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Serotonin 1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients

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ABSTRACT

Background: Several investigations have reported associations the serotonin 1A (5-HT1A) receptor to schizophrenia and psychotic disorders, making 5-HT1A receptor gene (*HTR1A*) an adequate candidate gene for the pathophysiology of schizophrenia and methamphetamine (METH)-induced psychosis. Huang and colleagues reported that rs6295 in *HTR1A* was associated with schizophrenia. The symptoms of methamphetamine (METH)-induced psychosis are similar to those of paranoid type schizophrenia. It may indicate that METH-induced psychosis and schizophrenia have common susceptibility genes. In support of this hypothesis, we reported that the V-act murine thymoma viral oncogene homologue 1 (AKT1) gene was associated with METH-induced psychosis and schizophrenia in the Japanese population. Furthermore, we conducted an analysis of the association of *HTR1A* with METH-induced psychosis.

Method: Using one functional SNP (rs6295) and one tagging SNP (rs878567), we conducted a genetic association analysis of case-control samples (197 METH-induced psychosis patients and 337 controls) in the Japanese population. The age and sex of the control subjects did not differ from those of the methamphetamine dependence patients.

Results: Rs878567 was associated with METH-induced psychosis patients in the allele/genotype-wise analysis. Moreover, this significance remained after Bonferroni correction. In addition, we detected an association between rs6295 and rs878567 in *HTR1A* and METH-induced psychosis patients in the haplotype-wise analysis. Although we detected an association between rs6295 and METH-induced psychosis patients, this significance disappeared after Bonferroni correction.

Conclusion: *HTR1A* may play an important role in the pathophysiology of METH-induced psychosis in the Japanese population. However, because we did not perform a mutation scan of *HTR1A*, a replication study using a larger sample may be required for conclusive results.

1. Introduction

Altered serotonergic neural transmission is hypothesized to be a susceptibility factor for schizophrenia (Geyer and Vollenweider, 2008; Meltzer et al., 2003). Several postmortem studies reported increased serotonin 1A (5-HT1A) receptor in the prefrontal cortex

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of schizophrenic patients (Burnet et al., 1996; Hashimoto et al., 1993, 1991; Simpson et al., 1996; Sumiyoshi et al., 1996). Huang and colleagues reported that rs6295 in an SNP (C-1019G: rs6295) in the promoter region of the 5-HT1A receptor gene (*HTR1A*), which regulate HTR1A transcription (Le Francois et al., 2008; Lemonde et al., 2003), was associated with schizophrenia (Huang et al., 2004). These facts suggest a crucial relationship between the 5-HT1A receptor and schizophrenia, and that *HTR1A* is an adequate candidate for the etiology of schizophrenia. *HTR1A* (OMIM*109 760, 1 exon in this genomic region spanning 2.069 kb) is located on 5q11.

The symptoms of methamphetamine (METH)-induced psychosis are similar to those of paranoid type schizophrenia (Sato et al., 1992). It may indicate that METH-induced psychosis and schizophrenia have common susceptibility genes (Bousman et al., 2009). In support of this hypothesis, we reported that the V-act murine thymoma viral oncogene homologue 1 (AKT1) gene was associated with METH-induced psychosis (Ikeda et al., 2006) and schizophrenia (Ikeda et al., 2004) in the Japanese population. Furthermore, we conducted an analysis of the association of these genes with METH-induced psychosis, using the recently recommended strategy of 'gene-based' association analysis (Neale and Sham, 2004).

2. Materials and methods

2.1. Subjects

The subjects in the association analysis were 197 METH-induced psychosis patients (164 males: 83.2% and 33 females; mean age ± standard deviation (SD) 37.6 ± 12.2 years) and 337 healthy controls (271 males: 80.4% and 66 females; 37.6 ± 14.3 years). The age and sex of the control subjects did not differ from those of the methamphetamine dependence patients. All subjects were unrelated to each other, ethnically Japanese, and lived in the central area of Japan. The patients were diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of medical records. METH-induced psychosis patients were divided into two categories of psychosis prognosis, the transient type and the prolonged type, which showed remission of psychotic symptoms within 1 month and after more than 1 month, respectively, after the discontinuance of methamphetamine consumption and beginning of treatment with neuroleptics; 112 patients (56.9%) were the transient type, and 85 patients (43.1%) were the prolonged type. One hundred thirty-seven subjects with METH-induced psychosis also had dependence on drugs other than METH. Cannabinoids were the most frequency abused drugs (31.4%), followed by cocaine (9.09%), LSD (9.09%), opioids (7.69%), and hypnotics (7.69%). Subjects with METH-induced psychosis were excluded if they had a clinical diagnosis of psychotic disorder, mood disorder, anxiety disorder or eating disorder. More detailed characterizations of these subjects have been published elsewhere (Kishi et al., 2008b). All healthy controls were also psychiatrically screened based on unstructured interviews. None had severe medical complications such as liver cirrhosis, renal failure, heart failure or other Axis-I disorders according to DSM-IV.

The study was described to subjects and written informed consent was obtained from each. This study was approved by the Ethics Committee at Fujita Health University, Nagoya University School of Medicine and each participating member of the Institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA).

2.2. SNPs selection and linkage disequilibrium (LD) evaluation

We first consulted the HapMap database (release#23.a.phase2, Mar 2008, www.hapmap.org, population: Japanese Tokyo: minor allele frequencies (MAFs) of more than 0.05) and included 3 SNPs (rs6449693, rs878567 and rs1423691) covering *HTR1A* (5′-flanking regions including about 1 kb from the initial exon and about 2 kb downstream (3′) from the last exon: HapMap database contig number chr5: 63287418...63291774). Then one tagging SNP was selected with the criteria of an r^2 threshold greater than 0.8 in 'pair-wise tagging only' mode using the 'Tagger' program (Paul de Bakker, http://www/broad.mit.edu/mpg/tagger) of the HAPLOVIEW software (Barrett et al., 2005).

HTR1A has also been reported to have one biologically functional SNP (C-1019G: rs6295) (Albert et al., 1996; Albert and Lemonde, 2004; Lemonde et al., 2003). Rs6295 (C-1019G) in the promoter region regulate *HTR1A* transcription (Le Francois et al., 2008; Lemonde et al., 2003). The C allele is a part of a 26 palindrome that connect transcription factors (Deaf-1, Hes1 and Hes5) by NUDR (nuclear deformed epidermal autoregulatory factor), whereas the G allele abolishes repression by NUDR (Le Francois et al., 2008; Lemonde et al., 2003). This would lead to elevated levels of 5-HT1A receptor in the presynaptic raphe nucleus in GG genotypes, compared with CC genotype (Le Francois et al., 2008; Lemonde et al., 2003). Since no information about rs6295 was shown in the HapMap database, we included this SNP. These two SNPs were then used for the following association analysis.

2.3. SNPs genotyping

We used TaqMan assays (Applied Biosystems, Inc., Foster City, CA) for both SNPs. Detailed information, including primer sequences and reaction conditions, is available on request.

2.4. Statistical analysis

Genotype deviation from the Hardy–Weinberg equilibrium (HWE) was evaluated by chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc., Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise association with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc., Tokyo, Japan), and haplotype-wise association analysis was conducted with a likelihood ratio test using the COCAPHASE2.403 program (Dudbridge, 2003). We used the permutation test option as provided in the haplotype-wise analysis to avoid spurious results and correct for multiple testing. Permutation test correction was performed using 1000 iterations (random permutations). In addition, Bonferroni's correction was used to control inflation of the type I error rate in the single marker association analysis and in the explorative analysis. For Bonferroni correction, we employed the following numbers for multiple testing: 2 for each sample set in allele- and genotype-wise analysis (2 examined SNPs). We had already performed a permutation test in the haplotype-wise analysis. Power calculation was performed using a genetic power calculator (Purcell et al., 2003).

The significance level for all statistical tests was 0.05.

3. Results

The LD from rs6449693, rs878567 and rs1423691 was tight in from the HapMap database samples ($r^2 = 1.00$). However, the LD structure of rs6295 (functional SNP) and rs878567 (tagging SNP) in our control samples was not tight ($r^2 = 0.160$). Genotype frequencies of all SNPs were in HWE (Table 1). Rs878567 was associated with METH-induced psychosis patients in the allele/genotype-wise analysis (P allele = 0.000122 and P genotype = 0.00103) (Table 1). Moreover, these significances remained after Bonferroni correction (P allele = 0.000244 and P genotype = 0.00203) (Table 1). In addition, we detected an association between rs6295 and rs878567 in *HTR1A* and METH-induced psychosis patients in the haplotype-wise analysis ($P = 0.0000643$) (Table 2). Although we detected an association between rs6295 and METH-induced psychosis patients (P allele = 0.0271), this significance disappeared after Bonferroni correction (P allele = 0.0542) (Table 1).

4. Discussion

We found associations between *HTR1A* and Japanese METH-induced psychosis patients. Therefore, we reasoned that *HTR1A* may play an important role in the pathophysiology of METH-induced psychosis in the Japanese population. However, our samples are small. Although Bonferroni's correction was used to control inflation of the type I error rate, we considered that there is a possibility of type I error in these results.

The 5-HT1A receptor is present in various regions of the brain, including the cortex, hippocampus, amygdala, hypothalamus and septum (Aznar et al., 2003; Barnes and Sharp, 1999; Le Francois et al., 2008; Varnas et al., 2004). Presynaptic 5-HT1A autoreceptors play an important role in the autoregulation of serotonergic neurons (Le Francois et al., 2008; Lemonde et al., 2003; Riad et al., 2000; Sotelo et al., 1990). The 5-HT1A receptor activation by serotonin induces the hyperpolarization of serotonergic neurons, decreasing their firing rate and consequently the release of serotonin in the brain (Le Francois et al., 2008; Lemonde et al., 2003; Riad et al., 2000; Sotelo et al., 1990). Also, the 5-HT1A receptor was associated hippocampal neurogenesis. The hippocampus is a part of the limbic system involved in cognitive function such as memory. Stimulation of 5-HT1A receptors has been known to reduce the

Table 1
Association analysis of *HTR1A* with methamphetamine-induced psychosis.

SNP[a]	Phenotype[b]	MAFs[c]	N	Genotype distribution[d]			*P*-value[f]			Corrected *P*-value[f,g]	
				M/M	M/m	m/m	HWE[e]	Genotype	Allele	Genotype	Allele
rs6295	Controls	0.254	336	192	117	27	0.132				
C > G	METH-induced psychosis	0.317	197	92	85	20	0.955	0.0657	**0.0271**		0.0542
rs878567	Controls	0.126	336	258	71	7	0.423				
C > T	METH-induced psychosis	0.216	197	124	61	12	0.233	**0.00103**	**0.000122**	**0.00203**	**0.000244**

[a] Major allele > minor allele.
[b] METH-induced psychosis: methamphetamine-induced psychosis.
[c] MAFs: minor allele frequencies.
[d] M: major allele, m: minor allele.
[e] Hardy–Weinberg equilibrium.
[f] Bold represents significant *P*-value.
[g] Calculated using Bonferroni's correction.

negative symptoms and cognitive dysfunction of schizophrenia (Meltzer et al., 2003; Meltzer and Sumiyoshi, 2008; Sumiyoshi et al., 2001, 2007). Mason and Reynolds (1992) reported that one of the major pharmacological therapeutic targets of clozapine is 5-HT1A receptors on cortical glutamatergic neurons. Several post-mortem studies reported increased 5-HT1A receptor in the prefrontal cortex of schizophrenic patients (Burnet et al., 1996; Hashimoto et al., 1993, 1991; Simpson et al., 1996; Sumiyoshi et al., 1996). NAN-190 (5-HT1A receptor antagonist) produced an inhibitory action on methamphetamine-induced hyperactivity (Ginawi et al., 2004; Millan and Colpaert, 1991). These facts suggest that altered serotonergic neural transmission caused by abnormalities in 5-HT1A receptor may be involved in the development of psychotic disorders such as schizophrenia and METH-induced psychosis (Geyer and Vollenweider, 2008; Meltzer et al., 2003).

Serretti et al. (2007) reported that rs878567 in *HTR1A* was associated with German and Italian suicidal attempters. Also, previous study have reported that rs878567 in *HTR1A* was found the interaction with childhood physical abuse in mood disorders (Brezo et al., 2009). These authors suggested rs878567 might influence hippocampus-mediated memory deficits in mood disorders (Brezo et al., 2009). The LD from rs6449693, rs878567 and rs1423691 was tight in from the HapMap database samples (r^2 = 1.00). As these results show, rs878567 covers a wide and important region including the exon and the promoter region in *HTR1A*. Because it is possible that rs878567 influences biological function in the brain, we suggest that functional analysis for rs878567 should be performed in future studies.

Rs6295 (C-1019G) in the promoter region regulate *HTR1A* transcription (Le Francois et al., 2008; Lemonde et al., 2003). The C allele is a part of a 26 palindrome that connect transcription factors (Deaf-1, Hes1 and Hes5) by NUDR (nuclear deformed epidermal autoregulatory factor), whereas the G allele abolishes repression by NUDR (Le Francois et al., 2008; Lemonde et al., 2003). This would lead to elevated levels of 5-HT1A receptor in the presynaptic raphe nucleus in GG genotyps, compared with CC genotype (Le Francois et al., 2008; Lemonde et al., 2003). This variant was associated with several studies, including major depressive disorder (Anttila et al., 2007; Kraus et al., 2007; Lemonde et al., 2003; Neff et al., 2009; Parsey et al., 2006) and panic disorder (Strobel et al., 2003) and antidepressant response in MDD (Arias et al., 2005; Hong et al., 2006; Lemonde et al., 2004; Parsey et al., 2006; Serretti et al., 2004; Yu et al., 2006). Huang et al. (2004) reported that rs6295 was associated with schizophrenia. Recent studies reported that rs6295 was associated with the improvement in negative symptoms from antipsychotics such as risperidone (Mossner et al., 2009; Reynolds et al., 2006; Wang et al., 2008) and that 5-HT1A receptor agonists such as tandospirone produced improvements in the cognitive impairment in schizophrenia (Meltzer and Sumiyoshi, 2008; Sumiyoshi et al., 2001, 2007).

A few points of caution should be mentioned with respect to our results. Firstly, the positive association may be due to small sample size. Ideal samples for this study are METH use disorder samples with and without psychosis. Because we had only a few METH use disorder samples without psychosis, and we wanted to avoid statistical error, we did not perform an association analysis with these samples. Secondly, we did not include a mutation scan to detect rare variants. We designed the study based on the common disease-common variants hypothesis (Chakravarti, 1999). However, Weickert et al. (2008) have shown associations between a common disease such as schizophrenia and rare variants. If the genetic background of METH-induced psychosis is described by the common disease-rare variants hypothesis, further investigation will be required, such as medical resequencing using larger samples. However, statistical power is needed to evaluate the association of rare variants. Lastly, our subjects did not undergo structured interviews. However, in this study patients were carefully diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of a review of medical records (Kishi et al., 2008a,c, 2009). In addition, when we found misdiagnosis in a patient, we promptly excluded the misdiagnosed case to maintain the precision of our sample. To overcome these limitations, a replication study using larger samples or samples of other populations will be required for conclusive results.

In conclusion, our results suggest that *HTR1A* may play a major role in the pathophysiology of METH-induced psychosis in the Japanese population. However, because we did not perform a mutation scan of *HTR1A*, a replication study using a larger sample may be required for conclusive results.

Table 2
Haplotype-wise analysis of *HTR1A*.

Haplotype rs6295-rs878567	Phenotype[a]	Individual haplotype frequency	Individual *P*-value[b]	Phenotype[a]	Global *P*-value[b]
C–C	Control	0.811			
	METH-induced psychosis	0.694	**0.0000364**	METH-induced psychosis	**0.0000643**
G–C	Control	0.189			
	METH-induced psychosis	0.306	**0.0000364**		

[a] METH-induced psychosis: methamphetamine-induced psychosis.
[b] Bold numbers represent significant *P*-value.

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Reduced emotional and corticosterone responses to stress in μ-opioid receptor knockout mice

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ABSTRACT

The detailed mechanisms of emotional modulation in the nervous system by opioids remain to be elucidated, although the opioid system is well known to play important roles in the mechanisms of analgesia and drug dependence. In the present study, we conducted behavioral tests of anxiety and depression and measured corticosterone concentrations in both male and female μ-opioid receptor knockout (MOP-KO) mice to reveal the involvement of μ-opioid receptors in stress-induced emotional responses. MOP-KO mice entered more and spent more time in the open arms of the elevated plus maze compared with wild-type mice. MOP-KO mice also displayed significantly decreased immobility in a 15 min tail-suspension test compared with wild-type mice. Similarly, MOP-KO mice exhibited significantly decreased immobility on days 2, 3, and 4 in a 6 min forced swim test conducted for 5 consecutive days. The increase in plasma corticosterone concentration induced by tail-suspension, repeated forced swim, or restraint stress was reduced in MOP-KO mice compared with wild-type mice. Corticosterone levels were not different between wild-type and MOP-KO mice before stress exposure. In contrast, although female mice tended to exhibit fewer anxiety-like responses in the tail-suspension test in both genotypes, no significant gender differences were observed in stress-induced emotional responses. These results suggest that MOPs play an important facilitatory role in emotional responses to stress, including anxiety- and depression-like behavior and corticosterone levels.

1. Introduction

Stress is hypothesized to be one of the triggering factors that causes mental illness, including anxiety and depression. Several brain areas are hypothesized to be involved in stress-induced emotional responses via corticosterone release by the hypothalamic-pituitary-adrenal (HPA) axis. Although several neurotransmitter systems, such as serotonin and catecholamines, have been hypothesized to be involved in these mechanisms, the precise molecular mechanisms are still unclear. Endogenous opioid peptides, such as endorphins, have been shown to modulate serotonergic and catecholaminergic neurotransmission (Chen et al., 2001; Hung et al., 2003; Ukai and Lin, 2002). Furthermore, pretreatment with naloxone, a nonselective opioid receptor antagonist, decreased immobility time in mice in a forced swim test (Amir, 1982). Chronic morphine facilitated immobility in a forced swim test (Molina et al., 1994). Opioids have also been reported to increase stress-related hormone levels (Mellon and Bayer, 1998). These previous reports indicate that the endogenous opioid system impacts behavioral responses to stress.

Opioid receptors have been classified into at least three subtypes, μ, δ, and κ (MOP, DOP, and KOP, respectively). Endomorphin-1 and -2, endogenous peptides that are selective for MOP, reportedly decreased immobility time in both the forced swim and tail-suspension tests (Fichna et al., 2007). A DOP selective agonist, SNC80, also decreased immobility time in a forced swim test (Broom et al., 2002). Furthermore, the KOP selective agonist U69593 increased, and the KOP selective antagonist nor-binaltorphimine decreased, immobility time in a forced swim test (Mague et al., 2003). Although three opioid receptor subtypes may be involved in stress-induced emotional responses, even the most selective ligands for a specific subtype (i.e., β-funaltrexamine for

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MOP, naltrindole for DOP, and nor-binaltorphimine for KOP) possess certain affinities for other subtypes (Newman et al., 2002) which may contribute to the discrepant findings about the role of opioid receptor subtypes in stress responses. Therefore, the precise molecular mechanisms underlying stress-induced emotional responses have not yet been clearly delineated by traditional pharmacological studies that use only selective ligands.

Recent success in developing knockout (KO) mice with MOP gene deletion has revealed the central role of MOPs, rather than other opioid receptor subtypes, in various opioid effects, including analgesia, reward, and tolerance (Ide et al., 2004; Kieffer, 1999; Loh et al., 1998; Sora et al., 2001, 1997). Although several compensatory changes might occur in KO animals, these animals have potential utility in investigating the *in vivo* roles of specific proteins. Opioid receptors have been shown to modulate responses to stress, including depression-like behavior (Filliol et al., 2000; McLaughlin et al., 2003). Thus, the use of MOP-KO mice has provided novel theories on the molecular mechanisms underlying stress-induced emotional responses. Both the forced swim test (Porsolt et al., 1977) and tail-suspension test (Steru et al., 1985) have been widely used to assess depression-like behavior, with several modifications. Many reports using these two tests have shown that the inescapable stress of swimming or suspending a mouse by its tail can provide valuable information about emotional responses in stressful situations. The present study investigated the contributory role of the MOP in emotional responses to height, tail-suspension, repeated forced swim, and restraint stress using MOP-KO mice.

2. Materials and methods

2.1. Animals

The present study used wild-type and homozygous MOP-KO mouse littermates on a C57BL/6J genetic background (backcrossed at least 10 generations) as previously described (Sora et al., 2001). The experimental procedures and housing conditions were approved by the Institutional Animal Care and Use Committee, and all animal care and treatment were in accordance with our institutional animal experimentation guidelines. Naive adult (>10 weeks old) male and female mice were group-housed in an animal facility maintained at 22 ± 2 °C and 55 ± 5% relative humidity under a 12 h/12 h light/dark cycle with lights on at 8:00 am and off at 8:00 pm. Food and water were available *ad libitum*. All behavioral tests and blood sample collections were conducted between 1:00 pm and 6:00 pm.

2.2. Elevated plus maze

The testing apparatus was a white plastic plus-shaped maze, elevated 80 cm from the floor. The maze consisted of two open arms (50 × 10 cm) and two closed arms (50 × 10 × 50 cm) without a roof. During testing, the time spent in the open arms and the number of entries into the open arms were recorded for 5 min. A mouse was considered to have entered an arm only if all four paws entered that arm.

2.3. Locomotor activity

Locomotor activity was assessed with an animal activity-monitoring apparatus equipped with an infrared detector (SUPERMEX, CompACT FSS, Muromachi Kikai Co., Tokyo, Japan). Mice were placed individually in 30 × 45 × 30 cm plastic cages, to which they had not been previously exposed, under dim light and sound-attenuated conditions. Locomotor activity was monitored for 3 h.

2.4. Tail-suspension test

For tail-suspension testing, mice were suspended by their tail which was taped on a metal hook in test chambers (20 × 20 × 25 cm) constructed of white plastic walls and floor. Each hook was connected to a computerized strain gauge that was adjusted to detect animal movements (Tail-suspension System, Neuroscience Inc., Osaka, Japan). The total duration of immobility was measured for 15 min per day for 2 consecutive days.

2.5. Forced swim test

For forced swim testing, animals were forced to swim in a cylindrical Plexiglas tank (30 cm height × 30 cm diameter) containing 20 cm deep water for 6 min per day for 5 consecutive days. The water temperature was maintained at approximately 25 °C. Immobility time was recorded with an animal activity-monitoring apparatus equipped with an infrared detector (SUPERMEX, CompACT FSS, Muromachi Kikai Co., Tokyo, Japan). After each session, the mice were immediately removed from the cylinder, dried with a towel, and kept under a heating lamp until completely dry, before being returned to their home cages.

2.6. Stress procedures and corticosterone enzyme immunoassay

After the 2 day tail-suspension test or 5 day forced swim test, blood samples (50 μl) were obtained from the tail vein. For restraint stress, mice were placed in a 50 ml conical centrifuge tube with multiple ventilation holes. Mice were restrained vertically in the tube for 12 h, followed by a 12 h rest with food and water available *ad libitum*. Mice were restrained again for 12 h, and then blood samples were obtained. All blood samples were immediately centrifuged for 20 min at 1000 × *g*. Plasma samples were stored at −80 °C until analysis. Plasma corticosterone levels were determined with a Corticosterone Enzyme Immunoassay Kit (Assay Design Inc., Ann Arbor, MI, USA).

2.7. Statistical analysis

Entry counts and time spent on the open arms of the elevated plus maze and stress-induced changes in plasma corticosterone concentrations were analyzed with Student's *t*-test. The results of other analyses were statistically evaluated with analysis of variance (ANOVA) followed by the Tukey–Kramer test. Values of $p < 0.05$ were considered statistically significant.

3. Results

We first assessed basal anxiety-like behavior of both mouse genotypes in the elevated plus maze (Fig. 1). Compared with wild-type mice, MOP-KO mice had significantly higher entry counts ($p < 0.05$, Student's *t*-test) and a longer time spent on the open arms ($p < 0.01$, Student's *t*-test) in both male and female mice. Although female mice tended to have more entry counts and more time spent in the open arms than male mice in both genotypes, no significant differences were observed.

When spontaneous locomotor activity of both wild-type and MOP-KO mice was analyzed (Fig. 2), MOP-KO mice displayed normal locomotor activity, similar to wild-types, during the 3 h test. A three-way, mixed-design ANOVA of spontaneous locomotor activity with two within-subjects factors (genotype and gender) showed no significant interactions (genotype: $F_{1,30} = 1.56$, $p = 0.221$; gender: $F_{1,30} = 0.08$, $p = 0.784$).

To test the influence of MOP-KO in stress-induced responses, immobility time in a 15 min tail-suspension test was analyzed every minute in wild-type and MOP-KO mice (Fig. 3). A three-way, mixed-design ANOVA of immobility time with two within-subjects factors (genotype and gender) revealed that immobility time was significantly different between genotypes in the tail-suspension test ($F_{1,22} = 6.92$, $p < 0.05$), although both genotypes showed time-dependent increases (Fig. 3a). The ANOVA also revealed that immobility time was not significantly different between male and female mice ($F_{1,22} = 3.01$, $p = 0.097$), although female mice tended to show less immobility than males. When the data of male and female mice were combined (Fig. 3b), significant differences were found in immobility time between genotypes ($F_{1,24} = 5.45$, $p < 0.05$, two-way, repeated-measures ANOVA). *Post hoc* tests revealed that MOP-KO mice had significantly less immobility time compared with wild-type mice from 7 to 9, 12 and 13 min after the tail-suspension test commenced. These differences in immobility time between wild-type and MOP-KO mice were not found during the second trial of the tail-suspension test on the next day (data not shown).

To test another type of stress stimulus, immobility time during the 6 min, 5-consecutive-day forced swim test was also analyzed in wild-type and MOP-KO mice (Fig. 4). Both genotypes and both male and female mice showed time-dependent increases in immobility time (Fig. 4a–d). Furthermore, immobility time during the 6 min forced swim test significantly increased, or tended to increase, in

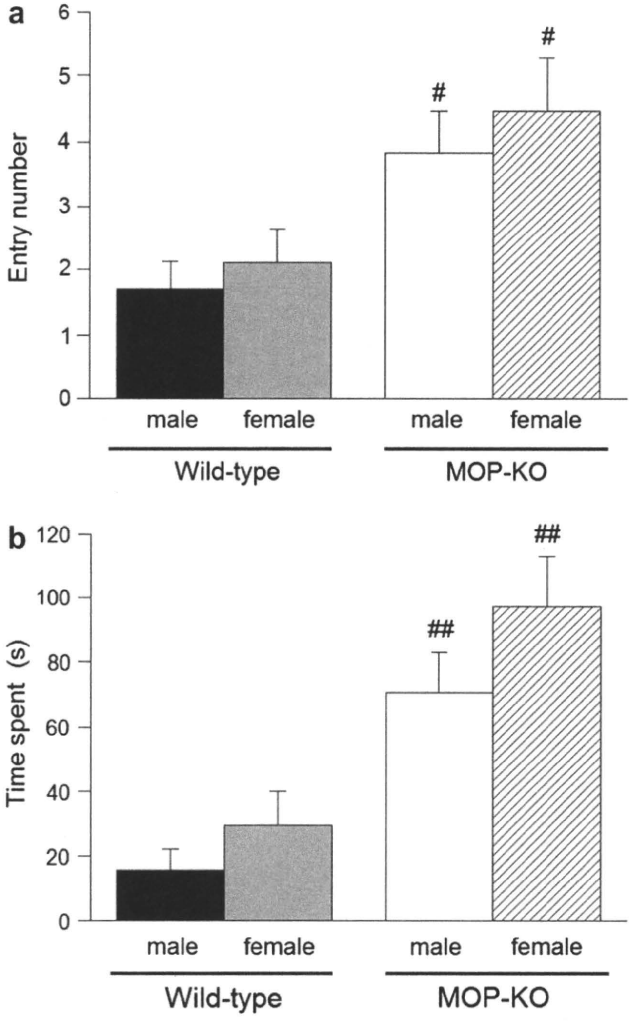

Fig. 1. Anxiety-like behavior in wild-type and MOP-KO mice in the elevated plus maze. The (a) number of entries and (b) time spent in the open arms of the elevated plus maze were measured for 5 min in wild-type mice (male, $n = 10$; female, $n = 9$) and MOP-KO mice (male, $n = 12$; female, $n = 13$). $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, significant difference from corresponding value in wild-type mice. Data are expressed as mean ± SEM.

a day-dependent manner (wild-type male mice: $F_{4,45} = 8.07$, $p < 0.001$; wild-type female mice: $F_{4,40} = 11.9$, $p < 0.001$; MOP-KO male mice: $F_{4,30} = 2.35$, $p = 0.077$; MOP-KO female mice: $F_{4,30} = 7.00$, $p < 0.001$; two-way, repeated-measures ANOVA). *Post hoc* comparisons revealed that immobility time on days 2–5 significantly increased compared with day 1 in both wild-type male and female mice ($p < 0.05$). Immobility time significantly increased on day 5 compared with day 1 in MOP-KO male mice and on days 4 and 5 compared with day 1 in MOP-KO female mice ($p < 0.05$). A three-way, mixed-design ANOVA of total immobility time during the 6 min tests on each of the 5 days with two within-subjects factors (genotype and gender) revealed that immobility time was significantly different between genotypes ($F_{1,29} = 10.9$, $p < 0.005$) but was not significantly different between genders ($F_{1,29} = 1.39$, $p = 0.248$) (Fig. 4e). Thus, when the male and female data were combined (Fig. 4f), MOP-KO mice showed significantly less immobility time compared with wild-type mice on days 2, 3, and 4.

We then analyzed stress-induced changes in plasma corticosterone concentrations in wild-type and MOP-KO mice (Fig. 5). The three types of stress significantly increased plasma corticosterone

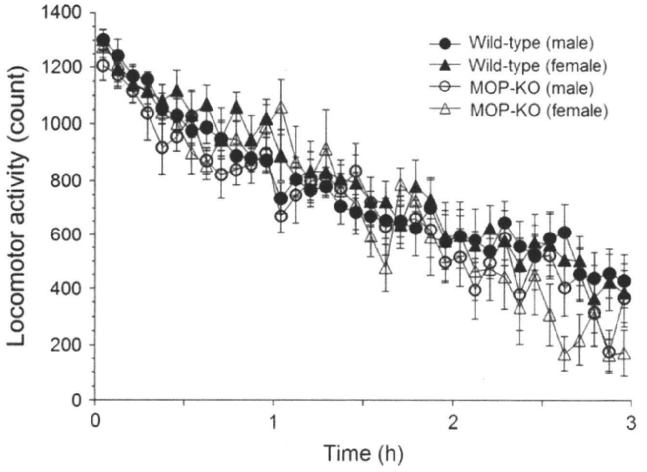

Fig. 2. Spontaneous locomotion in wild-type and MOP-KO mice. Spontaneous locomotion during 3 h habituation to a novel environment in wild-type mice (male, $n = 12$; female, $n = 9$) and MOP-KO mice (male, $n = 6$; female, $n = 7$). Each point represents the sum of 5 min locomotor activity. Data are expressed as mean ± SEM.

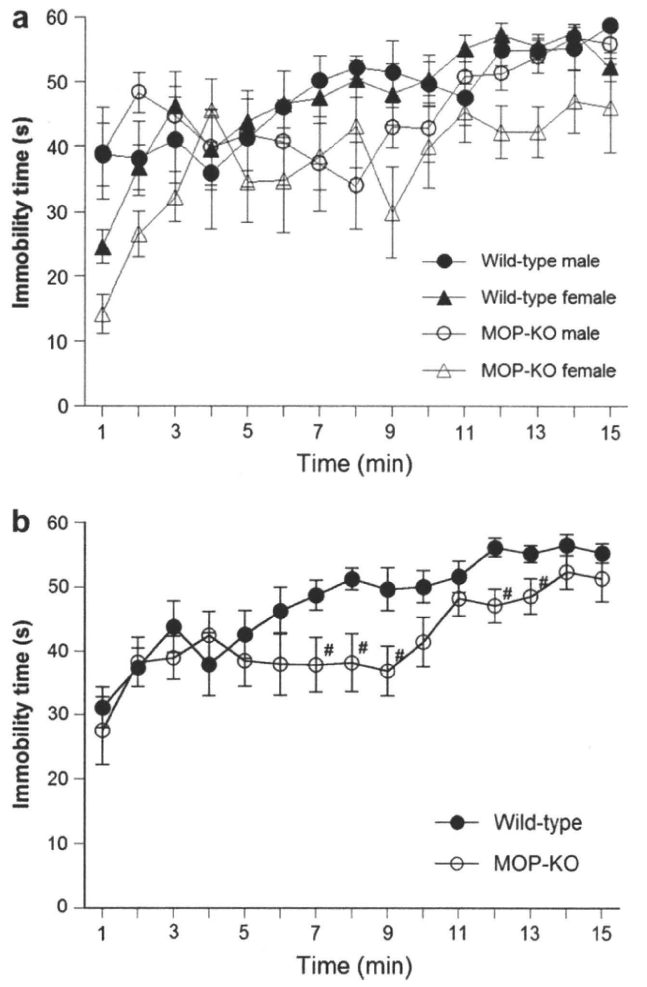

Fig. 3. Immobility in wild-type and MOP-KO mice in the 15 min tail-suspension test. (a) Immobility time was measured in wild-type mice (male, $n = 6$; female, $n = 7$) and MOP-KO mice (male, $n = 7$; female, $n = 6$). (b) Combined data of male and female mice in the 15 min tail-suspension test. $^{\#}p < 0.05$, significant difference from corresponding value in wild-type mice. Data are expressed as mean ± SEM.

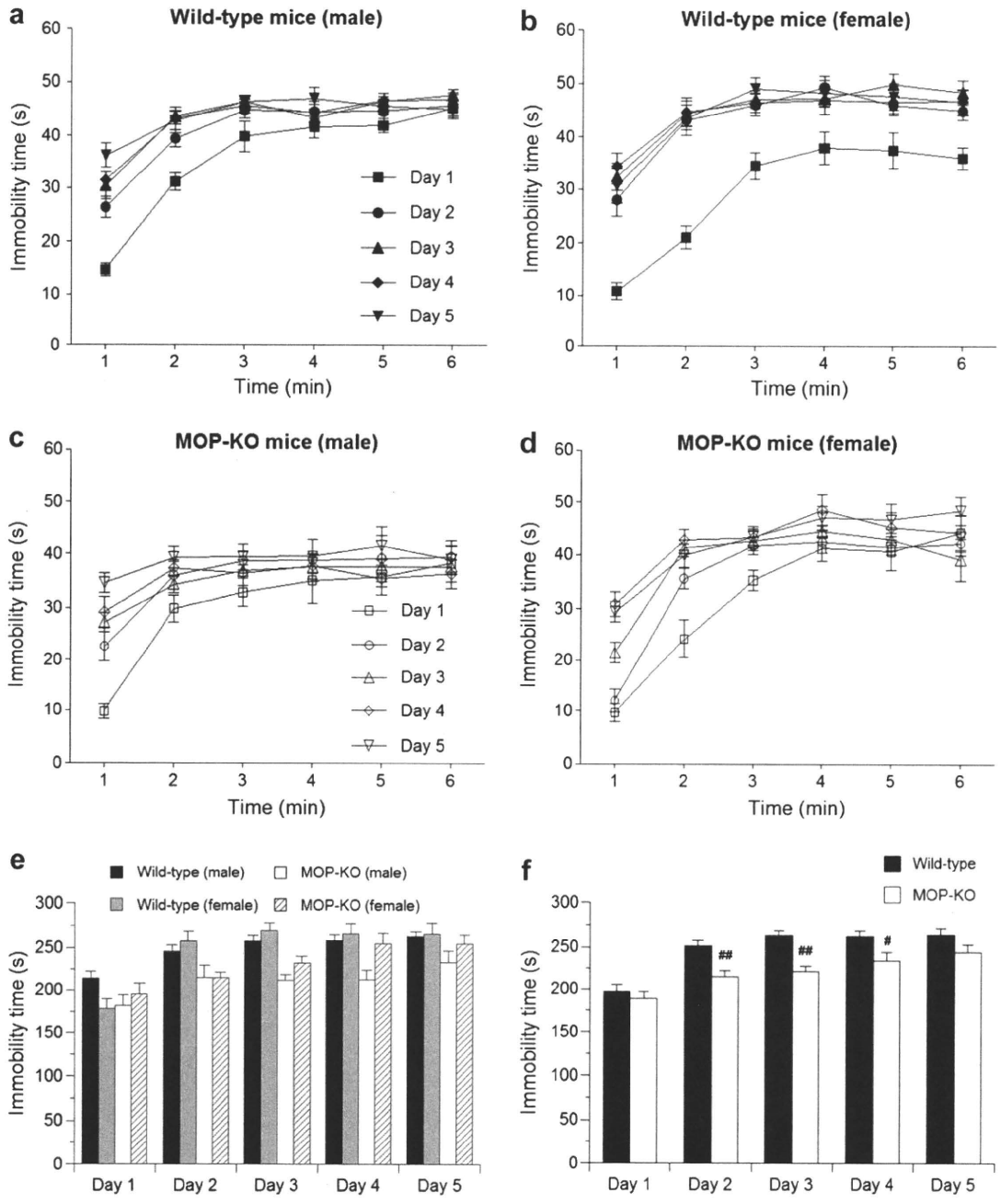

Fig. 4. Immobility in wild-type and MOP-KO mice in the 6 min, 5-consecutive-day forced swim test. Immobility time was measured in (a) wild-type male mice ($n = 10$), (b) wild-type female mice ($n = 9$), (c) MOP-KO male mice ($n = 7$), and (d) MOP-KO female mice ($n = 7$). (e) Sum of 6 min immobility time over 5 days. (f) Combined data of male and female mice. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, significant difference from corresponding value in wild-type mice. Data are expressed as mean ± SEM.

concentrations in both genotypes and in both male and female mice ($p < 0.05$, Student's t-test). Although no significant differences were observed in basal plasma corticosterone concentrations in naive mice, the stress-induced increases in plasma corticosterone concentrations were significantly different ($p < 0.05$, Student's t-test), or tended to be significantly different (restraint stress in female mice: $p = 0.065$, Student's t-test), between genotypes in both male and female mice. Both male and female MOP-KO mice had significantly lower plasma corticosterone concentrations compared with wild-type mice after the stress procedures. Although female mice tended to have slightly higher corticosterone concentrations than male mice (i.e., naive or after tail-suspension or restraint stress), no significant differences were observed (Student's t-test). Contrary to these findings, female mice tended to exhibit lower corticosterone concentrations than male mice after forced swim stress in both genotypes, although no significant differences were observed (Student's t-test).

4. Discussion

In the present study, MOP-KO mice displayed significantly decreased immobility time in both the tail-suspension and repeated forced swim tests and significantly reduced stress-induced increases in plasma corticosterone concentrations compared with wild-type mice. Moreover, MOP-KO mice also entered more, and spent more time in, the open arms of the

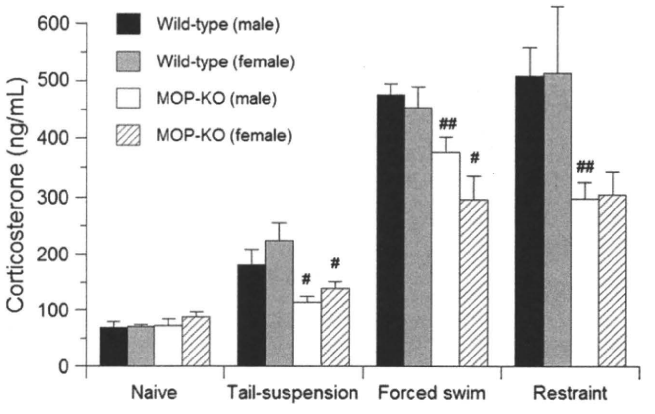

Fig. 5. Stress-induced increase in plasma corticosterone concentrations in wild-type and MOP-KO mice. Plasma corticosterone levels were analyzed (i) in naive wild-type mice (male, $n = 6$; female, $n = 5$) and MOP-KO mice (male, $n = 9$; female, $n = 8$), (ii) after the 2 day tail-suspension test in wild-type mice (male, $n = 6$; female, $n = 5$) and MOP-KO mice (male, $n = 9$; female, $n = 8$), (iii) after the 5 day forced swim test in wild-type mice (male, $n = 10$; female, $n = 8$) and MOP-KO mice (male, $n = 7$; female, $n = 7$), and (iv) after restraint stress in wild-type mice (male, $n = 6$; female, $n = 5$) and MOP-KO mice (male, $n = 9$; female, $n = 8$). $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, significant difference from corresponding value in wild-type mice. Data are expressed as mean ± SEM.

elevated plus maze. These results suggest that MOP-KO mice are resistant to stress exposure and exhibit fewer stress-induced emotional responses (i.e., anxiety- and depression-like behaviors) compared with wild-type mice, although the influences of other factors (e.g., response to novelty) should be considered in future studies.

No significant differences were observed in locomotor activity between wild-type and MOP-KO mice, although MOP-KO mice exhibited a slight tendency toward decreased locomotion. These results indicate that the present behavioral effects in MOP-KO mice were not attributable to variations in locomotor activity. MOP-KO mice entered more, and spent more time in, the open arms of the elevated plus maze in the present study. Similar results have been reported with another MOP-KO mouse strain in both the elevated plus maze test and light–dark box test (Filliol et al., 2000). This anxiolytic-like state of MOP-KO mice is consistent with a previous report in which the MOP-selective agonist DAMGO ([D-Ala^2, *N*-MePhe^4, Gly-ol]-enkephalin) induced anxiogenic-like activity in the elevated plus maze (Calenco-Choukroun et al., 1991). In contrast, several contradictory studies have reported an anxiolytic-like effect of morphine and MOP agonists (Asakawa et al., 1998; Koks et al., 1999). One of the reasons for this discrepancy using MOP-selective ligands might involve other opioid receptor subtypes. The most selective ligands for a specific opioid receptor subtype possess certain affinities for other subtypes (Newman et al., 2002). Although further studies using our and other MOP-KO mouse strains in various paradigms to assess anxiety-like responses (e.g., open field test) might be needed, the present results suggest that MOPs are involved in anxiety-like responses to height stress.

The decrease in immobility time in MOP-KO mice compared with wild-type mice in both the tail-suspension and repeated forced swim tests is consistent with previous reports. The decrease in immobility time in the forced swim test has been reported using another MOP-KO mouse strain (Filliol et al., 2000). These results suggest that MOP activation facilitates stress-induced, depression-like behavioral responses. Additionally, Fichna et al. (2007) reported contradictory findings in which intracerebroventricular treatment with endomorphin-1 and -2, endogenous MOP-selective peptides, decreased immobility time in both the forced swim and tail-suspension tests. Codeine, a relatively weak MOP agonist, also decreased immobility time in tail-suspension tests in mice (Berrocoso and Mico, in press). Although these reports might suggest that the MOP modulates depression-like behavior in contrast to our present results, other reports are consistent with our results. Chronic morphine facilitated immobility time in a rat forced swim test (Molina et al., 1994). Pretreatment with naloxone, a nonselective opioid receptor antagonist, decreased immobility time in a forced swim test in mice (Amir, 1982). Furthermore, intraperitoneal treatment of morphine enhanced immobility time in rats in a naloxone-sensitive manner (Zurita and Molina, 1999). These discrepant results might be attributable to differences in animals, mouse strains, time course, injection route, or other experimental conditions. Notably, different mouse strains have exhibited differential responses in forced swim tests (David et al., 2003). Further studies may reveal the reasons for these discrepant results.

To study the involvement of the MOP in emotional responses to repeated stress, the present study used both the 6 min forced swim test conducted for 5 consecutive days and the 15 min tail-suspension test conducted for 2 consecutive days, two regimens which were modified from typically used procedures in mice (Porsolt et al., 1977; Steru et al., 1985). When we analyzed immobility time from day 1 at 3–6 min in the forced swim test (excluding the data from the first 2 min), no significant differences were found between wild-type and MOP-KO mice. Additionally, no significant differences in immobility time were observed from day 1 for the first 6 min between wild-type and MOP-KO mice in the tail-suspension test. Although standard procedures for the analysis of depression-like behavior did not reveal significant differences, MOP-KO mice showed significant differences in depression-like behavior after repeated or longer stress exposure in the forced swim and tail-suspension tests. Our present results might suggest that MOPs facilitate emotional responses to repeated or longer stress exposure. In the present procedures, MOP-KO mice exhibited significantly decreased immobility time in the repeated forced swim test only on days 2, 3, and 4, and they only showed a tendency toward decreased immobility on day 5. In the tail-suspension test, MOP-KO mice had significantly decreased immobility time only after the first 5 min from the beginning of the test during the first trial, and no significant differences were observed during the second trial. Interestingly, the increase in plasma corticosterone concentrations in MOP-KO mice was still significantly lower than wild-type mice after the differences in behaviors between wild-type and MOP-KO mice in both tests disappeared. MOPs may facilitate the early behavioral responses to stress but are not necessary to fully express the behavioral responses after chronic stress procedures. Other neuronal systems might regulate the expression of stress-induced behavioral responses, and MOPs might facilitate this regulation.

At the hormonal level, one of the major responses to stress is an increase in corticosterone secretion caused by stimulation of the HPA axis. In the present study, plasma corticosterone concentration significantly increased after stress exposure in both wild-type and MOP-KO mice. The increased corticosterone levels after both forced swim and restraint stress were higher than after the tail-suspension test. This finding might be attributable to differences in the intensity of the stressors, although variations in the duration and frequency of these stressors might modify these levels. Additionally, the stress-induced increases in plasma corticosterone concentration were less in MOP-KO mice compared with wild-type mice. Our present results are consistent with previous reports. Endogenous opioids have been reported to have facilitatory effects on the HPA axis (Douglas et al., 1998). The increase in plasma corticosterone levels by morphine indicated activation of the HPA axis by MOP (Coventry et al., 2001; Ignar and Kuhn, 1990). In a different MOP-KO mouse strain, morphine- and restraint

stress-induced increases in plasma corticosterone levels were also reduced (Roy et al., 2001; Wang et al., 2002). Stress is well known to activate the HPA axis and increase norepinephrine release in the locus coeruleus. Moreover, stress-induced norepinephrine release in the locus coeruleus is partially regulated by both opioid and noradrenergic mechanisms (Nakai et al., 2002; Nestler et al., 1999; Valentino and Van Bockstaele, 2001), suggesting that MOPs may be involved in the activation of the HPA axis and locus coeruleus.

Knockout animals may be hypothesized to have potential utility in investigating the *in vivo* roles of specific proteins. Previous reports using gene mutant mice suggest that MOPs play an important role in various effects of opioids, such as antinociception, tolerance, reward, and locomotion (Ide et al., 2004; Matthes et al., 1996; Sora et al., 2001, 1997). Our present results also demonstrated the involvement of MOPs in stress-induced emotional responses. However, although no differences in DOP and KOP expression were evident in MOP-KO mice in the present study (Sora et al., 1997), several compensatory changes might occur in MOP-KO mice. These possible compensatory changes, especially with regard to neurotransmitter release and hormonal valence, could elicit changes in stress-induced emotional responses. Future studies, such as behavioral analyses using MOP-KO mice with viral expression of MOPs, may reveal the influences of compensatory changes in stress-induced emotional responses.

Gender differences in emotional responses may also exist (Toufexis, 2007; Toufexis et al., 2006). In the present study, several differences were found between male and female mice in stress-induced emotional responses, although these differences were not significant. In the elevated plus maze, female mice showed less anxiety-like behavior than male mice of both genotypes. These results are consistent with previous reports using rodents (Fernandes et al., 1999; Steenbergen et al., 1990) and suggest the presence of gender differences in anxiety-like behavior. However, no differences in immobility time were found between male and female wild-type mice in either the tail-suspension or forced swim tests. A previous report found that male and female C57BL/6J mice, the genetic background strain used in the present study, exhibited no differences in immobility time in either the tail-suspension or forced swim tests (Caldarone et al., 2003). Interestingly, female MOP-KO mice tended to exhibit less immobility in the tail-suspension test and more immobility in the forced swim test compared with male MOP-KO mice. Although the present study found no significant differences between genders, and additional studies may be required, MOPs may differentially modulate depression-like responses in both tests, especially in female mice.

In conclusion, we found decreased anxiety-like behavior in the elevated plus maze, decreased immobility in both the tail-suspension and forced swim tests, and reduced stress-induced plasma corticosterone concentrations in MOP-KO mice compared with wild-type mice. These results suggest that MOPs play an important facilitatory role in stress sensitivity and/or stress-induced emotional responses, including anxiety- and depression-like responses.

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Quality of life and cognitive dysfunction in people with schizophrenia

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ABSTRACT

The main purpose of the present study was to examine the relationship between quality of life (QOL) and cognitive dysfunction in schizophrenia. Subjects were 61 stabilized outpatients. Quality of life and cognitive function were assessed using the Quality of Life Scale (QLS) and the Brief Assessment of Cognition in Schizophrenia (BACS), respectively. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). The BACS composite score and the BACS Verbal memory score were positively correlated with the QLS total score and two subscales. The BACS Attention and speed of information processing score had positive correlation with the QLS total and all the subscales scores. The PANSS Positive and Negative syndrome scores also had significant correlations with the QLS total score and all of the subscales. In addition, the CDSS score was negatively correlated with the QLS total score and some of the subscales. Stepwise regression analysis showed that the BACS Attention and speed of information processing score was an independent predictor of the QLS total score but it was less associated with the QLS than the PANSS Negative syndrome score and the CDSS score. The results suggest that negative and depressive symptoms are important factors on patients' QOL and also support the view that cognitive performance provides a determinant of QOL in patients with schizophrenia.

1. Introduction

Quality of life (QOL) is thought to be one of the key outcome variables in the treatment of schizophrenia (**Matsui et al., 2008**), and the importance of evaluating it has been increasing in patient care and clinical research. Previous studies have revealed that several clinical factors such as negative and positive symptoms, depressive symptoms, and extrapyramidal adverse effect are associated with lowered QOL (**Browne et al., 1996; Dickerson et al., 1998; Smith et al., 1999; Norman et al., 2000; Fitzgerald et al., 2001; Rocca et al., 2005; Strejilevich et al., 2005; Bozikas et al., 2006; Hofer et al., 2006; Tomotake et al., 2006; Aki et al., 2008; Yamauchi et al., 2008**). Moreover,**Yamauchi et al. (2008)** reported that QOL correlated with dose of antipsychotics, and **Xiang et al. (2007) and Browne et al. (1996)** demonstrated that number of hospitalizations and duration of illness were associated with QOL.

Recently, cognitive dysfunction has been paid much more attention because they may lead to poor social functioning. Cognitive dysfunction is thought to be a core feature of schizophrenia (**Kraus and Keefe, 2007**), and it has been reported that cognitive functions of schizophrenia patients are of the order of one to two standard deviations below the mean of healthy controls in several cognitive dimensions, particularly memory, attention, verbal fluency, and executive function (**Heinrichs**

Abbreviations: BACS, the Brief Assessment of Cognition in Schizophrenia; CDSS, the Calgary Depression Scale for Schizophrenia; DIEPSS, the Drug-Induced Extrapyramidal Symptoms Scale; PANSS, the Positive and Negative Syndrome Scale; QLS, the Quality of Life Scale; QOL, quality of life.

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and Zakzanis, 1998; Gold, 2004; Kraus and Keefe, 2007; Savilla et al., 2008).

Previous research groups have studied the relationship between QOL and cognitive function in people with schizophrenia, and reported the significant correlations between QOL and some domains of cognitive function such as verbal memory, vocabulary, fluency performance, attention, social knowledge, and executive function (Dickerson et al., 1998; Addington and Addington, 2000; Bozikas et al., 2006; Ritsner, 2007; Matsui et al., 2008; Savilla et al., 2008). Although, considering the results of previous studies, it is clear that cognitive dysfunctions and some clinical symptoms are significantly correlated with lowered QOL in schizophrenia patients, it seems to remain unclear how much impact these factors have on patients' QOL. Some studies demonstrated that cognitive dysfunction has a greater influence on patients' QOL than do positive symptoms (Breier et al., 1991; Green, 1996; Ho et al., 1998). On the other hand, some reported that neuropsychological function had a little impact on patients' QOL in the presence of some clinical symptoms (Wegener et al., 2005; Matsui et al., 2008). The discrepancy among these studies might have been caused by differences of sample population, sample size, cognitive tests, and QOL scales (Breier et al., 1991; Green, 1996; Wegener et al., 2005; Matsui et al., 2008).

The purpose of the present study was to elucidate clinical determinants of QOL in schizophrenia patients with a special reference to cognitive dysfunction. Using a schizophrenia disease-specific QOL measure, we have already studied and reported significant correlations between QOL and negative factor, cognitive factor, and emotional discomfort factor which derived from the Positive and Negative Syndrome Scale (PANSS). But we did not assess cognitive function with a real neuropsychological battery in the study (Yamauchi et al., 2008). Hofer et al. (2007) demonstrated that clinical assessment of cognitive deficits on PANSS is not a viable alternative to neuropsychological testing to obtain information about cognitive functioning in schizophrenia. Therefore, in the present study, we assessed cognitive function using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004; Kaneda et al., 2007) that is a newly developed neuropsychological battery for assessing cognitive function of schizophrenia patient.

2. Methods

2.1. Subjects

Clinical data were collected at Department of Psychiatry, Tokushima University Hospital from 1 October 2007 to 31 March 2009. Treating psychiatrists consecutively asked 77 stabilized outpatients with a DSM-IV diagnosis of schizophrenia to participate in this study every weekday for the first 6 months and a particular day of the week for another 12 months. Subjects were excluded if they presented with any organic central nervous system disorder, epilepsy, mental retardation, severe somatic disorder, drug dependence, or alcohol dependence. Of 77 patients, 62 gave us written informed consent to participate in this study. As one subject did not complete all the assessments, data from 61 were used for analysis. This study was approved by the Ethics Committee of University of Tokushima.

All subjects had been regularly receiving outpatient treatment. The information on patients was obtained from both patients and family members living with them by treating psychiatrists. Their mean age was 40.1 years (SD = 12.2), ranging from 20 to 60 years old. The subjects had never been hospitalized during the previous 6 months, including 13 who had never had inpatient treatment. 45 had followed the same antipsychotic regimen for at least 6 months before recruitment. Although 16 subjects had slight changes in regimen during the previous six months, the 16 were judged as clinically stabilized by the treating psychiatrists.

2.2. Procedure

To assess QOL, we used the Quality of Life Scale (QLS) (Heinrichs et al., 1984, 2001). Cognitive function was evaluated using the BACS. Clinical symptoms were evaluated using the PANSS, the Calgary Depression Scale for Schizophrenia (CDSS), and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).

The QLS is a rating scale to assess QOL by means of semistructured interview. The ratings are based upon patients' self-report and observers' judgment about the functioning and life circumstances. This instrument includes four subscales measured by a total of 21 items, and each item is rated from 0 to 6. The four subscales are Interpersonal relations, Instrumental role, Intrapsychic foundation, and Common objects and activities. Higher scores indicate higher levels of QOL. Experienced psychiatrists who have been treating the patients for a long term and understood the patients' living conditions conducted the interviews according to the Evaluation Manual for the QLS (Heinrichs et al., 2001). They got information about the patients from family members and psychiatric social workers when it was necessary.

The BACS has been developed for clinical trials with a brief battery of tests for measuring cognition. It assesses the aspects of cognition that were found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The domains of cognitive function that are evaluated by the BACS are Verbal memory (List learning), Working memory (Digit sequencing task), Motor speed (Token motor task), Verbal fluency (Category instances and Controlled oral word association test), Attention and speed of information processing (Symbol coding), and Executive function (Tower of London). The BACS is fully portable, and is designed to be easily administered by a variety of testers, including nurses, clinicians, psychiatrists, neurologists, social workers, and other mental staff (Keefe et al., 2004; Kaneda et al., 2007). It was reported that the Japanese version of it was a reliable and practical scale to evaluate cognitive function in schizophrenia (Kaneda et al., 2007). In the present study, we used the Japanese version of the BACS and the BACS data were collected by clinical psychologists who were very experienced and well trained for the use of it.

The PANSS was originally designed as a rating scale that represents Positive, Negative and General psychopathology (Kay et al., 1987, 1991). The score ranges from 30 to 210 for the global score, and higher score indicates a greater level of symptom severity. Some of the authors who were all experienced psychiatrists conducted the interviews according to the Evaluation Manual for the PANSS (Kay et al., 1991).

The CDSS was specifically developed to distinguish depressive symptoms from positive and negative symptoms or antipsychotic-induced side effects. This scale is a 9-item questionnaire (depression, hopelessness, self-deprecation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicidality, and observed depression), and higher score indicates a greater level of depression. The reliability and validity of the scale have been verified (Addington et al., 1993; Kaneda et al., 2000).

The DIEPSS is composed of eight individual parameters (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia) and one global assessment constructed to assess extrapyramidal adverse effects, using 5-point scale that ranges from 0 to 4. Higher score indicates greater level of extrapyramidal adverse effects. In this study, the sum of eight individual parameters was considered the extrapyramidal symptoms score. Some of the authors assessed the drug-induced extrapyramidal symptoms according to the Rater's Manual for the DIEPSS (Inada, 1996).

2.3. Statistical analysis

Spearman rank correlation coefficients were calculated to study the relationship between the QLS and other clinical variables including the BACS scores, the PANSS Positive syndrome score, the

Table 1
Demographic characteristics of subjects (mean ± SD).

N (MW)		61(33/28)
Age (years)		40.1 ± 12.2
Duration of illness (yrs)		15.5 ± 9.3
Number of hospitalization		2.1 ± 2.3
Dose of antipsychotics (mg/day)*		642.3 ± 5011
Type of schizophrenia (n)		38
Paranoid		
	Residual	13
	Disorganized	5
	Catatonic	4
	Undifferentiated	1
Marital state (n)	Married	6
	Never married	52
	Divorced	2
	Widowed	1
Social state (n) Full time	14	
	Part time	8
	No employment	39
PANSS	Total	61.3 ± 164
	Positive	13.4 ± 4.8
	Negative	18.0 ± 6.6
DIEPSS (Total)		1.6 ± 2.4
	CDSS (total)	3.2 ± 3.1
BACS	Verbal memory	33.6 ± 18.1
	Working memory	17,1 ± 6.4
	Motor speed	66.9 ± 18.5
	Attention and speed of information processing	50.8 ± 12.9
	Verbal fluency	37.3 ± 10.6
	Executive function	14.9 ± 5.3
QLS	Total	62.8
	Interpersonal relations	22.7 ± 12.7
	Instrumental role	10.3 ± 6.9
	Intrapsychic foundations	22.5 ± 9.4
	Common objects and activities	7.4 ± 2.9

* Chlorpromazine equivalent.
PANF, Positive and Negative Syndrome Sale; DIEP, Drug Induced Extrapyramidal Symptoms Scale; CDSS, Calgary Depression Scale for Schizophrenia BACS, Brief Assessment of Cognition in Schizophrenia QLS, Quality of Li Scale.

PANSS Negative syndrome score, the CDSS score, the DIEPSS score, duration of illness, number of hospitalization, and dose of antipsychotics. As several data were non-normal distribution, we used non-parametric test for correlation analysis. Statistical significance was adjusted for multiple comparisons (Bonferroni correction). Then, the QLS total and the subscale scores were chosen as dependent variables. Using the clinical variables that showed significant correlations with each dependent variable, forward stepwise regression analyses were performed to assess which clinical variables were the best predictor of each dependent variable. Statistical analyses were done with the Statistical Package for the Social Sciences, version 14.0 J.

3. Results

Demographic characteristics and means and standard deviations of the clinical indices are presented in Table 1. All subjects were Japanese. 33 were males and 28 females. We used the chlorpromazine conversion chart to determine the dosage of antipsychotic medication (**Inagaki and Inada, 2006**).

The performance of subjects on each test of the BACS was standardized by creating z-scores whereby the healthy control mean was set to zero and the standard deviation set to one. The control data used to compare the performance of our subjects with that of healthy controls were collected by **Kaneda et al. (2008)**. The mean age of the healthy control subjects ($n = 76$) was 38.3 years (SD = 14.2). Z-score for Verbal memory is −1.68 (SD = 1.28), that for Working memory −1.23 (SD = 1.78), that for Motor speed −1.81 (SD = 1.64), that for Attention and speed of information processing −1.66 (SD = 1.19), that for Verbal fluency −0.82 (SD = 1.11), and that for Executive function −1.20 (SD = 1.95).

3.1. QOL and cognitive function

The correlations between the QLS scores and the BACS scores are shown in Table 2. The BACS composite score, Attention and speed of information processing score, and Verbal memory score showed significant and positive correlations with the QLS total and all or some subscale scores. The individual data points from the correlation between the QLS and the BACS composite score is presented in Fig. 1.

Table 2
Correlation between QLS and BACS and clinical indices.

	QLS				
	Total	Interpersonal relations	Instrumental role	Intrapsychic f oundation	Common objects and activities
BACS					
Verbal memory	0.419**	0.415**	0.311	0.422**	0.295
Working memory	0.281	0.283	0.142	0.290	0.259
Motor speed	0.196	0.175	0.126	0.222	0.228
Attention and speed of information processing	0.51	0.495**	0.372*	0.541**	0.418**
Verbal fluency	0.203	0.200	0.154	0.206	0.170
Executive function	0.168	0.174	0.103	0.131	0.175
Composite score[a]	0.341*	0.346*	0.205	0.341*	0.305
PANSS					
Positive	−0.478**	−0.475**	0.400**	−0.441**	0.394*
Negative	−0.640**	−0.632**	−0.363*	0.685	−0.650
CDSS	−0.381*	0.360*	0.440**	0.342*	−0.249
DIEPSS	−0.317	−0.290	−0.221	−0.346*	−0.463**
Duration of illness	−0.279	−0.294	−0.212	−0.298	−0.300
Number of hospitalization	0.088	0.133	−0.025	0.001	0.027
Dose of antipsychotics	−0.215	−0.192	−0.191	−0.259	−0.227

*P<005; **P<0.01. Spearman rank correlations (Bonferroni correction).
BACS, Brief Assessment of Cognition in Schizophrenia. QLS, Quality of Life Scale.

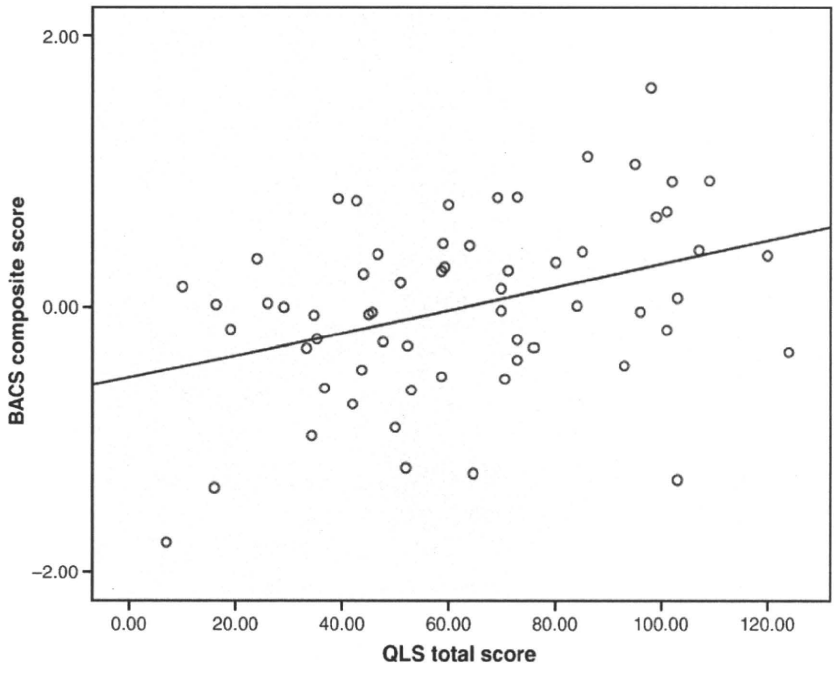

Fig. 1. Relationship between QLS total score and BACS composite score ($r = 0.341$, $p < 0.05$).

3.2. QOL and other clinical variables

The correlations between the QLS scores and clinical variables are shown in Table 2. The PANSS Positive syndrome scale score, the PANSS Negative syndrome scale score, the CDSS score, and the DIEPSS score had significant and negative correlations with the QLS total and all or some subscale score. However, there was no significant correlation between the QLS and duration of illness, number of hospitalization, and dose of antipsychotics. Figs. 2–4 show the individual data points from the correlations between the QLS total score and the PANSS Positive syndrome scale score, the PANSS Negative syndrome scale score, and the CDSS score, respectively.

3.3. Predictors of QOL

Table 3 shows the results of stepwise regression analyses. The QLS total score was significantly predicted by the PANSS Negative syndrome scale score, the CDSS score, and the BACS Attention and speed of information processing score. Interpersonal relations subscale score was significantly predicted by the PANSS Negative

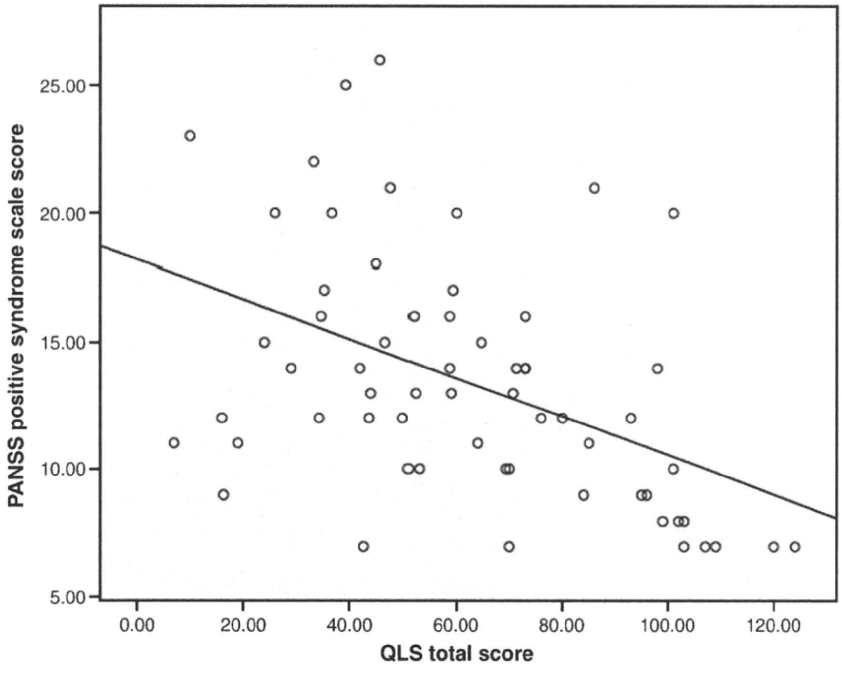

Fig. 2. Relationship between QLS total score and PANSS positive syndrome scale score ($r = -0.478$, $p < 0.01$).

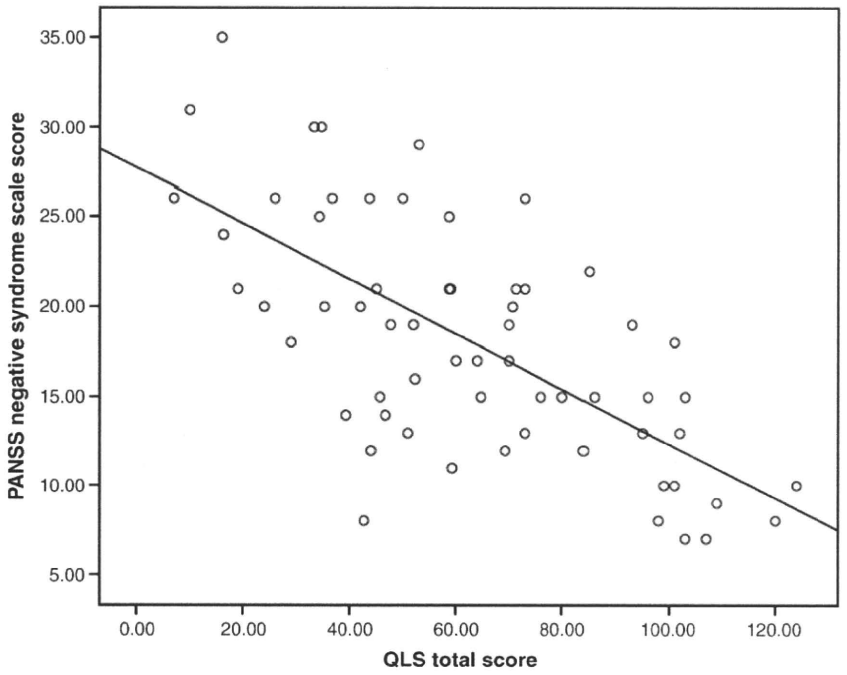

Fig. 3. Relationship between QLS total score and PANSS negative syndrome scale score ($r=-0.640$, $p<0.01$).

syndrome scale score and the CDSS score. The CDSS score and the PANSS Negative syndrome scale score significantly predicted Instrumental role subscale score. Moreover, the Intrapsychic foundation subscale score was significantly predicted by the PANSS Negative syndrome scale score, the CDSS score, and the BACS Attention and speed of information processing score. The only significant predictor of the Common objects and activities subscale score was the PANSS Negative syndrome scale score.

4. Discussion

As QOL is considered a very important outcome in the treatment of schizophrenia, greater attention has been paid to it in recent years. QOL is generally thought to include life satisfaction, social functioning, daily living activities, and physical health (**Aki et al., 2008; Yamauchi et al., 2008**). Some studies have demonstrated that QOL has significant correlations with cognitive dysfunctions, psychotic symptoms, and

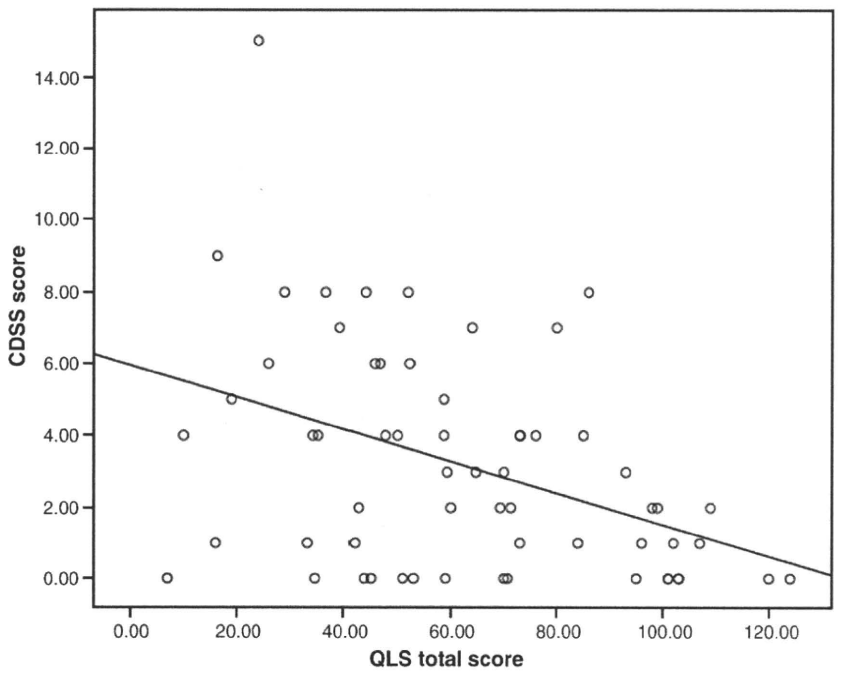

Fig. 4. Relationship between QLS total score and CDSS score ($r=-0.381$, $p<0.01$).

Table 3
Results of stepwise regression analyses on QLS.

Dependent variable	Independent variable	Adjusted R^2	B
Total	PANSS-negative	0.585***	−0.551***
	CDSS		−0.340***
	BACS-attention and speed of information processing		0.192*
Interpersonal relations	PANSS-negative	0.490***	−0.619***
	CDSS		−0.299**
Instrumental role	CDSS	0.302***	−0.429***
	PANSS-negative		−0.339**
Intrapsychic foundation	PANSS-negative	0.647***	0.625***
	CDSS		−0.304***
	BACS-attention and speed of information processing		0.176*
Common objects and activities	PANSS-negative	0.432***	−0.664***

*P<0.05; **P<0.01; ***p<0.001.
PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; BACS, Brief Assessment of Cognition in Schizophrenia; QLS, Quality of Life Scale. PANSS-negative, The PANSS negative symdrom scal score;BACS-attention and speed of information processing, Attention and speed of information processing score of BACS.

other clinical factors. However, there seems to be no unanimous predictors of schizophrenia patients' QOL. In the present study, we tried to elucidate the predictors and how much impact each predictor has on patients' QOL measured by the QLS. The QLS is schizophrenia disease-specific QOL scale and widely used in schizophrenia research, and it was originally designed to assess deficit symptoms and the dysfunctions related to them outside institutions (**Heinrichs et al., 1984**).

Cognitive impairments in schizophrenia have been reported repeatedly. **Keefe et al. (2006)** reported that the BACS composite score was significantly correlated with functional capacity and real-world functional outcome in schizophrenia. In the current study, the performance of subjects on each of the primary measures of the BACS demonstrated about one to two standard deviations below the healthy control mean. The degree of cognitive dysfunctions in the present sample was consistent with that of the previous studies (**Keefe et al., 2004**; **Kaneda et al., 2008**).

As for the relationship between QOL and cognitive function, the results of the present study were rather consistent with those of previous researches in terms of that cognitive dysfunction was on the whole related to lowered QOL (**George et al., 1996**; **Bozikas et al., 2006**; **Savilla et al., 2008**; **Yamauchi et al., 2008**). In the current study, the BACS composite score and Verbal memory score were significantly correlated with the QLS total and Interpersonal relations and Intrapsychic foundation subscales scores. The BACS Attention and speed of information processing score was strongly associated with the QLS total and all the subscale scores. These results have some different points from the previous findings (**Bozikas et al., 2006**; **Savilla et al., 2008**). The differences seem to reflect the differences in which types of cognitive tests researchers used and what types of subjects they investigated. In the study by **Bozikas et al. (2006)**, a different neuropsychological test battery consisted of nine tests for the putative neurocognitive domains was used. **Savilla et al. (2008)** investigated the relationship between the QLS and the BACS, and did not find the significant correlation between the QLS and the BACS Attention and speed of information processing domain. However, their subjects included schizophrenia patients with abuse of alcohol (25.8%) or other substances (29%). Moreover, there were differences of the patient's average ages and psychotic symptoms severity, which might cause the different results.

Regarding the associations between QOL and other clinical variables, our results showed that QOL was significantly correlated with positive, negative, depressive and extrapyramidal symptoms. On the other hand, no significant correlation was found between QOL and duration of illness, number of hospitalization, or dose of antipsychotics. **Yamauchi et al. (2008)** demonstrated that Negative factor derived from the PANSS was correlated significantly with the QLS total and all the subscales, and **Savilla et al. (2008)** reported that both the PANSS Positive and Negative symptoms scores were strongly associated with them. Moreover, **Rocca et al. (2005)** showed that the CDSS score was significantly correlated with the QLS scores. Our results seem to support these previous findings. However, the results may be affected by measurement overlap because the QLS and the PANSS have some similar items. Besides, there is a possibility that some significant correlation might be caused by the fact that some items of the PANSS are not scored simply on symptom severity but on the degree of functional disturbance the symptom causes. For example, score of 4 or more on the item of delusion of the PANSS positive syndrome scale is judged on both the symptom severity and the functional impairment the symptom causes, and score of 3 or more on the item of passive/apathetic social withdrawal of the PANSS negative syndrome scale is judged mainly on the impairment of social functioning. That may partly explain the significant correlation between the QLS and the PANSS. Therefore, in further study, it may be necessary to consider use of other scales such as the Scale for Assessment of Positive Symptoms (**Andreasen, 1984**) and the Scale for Assessment of Negative Symptoms (**Andreasen, 1983**) that hardly conflate functioning with symptoms.

Although there were several significant correlations between QOL and clinical variables in the present study, stepwise regression analyses clearly showed that negative and depressive symptoms and cognitive dysfunction in certain of domains were significant and independent predictors of QOL. Considering the beta coefficients of these predictors, it is clear that the negative symptom is the most important predictor of QOL and cognitive dysfunction also provides a determinant of QOL. **Wegener et al. (2005)** reported that neuropsychological variables were no longer significant predictors for QOL in the presence of psychiatric symptoms. **Narvaez et al. (2008) and Yamauchi et al. (2008)** also demonstrated that cognitive variable did not predict the QLS scores independently when doing multivariate analysis together with other clinical variables. However, we got a new finding that cognitive dysfunction in attention and speed of information processing domain is an independent predictor of QOL (the QLS total score) in people with schizophrenia. **Ritsner (2007)** reported a similar result that visual sustained attention was one of the independent predictors of Instrumental role subscale of the QLS but not that of the QLS total score. Our results suggest that cognitive dysfunction in attention and processing speed domain may be most strongly associated with lowered QOL in patients with schizophrenia.

The current study has some limitations. Considering the PANSS scores, our subjects seem to have rather mild psychotic symptoms,

which would cause the possibility that they did not represent the whole patients with schizophrenia. In addition, as the sample size was relatively small, we did not have an opportunity to assess subgroups of patients.

5. Conclusion

We investigated the independent predictors of QOL in people with schizophrenia, and found that not only negative and depressive symptoms but also cognitive dysfunction in attention and speed of information processing domain influenced patients' QOL. Our results support the view that cognitive performance provides a determinant of QOL in patients with schizophrenia. However, cognitive dysfunction had less association with the QLS than negative and depressive symptoms. Therefore, it is also suggested that treatment effort should be mainly paid to negative and depressive symptoms in order to improve patients' QOL.

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特集 統合失調症の予後改善に向けての新たな戦略

統合失調症治療におけるアウトカム指標*

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Key words

Schizophrenia, Outcome measure, Quality of life, Life skill, Cognitive function

はじめに

統合失調症治療のアウトカム指標として，疾病を持ちながらも心理的・社会的により健康的な生活が送れるようにという観点から quality of life (QOL) が重要視されるようになっている[21,22]。急性期治療においてある程度の精神症状の改善が得られ，薬物維持療法とリハビリテーションに移行する段階では，患者の QOL をできるだけよくするにはどうすればよいかという視点に立ち，治療を行うことが重要である。長期的な見通しを持った治療戦略を立てたり，その効果を評価するためには，QOL をはじめとして，生活技能や社会機能を適切に評価することが必要になる。

また，近年，就労などの社会的予後や QOL とも関連した重要な要因として認知機能障害が注目されるようになっている[13,30]。認知機能障害の存在は，社会復帰を目指した心理社会的治療がうまくいかない原因ともなるため，認知機能を適切に評価しておくことが，リハビリテーションの戦略を考えるうえでも重要になってきている。

本稿では，統合失調症治療におけるアウトカム指標として，QOL，生活技能・社会機能，認知機能について解説することとする。

QOL

統合失調症治療の重要なアウトカム指標の1つとして QOL が挙げられる。欧米では 1980 年代から統合失調症患者の QOL に関する研究が増えており，統合失調症患者の QOL は治療により改善が可能であること，他の精神症状評価尺度とは異なった変化をすること，最も患者指向の評価であること，などの理由からますますその重要性が増している。わが国でも 1990 年代後半の非定型抗精神病薬の臨床現場への登場以後，QOL への関心が高まってきている。従来の定型抗精神病薬と陽性症状に対する改善効果は同等であり，かつ，鎮静効果や錐体外路系の副作用が少なく陰性症状の改善効果も持つとされる非定型抗精神病薬の導入により，リハビリテーションを含めた心理

* Outcome Measures in the Treatment of Schizophrenia

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