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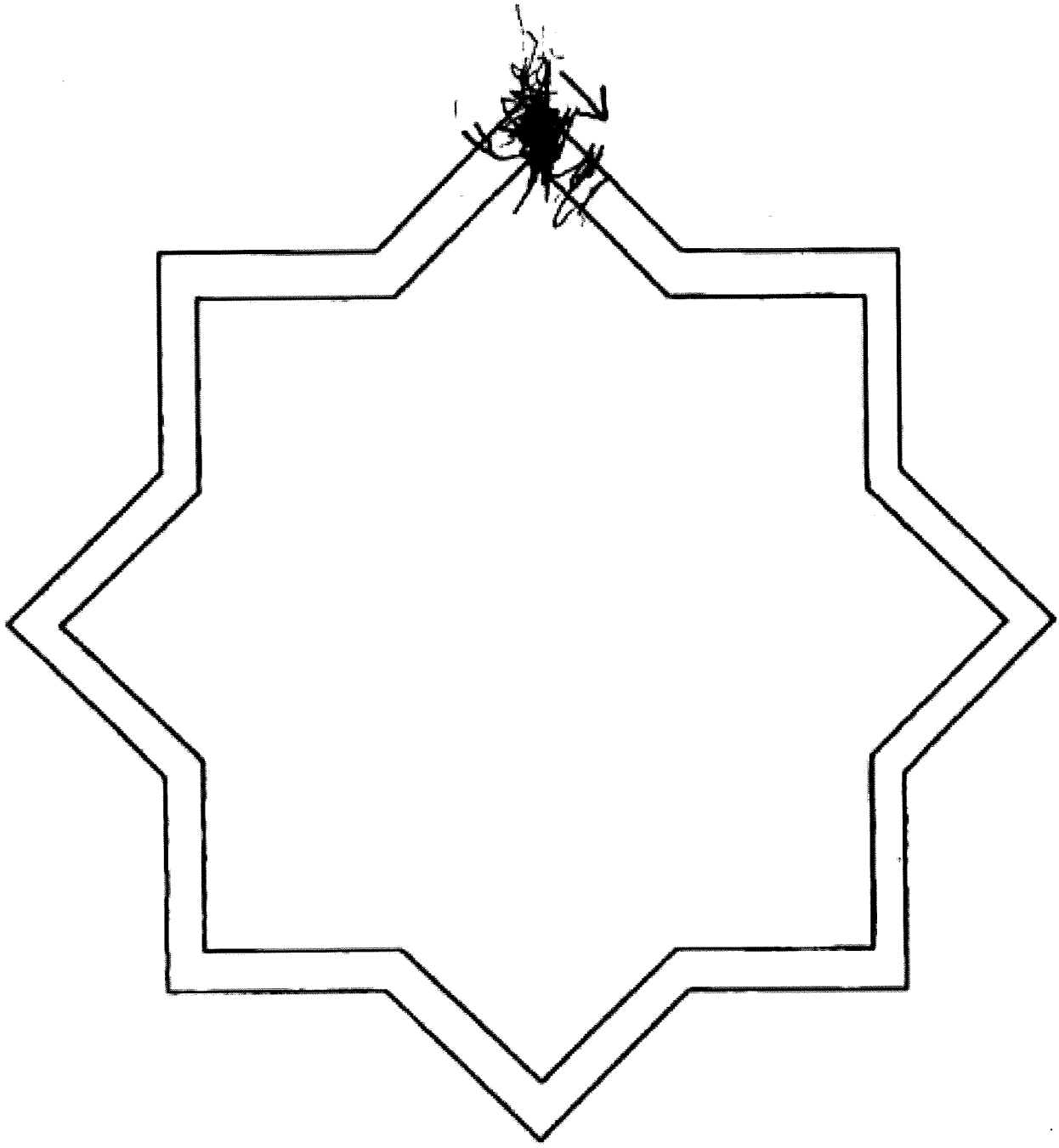

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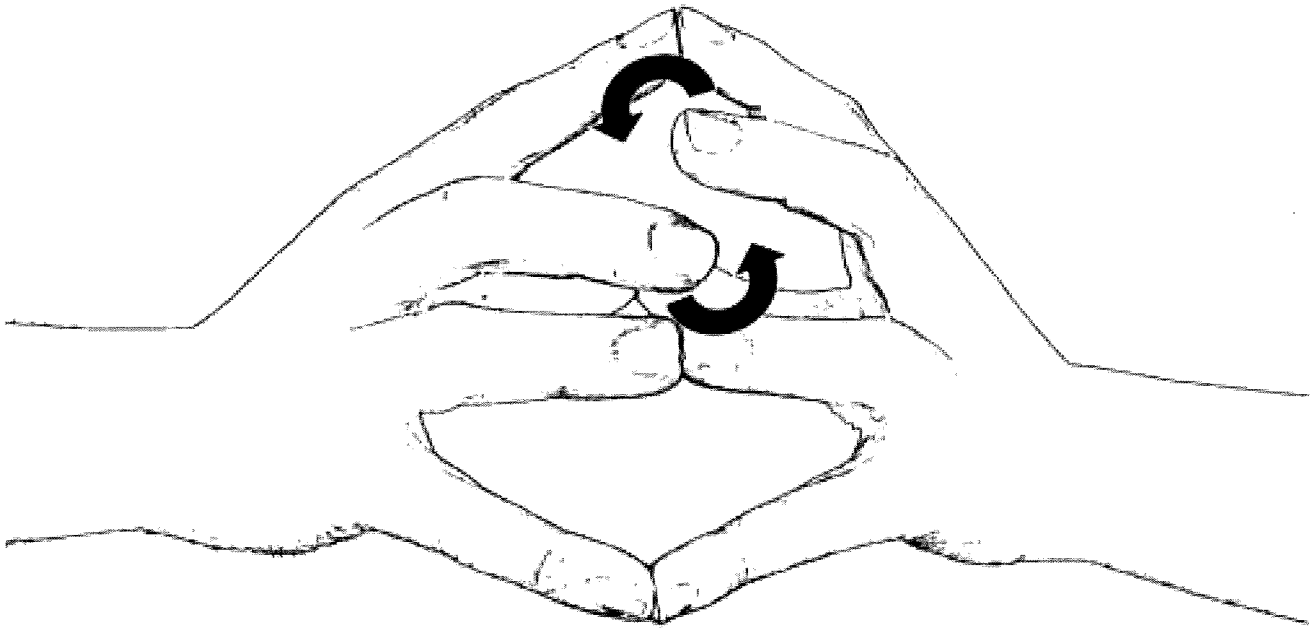


Table 1: Demographic characteristics of patients with schizophrenia and controls

			Control Group	Patient Group	Statistical value (*df*)	*P* value
n			49	27		
Age (years)						
Mean			37.4 ± 12.3	44.3 ± 12.7	t (74) = 2.1	0.039
Range			22–72	26–72		
Males/females			14/35	16/11	χ^2 (1) = 6.9	0.009
Handedness scale						
Right/Left			46/3	26/1		
Education level (years)						
Mean			16.6 ± 3.4	13.3 ± 2.4	t (73) = 4.4	0.00004
Range			12–24	9–18		
Family history +/–[a]				7/20		
Outpatient/inpatient				12/15		
Age of onset (years)						
Mean				23.4 ± 7.7		
Range				13–42		
Antipsychotic medication[b]						
Single dose	Typical	n = 7		782.2 ± 631.4		
	Atypical	n = 7		421.4 ± 196.1		
Dual dose	Typical	n = 13		529.1 ± 721.0		
	Atypical			702.6 ± 606.4		
Number of hospitalizations						
Mean			–	2.9 ± 2.7		
Range			–	0–11		
Hospitalized duration, months						
Mean			–	82.5 ± 150.8		
Range			–	0–624		

[a] Positive family history was defined as at least one schizophrenic individual within the second degree relatives.

[b] Chlorpromazine equivalent (mg/day).

Table 2: Comparisons in motor and cognitive tasks between patients with schizophrenia and controls

	Control group	Patient group	F [a]	P
A. Motor tasks				
Pegboard	67.0 ±11.6	132.3 ±65.6	19.9	3.0×10^{-5}
Normal Drawing	15.5 ±4.0	27.3 ±9.7	22.9	9.1×10^{-6}
Finger Movement	21.7 ±3.1	13.0 ±12.9	30.7	5.0×10^{-7}
B. Cognitive tasks				
WMS-R				
Verbal Memory	110.2 ±12.9	76.6 ±19.5	31.8	3.3×10^{-7}
Visual Memory	109.1 ±11.9	73.4 ±19.0	42.0	1.1×10^{-8}
General Memory	110.8 ±12.0	72.1 ±19.2	48.1	1.6×10^{-9}
Attention & Concentration	107.3 ±13.9	83.7 ±15.0	28.3	1.2×10^{-6}
Delayed Recall	112.0 ±10.1	69.2 ±18.5	79.0	4.3×10^{-13}
WAIS-R				
Verbal IQ	109.9 ±13.2	85.0 ±19.7	23.9	6.1×10^{-6}
Performance IQ	108.2 ±11.1	76.2 ±16.8	41.1	1.4×10^{-8}
Full scale IQ	109.9 ±11.4	79.3 ±18.9	40.6	1.7×10^{-8}
WCST [b]				
Categories Completed	4.1 ±1.98	2.1 ±2.17	4.0	0.051

[a] ANCOVA controlling for age, sex, and education years; $df_1 = 1$, $df_2 = 70$
[b] ANCOVA controlling for age, sex, and education years; $df_1 = 1$, $df_2 = 64$

Table 3: Comparisons in motor and cognitive tasks between patients with schizophrenia and controls matched for age and education level

	Controls	Patients	*df*	*t* value	*P* value
A Motor Tests					
Pegboard	67.8 ± 13.2	99.5 ± 31.3	16.1	3.4	< 0.01
Normal Drawing	16.9 ± 4.2	22.3 ± 7.7	18.7	2.2	< 0.05
Finger Movement	21.2 ± 3.1	14.8 ± 7.5	16.0	2.8	< 0.05
B Cognitive Tests					
WAIS-R					
Verbal Memory	107.8 ± 10.0	82.5 ± 21.9	16.9	3.8	< 0.01
Visual Memory	104.7 ± 15.4	80.6 ± 22.7	24.0	3.2	< 0.01
General Memory	107.8 ± 11.6	79.9 ± 21.0	24.0	4.2	< 0.001
Attention & Concentration	106.0 ± 13.6	83.1 ± 14.5	24.0	4.2	< 0.001
Delayed Recall	110.8 ± 10.4	74.0 ± 20.5	17.8	5.8	< 0.0001
WMS-R					
Verbal IQ	109.2 ± 12.6	90.2 ± 16.8	24.0	3.2	< 0.01
Performance IQ	105.9 ± 13.7	81.2 ± 16.2	24.0	4.2	< 0.001
Full Scale IQ	108.3 ± 12.2	84.9 ± 15.1	24.0	4.3	< 0.001
WCST					
Categories Completed	3.6 ± 2.3	2.5 ± 2.4	22.0	1.1	0.268

Table 4: Correlation of demographic and clinical characteristics with delayed recall and finger movement

	Delayed recall		Finger movement	
	r	*P*	*r*	*P*
Age	−0.05	0.81	−0.36	0.06
Education level (years)	0.51	0.01	0.05	0.80
Age of onset	0.17	0.39	0.03	0.90
Duration of illness	−0.18	0.38	−0.37	0.06
Antipsychotic medication [a]	−0.33	0.09	−0.04	0.84
Number of hospitalizations	−0.29	0.15	−0.25	0.20
Hospitalized duration	−0.00	1.00	−0.35	0.07

[a] Equivalent to chlorpromazine.

r = Pearson's product moment correlation coefficient.

Table 5: Relationship of categorical variables with delayed recall and finger movement

Categories (*n*)	Delayed Recall				Finger Movement			
	Mean	SD	*t* value [a]	*P* value	Mean	SD	*t* value [a]	*P* value
Male (16)	70.3	18.8	0.4	0.719	13.5	6.2	0.3	0.735
Female (11)	67.6	18.8			12.5	8.7		
Outpatient (12)	70.0	17.3	0.2	0.849	17.0	6.9	2.6	0.014
Inpatient (15)	68.6	19.9			9.	7.0		
Familial history + (7)	61.6	15.5	1.3	0.209	14.6	6.6	–0.6	0.559
Familial history − (20)	71.9	19.0			12.6	8.1		

[a] *t*-test for independent groups; $df = 2$

Table 6: Correlation of motor and cognitive functions with delayed recall and finger movement

	Delayed Recall		Finger Movement	
	r	*P*	*r*	*P*
Pegboard	− 0.27	0.18	− 0.51	0.01
Normal Drawing	− 0.44	0.02	− 0.32	0.10
Finger Movement	− 0.00	1.00	–	–
General Memory (WMS-R)	0.88	0.00	0.73	0.72
Attention and Concentration (WMS-R)	0.45	0.02	0.20	0.32
Delayed Recall (WMS-R)	–	–	− 0.00	1.00
Full Scale IQ (WAIS-R)	0.65	0.00	0.21	0.30
Completed Categories (WCST)	0.34	0.12	0.34	0.11

r = Pearson's product moment correlation coefficient

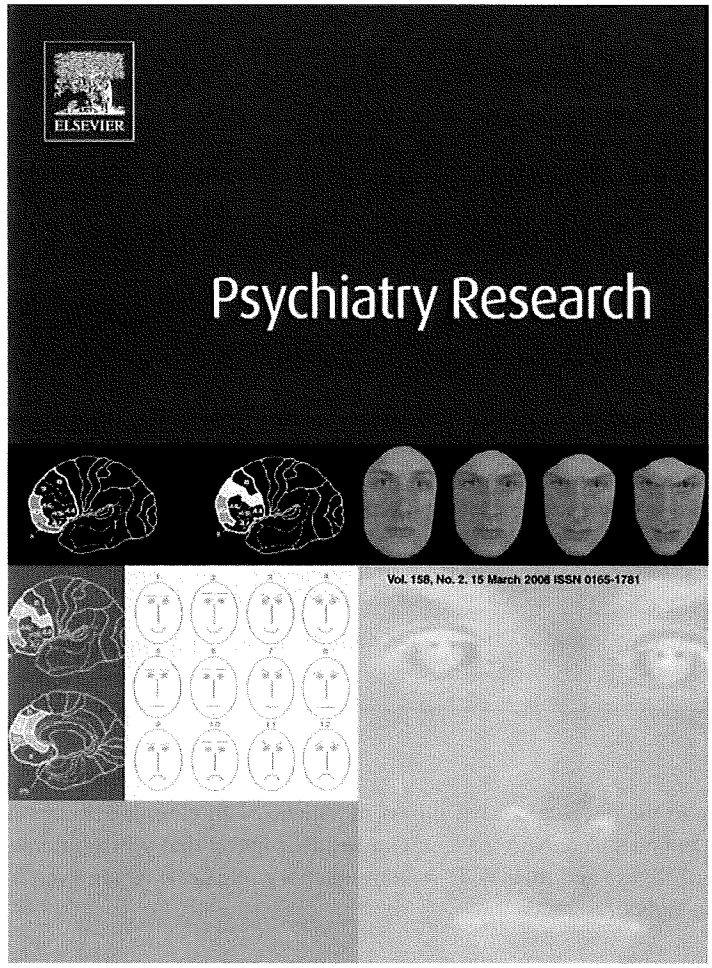
Figure Captions

Figure 1: An example of a drawing test result

This figure is a sample stimulus used in the normal drawing test and mirror drawing test. The figure was 10 cm in diameter and 3 mm in width. This upper, interrupted drawing was one patient's typical result of mirror drawing. He could not continue the drawing and gave up 2 min after starting the test.

Figure 2: Finger movement test

The subjects were asked to rotate each finger clockwise and counterclockwise with the remaining fingers extended and fixed. The figure presents the third-finger condition.



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Brief report

IQ decline and memory impairment in Japanese patients with chronic schizophrenia

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Abstract

The extent of IQ decline due to the development of illness in patients with chronic schizophrenia and the degree of memory impairment relative to such IQ decline still remain unclear. Our results suggest that schizophrenia patients experience marked IQ decline due to the development of illness and their wide-ranging memory impairments are even more severe than the IQ decline.

Keywords: Schizophrenia; IQ; Memory

1. Introduction

Cognitive impairment is a core feature of schizophrenia, with a great impact on patients' daily lives. Those therapies that have the potential to improve cognitive deficits of patients with schizophrenia, including cognitive remediation therapy (Medalia et al., 1998; Wykes et al., 2003), as well as the favorable effects of atypical antipsychotic drugs on cognition (Bilder et al., 2002; Harvey et al., 2006; Keefe et al., 2006), have been attracting increasing attention from researchers and clinicians. From this viewpoint, the precise delineation of cognitive impairments in schizophrenia patients is essential.

Intellectual deficits in patients with chronic schizophrenia have been reliably identified (Heinrichs and Zakzanis, 1998; Dickinson et al., 2004) with some ongoing debate as to "whether it is possible to be schizophrenic yet neuropsychologically normal" (Palmer et al., 1997; Kremen et al., 2000; Wilk et al., 2005); however, the extent of IQ decline caused by the development of schizophrenia remains unclear because the premorbid IQ scores of persons who later develop schizophrenia are lower than

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those of their peers (Fuller et al., 2002; Reichenberg et al., 2005). Impairments in memory, working memory, and attention in patients with schizophrenia are well documented (Aleman et al., 1999; Silver et al., 2003; Hori et al., 2006), but the relationship of these cognitive deficits to the possible decline in IQ has not been established. Here we assessed cognitive functions including intellectual and wide-ranging memory functioning in patients with chronic schizophrenia in relation to age- and premorbid IQ-matched healthy controls.

2. Materials and methods

Eighty-two patients who met the DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia participated in this study. All patients were receiving antipsychotic drugs at the National Center of Neurology and Psychiatry (NCNP), Musashi Hospital and were clinically stable at the time of the neuropsychological tests. Eighty-two age- and premorbid IQ-matched healthy volunteers were recruited from hospital staff and their associates and also from the community. Healthy participants were interviewed by a research psychiatrist using the Japanese version of the Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998) to confirm the absence of any psychiatric illnesses. A portion of the subjects were from our previous sample (Hori et al., 2006). Written informed consent was obtained from all subjects prior to their inclusion in the study. The study was approved by the ethics committee of the NCNP.

Premorbid IQ was estimated with the Japanese Adult Reading Test (JART, Matsuoka et al., 2002; 2006), a Japanese version of the National Adult Reading Test (NART, Nelson and Wilson, 1991). This test is considered to provide an estimate of premorbid IQ in schizophrenia patients (Uetsuki et al., 2006), which is consistent with the original NART (Crawford et al., 1992; O'Carroll et al., 1992). In this test, subjects were required to read out 100 idioms of Han-Chinese characters (Japanese kanji characters). JART-estimated premorbid IQ was calculated for each subject according to previous reports (Matsuoka et al., 2002, 2006). The full version of the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987; Sugishita, 2001) was administered to all participants. Outcome measures of the WMS-R were verbal memory, visual memory, delayed recall, auditory attention, visual attention, verbal working memory, and visual working memory. To precisely assess subjects' current intellectual function, a full version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R, Wechsler, 1981; Shinagawa et al., 1990) was administered, yielding age-corrected indices of verbal, performance, and full-scale IQs.

Schizophrenic symptoms were assessed by an experienced research psychiatrist in 46 of the 82 patients using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). Daily doses of antipsychotics and anticholinergic antiparkinsonian drugs were converted to chlorpromazine equivalents (CPZeq) and biperiden equivalents (BPDeq), respectively, using published guidelines (American Psychiatric Association, 1997; Inagaki et al., 1999; Minzenberg et al., 2004).

Results are reported as mean±standard deviation (S.D.). Demographic characteristics and cognitive test results were compared between groups. We used *t*-test or analysis of variance (ANOVA) to compare mean scores and the χ^2 tests to compare categorical variables. Analysis of covariance (ANCOVA) was used to compare means between groups, controlling for confounding variables. Statistical significance was set at two-tailed $P<0.05$. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Japan, Tokyo).

3. Results

Male/female ratios of patients and controls were 48/34 and 25/57, respectively, indicating that the patient group had a greater representation of males ($\chi^2(1)=13.06$, $P<0.001$). The mean ages of the patients and controls were 44.3±13.8 and 44.2±14.9, respectively ($t=0.05$, $df=162$, $P=0.96$). The mean years of education of the patients and controls were 13.4±2.5 and 14.1±2.2, respectively ($t=1.88$, $df=162$, $P=0.06$). The JART-predicted premorbid IQ scores of patients and controls were 102.2±11.6 and 102.3±7.4, respectively ($t=0.46$, $df=137.8$, $P=0.96$). Of the 82 patients, 56 were outpatients and 26 were inpatients. The mean age of illness onset was 24.7±8.8. Illness duration was 19.6±13.7 years, demonstrating that our patients were in the chronic phase of schizophrenia. CPZeq and BPDeq were 781.7±710.1 and 2.2±2.0, respectively. PANSS positive, negative, and total scores were 13.9±6.7, 19.1±7.1, and 62.1±17.9, respectively.

Verbal, performance, and full-scale IQs of patients with schizophrenia and healthy controls are presented in Supplementary Table 1. ANOVA showed that these three IQ indices in patients were significantly lower than those in controls (all $P<0.001$). The VIQ/PIQ ratios of patients and controls were 1.08±0.18 and 0.95±0.11, respectively ($F=22.5$, $df=1,160$, $P<0.001$, by ANCOVA with gender as a covariate). Scores of 13 subscales of the WMS-R in patients and controls are also shown in Supplementary Table 1. Patients performed significantly

more poorly than controls on all these cognitive domains (all $P<0.001$), except for auditory attention ($P=0.15$). Fig. 1(a) shows mean scores of the patients and controls on JART-estimated IQ, WAIS-R full-scale IQ, and the main three memory indices of the WMS-R. Dips of current IQ and all memory domains in patients are apparent, although the two groups are matched for the JART-estimated premorbid IQ.

To control for the current IQ and gender effects on these test results, ANCOVA was used with full-scale IQ and gender as covariates. It revealed that patients performed significantly more poorly than controls on verbal memory, visual memory, delayed recall, visual attention, and verbal working memory, even after controlling for full-scale IQ and gender (Supplementary Table 1). To confirm these results, additional comparisons were made between patients whose current IQ scores were within normal limit (IQ-WNL patients, defined as WAIS-R full-scale IQ ≥ equal to or greater than 85; $n=46$) and total controls ($n=82$). Fig. 1(b) summarizes the results, showing that there was no difference in current IQ between IQ-WNL patients (mean IQ: 98.85±8.55) and controls (mean IQ: 101.95±11.30), while these patients still showed significantly lower scores on all three memory indices compared with controls. On the other hand, the JART-estimated premorbid IQ of IQ-WNL patients was significantly higher than that of controls.

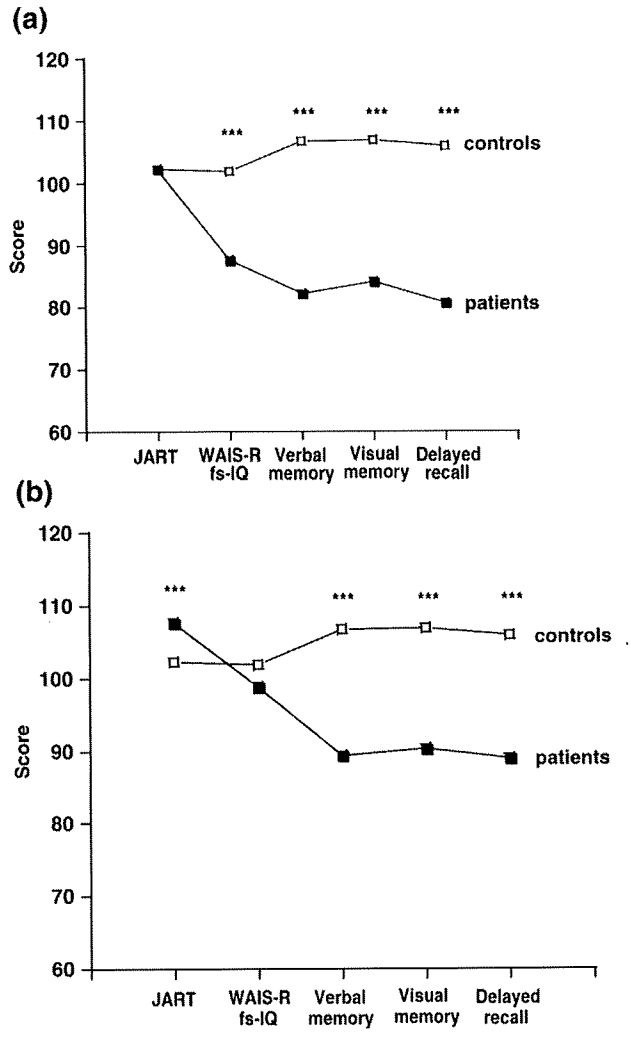

Fig. 1. Mean scores of patients and controls on JART IQ, WAIS-R full-scale IQ, Verbal memory, Visual memory, and Delayed recall indices (WMS-R). (a) total patients ($n=82$) vs. total controls ($n=82$) and (b) IQ-WNL patients (defined as WAIS-R full-scale IQ ≥ 85, $n=46$) vs. total controls ($n=82$).***$P<0.001$.

4. Discussion

In the present study we examined intellectual and memory functions in patients with chronic schizophrenia relative to age- and premorbid IQ-matched healthy controls. Our results confirmed that patients with chronic schizophrenia have wide-ranging cognitive impairments, consistent with the literature on schizophrenia.

The relationship of the development of schizophrenia to declining IQ scores has been confounded by findings that premorbid intelligence itself is likely to be lower in persons who later develop schizophrenia than in their peers (Fuller et al., 2002; Reichenberg et al., 2005). To address this issue, we employed a premorbid IQ-matched case-control sample. Although the cross-sectional nature of the present study does not allow any definite conclusions to be drawn concerning the time when the IQ decline actually occurred (i.e., during the prodromal stage, immediately after illness onset, or during the chronic course of illness), the observed differences in current IQs between patients and controls provide evidence for marked IQ decline due to the development of schizophrenia. Means of estimated premorbid IQ and current full-scale IQ in patients were 102.20 and 87.68, respectively, suggesting an approximate 1 S.D. decline in IQ score related to the development of illness. On the other hand, the subgroup of patients whose current IQ was within normal limits (and thus similar to that of controls) showed significantly higher premorbid IQ as estimated by the JART than controls (Fig. 1(b)), which favors the view that even neuropsychologically normal patients with chronic schizophrenia have compromised cognitive functioning relative to their presumed premorbid level of intellectual function (Kremen et al., 2000). Furthermore, in the present study performance IQ of the patients was more severely impaired than verbal IQ, congruent with prior reports (Heinrichs and Zakzanis, 1998).

Pervasive memory impairment in patients with schizophrenia relative to premorbid IQ-matched controls was

found, and most deficits remained significant even after current IQ was controlled for, supporting that memory impairment is a core feature of schizophrenia (Saykin et al., 1991; Heinrichs and Zakzanis, 1998; Aleman et al., 1999). The marked impairment in verbal memory is consistent with numerous studies (e.g., Saykin et al., 1991; Heinrichs and Zakzanis, 1998). Although visual memory deficits in schizophrenia have attracted less attention from researchers than verbal memory, several studies have reported substantial impairment of visual memory (Saykin et al., 1991; Aleman et al., 1999), consistent with the present study. The pronounced impairment in delayed recall observed here is also in line with prior reports (Aleman et al., 1999; Dickinson et al., 2004). Deficits of verbal and spatial working memory in schizophrenia tapped by the Wechsler digit span backward and spatial span backward subtests, respectively, are fairly consistent findings (Conklin et al., 2000; Silver et al., 2003; Dickinson et al., 2004), which were replicated in the current study. Previous studies have reported that the performance on the forward digit span task of schizophrenia patients is significantly poorer than that of healthy people, indicating impaired attentional function in schizophrenia (Conklin et al., 2000; Silver et al., 2003). The findings of the present study, by contrast, suggest that auditory attention as measured by the forward digit span subtest is preserved in schizophrenia. The discrepant findings regarding auditory attention in the present study relative to previous ones might be due in part to the distinct matching status between patients and controls regarding education and premorbid IQ.

In conclusion, our results suggest that patients with chronic schizophrenia have substantially lower intellectual function relative to their presumed premorbid level and that their memory impairment is even more severe than the IQ decline. To definitively delineate the lifetime course of cognitive decline in schizophrenia, longitudinal studies that range from childhood to the chronic phase are needed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2007.11.002.

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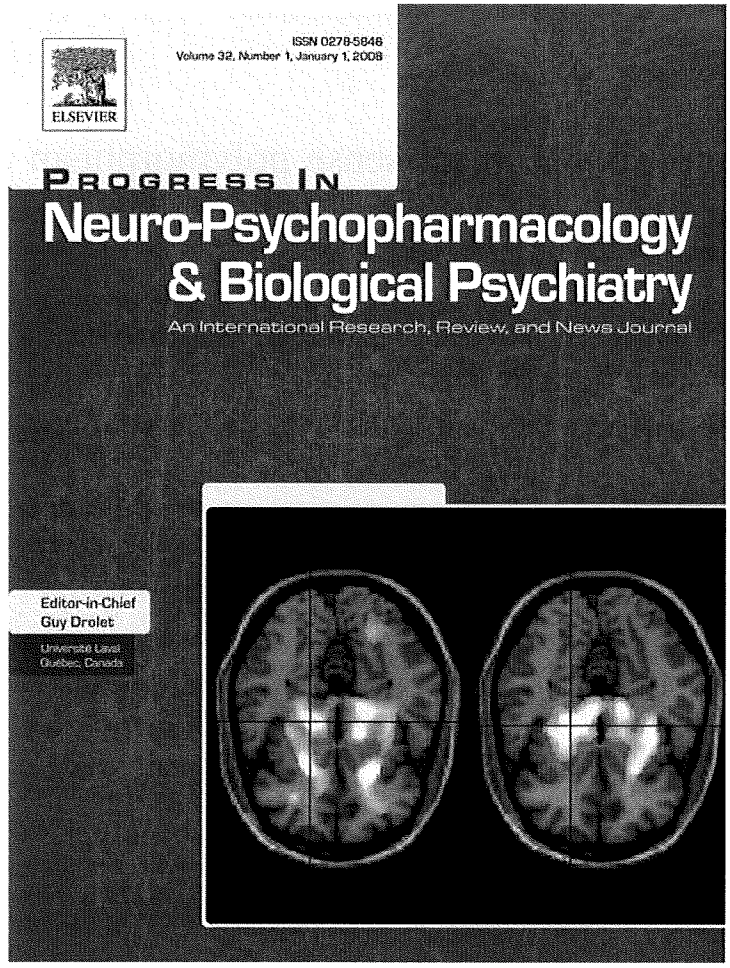

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A possible association between missense polymorphism of the breakpoint cluster region gene and lithium prophylaxis in bipolar disorder

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Abstract

Lithium is one of the most commonly used drugs for the treatment of bipolar disorder. To prescribe lithium appropriately to patients, predictors of response to this drug were explored, and several genetic markers are considered to be good candidates. We previously reported a significant association between genetic variations in the breakpoint cluster region (BCR) gene and bipolar disorder. In this study, we examined a possible relationship between response to maintenance treatment of lithium and Asn796Ser single-nucleotide polymorphism in the BCR gene. Genotyping was performed in 161 bipolar patients who had been taking lithium for at least 1 year, and they were classified into responders for lithium monotherapy and non-responders. We found that the allele frequency of Ser796 was significantly higher in non-responders than in responders. Further investigation is warranted to confirm our findings.

Keywords: BCR (breakpoint cluster region); Bipolar disorder; Lithium; SNP (single-nucleotide polymorphism)

1. Introduction

Bipolar disorder (BPD) is one of the most distinct syndromes in psychiatry, which is characterized by recurrent episodes of mania and depression. Three representative mood stabilizers, lithium, valproate and carbamazepine, are used worldwide for its treatment, and American Psychiatric Association guideline listed lithium as a first line agent (American Psychiatric Association, 2002). However, these treatments are associated with variable rates of efficacy and often with intolerable side effects. Therefore, many researchers explored psychopathological and biological markers for good response to lithium treatment (Gelenberg and Pies, 2003; Ikeda and Kato, 2003). To date, several studies investigated possible molecular predictors of lithium efficacy. The functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR) has been associated with lithium efficacy in two independent studies (Serretti et al., 2001;

Abbreviations: ANOVA, analysis of variance; BCR, breakpoint cluster region; BDNF, brain-derived neurotrophic factor; BPD, bipolar disorder; BP I, bipolar I disorder; BP II, bipolar II disorder; PH domain, pleckstrin homology domain; SNP, single-nucleotide polymorphism.

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