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Research Article

Cognitive Functions in Children of Persons with Schizophrenia

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ABSTRACT

Background: Cognitive deficits are a central feature of schizophrenia and occur in high-risk relatives of the patients.

Aim: We aimed to investigate whether children at-risk for schizophrenia also present neurocognitive deficits that are commonly observed in patients with schizophrenia.

Settings and Design: In a cross-sectional study, we assessed neurocognitive functioning in 15 at–risk children of schizophrenia patients with an equal number of healthy controls.

Materials and Methods: Offspring at-risk were compared with the control group on the measures of intelligence, verbal comprehension, perceptual reasoning, working memory, processing speed (assessed with Wechsler Intelligence Scale for Children – Fourth (India Edition), verbal working memory (Rey Auditory Verbal Learning Test) and executive function (Maze test).

Results: Participants in the study group obtained significantly lesser scores, compared to those in the control group, on all neurocognitive measures including verbal comprehension, working memory, processing speed and verbal working memory except for perceptual reasoning and executive function.

Conclusion: High-risk children had lower than average IQ and performed poorly on several neuropsychological measures in contrast to children in the control group.

Keywords: Schizophrenia; At-risk children; Cognitive deficits

INTRODUCTION

Cognitive dysfunction, a symptom of schizophrenia is a core and enduring feature of the illness [1]. Studies examining neurocognition in first-episode psychosis patients have found patients to perform significantly less well than normal, healthy controls on many cognitive functions including memory, attention and concentration, executive function, language skills, psychomotor speed, spatial abilities and general cortical functions [2-5].

Neurocognitive impairments are also present among non-ill relatives of patients with schizophrenia. Based on the theory of a genetic etiology, researchers began studying the offspring of individuals with schizophrenia in family studies and adoption studies and demonstrated that there was a genetic link between patients with schizophrenia, and their children [6-8].

Nearly 10-15% of offspring of parents with schizophrenia will be diagnosed with schizophrenia, reports Erlenmeyer-Kimling et al. [9]. The period of maximum risk for psychosis occurs during the ages of 20-30 [10]. Studying high-risk offspring during late childhood and adolescence, where the latter is a period in which great neuro-maturational changes occur [11]. Exploring probable abnormalities in cognitive functions may serve as new targets for early interventions as well [12].

Several studies have reported low IQ and deficits in specific cognitive functions among non-ill first and/or second-degree relatives aged less than 30 years [13] and among children/adolescents with an ill-parent [13-15]. Findings from these studies indicate that low IQ, poor scholastic achievement, deficits in verbal ability, attention, verbal memory and working memory assessed during childhood are associated with later development of schizophrenia [16-18].

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By studying neuropsychological performance of children genetically at-risk for schizophrenia, greater understanding may be obtained regarding the initial manifestation of schizophrenia and the progression of the disease. Deficits in neurocognitive functions have been documented in adults with schizophrenia, but it has been vastly understudied in children with genetic predisposition to schizophrenia.

In the current study, we aimed to determine whether children at-risk for schizophrenia display deficits in neurocognitive function like those observed in adults with schizophrenia. We hypothesize that relative to normal comparison groups, children genetically at-risk for schizophrenia would exhibit deficits on measures of intelligence, verbal comprehension, verbal memory, verbal working memory, processing speed, perceptual reasoning and executive function. With this background the present study is undertaken.

MATERIALS AND METHODS

Subjects

Study sampling was purposive, comprised 15 school going children (7 males, 8 females, age range=10-16 years) who had at least one parent meeting the ICD-10 criteria for schizophrenia. Proband parents with children ages 10-16 years old were then asked if their children would be willing to participate in the study. Of the 30 schizophrenia patients we approached, 3 (10%) stated that they were unwilling to participate in the study, 2 (6.67%) have no children, 5 (16.67%) were separated from their families and currently living alone and another 5 (16.67%) were excluded from participation as their children were older and could not meet the age-criteria of the study. The final sample comprised of 15 genetically at-risk children.

Children recruited into the study had never experienced a psychotic episode or taken anti-psychotic medication, and none presented with a neurological disorder, intellectual disability (IQ<70), or a diagnosis of autism or Asperger's disorder. The written informed consent for participation was taken from the mentally healthy parents and children provided written assent. Fifteen 10-to 16-year old control children matched for age and gender, were recruited from schools. The exclusion criteria for the study group were also applied to the control group. The parents of the healthy controls were screened by using the General Health Questionnaire (GHQ)

12 item version [19] for the possible presence of psychological distress. Consent/assent procedures were identical with those used for the index group. The medium of study of participants in both groups was English. The study period was January - March 2017 and approved by the Institutional Ethics Committee of our university. The sample characteristics have been described in Table 1.

Table 1: Sample characteristics.

Variables	Study group (n=15) (%)	Control group (n=15) (%)
Age (mean ± SD*)	13.37 ± 2.17	13.71 ± 2.10
10 – 12 years	5 (33)	5 (33)
13 – 16 years	10 (67)	10 (67)
Gender		
Male	7 (47)	7 (47)
Female	8 (53)	8 (53)
Education		
6 – 8 std	5 (33)	5 (33)
9 –10 std	7 (47)	8 (53)
11–12 std	3 (20)	2 (14)
Parent with mental illness		
Father	1 (7)	-
Mother	14 (93)	-
Marital status of parents		

Staying together	8 (53)	15 (100)
Separated	1 (7)	-
Divorced	1 (7)	-
Widowed	5 (33)	-

*SD – Standard deviation

Procedure

Eligible children were invited to participate in the study that incorporated a battery of neurocognitive assessments. Children completed the battery of neuropsychological assessment lasting approximately one hour in a single session. Neurocognitive assessments were administered by the second author (AK). Participants completed the neurocognitive tests with established reliability and validity for children aged between 10 and 16 years. They were administered the Wechsler Intelligence Scale for Children - Fourth (India Edition) [20] which is the Indian adaptation of WISC-IVUK, to estimate their intellectual functioning.

The WISC-IVINDIA provides a full-scale IQ to represent the overall cognitive ability of children aged between 6 years 0 months to 16 years 11 months. There are 10 core subtests divided among the four domains as follows: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index. The average split-half reliability coefficients ranged from 0.70 to 0.90 indicating good reliability.

Subtests from the W1SC- Fourth (India Edition), the Rey Auditory Verbal Learning Test [21] and the Maze test from the Wechsler Intelligence Scale for Children –Revised [22] were used to assess six domains of neurocognitive functions: verbal comprehension, perceptual reasoning, working memory, processing speed, verbal working memory and executive function. A brief description of each neurocognitive measure comprising the test battery is provided in Table 2.

Table 2: Summary of Neurocognitive subtests administered to participants.

Neurocognitive domain and subtest	Test description
Verbal Comprehension (WISC-IV India)	
Similarities	Identify similarities between pairs of words.
Vocabulary	Define orally and visually presented words.
Comprehension	Subjects are required to answer questions based on the understanding of general principles and social situations.
Perceptual Reasoning (WISC-IV India)	
Block Design	Replicate geometric patterns using two-colored cubes within a specified time limit.
Picture Concepts	Participants are presented with two or three rows of pictures to choose one picture from each row to form a group with a common characteristic.
Matrix Reasoning	Selecting one of five shapes to complete a pattern sequence.
Working Memory (WISC-IV India)	
Digit Span	Digit span forward requires the participant to repeat back the digits verbatim. Digit span backwards requires the participant to repeat back the digits in reverse order.
Letter-Number Sequencing	Reading a sequence of numbers and letters and recalling the numbers in ascending order and the letters in alphabetical order.
Processing Speed (WISC-IV India)	

Coding	Copying the symbols that are paired with numbers. Using the key, subjects are required to draw each symbol in its corresponding shape or box within a specified time limit.
Symbol Search	Participants are required to scan a search group and indicate whether the target symbol (s) matches any of the symbol (s) in the search group within a specified time limit.
Verbal Working Memory	
Rey Auditory Verbal Learning Test (RAVLT)	Reading a word list (list A) that is presented five times and being asked to freely recall items after each trial. This is followed by further list (list B) of new words with free recall. Another recall of list A with immediate and delayed recall of 20 minutes later.
Executive Function Mazes (WISC-R)	This test consists of nine paper-and-pencil mazes of increasing difficulty. Participants are instructed to find the way out without crossing any lines. The task is to be completed within a designated time limit and scored in terms of errors.

Statistical analysis

Data was analyzed using SPSS version 22 (IBM). The relations between test scores were tested with Mann – Whitney U test and P<0.05 was considered statistically significant.

RESULTS

Table 3 shows the means and standard deviations of the two groups on the performance of their intelligence using the Wechsler Intelligence Scale for Children – Fourth (India Edition). Significant overall group differences were obtained for full-scale IQ and verbal IQ. Children in the study group displayed lower full-scale and verbal IQ relative to control group.

The neuropsychological evaluation findings of the two groups are presented in Table 4.

Table 4 displays means and standard deviations for the 12 neurocognitive tests. As Table 4 shows, compared with controls, participants in the study group performed significantly more poorly on verbal comprehension, working memory, processing speed (symbol search; P=0.017) and verbal working memory (RAVLT; P=0.017 and P=0.035). There were no significant differences between study and control groups in terms of perceptual reasoning (as assessed with block design, picture concepts and matrix reasoning) and executive functions as assessed with maze test.

Table 3: Comparison of intelligence quotient between the two groups.

Subtest variables	Study group (n=15)	Controls (n=15)	Comparison
General Intelligence			
Full Scale IQ	83.87 ± 11.41	98.87 ± 10.78	P=0.002; MU*=37.00
Verbal comprehension	81.87 ± 7.25	96.53 ± 8.98	P=0.000; MU=22.50
Perceptual reasoning	95.00 ± 9.33	97.40 ± 11.54	P=0.163; MU=79.00
Working memory	77.40 ± 18.39	98.00 ± 15.98	P=0.005; MU=45.00
Processing speed	96.07 ± 10.24	107.93 ± 13.39	P=0.013; MU=53.00

*MU – Test statistic of the Mann Whitney U test

Table 4: Comparison of study group with healthy controls according to cognitive functions.

Neurocognitive domain (Tests used)	Study group (n=15)	Controls (n=15)	Comparison
Verbal Comprehension			
Similarities	8.13 ± 1.69	9.53 ± 1.77	P=0.049; MU =66.00
Vocabulary	5.93 ± 1.94	9.67 ± 2.23	P=0.000; MU=26.00

Comprehension	6.20 ± 2.04	8.93 ± 2.19	P=0.002; MU=37.50
Perceptual Reasoning			
Block design	8.93 ± 2.79	10.47 ± 3.74	P=0.260; MU=85.50
Picture concepts	9.20 ± 1.86	8.60 ± 2.23	P=0.556; MU=98.50
Matrix reasoning	9.40 ± 2.10	9.67 ± 2.44	P=0.720; MU=104.50
Working Memory			
Digit span	6.07 ± 3.71	9.47 ± 3.93	P=0.021; MU=57.00
Letter Number Sequencing	6.53 ± 2.78	9.87 ± 1.10	P=0.002; MU=37.50
Processing speed			
Coding	10.27 ± 1.87	11.80 ± 3.19	P=0.063; MU=68.00
Symbol search	8.40 ± 2.41	10.80 ± 2.65	P=0.017; MU=55.50
Verbal Working Memory (RAVLT)			
Total learning scores	47.20 ± 8.76	52.80 ± 7.46	P=0.068; MU=68.50
Immediate recall scores	10.40 ± 2.10	12.33 ± 1.80	P=0.017; MU =55.50
Delayed recall scores	10.87 ± 2.42	12.80 ± 2.08	P=0.035; MU=62.00
Executive Function Mazes (WISC – R)	11.07 ± 2.63	11.20 ± 2.11	P=0.851; MU=108.00

DISCUSSION

Cognitive deficits are part and parcel of schizophrenia. The high-risk relatives of the patients may also exhibit these deficits, which suggest that there is a genetic base. Davalos et al. [23] studied the cognitive functions in high-risk children aged 6-15 years and concluded that they manifest cognitive impairments in the domains of verbal- linguistic ability, working memory and response inhibition. In the present study, offspring at high-risk for schizophrenia, aged 10-16 years, demonstrated an overall difference in neurocognitive functioning compared to healthy controls. Deficits in intelligence, verbal comprehension, working memory, verbal working memory and processing speed were observed in the high-risk (index) group.

Individuals who later develop schizophrenia manifest lower childhood IQ relative to the control group, [24,25] and they were more likely to have receptive language impairments [26]. Our study also noted lower than average IQ scores [full scale and verbal] in the children in the index group. Lower childhood IQ may be a marker of neuroanatomical deficits that increase the vulnerability to certain mental disorders [27]. This might be because individuals with lower childhood IQs have less ability to cope with stressful life events, which makes them potentially vulnerable to develop various psychiatric disorders [28]. Also, children with parents who have psychosis are more likely to be exposed to stress, including financial and social challenges and stigma than the healthy peers [29]. Optimal development is impeded in these children as they are exposed to problematic parenting and face issues with the parent-child relationship [30].

In the present study, poor verbal comprehension has been identified in the children in the index group with a first-degree relative with schizophrenia. Similar findings have been reported by other researchers [13,31]. These specific cognitive impairments may represent generalized markers for later psychosis that span genetic (individuals with a first-degree affected relative) and clinical high-risk groups. The poor verbal abilities observed in the index group are in accordance with findings of a previous study which observed that verbal abilities may be one of the first cognitive processes to show impairment in children who subsequently develop schizophrenia [32].

Our study noted that offspring at-risk for schizophrenia have shown verbal working memory impairment. These findings have been reported in other studies, such as those by Addington & Barbato [31] and Fusar Poli et al. [33]. Moreover, verbal working memory deficits predict conversion to later psychosis among young offspring of individuals with schizophrenia [34-36]. Previous studies have observed verbal working memory impairments among individuals with a family history of schizophrenia [37] or the ultra-high risk group only [38]. The findings of the present study and those of previous reviews of cognitive impairment among first-degree family members of affected individuals aged 30 years and younger [13] indicate that

poor verbal working memory may represent a possible genetic vulnerability indicator for schizophrenia.

Further, the children in the index group performed significantly less well on two working memory tasks (Digit Span Test and Letter Number Sequencing Test) than the control group. The tasks used in this study that elicited impairment in the index group are the ones that meet the D'Esposito et al. [39] criteria for maintenance-plus tasks, thus suggesting dorsolateral prefrontal cortex (DLPFC) involvement. Developmental dysmaturation of the prefrontal cortex associated with vulnerability to the illness [40] appears to characterize working memory deficits in this population. [41]. The maintenance and manipulation components associated with working memory are largely associated with dorsal prefrontal processing [42]. It was reported that, in healthy subjects, increased proficiency in working memory is reflected in greater dorsal prefrontal engagement and this pattern is absent in schizophrenic patients [43,44].

In our study, offspring at-risk for schizophrenia have shown deficits in the speed of working memory relative to normal comparison subjects. Deficits in information processing have been reported by earlier researchers in clinically unaffected relatives of schizophrenia [45]. In fact, the information processing literature supports the hypothesis that the schizophrenia diathesis carries with it a vulnerability to attentional and information-processing dysfunction, supporting the existence of trait-linked deficits in schizophrenic patients [46-48]. Using the digit-symbol subtest, it was found that processing speed was the most severely impaired function in chronic schizophrenia patients [49]. In the current study also, children in the index group have shown poor performance in the symbol search subtest. The poor performance of children in the index group on symbol search subtest appears to reflect their greater deficit in perceptual motor speed and speed of working memory. Similar findings were observed in high-risk adolescents [50] and adult patients with schizophrenia [51]. Contrary to the hypothesis, the current study found no significant group differences on perceptual reasoning domain (as assessed by block design, picture concepts and matrix reasoning subtests) as well as on executive functions using the maze test. In perceptual reasoning, the children in the index group have shown normal performance in perceptual and visuospatial abilities. Similar findings have been reported by Snitz et al. [52] in a study involving unaffected first-degree relatives of schizophrenia patients. The offspring at-risk for schizophrenia in our study have shown no deficits in executive functions also indicating that their planning abilities are well preserved. The above findings are in accordance with the findings of Cannon et al. [53] who reported that study members with subsequent diagnosis of schizophrenia form disorder performed well in the maze test from Wechsler Intelligence Scale for Children.

The robustness of this study is limited by the small sample size. Despite limited statistical power, the results indicate that children at-risk for schizophrenia present with poor neurocognitive performance than matched peers. As neurocognitive dysfunction is observed at illness onset and during prodrome phase of schizophrenia, this study lends support to the proposition that at-risk children may experience elevated risk of developing schizophrenia. 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 endophenocognitype concept and serve as new targets for early interventions.

CONCLUSION

In the present study, the offspring at high-risk for schizophrenia displayed significantly lower full-scale IQ with poor performance in cognitive functions, such as verbal comprehension, working memory, verbal working memory and processing speed. However, no group differences were detected either on perceptual reasoning or executive functions.

REFERENCES

1. Bleuler E. Dementia praecox or the group of schizophrenias. International Universities Press, New York, USA, 1950.
2. Bilder RM, Lipschutz LB, Reiter G, Geisler SH, Mayerhoff DI, Lieberman JA. Intellectual deficits in first-episode schizophrenia: Evidence for progressive deterioration. Schizophr Bull. 1992;18:437-448.
3. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafniack P, et al. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry. 1994;51:124-131.
4. Censits DM, Ragland JD, Gur RC, Gur RE. Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: A longitudinal study. Schizophr Res. 1997;24:289-298.
5. Riley EM, McGovern D, Mockler D, Doku V, O'Cealleigh S, Fannon DG, et al. Neuropsychological functioning in first-episode psychosis: Evidence of specific deficits. Schizophr Res. 1999;43:47-55.
6. Kallmann FJ, Falek A, Hurzeler M, Erlenmeyer-Kimling J. The developmental aspects of children with two schizophrenic parents. In: Solomon P, Glueck BD, eds. Recent research on schizophrenia, Psychiatric Research Report, American Psychiatric Association, 1964;19:216-263.
7. Heston LL. Psychiatric disorders in foster home reared children of schizophrenic mothers. Br J Psychiatry. 1966;112:819-826.
8. Kety SS, Rosenthal D, Wender PH. Mental illness in the biological and adoptive families of schizophrenics. Am J Psychiatry. 1971;3:302-306.
9. Erlenmeyer-Kimling L, Hilldoff Adamo UH, Rock D, Roberts SA, Bassett AS, Squires-Wheeler E, et al. The New York High-Risk Project. Prevalence and comorbidity of axis 1 disorders in offspring of schizophrenic parents at 25-year follow-up. Arch Gen Psychiatry. 1997;54:1096-1102.
10. Seidman LJ, Giuliano CW, Smith WS, Stone SJ, Glatt E, Meyer SV, et al. Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: Results from the Harvard and Hillside adolescent high risk studies. Schizophr Bull. 2006;32:507-524.
11. Keshavan MS. Development, disease and degeneration in schizophrenia: A unitary pathophysiological model. J Psychiatry Res. 1999;33:513-521.

12. Stone WS, Faraone SV, Tsuang MT. Early clinical intervention and prevention of schizophrenia. Humana Press, Totowa, NJ, USA, 2004.
13. 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;18:1-39.
14. Erlenmeyer-Kimling L. Neurobehavioural deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. Am J Med Genet. 2000;97:65-71.
15. Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lonnqvist JK. Childhood developmental abnormalities in schizophrenia: Evidence from high-risk studies. Schizophr Res. 2003;60:239-258.
16. Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, et al. Attention, memory and motor skills as childhood predictors of schizophrenia-related psychoses: The New York High-Risk Project. Am J Psychiatry. 2000;157:1416-1422.
17. Sorensen HJ, Mortensen EL, Parnas J, Mednick SA. Premorbid neurocognitive functioning in schizophrenia spectrum disorder. Schizophr Bull 2006;32:578-583.
18. Seidman LJ, Cherkerzian S, Goldstein JM, Agnew-Blais J, Tsuang MT, Buka SL. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. Psychol Med 2013;43:119-131.
19. Goldberg D, Williams P. A User's Guide to the General Health Questionnaire. NFER-Nelson, 1988.
20. Wechsler D. Wechsler Intelligence Scale for Children-Fourth [India Edition). NCS Pearson; India: 2012.
21. Schmidt M. Rey Auditory Verbal Learning Test: A Handbook. Western Psychological Services, USA: 2004.
22. Wechsler D. Wechsler Intelligence Scale for Children-Revised. The Psychological Corporation, USA: 1974.
23. Devalos DB, Compagnon N, Heinlein S, Ross RG. Neuropsychological deficits in children associated with increased familial risk for schizophrenia. Schizophr Res. 2004;67:123-130.
24. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: A meta-analytic review. Am J Psychiatry. 2008;165:579-587.
25. Dickson H, Laurens KR, Cullen AE, Hodgins S. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. Psychol Med. 2012;42:743-755.
26. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, et al. Evidence for early-childhood, Pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry. 2002;59:449-456.
27. Gray JR, Thompson PM. Neurology of intelligence: Science and ethics. Nat Rev Neurosci. 2004;5:471-482.
28. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. Psycho Bull. 2006;132:477-493.
29. Chernomas WM, Clarke DE, Chisholm FA. Perspectives of women living with schizophrenia. Psychiatr Serv. 2000;51:1517-1521.
30. Wan MW, Salmon MP, Riordan DM, Appleby L, Webb R, Abel KM. What predicts poor mother-infant interaction in schizophrenia? Psychol Med. 2007;37:537-546.
31. Addington J, Barbato M. The role of cognitive functioning in the outcome of those at clinical high risk for developing psychosis. Epidemiol Psychiatr Sci 2012;21:335-342.
32. Reichenberg A, Caspi A, Harrington BS, Houts R, Keefe RSE, Murray RM, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am J Psychiatry. 2010;167:160-169.
33. Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes OD, et al. Cognitive functioning in prodromal psychosis: A meta-analysis. Arch Gen Psychiatry. 2012;69:562-571.
34. Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, et al. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry. 2005;162:71-88.
35. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, et al. Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry. 2006;59:863-871.
36. Simon AE, Gradel M, Cattapan-Ludewig K, Gruber K, Ballinari P, Roth B, et al. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. Schizophr Res. 2012;142:108-115.
37. Myles-Worsley M, Ord M, Ngiralmau H, Weaver S, Blalles F, Faraone SV. The Palau early psychosis study: neurocognitive functioning in high-risk adolescents. Schizophr Res. 2007; 89:299-307.
38. Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, et al. Neuropsychology of the prodrome to psychosis in the napls consortium: relationship to family history and conversion to psychosis. Arch Gen Psychiatry. 2010;67:578-588.
39. D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res. 1998;7:1-13.
40. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci. 2002;25:409-432.
41. Diwadkar V, Sweeney J, Boarts D, Montrose D, Keshavan M. Oculomotor delayed response abnormalities in young offspring and siblings at risk for schizophrenia. CNS Spectr. 2001;6:899-903.
42. Wager TD, Smith EE. Neuroimaging studies of working memory: A meta-analysis. Cogn Affect Behav Neurosci. 2003;3:255-274.
43. Schneider F, Habel U, Reske M, Kellermann T, Stocker T, Shah NJ, et al. Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study. Schizophr Res. 2007;89:198-210.
44. Tan HY, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, et al. Dysfunctional prefrontal regional specialization and compensation in schizophrenia. Am J Psychiatry. 2006;163:1969-1977.
45. Cornblatt BA, Erlenmeyer-Kimling L. Global attentional deviance as a marker of risk for schizophrenia: Specificity and predictive validity. J Abnorm Psychol. 1985;94:470-486.
46. Cadenhead K, Geyer M, Braff D. Impaired startle prepulse inhibition and habituation in schizotypal personality disordered patients. Am J Psychiatry. 1993;150:1862-1867.
47. Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ et al. Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Arch Gen Psychiatry. 1994;51:651-666.
48. Freedman LR, Rock D, Roberts SA, Cornblatt BA, Erlengmeyer Kimling L. The New York high – risk project: Attention, anhedonia and social outcome. Schizophr Res. 1998;30:1-9.
49. Dickinson D, Ramsey MB, Gold JM. Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry. 2007;64:532-542.

50. Cornblatt BA, Malhotra AK. Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. Am J Med Genet. 2001;105:11-15.
51. Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, et al. The inheritance of neuropsychological dysfunction in twins discordant of schizophrenia. Am J Hum Genet. 2000; 67:369-82.
52. Snitz BE, Macdonald AW, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. Schizophr Bull. 2006;32:179-194.
53. Cannon M, Moffitt TE, Caspi A, Murray RM, Harrington N, Poulton R. Neuropsychological performance at the age of 13 years and adult schizophreniform disorder: A prospective birth cohort study. BJP. 2006;189:463-464.