Verbal Memory and Working Memory Impairment in Healthy Siblings of Patients with Schizophrenia

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Article info:
Received: 02 May 2014
Accepted: 18 Oct. 2014

Keywords:
Schizophrenia, Endophenotypes, Verbal memory, Working memory

ABSTRACT

Objective: This study aimed to investigate the verbal memory and working memory impairment in healthy siblings of patients with schizophrenia.

Methods: The purpose of this study was to compare cognitive deficits in siblings of the patients with schizophrenia and control group. A total of 35 unaffected siblings of patients with schizophrenia were selected from the relatives of the patients referred to Shoosh clinic and 35 matched healthy controls were selected from the staff of the same clinic. This sample was chosen accessible. Then, the subjects completed Verbal Paired Association Test, Logical Memory Test, Wechsler Memory Scale-Revised, and N-back working memory Test. Data were analyzed by Chi-square, t test, and Multivariate analyses of variance (MANOVA). Statistical analysis was performed using SPSS version 20.

Results: The results indicated that there were significant differences between the siblings of the patients with schizophrenia and control group with respect to the cognitive functions ($P<0.05$). Siblings of the patients with schizophrenia performed low in both verbal and working memory compared to the control group.

Conclusion: In this study, our results supported this hypothesis that verbal and working memory impairment could be considered endophenotype of schizophrenia.

1. Introduction

Schizophrenia is a chronic and genetically complex disorder and its pathophysiology is poorly understood. Neurocognitive impairments have been recognized as one of the core features of schizophrenia in the majority of patients (Reichenberg et al., 2009). These impairments seem to be stable along the course of the disease and manifest in multiple neuropsychological domains (Galderisi et al., 2009; Sánchez-Torres et al., 2013). Siblings of individuals with schizophrenia have an 8 to10 fold higher risk of developing the disorder compared to the general population (Gottesman & Gould, 2003). In addition, schizophrenia patients and their healthy siblings share similar genetic backgrounds and early-life environments, as schizophrenia has been recognized as a neurodevelopmental disorder (Insel, 2010; Rapoport, Addington, Frangou, & Psych, 2005). Making it likely that different sets of genetic or early environmental factors influence the etiology of schizophrenia in different populations and they could alter the size and shape of developing neural structures.

Some characteristics, which are heritable and shared with the relatives of the patients, could be considered endophenotypes. In recent years, endophenotype (intermediate phenotype) approaches have been adopted to study complex neuropsychiatric disorders (Braff, Freedman, Schork, & Gottesman, 2007). There are 5 criteria for identifying credible endophenotypes in psychiatry: 1) the endophenotype should be associated with the

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illness in the population; 2) the endophenotype should be heritable; 3) the endophenotype should be primarily state independent; 4) within families, the endophenotype and the illness should co-segregate; and 5) the endophenotype should be found in unaffected family members at a higher rate than in general population (Chan & Gottesman, 2008). Structural and functional neuroimaging, neurophysiological, neuromotor, and neurocognitive abnormalities have been found as possible endophenotypes of schizophrenia (Massuda et al., 2013).

Numerous studies have demonstrated that patients with schizophrenia have significant impairments across several cognitive domains, especially in working memory, attention, and executive functions (Smith, Eich, Cebenoyan, & Malapani, 2011). Although the criteria for the diagnosis of schizophrenia do not currently include symptoms of cognitive impairment, several symptoms of frontal lobe functioning are incorporated in the negative symptoms, including apathy, failure of abstract reasoning, difficulty in making decisions, and set-shifting. Furthermore, cognitive dysfunction, including deficits in working memory, verbal memory, and executive functions are often present in first-degree relatives of patients with schizophrenia, and have fueled the scientific proposal that cognitive pathology may serve as an endophenotype for this disorder.

The presence of cognitive deficits in first-degree relatives of schizophrenia patients likely occurs at a higher rate than in the general population (Torniainen et al., 2011; Trandafir, Méary, Schürhoff, Leboyer, & Szöke, 2006). Heritability in the general population is an important criterion for a disease-related endophenotype, and there is much evidence to support the heritability of neurocognition. Heritability for working memory has been estimated at 33%-64% (Greenwood et al., 2007; Kremen et al., 2007). Recent results from a multi-site study of neurocognition, the consortium on the genetics of schizophrenia, have added support to the hypothesis that neurocognition is a schizophrenia-related endophenotype (Allen, Griss, Folley, Hawkins, & Pearlson, 2009), and suggested that both genetic and environmental factors can influence neurocognitive performance in patients with schizophrenia and their relatives (Greenwood et al., 2007). Therefore, as researchers delineate the associations between specific cognitive deficits and their behavioral effects among first-degree relatives of schizophrenia patients, the issue of cognitive dysfunction as a heritable endophenotype in schizophrenia is supported more.

By studying verbal memory and working memory in relatives of schizophrenia patients, we can identify whether verbal memory (VM) and working memory (WM) are endophenotypic markers of schizophrenia and lead to further genetic studies. In addition, we can provide cognitive remediation therapy to improve the VM and WM difficulties in this high risk group. The present study, therefore, aimed to explore the VM and WM performance in these relatives. We hypothesized that the relatives would significantly perform more poorly compared to the control group.

2. Methods

This was a cross-sectional comparative and Expos facto study. All participants were informed about the procedure and signed the informed consent prior to participation. A total of 35 unaffected siblings of patients and 35 healthy controls matched by age and years of education were enrolled in the study. This sample was chosen accessible. The sample size was determined according to the formula provided for the comparison groups sample size (Rafiey, 2008). Siblings of the patients were recruited from Shoosh clinic in Tehran, Iran and healthy controls were selected from the clinic staff. The inclusion criteria for the siblings of the patients consisted of age between 18 and 60 years and having a sibling with confirmed diagnosis of schizophrenia based on the Statistical Manual of Mental Disorders Fourth Edition (DSM-IV-TR). The control group consisted of healthy volunteers who had neither current or previous history, nor first-degree family history of a major psychiatric disorder, including dementia or mental retardation. All the subjects were assessed by the Structured Clinical Interview for DSM-IV-TR. Exclusion criteria for both of the groups were history or presence of psychiatric and neurological disease or mental retardation, actual use or abuse of drugs, and brain tumor.

Verbal Paired Association Test: Verbal paired association is one of the Wechsler memory scale-revised test containing 8 pairs of words. After reading these words, the tester reads out the first word of each pair and participants should recall the second word. The test can be replicated up to 6 times. After the 8 pairs were recalled correctly at each step, the test has been finished. The maximum score is 24. Reliability subtests have been demonstrated (range 0.74 to 0.93) (Wechsler, 1987).

Logical Memory Test: Logical memory test is one of the Wechsler memory scale-revised tests containing two story synopses. They are read out to the participants and then the participants recall the stories by heart. The tester

Table 1. Demographic characteristics of the groups.

		Healthy controls (n=35)		Siblings (n=35)		P-value
		Mean(SD)	Frequency(percent)	Mean(SD)	Frequency(percent)	
Gender	Male		17(48.6)		18(51.4)	0.81*
	Female		18(51.4)		17(48.6)	
Education(year)	elementary		7(20)		5(14.3)	0.906*
	secondary		7(20)		7(20)	
	diploma		16(45.7)		18(51.4)	
	After diploma		5(14.3)		5(14.3)	
Age(year)		39.02(10.12)		39.31(9.99)		0.978**

* chi-square
** t test

reads out each story and asks the participant to listen to the story. Then the participant is asked to recount the story by heart. Any word would get a score if it was recited correctly. The highest score for each story is 25. Reliability has been demonstrated (0.89) (Orangi, Atefvahid, & Ashayeri, 2002).

N-Back Working Memory Test: The n-back working memory test was used to measure working memory. In this study, the computerized version of the 1-back task was used in which 120 digits from 1 through 9 appear on the center of the screen in a semi-random manner within an interval of 2 seconds. If any digit is the same as the previous one, the participant is supposed to press the right indicator key on the computer and if they are different, the left indicator key. Each digit remains on the screen for 1500 ms. What presented at the end of the task as the result of the participants performance, is actually the total correct answers and the reaction time. This measure has demonstrated good reliability and validity (range 0.051 to 0.076) (Ghadiri, Jazayeri, Ashyeri, & Ghazi Tabatabaei, 2007; Jaeggi, Buschkuehl, Perrig, & Meier, 2010).

Statistical analysis was performed using SPSS 20. Demographic characteristics were analyzed using Chi-square and t test. In order to analyze the data, we used descriptive statistics (mean and standard deviation). Multivariate Analyses of Variance (MANOVA) was used to examine the group difference in verbal memory and working memory. $P<0.05$ was considered significant.

3. Results

Demographic characteristics were analyzed using chi-square and t test. Healthy controls and siblings were not

Table 2. Mean and standard deviation of scores.

Variable	Group	Mean	SD
Verbal memory			
Immediate recall	Siblings	53.42	10.10
	Healthy controls	59.28	5.61
Delayed recall	Siblings	50.05	9.40
	Healthy controls	57.62	5.65
Working memory			
Correct responses	Siblings	87.02	23.11
	Healthy controls	102.11	13.54
Reaction time (ms)	Siblings	671.31	144.24
	Healthy controls	595.71	148.79

different in age, gender, and years of education. Demographic information of the participants is shown in Table 1.

Table 2 shows mean and standard deviation of verbal memory (immediate recall, delayed recall), and working memory (correct responses, reaction time) scores. As Table 2 shows, the average number of correct answers of immediate verbal memory and delayed verbal memory for the healthy control group (in the Wechsler scale) is higher compared to the other group. As in n-back test, the average number of correct answers for the healthy control group is higher compared to the other group.

T^2 Hotelling's trace was used to investigate the significant difference between immediate recall memory, delayed recall memory, and working memory in both groups of siblings and healthy control in Wechsler memory scale and n-back test. Yet, before doing that, it was necessary to investigate its important assumptions. One of the assumptions of multivariate analysis of variance was the homogeneity of covariance matrices. Based on the Boxes Test results, which was statistically significant, the observed covariance matrices of the variables were not equal for different levels of independent variables, including siblings and healthy control groups ($P<0.001$, Box's M=36.19). Likewise, the results of Bartlett's test were statistically significant (Chi-square=865.82, $P<0.001$), which suggested sufficient correlation between the dependent variables for further analysis.

Levene's test was used to check the assumption of equality of error variances. The results confirmed the assumption of equality of error variances for all scales except the number of correct answers in n-back test ($P>0.05$).

The results of multivariate analysis are presented in Table 3 Given the significance of Box's M test, which indicated the heterogeneity of variance-covariance matrices, Pillai's trace was reported.

The results of multivariate analysis of variance are shown in Table 3 too. The Pillai's trace value was equal to 0.354, which was significant at the error level smaller than 0.05 and F=8.899. Therefore, the difference between two groups of siblings and healthy controls was significant regarding immediate verbal memory, delayed verbal memory, and working memory. Similarly, partial eta squared value was equal to 0.354; i.e. 0.354 of the dependent variable variance was explained by sibling and healthy control groups.

In Table 4, the results of the multivariate analysis are presented according to the scales of the dependent variables. Based on the results of Table 4, there is a difference between the two group of siblings and healthy controls regarding immediate and delayed verbal memory i.e. the healthy controls had a higher number of correct answers and better performance. As in the n-back test, there is a difference between the two groups of siblings and healthy control in the number of correct answers and reaction time in such a way that the healthy controls had more correct answers in less reaction times compared to siblings group.

4. Discussion

The main purpose of this study was to examine working memory and verbal memory in the first-degree relatives of the patients with schizophrenia. The findings of the test measuring working memory (n-Back) showed that the siblings of patients with schizophrenia had lower performance compared to the healthy control group. These finding was consistent with the findings of previous studies indicative of poor performance of siblings of schizophrenic patients compared to controls on the working memory (Brahmbhatt, Haut, Csernansky, & Barch, 2006; Callicott et al., 2014; Conklin, Curtis, Calkins, & Iacono, 2005; de Leeuw, Kahn, Zandbelt, Widschwendter, & Vink, 2013; Whitfield-Gabrieli et al., 2009). Working memory is related to the activity of dopamine receptors in the prefrontal regions (de Leeuw et al., 2013). Reduction in size of these structures has been reported in patients with schizophrenia (Abi-Dargham

Table 3. Results of the multivariate analysis for verbal memory and working memory.

Effect	Value	F	Hypothesis df	Error df	Sig.	Partial Eta squared
Pillai's Trace	0.354	8.899	4	65	0.0001	0.354
Wilks's lambda	0.646	8.899	4	65	0.0001	0.354
Hotelling's Trace	0.548	8.899	4	65	0.0001	0.354
Roy's largest Root	0.548	8.899	4	65	0.0001	0.354

Table 4. Results of the multivariate analysis respectively dependent variables.

Variable	Type sum of squares	df	Mean square	F	Sig	Partial squared
Immediate recall (WMS-III)*	600.35	1	600.35	8.981	0.004	0.117
Delayed recall (WMS-III)	1003.21	1	1003.21	16.655	0.000	0.197
Correct responses (n-back)**	3982.629	1	3982.62	11.097	0.001	0.140
Reaction time (n-back)	100018.8	1	100018.8	4.658	0.034	0.064

*WMS-III, Wechsler adult memory Scale
** N- Back, N-back Working Memory Test

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et al., 2002). The presence of this memory dysfunction in their relatives helps study neural messengers because dysfunction in dopamine receptors of patients with schizophrenia have been reported. In this regard, the question arises as to whether patients' next of kin has abnormality of the nervous messengers and their receptors as well. Functional MRI studies consistently report a corticostriatal network subserving working memory processes, which includes dorsolateral prefrontal cortex, parietal cortex, and striatum (Murty et al., 2011). In unaffected siblings of the patients with schizophrenia, fMRI studies of these working memory shows hyperactivity in related areas compared to healthy controls (Guo et al., 2014). Anticevic, Repovs, and Barch (2011) suggest that siblings of the patients with schizophrenia show impairment in encoding and retrieving of information, but not in maintaining that information.

In investigation of verbal memory, findings of our study showed that siblings of the patients with schizophrenia were weaker in immediate verbal memory and delayed verbal memory compared to the control group. The same finding has been also reported in the literature (MacDonald, Thermenos, Barch, & Seidman, 2009; Mazhari, 2006; O'Driscoll et al., 2001; Simons & van Winkel, 2012; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Unschuld et al., 2014). Verbal memory is one of the most impaired cognitive domains in schizophrenia (Toulopoulouand & Murray, 2004). Functional imaging studies have reported alterations of functional connectivity in siblings of the patients with schizophrenia, especially in prefrontal cortex regions and parahippocampus (Unschuld et al., 2014; Woodward et al., 2009).

Genetic studies have associated polymorphisms with verbal memory deficit in patients with schizophrenia and their unaffected siblings (Jablensky et al., 2011; Simons & van Winkel, 2012). Furthermore, the verbal memory impairments of healthy relatives have been found to be associated with impaired encoding and manipulation of information, rather than increased rates of forgetting (Gold et al., 2000; Trandafir et al., 2006).

Important areas of memory function are hippocampus, amygdala, and frontal cortex. Accordingly, finding memory deficits in patients helps discover the exact brain structures connected with schizophrenia. Diagnosis of memory dysfunction in first-degree relatives who are genetically similar, not only helps clarify endophenotypes but also can somewhat determine the involved brain structures in the patients' relatives. O'Driscoll et al. (2001) observed that hippocampus and amygdala of relatives of the patients with schizophrenia have abnormalities in terms of volume.

Finally, cognitive deficits that are found in patients and their relatives can provide us with hypotheses about the brain regions involved in schizophrenia. The results of our study showed deficiencies in the domains of verbal memory and working memory among the relatives of the patients. These cognitive functions are associated with frontal and temporal lobe dysfunctions (Unschuld et al., 2014). The shared genetics of the patients with schizophrenia and their unaffected first-degree relatives may elucidate frontal lobe deficits in patients with schizophrenia and memory impairments in their relatives. This finding is consistent with the idea that certain cognitive deficiencies in relatives are caused by familial predisposition to schizophrenia and that these deficiencies might be putative endophenotypes for schizophrenia (Massuda et al., 2013).

This study had some limitations too. First, the sample size of the experimental group is small so more participants should be recruited in future studies. Second limitation was the implementation of tests in a clinic. Although efforts were made to test the relatives of the patients in a quiet atmosphere, presence in a hospital could disturb the participants' concentration. Moreover, it is possible that the n-Back test and WMS-III were limited to access working memory and verbal memory impairment in siblings of patients with schizophrenia. Other studies

with different neuropsychological tests are necessary to access sensible cognitive deficits. We suggest that future research apply a complete set of software packages of cognitive tests to achieve a better understanding of cognitive deficits and using this knowledge in patients' rehabilitation program. In addition, these findings suggest the significance of the study that address memory disorder and brain imaging of the patients and their first-degree relatives so as to determine the precise relationship between these disorders and organic changes in the brain. In spite of these limitations, the current study presented promising data on verbal and working memory performance of non-psychotic first-degree relatives of the patients with schizophrenia and suggests that VM and WM may be a potential endophenotype for schizophrenia.

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