A Preliminary Study of Memory Functions in Unaffected First-Degree Relatives of Schizophrenia

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Abstract. Schizophrenia is a neuropsychiatric disorder with etiologies caused by both genetic and environmental factors. However, very few studies have been done to examine the differential pattern of working memory dysfunction in individuals at risk for schizophrenia. The current study aimed to examine the different modalities of working memory performances in the first-degree relatives of patients with schizophrenia. Results showed that unaffected first-degree relatives characterized by high but not low schizotypal traits demonstrated significantly poorer performances in the verbal 2-back tasks, the immediate and delayed recall of logical memory compared to healthy controls. These preliminary findings suggest memory function impairment was more closely associated with schizotypal traits in unaffected first-degree relatives of schizophrenia patients.

Keywords: unaffected first-degree relatives, schizophrenia, memory, working memory.

1 Introduction

Schizophrenia is a neuropsychiatric disorder with etiologies caused by both genetic and environmental factors [1-4]. It is a spectrum of disorders covering both patients with psychotic symptoms fulfilling the diagnostic criteria for schizophrenia and those with mentally at-risk for psychoses [5, 6]. Substantial evidence has suggested that these at-risk individuals also demonstrate similar impairments with their psychotic probands, including attention, memory and executive functions [7-14].

Working memory has been considered to be one of the core features of cognitive impairments in schizophrenia [15-23]. This kind of impairment has been demonstrated in individuals with prodromal symptoms [24-26] and unaffected siblings of patients with schizophrenia [27-29]. Recent studies also suggest working memory is a potential endophenotype for schizophrenia [30-34].

Theoretically, Baddeley and Hitch (1974) have put forward a multi-componential concept of working memory comprising the central executive system, and two slave

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D.-S. Huang et al. (Eds.): ICIC 2013, LNAI 7996, pp. 11–19, 2013.

subsystems subserving for two independent route, namely the visuo-spatial sketchpad, and the phonological loop. Empirical findings from neuroimaging also showed that verbal task mainly evoked activation of left hemisphere [35-38] while spatial materials activated the right hemisphere of right-handers [39-43].

Recent meta-analysis of working memory in schizophrenia suggested that there may be differential effects of impairment of different modalities of working memory in this clinical group, with larger effect size demonstrated in spatial modalities than verbal modalities [18]. However, very few studies have been done to examine the differential pattern of working memory dysfunction in individuals at risk for schizophrenia. The current study aimed to examine the different modalities of working memory performances in the unaffected first-degree relatives of patients with schizophrenia. Given the similarity of neuropsychological dysfunctions demonstrated in biological relatives of patients with schizophrenia, it was hypothesized that the unaffected first-degree relatives of schizophrenia would demonstrate similar deficits in different components of working memory as compared to healthy controls.

2 Materials and Methods

2.1 Participants

Thirty-one unaffected first-degree relatives (including parents, siblings or off-springs) of patients with schizophrenia were recruited from the Mental Health Center, Shantou University, Shantou, Beijing Anding Hospital, Beijing Hui-long-guan Hospital, and the Institute of Mental Health of Peking University. All the relatives were interviewed by experienced psychiatrists to ascertain they did not suffer from any psychiatric illness, and had no history of neurological disorders and substance abuse. Thirty-one healthy volunteers were also recruited from the community. A semi-structured interview was conducted by a trained research assistant to ascertain that the volunteers had no family history of psychiatric and neurological disorders. All the participants were administered the Schizotypal Personality Questionnaire (SPQ) [44,45] to reflect the tendency of schizotypal personality trait. IQ was estimated by the short-form of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [46].

This current study was approved by the local ethical committees of the related hospitals stated above. Written consent was obtained from each participant before the administration of the test and questionnaires.

2.2 Tasks

The verbal 2-back [47] and the visuo-spatial 2-back [48] tasks were applied in the present study to capture the updating ability in visuo-spatial domain. The participants' correct response rate and correct response time were recorded. The Chinese version of the Letter–Number Span Test[49] was also applied to assess the participants' working memory function that the total items and the longest item were recorded. Moreover,

the Logical Memory and Visual Reproduction subtests from the Chinese version [50] of the Wechsler Memory Scale-Revised [51] were also administered to all the participants.

2.3 Data Analysis

Chi-square and one-way analysis of variance (ANOVA) were used to examine the differences of demographics between relatives of schizophrenia and healthy controls. Then multivariate analysis of covariance（MANCOVA）controlling for age and education was used to examine the main effect of factor group and potential interaction of independent factors. Subsequent one-way ANOVA was conducted to further examine the exact differences observed between relatives and controls. To explore the possible impact of schizotypal personality trait upon working memory in the unaffected first-degree relatives of schizophrenia, they were further classified into two subgroups according to the the median split of the SPQ score. Cohen's d values (low,0.2~0.3; medium,0.5; high,0.8 and above) and partial Eta-squared (η_p^2, low, 0.01; medium, 0.06; high, 0.14 and above) were calculated to estimate effect size and the extent of differences found between groups.

3 Results

Table 1 summarizes the demographic information of the participants. There were no significant differences found between the first-degree relatives of schizophrenia patients and healthy controls in age, number of years of education, gender proportion, and IQ estimates. Results from MANCOVA (Table 2) controlling for age and education showed that relatives of schizophrenia patients performed significantly poorer than the healthy controls in the correct response rate ($F_{(1,61)}=4.65$, $p=0.035$, $\eta_p^2=0.077$) and reaction time ($F_{(1,61)}=7.64$, $p=0.008$, $\eta_p^2=0.120$) in the verbal 2-back task. Moreover, the first-degree relatives also showed significantly poorer performances in both the immediate ($F_{(1,61)}=10.86$, $p=0.002$, $\eta_p^2=0.162$) and delayed ($F_{(1,61)}=8.75$, $p=0.005$, $\eta_p^2=0.135$) scores of logical memory than healthy controls. A check on the Cohen's d also indicated a range of medium to large effect sizes between the two (0.4~0.8).

Table 1. Demographics of relatives of schizophrenia and healthy controls

	HC (N = 31)		REL (N=31)		χ^2/t	*p*
	Mean	SD	Mean	SD		
Gender (M/F)	20/11		11/18		3.175	0.075
Age	38.55	10.14	42.90	12.17	-1.53	0.131
Education	11.45	2.61	11.94	2.78	-0.71	0.482
IQ _estimate	104.90	13.06	104.97	12.99	-0.02	0.985

Note: F=females, M=males; HC= healthy controls, REL= relatives of schizophrenia

Table 2. Differences over memory function between relatives of schizophrenia and healthy controls

	HC (n=31)	REL (n=31)	$F_{(1,61)}$	*P*	η_p^2	*Cohen's d*
	Mean (SD)	Mean (SD)				
Verbal 2-back Task						
Correct Response Rate	0.44 (0.2)	0.36 (0.17)	4.65	0.035	0.077	0.414
Mean Reaction Time	587.64 (218.23)	775.6 (240.53)	7.64	0.008	0.12	-0.818
Spatial 2-back Task						
Correct Response Rate	0.56 (0.17)	0.56 (0.22)	0.06	0.809	0.001	0.018
Mean Reaction Time	1048.2 (226.07)	1051.32 (206.07)	0.02	0.887	0	-0.014
Letter-Number Span						
Longest span passed	5.65 (1.2)	5.38 (1.18)	1.86	0.178	0.032	0.224
Total Scores	13.74 (3.4)	12.76 (2.89)	0.79	0.378	0.014	0.312
Logical Memory						
Immediate recall	13.03 (3.95)	10.14 (3.86)	10.86	0.002	0.162	0.741
Delayed recall	10.74 (4.08)	8.24 (3.5)	8.75	0.005	0.135	0.658
Visual Memory						
Immediate recall	22.45 (3.12)	23.07 (1.73)	1.07	0.305	0.019	0.245
Delayed recall	21.87 (3.95)	22.45 (2.5)	0.33	0.566	0.006	0.175

Note: HC for healthy controls, REL for relatives of schizophrenia

Table 3 shows the demographic summary of the subdivision of the first-degree relatives into the high-SPQ group (n=15) and low-SPQ group (n=17) with a median split of for the total SPQ (score of 17).

Table 3. Demographics of healthy controls and two subtypes of relatives of schizophrenia according to SPQ scores

	HC (N = 31)	High-SPQ REL (N=14)	Low-SPQ REL (N=17)	χ^2/F	*P*
	Mean (SD)	Mean (SD)	Mean (SD)		
Gender (M/F)	20/11	6/8	7/10	3.183	0.204
Age	38.55 (10.14)	41.53 (13.78)	44.57 (10.15)	1.44	0.244
Education	11.45 (2.61)	12.00 (2.32)	11.86 (3.35)	0.26	0.775
IQ _estimate	104.90 (13.06)	108.59 (11.25)	100.57 (13.99)	1.5	0.231

Note: HC for healthy controls, REL for relatives of schizophrenia

Results from MANCOVA (Table 4) showed that there were significant differences found between the reaction time ($F_{(2,61)}$=9.83, p<0.0001, η_p^2=0.263) of verbal 2-back, immediate as well as delayed logical memory ($F_{(2,61)}$=5.52 and 4.48; p=0.007 and 0.016, η_p^2=0.167 and 0.14). Further paired comparisons by Bonferroni correction found that the high-SPQ relatives performed significantly poorer than healthy controls over these variables. It was also noted that there was a trend of significant among the three groups in the correct response of the verbal 2-back ($F_{(2,61)}$=2.84, p=0.08, η_p^2=0.088), with a relatively large effect size observe between the high-SPQ relatives and controls (Cohen's d 0.798).

Table 4. Differences over memory function among healthy controls and two subtypes of relatives of schizophrenia

	HC	REL					*p*_value (Cohen's d) for paired comparisons		
	(N=31)	High-SPQ (N=14)	Low-SPQ (N=17)	$F_{(2,61)}$	*p*	η_p^2			
	Mean (SD)	Mean (SD)	Mean (SD)				HC vs. High-SPQ	HC vs. Low-SPQ	Low-SPQ vs. High-SPQ
Verbal 2-back Task									
Correct Response Rate	0.44 (0.2)	0.3 (0.15)	0.4 (0.17)	2.64	0.08	0.088	0.095 (0.798)	0.545 (0.175)	1 (0.667)
Mean Reaction Time	587.64 (218.23)	916.42 (178.12)	616.6 (238.5)	9.83	<0.001	0.263	<0.001 (1.651)	1 (0.127)	0.006 (1.424)
Spatial 2-back Task									
Correct Response Rate	0.56 (0.17)	0.5 (0.21)	0.6 (0.23)	0.38	0.687	0.014	1 (0.324)	1 (0.161)	1 (0.432)
Mean Reaction Time	1048.2 (226.07)	986.86 (230.48)	1084.01 (194.44)	0.79	0.459	0.028	1 (0.269)	1 (0.17)	0.651 (0.456)
LNS task									
Longest span passed	5.65 (1.2)	4.93 (0.92)	5.75 (1.24)	1.36	0.265	0.047	0.38 (0.672)	1 (0.086)	0.514 (0.754)
Total Scores	13.74 (3.4)	12 (3.09)	13.31 (2.57)	0.93	0.399	0.033	0.712 (0.537)	0.927 (0.143)	1 (0.462)
Logical Memory									
Immediate recall	13.03 (3.95)	9.14 (4.44)	10.88 (3.1)	5.52	0.007	0.167	0.014 (0.926)	0.055 (0.608)	1 (0.453)
Delayed recall	10.74 (4.08)	7.29 (3.29)	8.88 (3.59)	4.48	0.016	0.14	0.029 (0.932)	0.106 (0.485)	1 (0.461)
Visual Memory									
Immediate recall	22.45 (3.12)	22.93 (1.59)	23.06 (1.91)	0.64	0.531	0.023	0.823 (0.193)	1 (0.236)	1 (0.076)
Delayed recall	21.87 (3.95)	21.93 (2.73)	22.44 (2.94)	0.19	0.828	0.007	1 (0.017)	1 (0.163)	1 (0.179)

Note: HC for healthy controls, REL for relatives of schizophrenia

4 Discussion

This study showed that there were significant differences found between the unaffected first-degree relatives and healthy controls in the verbal 2-back task, and the immediate and delayed logical memory. These findings were particularly demonstrated in the relatives characterized by high schizotypal trait. The findings are in general consistent with the existing literature concerning the working memory

function in the unaffected first-degree relatives with schizophrenia [52-57]. Our current study did not show that the unaffected first-degree relatives of schizophrenia as a whole demonstrated significant spatial working memory deficits as compared to healthy controls. At a first glance, these findings seem to be inconsistent with the existing literature concerning the working memory deficits observed in unaffected first-degree relatives of schizophrenia [15]. However, we found that these kinds of deficits, especially the verbal working memory and semantic memory, were only demonstrated in the relatives associated with higher schizotypal traits. These findings highlight the importance of schizotypy contributing to the cognitive impairments in genetically at-risk individuals for schizophrenia.

The current study has a number of methodological limitations. First, we only recruited a relatively small sample size that might have limited the power of discriminating the true differences of memory functions found between the participants. Second, although we attempted to measure the different modalities of working memory function in our current study, we only adopted a narrow range of tests to capture the verbal and visuo-spatial modalities of working memory. These relatively simple behavioral tasks might not be sensitive enough to detect any differences demonstrated in at-risk individuals. Future study should recruit a larger sample size with a wider range of tests to cover different modalities of working and semantic memory functions in unaffected first-degree relatives. Target participants should extend to the patients with schizophrenia. Neuroimaging or electrophysiological paradigms may be more sensitive to detect such a subtle impairment in at-risk individuals for schizophrenia.

Acknowledgement. This work was supported a grant from the Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences. The authors would like to acknowledge the staff of the Mental Health Center, Shantou University, Beijing Anding Hospital, Beijing Hui-long-guan Hospital, and the Institute of Mental Health of Peking University for their recruitment of clinical cases.

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