805 (0.079)	2.361 (0.104)	0.076	SP > HC, SP > US, US=HC
BVMT-R delay	6.6 (5.2-7.9)	4.5 (3.0-6.0)	7.2 (5.6-8.7)	2.090 (0.043)	0.615 (0.542)	2.589 (0.014)	3.910 (0.026)	0.121	SP > HC, SP=US, US=HC
HVLT-R									
HVLT-R trial 1	5.8 (5.4-6.2)	5.0 (4.4-6.2)	6.8 (6.0-7.5)	2.421 (0.020)	2.437 (0.020)	4.073 (<0.001)	10.330 (<0.001)	0.266	SP > US, SP > HC, US > HC
HVLT-R trial 2	7.0 (6.6-7.4)	6.4 (5.7-7.1)	8.1 (7.5-8.6)	1.511 (0.139)	3.0376 (0.002)	3.937 (<0.001)	9.733 (<0.001)	0.255	SP > US, SP > HC, US > HC
HVLT-R trial 3	7.6 (7.0-8.1)	7.2 (6.5-7.9)	9.1 (8.5-9.7)	0.790 (0.434)	3.796 (0.001)	4.133 (<0.001)	10.684 (<0.001)	0.273	SP > US, SP > HC, US > HC
HVLT-R delayed recall	7.0 (6.6-7.4)	5.5 (4.8-6.1)	8.0 (7.1-8.9)	4.192 (<0.001)	2.128 (0.040)	4.923 (<0.001)	15.828 (<0.001)	0.357	SP > US, SP > HC, US=HC
WAIS DST									
Digit substitution test	54.0 (47.9-60.0)	42.3 (36.1-48.4)	52.45 (45.3-59.5)	2.827 (0.007)	0.347 (0.730)	2.263 (0.029)	4.239 (0.019)	0.129	SP > US, SP > HC, US=HC

WCST – Wisconsin card sorting test, WAIS DST – Wechsler adult intelligence scale digit symbol test; HVLT-R – Hopkins verbal learning test-revised; BVMT-R – Brief visuospatial memory test-revised; CI – Confidence interval; @-the differences indicated by ">" were significant at least at p value <0.05 and the differences indicated by "=" were not significant

disorder, occurring in all phases of the illness.[3] Studying the FDRs of patients with schizophrenia has been extensively used to understand the presumed genetic risk, as this helps in identification of cognitive vulnerability markers for schizophrenia in the absence of any psychotic symptoms.[3]

This study compared the neurocognitive dysfunction

of unaffected siblings of patients with schizophrenia, patients with schizophrenia and a healthy control group. By design, all the study groups were matched on the sociodemographic variables, so as to remove the confounding effect of these variables on the findings of the study.

The neurocognitive assessment included evaluation of cognitive domains of executive functioning, visual memory, verbal memory and learning, psychomotor speed, concentration and graphomotor abilities. These domains were evaluated as these are considered to be affected in patients with schizophrenia and also in their FDRs.[1,4]

The present study suggests that compared to healthy controls, the unaffected siblings and patients with schizophrenia perform poorly on various neurocognitive tests. However, significant differences were noted only on the tests of short-term verbal learning and memory (HVLT). These findings are in accordance with the existing literature that suggest that compared to health controls, unaffected siblings/FDRs have more deficits in the domains of learning, episodic memory and working memory.[1] However, it is important to note that the deficits in the domains of executive functions and sustained attention have not been reported consistently in the literature.[1,4] In the recent meta-analysis, too modest effect sizes were seen for the domains of declarative memory and working memory.[3] Similarly, findings of the present study do not concur with some of the previous studies which have reported significantly higher deficits in the unaffected siblings/FDRs when compared with healthy controls in the domains of executive functions and sustained attention.[1] These differences can be possibly be due to the small sample size and variance in the genetic loading of schizophrenia.

Findings of the present study also shows that when compared with healthy controls and FDRs patients with schizophrenia have significantly more severe cognitive deficits in the domains of executive functions, immediate recall, delayed recall, learning and recognition for visuospatial information, short-term verbal learning and memory, psychomotor speed, concentration, and graphomotor abilities. These findings are line with the existing literature.[4] Taken together, it can be said that performance of FDRs of patients with schizophrenia is intermediate between healthy controls and patients of schizophrenia. Accordingly, present study substantiates the fact that cognitive deficits in FDRs are seen in the absence of overt clinical features and these can be considered as an important endophenotypes for psychosis.

Findings of the present study must be interpreted in the light of its limitations. This study evaluated the FDRs of patients with schizophrenia attending a tertiary care hospital. The study did not involve assessment of IQ, which has been shown to have largest effect sizes in the literature when FDRs of patients of schizophrenia are compared with health controls.[3] The present study did not involve assessment of twin-pairs who have highest level of genetic matching. Further, the sociodemographic profile of various study groups was group matched rather than case to case matched. Further, few of the subjects included in the present study were aged more than 30 years, which is considered a cut off for considering the unaffected relatives to be high-risk subjects.

To conclude, this study suggests that certain cognitive markers can distinguish unaffected siblings of schizophrenia from healthy controls. This can be useful in clinical practice to ascertain the genetic liability in an index case.

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Conflicts of interest
There are no conflicts of interest.

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