



Plasma levels of matrix metalloproteinase-9 (MMP-9) are associated with cognitive performance in patients with schizophrenia

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Abstract

Aim: Matrix metalloproteinase-9 (MMP-9) has been shown to modulate synaptic plasticity and may contribute to the pathophysiology of schizophrenia. This study investigated the peripheral levels of MMP-9 and its association with cognitive functions in patients with schizophrenia to see the possible involvement of MMP-9 in pathophysiology of schizophrenia, especially in cognitive decline.

Methods: We measured the plasma levels of MMP-9 in 257 healthy controls and 249 patients with schizophrenia, including antipsychotic drug-free patients. We also explored the possible association between plasma MMP-9 levels and cognitive performance in healthy controls and patients with schizophrenia using the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), the Wechsler Memory Scale-Revised (WMS-R), and the Rey Auditory Verbal Learning Test (AVLT).

Results: We found that the plasma levels of MMP-9 were significantly higher in patients with schizophrenia, including antipsychotic drug-free patients, than in healthy

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controls. We found a significant negative association between plasma MMP-9 levels and cognitive performance in controls and patients with schizophrenia.

Conclusion: Together, these convergent data suggest a possible biological mechanism for schizophrenia, whereby increased MMP-9 levels are associated with cognitive impairment.

KEYWORDS

cognitive performance, matrix metalloproteinase-9, schizophrenia, Wechsler Adult Intelligence Scale, Wechsler Memory Scale

1 | INTRODUCTION

The extracellular matrix (ECM) in the brain has emerged as an important reservoir of signaling molecules that can influence synaptic plasticity, synaptogenesis, neurite outgrowth, and other processes occurring in the central nervous system. Matrix metalloproteinases (MMPs) are among the major modulators of the ECM. Matrix metalloproteinase-9 (MMP-9) is the best characterized MMP in the central nervous system. MMP-9 is expressed in adult brain structures such as the hippocampus, cerebral cortex, and cerebellum. It is mostly produced by neurons, but to some extent, it is also produced by glia. Matrix metalloproteinase-9 has been implicated in synaptic plasticity, learning, and memory.^{1,2}

Matrix metalloproteinase-9 has been shown to be associated with schizophrenia. For example, the MMP-9 C1562T gene promoter polymorphism has been shown to be associated with schizophrenia.^{3,4} An interesting example of a gene-schizophrenia association is the rs20544 C/T SNP that has been demonstrated to be strongly linked to the delusional symptoms associated with schizophrenia. This polymorphism is located within MMP-9 3'-UTR mRNA, and the authors have also shown that it affects RNA structure and binding to Fragile X mental retardation protein (FMRP) as well as synaptic MMP-9 availability and morphology of dendritic spines.⁵ Several studies have demonstrated that patients with schizophrenia have increased peripheral levels of MMP-9.⁶⁻⁸ We also previously reported that patients with schizophrenia have increased levels of plasma MMP-9.⁹ Similarly, MMP-9 gene expression in blood mononuclear cells was found to be upregulated in schizophrenia patients who did not undergo treatment.¹⁰ Another independent study reported increased MMP-9 activity in the blood of schizophrenia patients.¹¹

Many studies have reported that patients with schizophrenia, compared with those without schizophrenia, demonstrate cognitive decline.¹²⁻¹⁵ Increased serum MMP-9 levels have been reported in elderly patients with postoperative cognitive dysfunction after general anesthesia.¹⁶ Increased serum MMP-9 levels have also been reported to be associated with cognitive impairment after acute ischemic stroke.¹⁷ Another study reported that MMP-9 serum levels were associated with decision-making abilities in bulimia nervosa patients.¹⁸ Together, these findings

indicate that MMP-9 might be involved in the pathophysiology of schizophrenia, especially in cognitive decline. However, the correlations between peripheral MMP-9 levels and cognitive functioning have not been thoroughly investigated in patients with schizophrenia.

The aim of this study was to investigate the plasma levels of MMP-9 in patients with schizophrenia in a large Japanese cohort that included antipsychotic drug-free patients. We further investigated the possible associations between plasma levels of MMP-9 and cognitive functioning in patients with schizophrenia.

2 | MATERIALS AND METHODS

2.1 | Subjects

A total of 249 patients with schizophrenia and 257 healthy controls were included in this study. The patients and healthy controls were age and sex matched (Table 1). Blood samples were collected, and the plasma was used for the analysis. Most patients were recruited at the Osaka University hospital. One set of the Osaka samples, including 22 treatment-resistant patients with schizophrenia and 22 healthy controls, was the same sample used in the previous study that showed a significant increase in plasma MMP-9 in patients.⁹ In all, 79 patients with schizophrenia and 79 healthy controls were recruited at Chiba University Hospital and Tokushima University Hospital. Each subject had been diagnosed and assessed by at least two trained psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria based on a structured clinical interview for DSM-IV axis I disorders (SCID-I). Patients with comorbidities of substance-related disorders or mental retardation were excluded. Symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (PANSS) (Table 1). PANSS subscales are shown in Table S1. The total prescribed antipsychotic drug dose was calculated as chlorpromazine (CPZ) equivalents (mg/d)¹⁹ (Table 1). Other prescribed drug doses of imipramine, diazepam, and biperiden equivalents are shown in Table S1. Relatives living with patients or hospital staffs confirmed that the adherence rates are 100%. Rate of smokers and inpatients/outpatients rate are also

**TABLE 1** Demographic data of the subjects

Variables	Osaka-1		Osaka-2		Osaka-3		Drug free
	HC	SCZ	HC	SCZ	HC	SCZ	HC
	N = 35	N = 32	N = 40	N = 39	N = 40	N = 40	N = 40
Age (y)	54.5 ± 5.9	57.3 ± 11.9	37.8 ± 12.2	38.0 ± 12.3	42.3 ± 12.2	41.4 ± 11.8	35.5 ± 12.3
Sex (male/female)	15/20	11/21	20/20	20/19	20/20	20/20	23/17
Age of onset		36.1 ± 15.2		26.6 ± 11.1		N/A	
Duration of illness		20.5 ± 15.1		11.4 ± 9.9		N/A	
CPZ dose (mg)		608.8 ± 505.4		562.6 ± 398.3		N/A	
PANSS total		72.7 ± 25.5		79 ± 23.1		N/A	

Note: The mean ± SD is shown.

Abbreviations: CPZ, chlorpromazine; HC, healthy control; N/A, not available; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia.

shown in Table S1. The “drug-free” patients took no antipsychotics for over a week. The “drug-free” patients include the patients who have never taken antipsychotics. The “treatment-resistant” patients were defined according to the following criteria mentioned in clozapine drug information in Japan: (a) No or little response to treatment from at least two adequately dosed antipsychotic trials for at least 4 weeks (including at least one second-generation antipsychotic, >600 mg/d of chlorpromazine equivalent), and patients never had global assessment of functioning (GAF) scores that were higher than 40. (b) Intolerance to at least two second-generation antipsychotics because of uncontrolled extrapyramidal symptoms. All subjects included in this study met the criteria of no or little response. The controls were recruited through local advertisements. Psychiatrically, medically, and neurologically healthy controls were evaluated via the DSM-IV structured clinical interview, nonpatient version (SCID-I/NP) that included an assessment of whether the subject had physical problems. Subjects were excluded if they had neurological or medical conditions that could potentially affect the central nervous system, such as atypical headache, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active stage cancer, cerebrovascular disease, epilepsy, or seizures. Neurological and medical conditions were assessed mainly by interview. In the case of patients, blood tests were also conducted to confirm medical conditions.

2.2 | Determination of plasma MMP-9 levels

Peripheral blood samples were collected from each subject using VENOJECT II vacuum blood collection tube, EDTA-2Na, 7 mL (TERUMO). The samples were centrifuged, and the plasma was preserved at -80°C until further testing. Plasma levels of MMP-9 were determined with Quantikine human ELISA kits from R&D Systems. According to the manufacturer's instructions in the ELISA kits, the intra-assay and interassay coefficients of variation for the MMP-9 ELISAs, as measured in 20 plasma samples, averaged 2.3% and 7.5%, respectively. The minimum detectable dose of human MMP-9 was

0.156 ng/mL, and all values obtained from our plasma samples were above the minimum detectable dose.

2.3 | Assessment of cognitive function

Cognitive function was assessed with the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III),^{20,21} the Wechsler Memory Scale-Revised (WMS-R),²² and the Rey Auditory Verbal Learning Test (AVLT). The numbers of subjects who underwent testing with the WAIS-III, WMS-R, and AVLT are shown in Table 3. In case of healthy controls, cognitive tests were done on the same day of blood sampling. As for patients, cognitive tests were done as soon as after blood sampling. The period between blood sampling and cognitive tests in patients averaged 102 ± 242 days in WAIS-III and 55 ± 150 days in WMS-R.

2.4 | Statistical analysis

The statistical analysis was performed with SPSS 20.0 software for Windows (SPSS Japan Inc). The variables are expressed as the mean ± standard deviation (SD). Data normality was assessed via the Kolmogorov-Smirnov and Shapiro-Wilk tests, and the plasma MMP-9 levels did not show a Gaussian distribution. The differences in clinical characteristics between the patients and controls were analyzed using χ^2 tests for categorical variables and Mann-Whitney *U* tests for continuous variables. The groups did not differ with respect to age or sex (*P* > .05). Differences in the plasma levels of MMP-9 between the patients and controls were analyzed via the Mann-Whitney *U* test. Correlations were examined with Spearman's rank correlation. Potential confounders of plasma MMP-9 (age, sex, and smoking status) were investigated with nonparametric tests (Mann-Whitney *U* test and Spearman's rank correlation), and the *P*-values for sex were lower than .05. Sex was controlled for using partial correlations. The Bonferroni correction was used for multiple comparison corrections. Differences were considered statistically significant for *P*-values < .05.

SCZ	Treatment-resistant SCZ		Tokushima		Chiba		Total	
	HC	SCZ	HC	SCZ	HC	SCZ	HC	SCZ
N = 37	N = 22	N = 22	N = 39	N = 40	N = 40	N = 39	N = 257	N = 249
35.5 ± 13.1	38.1 ± 12.9	39.1 ± 13.3	52.2 ± 7.2	55.2 ± 6.1	32.4 ± 6.2	31.8 ± 5.7	41.8 ± 12.7	42.5 ± 14.0
23/14	12/10	12/10	19/20	20/20	20/20	20/19	130/127	126/124
26.6 ± 11.8		21.8 ± 8.4		N/A		24.9 ± 5.1		27.1 ± 11.4
9.5 ± 7.4		17.3 ± 11.2		N/A		6.9 ± 4.2		12.3 ± 10.8
0		993.2 ± 236.2		N/A		N/A		680.4 ± 442
79.9 ± 25.8		102.1 ± 17.9		N/A		N/A		81.9 ± 25.3

TABLE 2 MMP-9 levels in plasma

Variables (HC vs SCZ)	Osaka-1 (35 vs 32)	Osaka-2 (40 vs 39)	Osaka-3 (40 vs 40)	Drug free (40 vs 37)	Treatment-resistant SCZ (22 vs 22)	Tokushima (39 vs 40)	Chiba (40 vs 39)	Total (256 vs 249)
HC (ng/mL)	22.2 ± 10.1	19.3 ± 7.7	19.1 ± 9.3	21.9 ± 10.5	29.8 ± 17.4	44.5 ± 23.2	29.7 ± 19.5	26.4 ± 17.1
SCZ (ng/mL)	38.4 ± 20.0	27.6 ± 18.8	50.9 ± 53.7	31.3 ± 15.8	43.0 ± 22.4	43.5 ± 29.6	37.7 ± 24.8	38.8 ± 30.4
P value	3.6 × 10 ⁻⁵ **	0.015*	2.3 × 10 ⁻⁵ **	2.8 × 10 ⁻³ **	0.016*	n.s.	0.048*	4.0 × 10 ⁻¹⁰ **

Note: The mean ± SD is shown.

Abbreviations: HC, healthy control; SCZ: schizophrenia.

*P < .05.

***P < .005.

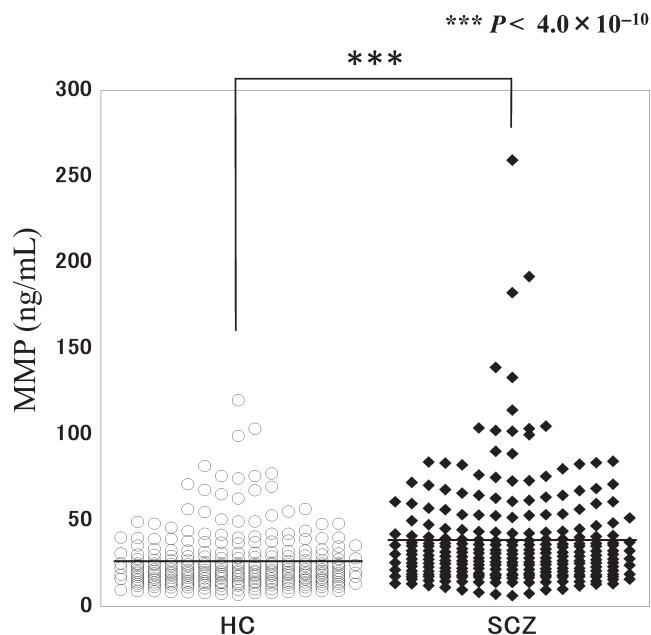


FIGURE 1 Distribution of plasma levels of MMP-9. The plasma levels of MMP-9 were measured in healthy controls (HC) and schizophrenia patients (SCZ) (healthy controls, n = 257; patients with schizophrenia, n = 249). The bars represent mean values. ***P < .001 by Mann-Whitney U test

3 | RESULTS

3.1 | Plasma levels of MMP-9

First, the plasma levels of MMP-9 were compared between the antipsychotic drug-free schizophrenia patient group (n = 37) and the age- and sex-matched control group (total n = 40) from Osaka. The plasma levels of MMP-9 were significantly higher in the patients than in the controls (Table 2). This result suggests that the higher plasma levels of MMP-9 in patients are not the result of medication, and we further investigated the plasma levels of MMP-9 in medicated schizophrenia patient group (total n = 194) and the control group (total n = 190). Five sets of samples were investigated, including 3 sets of samples from Osaka, 2 sets of samples from Tokushima and Chiba (Table 1). All sample sets were age and sex matched. In 4 of the 5 sets of samples, the plasma levels of MMP-9 were significantly higher in the patients than in the controls (Table 2). Finally, we investigated the plasma levels of MMP-9 in treatment-resistant schizophrenia patients who were treated by clozapine (n = 22) and the age- and sex-matched control group (total n = 22) from Osaka to see the possibility of MMP-9 involvement in pathophysiology of treatment-resistant schizophrenia. The plasma levels of MMP-9 were also significantly higher in the

**TABLE 3** Correlations between plasma MMP-9 levels and cognitive function

			Total				Schizophrenia				Healthy control			
			n	r	P	Corrected P value	n	r	P	Corrected P value	n	r	P	Corrected P value
IQ	WAIS	VIQ	264	-0.18	$3.8 \times 10^{-3**}$	0.049*	87	-0.04	n.s.	n.s.	177	-0.03	n.s.	n.s.
		PIQ	264	-0.19	$1.9 \times 10^{-3***}$	0.025*	87	-0.06	n.s.	n.s.	177	-0.04	n.s.	n.s.
		FIQ	264	-0.20	$1.3 \times 10^{-3***}$	0.017*	87	-0.05	n.s.	n.s.	177	-0.04	n.s.	n.s.
		VC	264	-0.16	$8.6 \times 10^{-3**}$	n.s.	87	0.02	n.s.	n.s.	177	-0.07	n.s.	n.s.
		PO	264	-0.16	0.011*	n.s.	87	-0.10	n.s.	n.s.	177	-0.01	n.s.	n.s.
		WM	261	-0.18	$3.3 \times 10^{-3***}$	0.043*	84	-0.08	n.s.	n.s.	177	-0.04	n.s.	n.s.
		PS	261	-0.22	$3.1 \times 10^{-4***}$	$4.0 \times 10^{-3***}$	84	0.08	n.s.	n.s.	177	-0.10	n.s.	n.s.
Memory	WMS AVLT	VerM	268	-0.24	$9.4 \times 10^{-5***}$	$1.2 \times 10^{-3***}$	91	-0.04	n.s.	n.s.	177	-0.13	n.s.	n.s.
		ViM	268	-0.14	0.027*	n.s.	91	0.01	n.s.	n.s.	177	-0.06	n.s.	n.s.
		GM	268	-0.24	$8.8 \times 10^{-5***}$	$1.1 \times 10^{-3***}$	91	-0.06	n.s.	n.s.	177	-0.13	n.s.	n.s.
		A/C	268	-0.20	$8.4 \times 10^{-4***}$	0.011*	91	-0.12	n.s.	n.s.	177	-0.05	n.s.	n.s.
		DR	268	-0.24	$9.5 \times 10^{-5***}$	$1.2 \times 10^{-3***}$	91	-0.11	n.s.	n.s.	177	-0.11	n.s.	n.s.
		total recall	258	-0.21	$7.3 \times 10^{-4***}$	$9.5 \times 10^{-3**}$	81	-0.14	n.s.	n.s.	177	-0.08	n.s.	n.s.

Abbreviations: A/C, attention and concentration; DR, delayed recall; FIQ, full-scale IQ; GM, general memory; n.s., not significant; PIQ, performance IQ; PO, picture completion block design and matrix reasoning; PS, block design and matrix reasoning; VerM, verbal memory; ViM, visual memory; VIQ, verbal IQ; WM, arithmetic digit span and letter-number sequencing.

* $P < .05$.

** $P < .01$.

*** $P < .005$.

treatment-resistant schizophrenia patients than in the controls (Table 2). In total, the plasma levels of MMP-9 were significantly higher in the patients than in the controls (Figure 1, Table 2; Mann-Whitney U test: $z = -6.26$, $P = 3.96 \times 10^{-10}$).

3.2 | MMP-9 and cognitive and memory function

The relationship between plasma MMP-9 levels and cognitive function was investigated via the WAIS- III. Plasma MMP-9 levels were significantly and negatively correlated with the WAIS verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FIQ) scores (Figure 2A); arithmetic, digit span and letter-number sequencing (WM) scores; and block design and matrix reasoning (PS) scores in all samples (patients with schizophrenia and healthy controls) after Bonferroni correction (Table 3; VIQ: $r = -0.18$, $P = 3.8 \times 10^{-3}$, corrected $P = .049$; PIQ: $r = -0.19$, $P = 1.9 \times 10^{-3}$, corrected $P = .025$; FIQ: $r = -0.20$, $P = 1.3 \times 10^{-3}$, corrected $P = .017$; WM: $r = -0.18$, $P = 3.3 \times 10^{-3}$, corrected $P = .043$; PS: $r = -0.22$, $P = 3.1 \times 10^{-4}$, corrected $P = 4.0 \times 10^{-3}$). No significant correlations were observed between MMP-9 levels and cognitive function as assessed via the WAIS- III in patients with schizophrenia or in healthy controls (Figure S1, Table 3). To exclude the effects of sex, we conducted a partial correlation analysis between the plasma MMP-9 levels and cognitive function as assessed via the WAIS- III using sex as a control variable. Plasma MMP-9 levels were significantly and negatively correlated with the PIQ and PS scores in all sample (patients with schizophrenia and healthy controls), as shown in Table S1.

We also investigated the relationship between plasma MMP-9 levels and memory functions using the WMS-R and AVLT. Plasma MMP-9 levels were significantly and negatively correlated with the WMS-R verbal memory (VerM) and general memory (GM) subscales (Figure 2B) as well as the attention and concentration (A/C), delayed recall (DR), and total recall scores on the AVLT in all sample (patients with schizophrenia and healthy controls) after Bonferroni correction (Table 3; VerM: $r = -0.24$, $P = 9.4 \times 10^{-5}$, corrected $P = 1.2 \times 10^{-3}$; GM: $r = -0.24$, $P = 8.8 \times 10^{-5}$, corrected $P = 1.1 \times 10^{-3}$; A/C: $r = -0.20$, $P = 8.4 \times 10^{-4}$, corrected $P = .011$; DR: $r = -0.24$, $P = 9.5 \times 10^{-5}$, corrected $P = 1.2 \times 10^{-3}$; AVLT: $r = -0.21$, $P = 7.3 \times 10^{-4}$, corrected $P = 9.5 \times 10^{-3}$). No significant correlations were observed between MMP-9 levels and memory functions as assessed via the WMS-R and AVLT in patients with schizophrenia or in healthy controls (Figure S2, Table 3). To exclude the effects of sex, we conducted a partial correlation analysis between the plasma MMP-9 levels and memory functions as assessed via the WMS-R and AVLT using sex as a control variable. Plasma MMP-9 levels were significantly and negatively correlated with GM, A/C, and DR in the entire sample (patients with schizophrenia and healthy controls), as shown in Table S1.

4 | DISCUSSION

In this study, we confirmed that the plasma levels of MMP-9 were significantly increased in patients with schizophrenia in a large

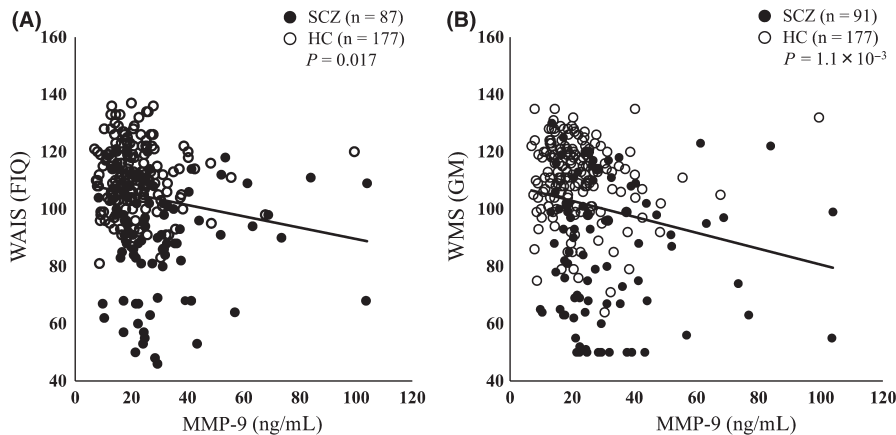


FIGURE 2 Correlation between plasma MMP-9 levels and cognitive function. Correlations of the plasma levels of MMP-9 with the WAIS full-scale IQ (FIQ) scores (A) and the WMS general memory (GM) scores (B). MMP-9 was negatively correlated with both FIQ and GM

Japanese cohort that included antipsychotic drug-free patients and treatment-resistant patients. Our data showing higher plasma MMP-9 levels in patients with schizophrenia are consistent with the results of previous studies. To the best of our knowledge, this is the first study to demonstrate that plasma MMP-9 levels are significantly increased in antipsychotic drug-free patients with schizophrenia, suggesting that higher levels of MMP-9 in patients with schizophrenia are not the result of medication.

It has been reported that higher peripheral levels of MMP-9 were associated with worse cognitive function in elderly patients after general anesthesia¹⁶ and in acute ischemic stroke¹⁷ and bulimia nervosa patients.¹⁸ However, an association between plasma MMP-9 levels and cognitive function has not been investigated in patients with schizophrenia. We found that higher plasma MMP-9 levels were associated with worse cognitive function in patients with schizophrenia and healthy controls. Most subcategories of both the WAIS and WMS-R were associated with plasma MMP-9 levels, suggesting that MMP-9 is associated with general cognitive and memory functions rather than specific functions.

The results of this study should be evaluated in light of certain limitations. First, plasma sampling conditions, such as the time of sampling and diet, might modulate the plasma levels of the investigated marker. However, these conditions were not controlled for in this study. Second, patients used different antipsychotic drugs that might affect the plasma MMP-9 levels and cognitive functions. Third, a significant association was observed mainly in all sample (patients with schizophrenia and healthy controls), and we did not detect a significant association when only the patients with schizophrenia were included. This finding might be due to reduced statistical power, as the sample size of the patients was less than a third of the total sample size. Another possibility is that the observed associations between MMP-9 and cognitive functions in the whole sample analysis were driven by the higher plasma levels of MMP-9 and worse cognitive functions in patients with schizophrenia compared to controls. Thus, further studies are needed to elucidate the role of MMP-9 in schizophrenia with respect to cognitive impairment.

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CONFLICT OF INTERESTS

None to declare.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and the recommendations of Ethical Guidelines for Medical and Health Research Involving Human Subjects, Ministry of Health.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by the Research Ethical Committee of Osaka University, Chiba University and Tokushima University.

INFORMED CONSENT

Written informed consent was obtained from all subjects after the procedures had been fully explained.

DATA AVAILABILITY STATEMENT

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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