Neurocognitive Impairments in Unaffected First-degree Relatives of Schizophrenia

Virupaksha Shanmugam Harave, Venkataram Shivakumar, Sunil V. Kalmady, Janardhanan C. Narayanaswamy, Shivarama Varambally, Ganesan Venkatasubramanian

ABSTRACT

Background: Neurocognitive impairments of attention and executive functioning are trait abnormalities in schizophrenia, and these are considered to be endophenotypes. These deficits have been convincingly linked to prefrontal cortical functioning. In this study, we examined the cognitive performance in the domains of attention and executive functioning among first-degree relatives of Indian people with schizophrenia (high-risk [HR] patients) compared to healthy controls (HC). Materials and Methods: Siblings of patients with DSM-IV schizophrenia, HR patients (n = 17), were compared with HC (n = 30) (matched as a group for age, sex, years of education, and handedness) using the following neurocognitive tests for attention and executive function – digit span test (DST), trail making test, letter-number sequencing (LNS), and spatial span test. Results: HR patients had significantly deficient performance in attention and executive function tasks (DST-forward [P < 0.001], DST-backward [P < 0.001], spatial span-forward [P < 0.001], spatial span-backward [P < 0.001], and LNS [P < 0.001]). Conclusions: This study replicates the findings that neurocognitive deficits involving executive function task performance, attention, and working memory, which are considered as principal features in patients with schizophrenia, are also significantly present in the first-degree relatives of patients. Thus, these neurocognitive parameters can be considered as potential endophenotypes in schizophrenia.

Key words: Attention, endophenotype, high-risk subjects, neurocognitive, schizophrenia

INTRODUCTION

Schizophrenia is a complex disorder with a multifactorial inheritance, and the presence of an affected first-degree relative is considered as a significant risk factor.[1] Neurocognitive deficits, which are consistently reported in schizophrenia patients, have been postulated as a potential endophenotype in schizophrenia.[2] Neurocognitive impairments have been demonstrated in all stages of schizophrenia and are intricately linked to the functional outcome of the illness.[3] Such cognitive deficits have also been demonstrated...

Department of Psychiatry, Translational Psychiatry Laboratory, The Schizophrenia Clinic, Neurobiology Research Centre, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Ganesan Venkatasubramanian
Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru - 560 029, Karnataka, India.
E-mail: venkat.nimhans@yahoo.com
Prospective studies in HR patients have shown that verbal working memory, performance attention, and gross motor skills have predictive potential regarding conversion to psychosis. Examining the cognitive endophenotypes in HR patients could help in evaluating the cognitive vulnerability markers without the effects of illness-related confounding factors. Previous studies including meta-analyses have demonstrated deficits in attention, working memory, and executive functioning in adult HR compared to healthy volunteers. Studies from India have been sparse in this area. In a recent study from India, it was demonstrated that the siblings performed significantly poor as compared to the healthy controls (HCs) on Wisconsin card sorting test, continuous performance test, and spatial working memory test. In this study, we sought to examine the neurocognitive performance in attention and executive functioning among siblings of patients with schizophrenia (HR) who attended a tertiary care psychiatric hospital in South India compared to matched HC.

MATERIALS AND METHODS

We recruited HR patients (n = 17) who are siblings of patients with DSM-IV schizophrenia who attended the clinical services of both inpatient and outpatient services of National Institute of Mental Health and Neurosciences, India. Age-, sex-, education-, and handedness-matched volunteering HCs (n = 30) were recruited through word of mouth. After complete description of the study to the participants, written informed consent was obtained. The Institute’s Ethics Committee approved the study. All the participants were assessed using Mini International Neuropsychiatric Interview (MINI) Plus to rule out the presence of axis I psychiatric diagnoses. At least one sibling with diagnosis of DSM-IV schizophrenia established by MINI and ascertained by a qualified psychiatrist was ensured for HR patients. None of these patients had clinical features suggestive of substance abuse/dependence. None had comorbid medical/neurological diagnosis. All the participants were right-handed as established using Edinburgh handedness inventory. All the participants had formal education till at least 10th standard and had a score >25 on the Mini Mental Status Examination.

Neurocognitive assessment was conducted for all the study participants in a single session (lasting for approximately 1 h), in a fixed order and in the same quiet room. The following neuropsychological tests were administered.

Tests of attention
- Trail making test: This examines for attention, sequencing, mental flexibility, and psychomotor speed (visual search and motor function) and consists of two parts: a. Part A – requires participant to make connection of circles containing numbers (digits) in ascending order, arranged randomly on paper; b. Part B – requires participant to make connection of circles containing numbers (digits) and letters (alphabets) in alternating order, arranged randomly on paper.

Tests of executive functions
- Wechsler memory scale (WMS)-letter-number sequencing (LNS): This measures working memory using auditory stimuli. The participant listens to a combination of numbers and letters and is asked to repeat them, saying the numbers first in an ascending order, and then the letters in the alphabetical order.

- WMS-spatial span: This is a test for spatial working memory. The spatial span board has ten cubes and consists of two subtests – spatial span-forward and spatial span-backward. In spatial span-forward, the participant is asked to tap the sequence in reverse order as had been tapped by the examiner; while in the spatial span-backward, the participant has to tap the sequence in reverse order as had been tapped by the examiner.

Analysis of covariance controlling for age, sex, and years of education was employed to examine the difference in neurocognitive task performance between HR and...
HC. Bonferroni corrected \( P < 0.007 \) was considered statistically significant, taking into account seven tests of comparison made between the groups [Table 1].

**RESULTS**

The HR patients were matched to HCs based on age (25.3 ± 4.6 vs. 24.9 ± 3.7, \( t = 0.3, P = 0.73 \)), sex (male:female = 12.5 vs. 21.9, \( \chi^2 = 0.02, P = 0.97 \)), handedness (all subjects were right handed), and years of education (13.4 ± 2.5 vs. 13.1 ± 2.6, \( t = 0.3, P = 0.78 \)). As shown in Table 1, HR patients had significantly deficient performance in attention and executive function tasks (digit span [forward] \( P < 0.001 \), digit span [backward] \( P < 0.001 \), spatial span [forward] \( P < 0.001 \), spatial span [backward] \( P < 0.001 \), and LNS \( P < 0.001 \)).

**DISCUSSION**

In this study, HR patients demonstrated significant deficits in the neurocognitive measures of attention and executive functioning when compared with matched HCs.

Several previous studies have revealed that attention and executive functioning have been found to be among the most affected cognitive domains in schizophrenia.[14] Neurocognitive deficits involving executive function task performance, attention, and working memory could be considered as principal features in patients with schizophrenia since these aberrations are noticeable from the first episode of psychosis.[22] These domains are also found to be affected in first-degree relatives of patients with psychosis.[15] Examining the studies with HR patients (mean age between 15 and 29 years), Bora et al. in their recent meta-analysis reported that significant neurocognitive deficits are present in HR compared to HC in various domains.[23] In a recent study, Üçok et al. reported that HR patients performed poorly in attention, executive functions, and working memory than HC and the neurocognitive performance of HR was almost comparable to participants with the first episode psychosis.[24]

First-degree relatives of patients with schizophrenia or HR patients have been noted to have a significant predisposition to develop schizophrenia where some studies have noted the conversion rate as high as 40%.[23] Endophenotypes, also known as intermediate phenotypes, are measurable stable biological deficits or factors which could indicate inherited vulnerability to the disease in question. Hence, they co-segregate within the families of patients,[26] and as replicated in this study, neurocognitive impairments involving attention and executive functions can be considered to be endophenotypes.

Schizophrenia is probably not understood as dysfunction due to single brain area; rather, it is considered to be a disorder of brain networks.[27] Many brain areas such as prefrontal cortex, hippocampus, and parietal lobe structures are consistently reported to be associated with cognitive function deficits, especially the attention and executive function impairments.[28-30] It has been shown that the vulnerability to develop schizophrenia might reveal regional gray matter density alterations in functionally relevant brain circuits, especially involving the prefrontal regions.[31] Neuro-hemodynamic changes involving frontal brain regions which form a part of the attentional network has been found to be an important endophenotype marker of schizophrenia.[32] Indeed, many of the frontal lobe-mediated neurocognitive functions have been found to have significant heritability estimates.[33] Albeit in a relatively smaller number of HR patients, our study further adds evidence supporting that attention and executive functioning are cognitive endophenotypes of schizophrenia.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Waddington JL, Corvin AE, Donohoe G, O’Tuathaigh CM, Mitchell KJ, Gill M. Functional genomics and schizophrenia: Endophenotypes and mutant models. Psychiatr Clin North Am 2007;30:365-99.
2. Allen AJ, Griss ME, Folley BS, Hawkins KA, Pearson GD. Endophenotypes in schizophrenia: A selective review. Schizophr Res 2008;109:24-37.
3. Lepage M, Bodnar M, Bowie CR. Neurocognition: Clinical and functional outcomes in schizophrenia. Can J Psychiatry 2014;59:5-12.
4. Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull 1998;24:425-35.
5. Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. Handb Exp Pharmacol 2012;213:11-37.
6. Conklin HM, Curtis CE, Calkins ME, Iacono WG. Working memory functioning in schizophrenia patients and their first-degree relatives: Cognitive functioning shedding light on etiology. Neuropsychologia 2005;43:930-42.
7. Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 2005;57:688-91.
8. Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: A quantitative and qualitative review. Cogn Neuropsychiatry 2013;18:44-82.
9. Dickson H, Cullen AE, Reichenberg A, Hodgins S, Campbell DD, Morris RG, et al. Cognitive impairment among children at-risk for schizophrenia. J Psychiatr Res 2014;50:92-9.
10. Keshavan MS, Kulkarni S, Bhojraj T, Francis A, Diwadkar V, Montrose DM, et al. Premorbid cognitive deficits in young relatives of schizophrenia patients. Front Hum Neurosci 2010;3:62.
11. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: An overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull 2007;33:21-32.
12. Erlenmeyer-Kimling L. Neurobehavioral deficits in offspring of schizophrenic parents: Liability indicators and predictors of illness. Am J Med Genet 2000;97:65-71.
13. Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. Psychol Bull 2007;133:833-58.
14. Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: A meta-analysis. Schizophr Res 2004;71:285-95.
15. Smit BE, Macdonald AW 3rd, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. Schizophr Bull 2006;32:179-94.
16. Garg R, Trivedi JK, Dalal PK, Nischal A, Sinha PK, Varma S. Assessment of cognition in non-affected full biological siblings of patients with schizophrenia. Indian J Psychiatry 2013;55:331-7.
17. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33.
18. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 1971;9:97-113.
19. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
20. Reitan R, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Tucson: Neuropsychology Press; 1985.
21. Wechsler D. Wechsler Memory Scale. 3rd ed. San Antonio: The Psychological Corporation; 1997.
22. Ma X, Wang Q, Sham PC, Liu X, Rabe-Hesketh S, Sun X, et al. Neurocognitive deficits in first-episode schizophrenic patients and their first-degree relatives. Am J Med Genet B Neuropsychiatr Genet 2007;144B: 407-16.
23. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: A systematic review and meta-analysis. Acta Psychiatr Scand 2014;130:1-15.
24. Üçok A, Direk N, Koyuncu A, Keskin-Ergen Y, Yüksel Ç, Güler J, et al. Cognitive deficits in clinical and familial high risk groups for psychosis are common as in first episode schizophrenia. Schizophr Res 2013;151:265-9.
25. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: Psychopathology and clinical features. Schizophr Res 2004;67:131-42.
26. Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etiology and strategic intentions. Am J Psychiatry 2003;160:636-45.
27. Mesulam MM. Schizophrenia and the brain. N Engl J Med 1990;322:842-5.
28. Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey’s dorsolateral prefrontal cortex. J Neurophysiol 1989;61:331-49.
29. Shapiro ML, Eichenbaum H. Hippocampus as a memory map: Synaptic plasticity and memory encoding by hippocampal neurons. Hippocampus 1999;9:365-84.
30. Hart SJ, Bizzeii J, McMahon MA, Gu H, Perkins DO, Belger A. Altered fronto-limbic activity in children and adolescents with familial high risk for schizophrenia. Psychiatry Res 2013;212:19-27.
31. Habets P, Krabbendam L, Hofman P, Suckling J, Oderwald F, Baram TZ, et al. Cognitive performance and grey matter density in psychosis: Functional relevance of a structural endophenotype. Neuropsychobiology 2005;58:136-37.
32. Filbey FM, Russell T, Morris RG, Murray RM, McDonald C. Functional magnetic resonance imaging (fMRI) of attention processes in presumed obligate carriers of schizophrenia: Preliminary findings. Ann Gen Psychiatry 2008;7:18.
33. Gurr RE, Nimmo-smith L, Almasy L, Calkins ME, Hagland JD, Pogue-Geile MF, et al. Neurocognitive endophenotypes in a multiplex multigenational family study of schizophrenia. Am J Psychiatry 2007;164:813-9.