healthy controls). IBM SPSS statistical software, version 20, was used for all analyses. We compared sex, age, education, CPZ equivalent doses, age at onset, duration of illness, positive scale, negative scale and General Psychopathology Scale between schizophrenia cases and control subjects using a Fisher's exact test, two-tailed t-test and Welch's t-test. Next, we compared d' in the CPT and CA, PEM, PEN, TE in the WCST between the case and control groups using a two-tailed t-test and Welch's test (*Table III*).

Patients' records were used to obtain relevant clinical information (e.g. age, education, CPZ equivalent doses, age at onset and duration of illness). Medication status of patients was investigated on the day when cognitive tests were conducted. Patients' medication status and positive and negative symptom scale (PANSS) (32) scores were obtained at the time of cognitive assessment.

Significance level in clinical information was set at p=0.0055 after Bonferroni correction (p=0.05/9). Significance level in five cognitive outcomes was set at p=0.01 after Bonferroni correction (p=0.05/5).

Results

In JGWAS and replication sample set, we did not detect any association in 2 SNPs (rs672607 and rs10494252) and schizophrenia (*Table I*). Joint analysis by PLINK also did not show significantly low p-value in both SNPs (*Table II*). Meta-analysis of the Japanese total sample and Chinese sample in rs672607 showed a significant association (p-value 0.012, odds ratio 0.855).

We investigated the genetic effects of rs672607 and rs10494252 on the CPT-IP and WCST. There was no significant (p<0.0055) difference in clinical information. There was a significant (p<0.01) difference between the A/A and G carrier group of rs672607 in CPT mean d' (p=0.0092) (*Table III*).

Discussion

In this study, we investigated the association between two SNPs within *BCL9* and schizophrenia in the Japanese population. We detected a significant (p=0.012) association between *BCL9* and schizophrenia in the meta-analysis of Japanese and Chinese sample set, however, as the Chinese GWAS dataset was included in the meta-analysis, evidence for the association might be overestimated. The minor allele of rs672607 may be a common variant associated with schizophrenia in the Asian population. Thus, further studies in different populations are needed.

In addition, one of the main obstacles in the identification of genetic variants for schizophrenia is its heterogeneous diagnostic entity, which is clinically relevant, though less appropriate for etiological and genetic research. Therefore, it was of interest to focus on alternative indicators of liability, or endophenotypes. We chose the CPT-IP that is designed to assess highly heritable traits (working memory and visual sustained attention) that are shown to be impaired in schizophrenic patients (33). The WCST was selected in order to evaluate executive function. We tested the association between candidate SNPs from our meta-analysis and cognitive performance measured by the

Table I Association study in JGWAS and the replication sample set.

		Case N	Control N	Total N	Case[b]	Control[b]	p-value[c]	Or[d]	L95[e]	U95[e]	HWEp[f]
rs672607 A>G (Ch1, 145519964a)	JGWAS	548	552	1100	0.375	0.393	0.37	0.92	0.78	1.10	0.47
	Replication	1464	1171	2635	0.374	0.392	0.22	0.93	0.83	1.05	0.87
rs10494252 C>A (Ch1, 145483560a)	JGWAS	548	552	1100	0.190	0.226	0.04	0.80	0.65	0.99	0.06
	Replication	1464	1171	2635	0.221	0.221	1.00	1.00	0.87	1.15	0.53

a. based on NCBI 36
b. minor allele frequency
c. p-value of Fisher's exact test
d. Odds ratio
e. Lower (L95) and upper (U95) 95% confidence intervals
f. Hardy-Weinberg Equilibrium test p-value in control

Table II Joint analysis of JGWAS and the replication sample set.

	Case N	Control N	Total N	p-value[a]	OR[b]	L95[c]	U95[c]	BDp[d]
rs672607 A>G	2012	1723	3735	0.13	0.93	0.84	1.02	0.95
rs10494252 C>A	2012	1723	3735	0.26	0.94	0.83	1.05	0.08

a. p-value of Cochran–Mantel–Haenszel stratified analysis by PLINK v1.07
b. Odds ratio
c. Lower (L95) and upper (U95) 95% confidence intervals
d. p-value of Breslow-Day test

Table III Cognitive performance of two SNPs in BCL9.

	rs672607 A>G						rs10494252 C>A					
	Cases (n=110)			Controls (n=76)			Cases (n=110)			Controls (n=76)		
	A/A[a] (n=31)	G carrier (n=79)	p-value[b]	A/Aa (n=21)	G carrier (n=55)	p-value[b]	C/Ca (n=61)	A carrier (n=49)	p-value[b]	C/Ca (n=48)	A carrier (n=28)	p-value[b]
Sex (Males/Females)	21/10	49/30	0.66	13/8	36/19	0.79	37/24	33/16	0.55	26/22	23/5	0.024
Age (years)	48.2	44.8	0.25	26.6	27.2	0.76	44.4	47.5	0.25	26.2	28.4	0.24
	13.6	14.2		7.6	8.1		13.5	14.6		6.9	9.3	
Education (years)	12.1	12.1	0.94	15.6	15.3	0.66	12.2	11.9	0.53	15.4	15.4	0.96
	2.5	2.2		2.8	2.5		2.4	2.2		2.5	2.7	
CPZeq (mg/day)[c]	630.5	627.5	0.97				640.6	612.9	0.69			
	378.4	355.1					340.9	386.1				
Age at onset (years)	26.6	26.7	0.97				25.9	27.5	0.43			
	10.7	10.3					9.0	11.9				
Duration of illness (years)	21.5	18.0	0.24				18.3	19.8	0.58			
	13.9	14.0					13.4	14.8				
PANSS[d] Positive (7–49)	15.5	16.0	0.63				16.4	15.1	0.12			
	4.8	4.3					4.7	4.0				
PANSS[d] Negative (7–49)	20.0	18.5	0.19				19.8	17.8	0.05			
	5.7	5.2					5.6	4.9				
PANSS[d] General (16–112)	36.2	35.8	0.82				36.8	34.9	0.25			
	10.2	7.7					8.9	7.9				
CPT-IP[e] mean d'	0.9	1.4	0.009	2.9	2.7	0.33	1.2	1.3	0.74	2.7	2.8	0.60
	0.9	0.8		0.7	0.7		0.8	0.9		0.7	0.8	
WCST CA[f]	2.6	3.5	0.08	5.7	5.7	0.82	3.1	3.5	0.36	5.7	5.7	0.93
	2.1	2.1		0.5	0.4		2.1	2.2		0.5	0.5	
WCST PEN[g]	7.6	7.3	0.86	0.7	0.6	0.69	7.4	7.4	0.99	0.7	0.5	0.38
	5.8	7.1		1.1	0.9		6.7	6.9		1.1	0.9	
WCST PEM[h]	5.8	4.8	0.54	0.4	0.3	0.98	5.7	4.3	0.31	0.4	0.3	0.77
	5.9	7.6		0.5	0.6		8.6	4.9		0.6	0.5	
WCST TE[i]	23.1	21.3	0.44	11.0	10.8	0.74	22.2	21.2	0.60	10.7	11.0	0.63
	10.1	10.2		1.2	2.1		9.9	10.5		1.9	1.9	

a. Results shown as mean and standard deviation (absolute number for row »sex«)
b. P-value of Student's t-test (p-value of Fisher exact test for row »Sex«/p-value of Welch's t test for row WCST PEN)
c. Chlorpromazine equivalent dose
d. *Positive and negative syndrome scale*
e. Continuous performance test–identical pairs version
f. Wisconsin card sorting test categories achieved
g. Wisconsin card sorting test perseverative errors – Nelson's type
h. Wisconsin card sorting test perseverative errors – Milner's type
i. Wisconsin card sorting test total errors

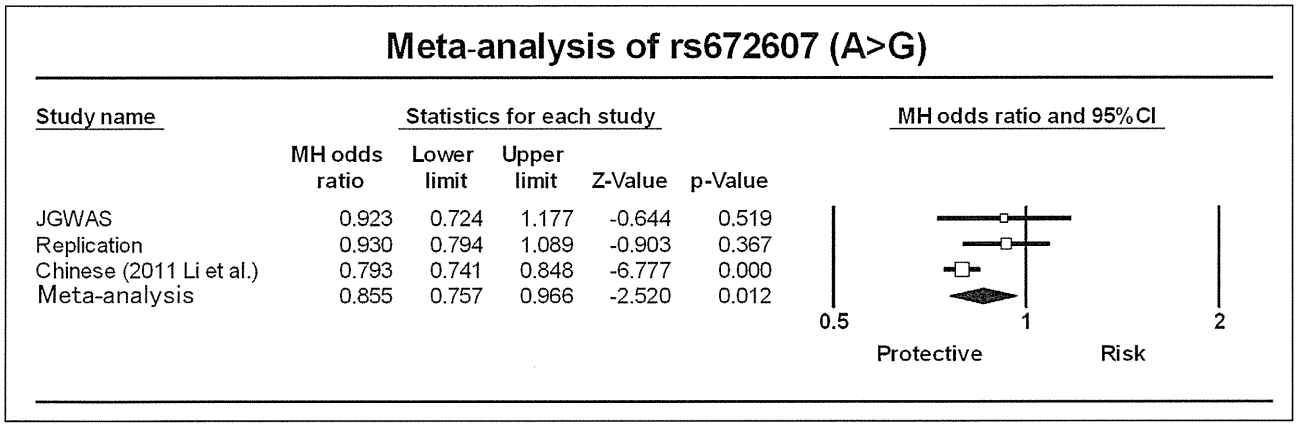

Figure 1 Meta-analysis of the Japanese and Chinese sample set in rs672607. MH: Cochran–Mantel–Haenszel test; lower limit: 95% confidence intervals; upper limit: 95% confidence intervals.

CPT and WCST. In the CPT-IP, the group with the minor allele of rs672607 (protective allele, odds ratio= 0.855 in our meta-analysis of Japanese and Chinese sample sets) showed significantly impaired working memory in schizophrenia patients.

Several caveats should be noted. Firstly, we did not include a systematic genome-wide mutation scan in either the 5 flanking region or exon regions to search for novel functional variants that may exist within the BCL9 locus, but had not been registered in the databases of common variants. Secondly, our phenotypic diagnosis is not based on structured interviews, and the control samples are significantly younger than the case samples. Thirdly, the sample sizes of cognitive tests were relatively small and the results of cognitive tests may be biased.

As a conclusion, we were able to detect evidence for an association between rs672607 in BCL9 and schizophrenia in the meta-analysis of Japanese and Chinese populations. Additionally, this common variant may affect cognitive performance, as measured by the CPT-IP in schizophrenia patients. Further studies using the sample collected in a non-Asian population are needed.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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SHORT COMMUNICATION

Effects of repeated dosing with mirtazapine, trazodone, or placebo on driving performance and cognitive function in healthy volunteers

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Objective This study aimed to evaluate the effects of repeated treatments with the sedative antidepressants mirtazapine and trazodone on driving performance and cognitive function.
Methods Nineteen healthy men received continuous nocturnal doses of 15-mg mirtazapine , 25-mg trazodone, or placebo for 8 days in a double-blinded, three-way crossover trial. Subjects were asked to perform three driving tasks (road tracking, car following, and harsh braking) using a driving simulator and cognitive tasks (the Wisconsin Card Sorting Test, Continuous Performance Test, and N-back Test) at baseline and on Days 2 and 9. Stanford Sleepiness Scale scores were also assessed.
Results Mirtazapine significantly increased the standard deviation of lateral position in the road-tracking task as compared with trazodone on Day 2. Mirtazapine significantly increased Stanford Sleepiness Scale scores as compared with trazodone and placebo. For the remaining tasks, no significant effects of treatment were observed.
Conclusions Acute treatment of mirtazapine impaired road-tracking performance and increased sleepiness, but sedative effects disappeared under repeated administrations. Trazodone did not affect driving performance or cognitive function under acute or repeated administrations. Both initial sedative effects and pharmacological profiles should be taken into consideration when using sedative antidepressants. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—sedative antidepressant; mirtazapine; trazodone; driving performance; cognitive function

INTRODUCTION

Many antidepressants are available for psychiatric treatment, but pharmacological profiles of these drugs differ widely. The choice of antidepressant is determined by safety, tolerability, efficacy, payment, and simplicity, which are summarized by the mnemonic STEPS (Preskorn, 1996). Although sedation is one of the unpleasant side effects (Bourin and Briley, 2004), sedative antidepressants can represent a useful treatment option for some patients with agitation or insomnia (Mann, 2005; Linden and Westram, 2010).

Among the sedative antidepressants, tricyclic antidepressants (TCAs) show anticholinergic properties as well as sedative properties. Because of these properties, TCAs have been repeatedly shown to impair cognitive and psychomotor performance (Serretti *et al.*, 2010), including car driving (Ramaekers, 2003; Iwamoto *et al.*, 2008). Thus, non-sedating antidepressants may represent a better option (Bourin and Briley, 2004; Versiani *et al.*, 2005). However, the sedative antidepressants trazodone and mirtazapine are among the most commonly used drugs for chronic insomnia in the USA because of safety and lower dependence potential. Therefore, these two drugs need to be examined with respect to psychomotor performance in daily life, including car-driving skills.

Previous studies have suggested that mirtazapine could impair road-tracking performance (Wingen *et al.*, 2005). However, the effects of mirtazapine on driving skills associated with traffic accidents have not been fully investigated. Moreover, the effects of trazodone on

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driving skills have rarely been studied (Roth *et al.*, 2011). The aim of the study was to evaluate the effects of repeated treatment with mirtazapine or trazodone on driving performance using methods designed to test the risk of rear-end collisions, the most common type of traffic accidents.

MATERIAL AND METHODS

Nineteen healthy male volunteers (26–49 years old, mean ± standard deviation, 38.8 ± 6.8 years) were included through health interviews and the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. All participants had a driving license for ≥5 years and regularly drove a car (minimum, 5000 km/year). The study was approved by the ethics committee of the Nagoya University Graduate School of Medicine and Nagoya University Hospital, and written informed consent was obtained from each individual before participation.

This study used a double-blind, placebo-controlled, three-way crossover design. Each subject received 8 days of continuous bedtime dosing with either 15-mg mirtazapine, 25-mg trazodone, or matched placebo in identical capsules across three different treatment series. The doses selected were clinical recommended starting doses (Sadock *et al.*, 2005). Dosing started at bedtime on Day 1, preceding the first test day (Day 2). A washout period of ≥7 days was provided between treatment series.

Baseline assessments were conducted only once before the treatment session. After baseline assessments without treatment, subsequent assessments were performed on Days 2 and 9 at 09:30 AM for each treatment series. We used a driving simulator (DS) (Toyota Central R&D Labs, Nagakute, Japan) to examine three driving skills that appeared to be associated with traffic accidents, including frequent rear-end collisions. The details of DS configuration and tasks have been described previously (Iwamoto *et al.*, 2008). The road-tracking test measures the standard deviation of lateral position (SDLP) on a gently winding road at a constant speed of 100 km/h. The car-following test measures the coefficient of variation of the distance between a preceding car and subject's own (Uchiyama *et al.*, 2003). Subjects were required to maintain a constant distance between cars. The harsh-braking test measures mean brake reaction time in seven braking trials to avoid crashing into the humanoid models that randomly ran into the road. Each test was recorded every 20 ms and lasted for 5 min. The three cognitive tests, described in detail previously (Iwamoto *et al.*, 2008), were examined using a computer. The modified version of the Wisconsin Card Sorting Test (Heaton, 1981) was used to measure executive function. This performance was measured by category achievement, perseverative errors of Nelson, and difficulty of maintaining set. The Continuous Performance Test, Identical Pairs version (Cornblatt *et al.*, 1988), was used to measure sustained attention. A series of four-digit stimuli were used, and performance was measured by the signal detection index *d*-prime, a measure of discriminability computed from "hits" and "false alarms." The *N*-back test (Callicott *et al.*, 2000, 2003) was used to assess working memory. A two-back condition was used, and performance was measured as the percentage of correct responses. All subjects were trained in both driving and cognitive tests 1–2 weeks before first testing until the plateau level. The Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) is used to examine the level of alertness.

A two-way repeated-measures analysis of variance with time and drug as factors was used to analyze percentage changes in outcome variables over 8 days. If a significant interaction between factors was observed, these variables at each evaluation point were examined with one-way repeated-measures analysis of variance, followed by the Bonferroni *post hoc* test. All tests were two tailed, and the alpha value was set at 0.05.

RESULTS

In the road-tracking test, one subject administered mirtazapine failed to complete the test on Day 2. Because of technical malfunctions, car-following test, road-tracking test, and Continuous Performance Test data were incomplete for one subject, and harsh-braking test data were incomplete for two subjects. Only complete data sets were included in the analyses.

A summary of the results is shown in Table 1. There is a significant Drug × Time interaction in the road-tracking test ($F = 3.520$, $df = 2, 46$, $p = 0.023$). The SDLP of the mirtazapine condition was significantly greater than that observed in the trazodone condition on Day 2 ($p = 0.001$). The results of SDLP are presented in Figure 1. There is no significant Drug × Time interaction in other driving tests and cognitive tests.

There is a significant Drug × Time interaction in sleepiness ($F = 10.630$, $df = 1, 34$, $p < 0.001$). SSS scores under mirtazapine conditions were significantly greater than those observed under trazodone and placebo conditions on Day 2 ($p < 0.001$ each). Results of the SSS are presented in Figure 2.

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Table 1. Summary of the results of driving tests, cognitive tests, and subjective measurements in healthy subjects enrolled in a crossover trial of 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 19$)

Measure	Test time	Mean (*SD*)		
		Placebo	Mirtazapine (15 mg)	Trazodone (25 mg)
Driving test				
SDLP (cm)[a]	Baseline	42.4 (11.02)		
	Day 2	42.2 (12.32)	48.5 (11.61)	41.1 (11.65)
	Day 9	42.2 (11.26)	43.1 (10.69)	39.9 (9.59)
DCV[b]	Baseline	37.4(24.50)		
	Day 2	55.6 (87.45)	64.8 (75.46)	37.7 (30.79)
	Day 9	31.1 (19.45)	32.2 (26.33)	44.5 (42.44)
BRT (ms)[a]	Baseline	536.5 (46.57)		
	Day 2	528.4 (70.81)	539.6 (44.20)	526.5 (43.31)
	Day 9	524.1 (49.04)	543.6 (52.24)	529.8 (41.22)
Cognitive test				
CPT (d')[b]	Baseline	2.9 (0.75)		
	Day 2	3.3 (0.71)	3.0 (0.80)	3.3 (0.75)
	Day 9	3.2 (0.81)	3.2 (0.85)	3.4 (0.61)
WCST (CA)[c]	Baseline	5.6 (0.67)		
	Day 2	5.7 (0.71)	5.7 (0.64)	5.8 (0.52)
	Day 9	5.7 (0.57)	5.7 (0.57)	5.8 (0.67)
WCST (PEN)[c]	Baseline	0.7 (1.07)		
	Day 2	0.7 (1.07)	1.0 (2.27)	0.4 (0.67)
	Day 9	1.1 (1.48)	0.7 (1.16)	0.5 (0.94)
WCST (DMS)[c]	Baseline	0.3 (0.73)		
	Day 2	0.2 (0.52)	0.2 (0.49)	0.3 (0.73)
	Day 9	0.1 (0.31)	0.3 (0.57)	0.3 (0.44)
Two-back (accuracy, %)[c]	Baseline	93.6 (15.35)		
	Day 2	94.4 (10.76)	90.6 (12.05)	87.2 (23.12)
	Day 9	97.0 (6.27)	92.1 (12.67)	94.0 (11.65)
Subjective measurement (SSS)[c]	Baseline	2.3 (0.46)		
	Day 2	2.4 (0.74)	3.8 (1.15)	2.3 (0.46)
	Day 9	2.4 (0.49)	2.7 (0.65)	2.4 (0.58)

Baseline data were assessed once before treatment.
SDLP, standard deviation of lateral position; DCV, distance coefficient of variation; BRT, brake reaction time; CPT, Continuous Performance Test; WCST, The Wisconsin Card Sorting Test; CA, category achievement; PEN, perseverative errors of Nelson; DMS, difficulty of maintaining set; SSS, Stanford Sleepiness Scale.
[a] $n = 17$
[b] $n = 18$
[c] $n = 19$

DISCUSSION

The present results demonstrated that mirtazapine significantly impaired road-tracking performance and increased subjective sleepiness in acute dosing. No other performances were significantly affected by any treatment condition during the 8 days. The effects of mirtazapine on diving performances in this study are roughly consistent with data shown in previous studies (Ramaekers *et al.*, 1998; Ridout *et al.*, 2003; Wingen *et al.*, 2005).

Mirtazapine also did not impair car-following performance in this study. To the best of our knowledge, this represents the first study to demonstrate the effects of mirtazapine on car-following performance. Whereas the road-tracking test requires subjects to handle a wheel rather than manipulate the pedals, the car-following test requires subjects to constantly switch between accelerator and brake pedal rather than handle a wheel. This means that the road-tracking test is a comparatively monotonous visuomotor task, whereas the car-following test is a more complex executive function task. Wezenberg *et al.* (2007) suggested that mirtazapine was likely to impair simpler cognitive tasks requiring less cognitive effort. Mirtazapine may tend to affect monotonous driving tasks such as the road-tracking test. Meanwhile, amitriptyline, a TCA, impaired both road-tracking and car-following performances in our DS (Iwamoto *et al.*, 2008). Its anticholinergic activity may harm car-following performance, as more cognitive effort is required (Sakulsripong *et al.*, 1991, Curran *et al.*, 1998). The difference of the effects of these sedative antidepressants on driving performance may be explained by the pharmacological properties. On the other hand, for braking performance, mirtazapine and amitriptyline did not impair brake reaction time (Iwamoto *et al.*, 2008), but diazepam, a benzodiazepine,

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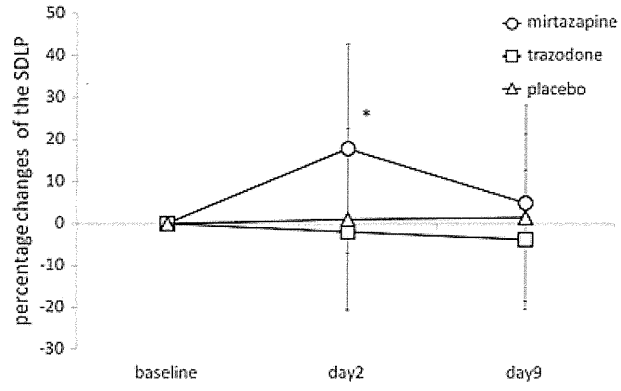

Figure 1. Mean (standard deviation) standard deviation of lateral position (SDLP) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 17$). Differences in SDLP were examined by a two-way repeated-measures analysis of variance. Differences in SDLP at each evaluation point were examined with a one-way repeated-measures analysis of variance followed by a Bonferroni test (*post hoc* test). A significant Drug × Time interaction was noted among the three conditions ($F = 3.520$, $df = 2,46$, $p = 0.023$). **Post hoc* testing demonstrated that SDLP of the 15-mg mirtazapine condition was significantly greater than that of the 25-mg trazodone condition on Day 2 ($p = 0.001$).

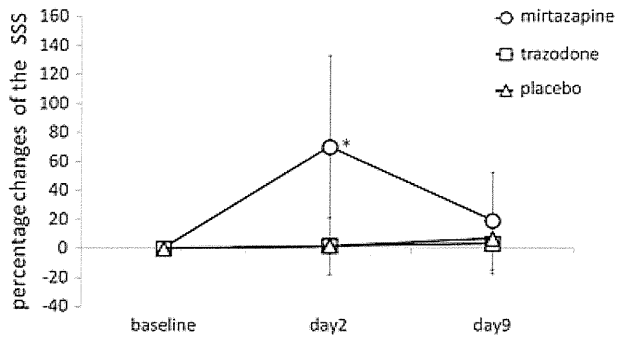

Figure 2. Mean (standard deviation) Stanford Sleepiness Scale (SSS) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N = 19$). Differences in SSS were examined by a two-way repeated-measures analysis of variance. Differences in SSS at each evaluation point were examined by a one-way repeated-measures analysis of variance followed by a Bonferroni test (*post hoc* test). Significant Drug Time interactions were seen among the three conditions ($F = 10.630$, $df = 1$, 34, $p < 0.001$). **Post hoc* testing demonstrated that SSS of the 15-mg mirtazapine condition was significantly greater than that observed in the placebo and 25-mg trazodone conditions on Day 2 ($p < 0.001$ each).

did result in impairments (Takahashi *et al.*, 2010). The harsh-braking task is likely to be affected by a peripheral muscle relaxant effect rather than a cognitive detrimental effect. Because subjective assessments and psychometric tests did not fully predict drug effects on driving performance (Verster and Roth, 2012a, 2012b), further researches are needed to elucidate the impact of psychotropics on car-driving performance.

The present study showed that 25-mg trazodone did not impair both driving and cognitive performances, although the previous study showed that 50-mg trazodone did not impair driving performance but affected memory and learning (Roth *et al.*, 2011) and that more than 100 mg of trazodone affected memory and attention (Curran *et al.*, 1998; Sakulsripong *et al.*, 1991). Although these differences may be attributable to the dosage of trazodone and cognitive tasks, pharmacological profiles of trazodone may be also in part responsible for these results. The sedative effect of trazodone is associated with its high affinity to the histamine H1 receptor; however, trazodone has features of a weak anticholinergic activity and short half-life (Bryant and Ereshefsky, 1982). Therefore, a low dose of trazodone may produce no detrimental effects on psychomotor performance as antihistamines have dose-dependent effects on psychomotor performance including driving performance (Theunissen *et al.*, 2004).

In the present study, the sedative effects of mirtazapine were no longer apparent on Day 9. According to pharmacological profiles, mirtazapine is a strong histamine H1 receptor antagonist without anticholinergic activity, and its activity contributed to detrimental effects. In assessing sedative properties with medications, an important issue is the degree to which tolerance to the sedative effect develops. Tolerance to sedative effects of mirtazapine may develop rapidly, as with histamine H1 antihistamines (Richardson *et al.*, 2002). Development of tolerance may apply equally to repeated doses of trazodone. Meanwhile, TCAs often exert an anticholinergic activity that can cause different detrimental effects on cognitive performance. In the case of amitriptyline, tolerance to sedative effects, based on subjective and behavioral measures, develops within 1–2 weeks (Deptula and Pomara, 1990; Veldhuijzen *et al.*, 2006), although several studies have indicated intolerance of amitriptyline based on several cognitive measures (Sakulsripong *et al.*, 1991; van Laar *et al.*, 2002). Anticholinergic properties should thus be considered in cases of tolerance to sedative antidepressants.

The effects of antidepressant on driving performance are different in healthy subjects and psychiatric patients and are also influenced by age and gender of the subjects. In addition, both the psychopharmacological treatment and the pathology itself may impair driving ability. Recent epidemiological studies showed that exposure to antidepressants including selective serotonin reuptake inhibitors was associated with an increased risk of motor vehicle accidents, unlike with past studies (Meuleners *et al.*, 2011; Chang *et al.*, 2013). As for the experimental studies, newer antidepressants, unlike TCAs, have no detrimental effects on driving performance (Ramaekers, 2003), and mirtazapine could also improve driving ability in depressed patients (Brunnauer *et al.*, 2008; Shen *et al.*, 2009). These discrepancies may

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be explained in part by age, dosage, dosing period, active depressive symptom, comorbid psychotropic drugs, and methodological variances (Sansone and Sansone, 2009). Especially, benzodiazepines often prescribed in clinical settings may increase the risk of motor vehicle accidents (Dassanayake *et al.*, 2011). Meanwhile, many depressed patients before hospital discharge showed impairments in psychomotor functions related to driving abilities, and those were influenced by different classes of antidepressants (Brunnauer *et al.*, 2006). The effects of antidepressants on driving ability in depressed patients under treatment have not yet been fully defined because of many confounding factors such as psychopharmacological treatment and the depression itself. Thus, it is important to examine the effects of antidepressants on driving performance in healthy subjects to find the inherent influences of antidepressants for driving impairments. However, future studies need to elucidate the impact of similar antidepressants in depressed patients in a similar experimental line and make a comparison with depressed patients.

The present study has several limitations. First, participation was restricted to healthy adult volunteers, and the sample size is relatively small. Neither elderly nor patient populations were included in the study. The elderly are more vulnerable to the side effects of pharmacological treatments. In addition, depression and insomnia can affect driving performance (Brunnauer *et al.*, 2008; Shen *et al.*, 2009) and cognitive function. Both properties of antidepressant and disorder should be considered in clinical settings. Second, the validity and sensitivity of the DS need to be considered; however, our past results using same DS are roughly consistent with preceding results (Iwamoto *et al.*, 2008; Takahashi *et al.*, 2010). Although cognitive tasks used in this study were employed in many psychiatric researches and our past studies, the sensitivity of these tasks regarding the assessment for drug effects should be considered, too. Third, dosage selection may be lower than that of past studies, because we used the initial starting dose for clinical practice. Considering an affinity for histamine H1 receptor in particular, the dose of trazodone may be low in comparison with that of mirtazapine.

Finally, acute treatments of mirtazapine did not impair car-following or harsh-braking performances but did impair road-tracking performance, although this impairment disappeared under repeated administrations. The lower dose of trazodone did not affect driving or cognitive performances under acute or repeated administrations. Both initial sedative effects and pharmacological profiles should be taken into consideration in prescribing sedative antidepressants.

CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this study.

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ORIGINAL INVESTIGATION

Effects of sedative antidepressants on prefrontal cortex activity during verbal fluency task in healthy subjects: a near-infrared spectroscopy study

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Abstract
Rationale Japanese researchers have recently conducted studies using near-infrared spectroscopy (NIRS) to help diagnose psychiatric disorders based on changes in brain activity. However, the influence of psychotropic drugs on NIRS measurements has not been clarified.
Objective To assess the effects of sedative antidepressants on prefrontal cortex activity in healthy subjects using NIRS in a double-blinded, placebo-controlled, crossover trial.
Methods Nineteen healthy males received nocturnal doses of mirtazapine 15 mg, trazodone 25 mg, or placebo for eight consecutive days in rotation, with a washout period of more than 1 week between each rotation. Subjects performed a verbal fluency task during NIRS on a total of seven occasions during the study period: more than a week prior to receiving the first dose of the first medication; and on days 2 and 9 of each rotation. The number of words correctly generated during the task (behavioral performance) was also recorded. Stanford Sleepiness Scale (SSS) scores were determined each day.
Results Mirtazapine 15 mg significantly increased oxyhemoglobin (oxy-Hb) concentration change in NIRS on day 9, compared to trazodone 25 mg and placebo. Mirtazapine 15 mg significantly increased SSS on day 2, compared to the other conditions. No significant differences in behavioral performance were observed.
Conclusions Administration of mirtazapine for eight consecutive days affected oxy-Hb changes on NIRS. This result indicates that researchers should consider how certain types of antidepressant could influence brain function when the brain activity of patients with psychiatric disorders is assessed.

Keywords Antidepressant · Mirtazapine · Trazodone · Near-infrared spectroscopy (NIRS) · Brain activity · Sleepiness · Neuroimaging

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Introduction

Near-infrared spectroscopy (NIRS) is a noninvasive functional brain imaging technique that utilizes the absorbance of light in the near-infrared spectrum by hemoglobin (Hb) to determine blood volumes in an anatomical region of interest. NIRS has been gaining attention recently because of its relatively high temporal resolution and the compactness of the measurement devices. These features make NIRS

suitable for testing, as experimental procedures can be performed under conditions that are close to natural. Many studies have confirmed the suitability of NIRS for various types of investigations. Frontal lobe activity as measured by NIRS has been suggested to be decreased in many psychiatric disorders (i.e., major depressive disorder, bipolar disorder, schizophrenia, panic disorder, eating disorder, attention deficit hyperactivity disorder, Alzheimer's dementia, and alcoholism).(Kameyama et al. 2006; Schecklmann et al. 2007; Suda et al. 2010; Suto et al. 2004).

Age, sex, and sleepiness have been indicated as factors that may influence Hb concentration changes in NIRS, in addition to the influences attributable to disease (Kameyama et al. 2004; Suda et al. 2008). We have previously reported that insufficient sleep could lower the peak oxyhemoglobin (oxy-Hb) concentration in the lateral frontal lobes (Miyata et al. 2010). In addition, the effects of psychotropic drugs on NIRS measurements have yet to be clarified.

Many studies have investigated the influence of drugs on brain function using functional brain imaging. Such studies have been performed using positron emission tomography (PET), single photon emission computed tomography, and functional magnetic resonance imaging (fMRI). Conversely, only a few studies have used NIRS to directly verify these influences. Tsujii et al. (2009, 2007) examined the effects of antihistamines on brain activity. Comparing the first-generation histamine H1-receptor antagonist ketotifen to the second-generation epinastine, they revealed that ketotifen significantly impaired cortical activation in the lateral prefrontal cortex.

Given these findings, the present study used NIRS to examine whether taking an antidepressant for consecutive days can affect brain activity in healthy subjects. In light of revelations from previous studies that insufficient sleep could lower cortical activation and that the sedative effects of antihistamines impair neural response, we verified the effects of an antidepressant itself on brain activity in healthy volunteers using multichannel NIRS with the sedative antidepressants mirtazapine and trazodone, both of which exert strong sedative/hypnotic effects.

Subjects and methods

Subjects

Participants in this study comprised 19 healthy, male Japanese volunteers who were right-handed (mean age, 38.8 years; SD, 6.8 years; range, 26–49 years). The study protocol was approved by the ethics review committees at Nagoya University Graduate School of Medicine and Nagoya University Hospital. Written informed consent was obtained from all participants prior to enrolment in the study. All subjects were interviewed to confirm the absence of any psychiatric disorders using the Structured Clinical Interview for DSM-IV by one of the experimenters. All subjects were found to be in good health without any significant clinical history of physical or mental illness and were not receiving any concomitant medications likely to affect brain function.

Drug administration and study design

A double-blind, placebo-controlled, crossover design was used. Before going to bed, subjects took orally either mirtazapine 15 mg, trazodone 25 mg, or placebo for eight consecutive days. After finishing eight consecutive days of the first drug, the subject then went more than 1 week without medication as a washout period before proceeding to the next drug. The second and third drugs were administered in the same manner as the first drug. The order of drugs that subjects took was allocated based on a pre-determined randomization schedule. In total, subjects were required to come to the study room seven times. The first visit was more than a week prior to receiving the first medication (day-pre). Subsequently, each subject came on day 2 (three times during the study) and day 9 (three times during the study) during administration. The study schedule is shown in Fig. 1. Doses were determined according to the initial dosages recommended in a manual for psychiatric drug treatment, because we considered that one of the aims of this study was to evaluate sleepiness as a side effect (Sadock et al. 2005). Each examination started at 0900 hours. Subjects completed a verbal fluency task, during which prefrontal cortical activity was measured using a NIRS recorder. In addition, subjective sleepiness at the time of the examination was evaluated using the Stanford Sleepiness Scale (SSS).

Activation task

Hb concentration changes were measured during a letter-version verbal fluency task that has been administered in many previous studies. The subject sat on a comfortable chair in a

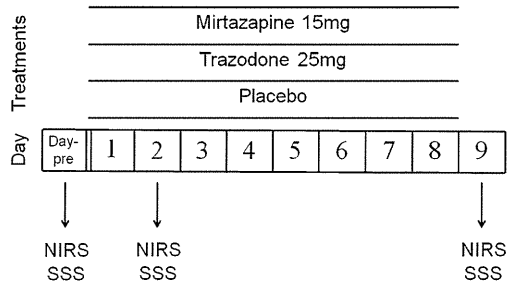

Fig. 1 Study design. Subjects were to be measured more than a week prior to receiving the first medication (day-pre), on days 2 (three times during the study) and 9 (three times during the study). *NIRS* NIRS measurement, *SSS* Stanford Sleepiness Scale

sunlit room with the eyes open throughout the measurement. During the task, subjects were instructed orally to vocally generate as many nouns as possible beginning with the Japanese syllables "a", "ki", "ha", "to", "se", "o", "i", "no" or "ta", without repetitions or resorting to proper nouns. Stimulus syllables were counterbalanced for each treatment condition. The subject performed a verbal fluency task consisting of a 30-s pre-task, 60-s verbal fluency task, and 60-s post-task. The number of words generated during the verbal fluency task was determined as a measure of task performance. Subjects were instructed to repeat the vowels "a", "i", "u", "e" and "o" during the pre-task and post-task periods as the Japanese counterparts of A, B, and C in English (Kameyama et al. 2006). Prior to the main examination when the NIRS response was recorded, practice sessions were conducted until the experimenter judged that the subjects understood the procedure.

NIRS measurements

Relative changes in oxy-Hb and deoxy-Hb were measured using a FOIRE-3000 functional NIRS system (Shimadzu, Kyoto, Japan) at three wavelengths (780, 805, and 830 nm). A NIRS shell with 3×5 arrays of light emitters and detectors were used (distance between probes, 3 cm). This apparatus could measure the relative concentrations of oxy-Hb and deoxy-Hb at 22 measurement points in a 9×15 cm area (Fig. 2). The NIRS shell was placed over the frontal region. The location of the shell was determined according to the International 10–20 system used in electroencephalography, with the lowest probes positioned along the Fp1-2 line (Okamoto et al. 2004).

Data analysis and statistics

We analyzed oxy-Hb values in the 22 channels located above the prefrontal cortex. We focused on oxy-Hb concentrations, since oxy-Hb change is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood oxygenation level-dependent signal measured by fMRI (Strangman et al. 2002). Near-infrared light absorption was measured with a temporal resolution of 0.1 s. Waveforms of oxy-Hb changes were acquired from all subjects in all of the 22 channels during the task. NIRS data that clearly contained motion artifacts as determined by close observation of the subject were excluded from further statistical analysis (one subject in total). A low-pass filter with a high cutoff of 0.1 Hz was used to exclude short-term motion artifacts from the data for analysis. In addition, oxy-Hb data in the following channels showing low signal-to-noise (S/N) ratios were excluded from further analysis: channels 1, 5, 14, 18, 19, 20, 21, and 22. Oxy-Hb concentrations were averaged during the 60-s verbal fluency task period. The pretask baseline was determined by employing the mean across the last 10 s of the whole 30-s pretask period. Oxy-Hb concentration changes during the verbal fluency task observed on days 2 and 9 were statistically tested after subtracting changes between the task period and pre-task period from day-pre measurements. We utilized repeated-measures analysis of variance (ANOVA) for the drugs (mirtazapine, trazodone, and placebo) on days 2 and 9, followed by post hoc multiple comparison with Fisher's protected least significant difference.

The number of words correctly generated was statistically tested using repeated-measures ANOVA for the drugs (mirtazapine, trazodone, and placebo) on days 2 and 9.

SSS scores were statistically tested using Friedman's test followed by multiple comparison adjustment using the Bonferroni method. Exploratory correlational analysis between oxy-Hb concentration change and SSS was performed for each channel with Spearman's ρ. Values of $p<0.05$ were considered statistically significant for all analyses.

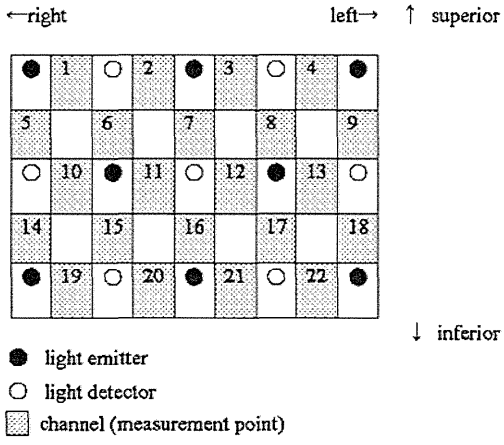

Fig. 2 Placement of NIRS shells

Results

Behavioral performance

The numbers of words correctly generated during the 60-s verbal fluency task period for each administration condition are summarized in Table 1. Repeated-measures ANOVA revealed no significant difference between day-pre, day 2, and day 9.

SSS

Mean SSS for mirtazapine (Table 1) on day 2 was significantly higher than any other scores ($p=0.00$). Changes in

Table 1 Number of words correctly generated and subjective sleepiness (mean ± SD)

	Pre	Mirtazapine		Trazodone		Placebo	
		Day 2	Day 9	Day 2	Day 9	Day 2	Day 9
BP	15.3±4.2	15.9±3.6	14.7±4.2	16.3±3.7	14.9±4.2	16.4±3.8	14.8±4.5
SSS	2.3±0.5	3.7±1.2	2.7±0.7	2.3±0.5	2.4±0.6	2.4±0.8	2.4±0.5

BP behavioral performance, *SSS* Stanford Sleepiness Scale

oxy-Hb concentration did not correlate with SSS in any channels.

NIRS response

For oxy-Hb, repeated-measures ANOVA for day 2 revealed no significant difference between drugs. However, repeated-measures ANOVA for day 9 revealed significant differences in ch8 (F=4.50, p=0.02), ch12 (F=4.59, p=0.02), ch13 (F=2.80, p=0.08), ch15 (F=3.04, p=0.06), ch16 (F=3.46, p=0.04), and ch17 (F=3.03, p=0.06). Post hoc testing for day 9 showed that oxy-Hb increases with mirtazapine were larger than those with trazodone in ch8 (p=0.02), ch12 (p=0.02), ch13 (p=0.06), ch15 (p=0.02), ch16 (p<0.01), and ch17 (p=0.04) and were larger than those with placebo in ch8 (p=0.05) and ch12 (p=0.03) (Fig. 3).

Discussion

We examined the effects of two types of sedative antidepressants on brain activity, performed the verbal fluency task, and used NIRS to measure changes in oxy-Hb concentration. No significant differences were detected between mirtazapine, trazodone, and placebo on day 2 for oxy-Hb. However, activation was significantly increased with mirtazapine in comparison to the other drugs in 6 of 22 channels.

Results for the SSS indicated that sleepiness on day 2 was significantly increased with mirtazapine compared to other conditions. No significant difference between drugs was seen for the number of words correctly uttered during the task, representing behavioral performance.

We assumed in this study that the superior frontal gyrus was the area activated in oxy-Hb concentration change, as

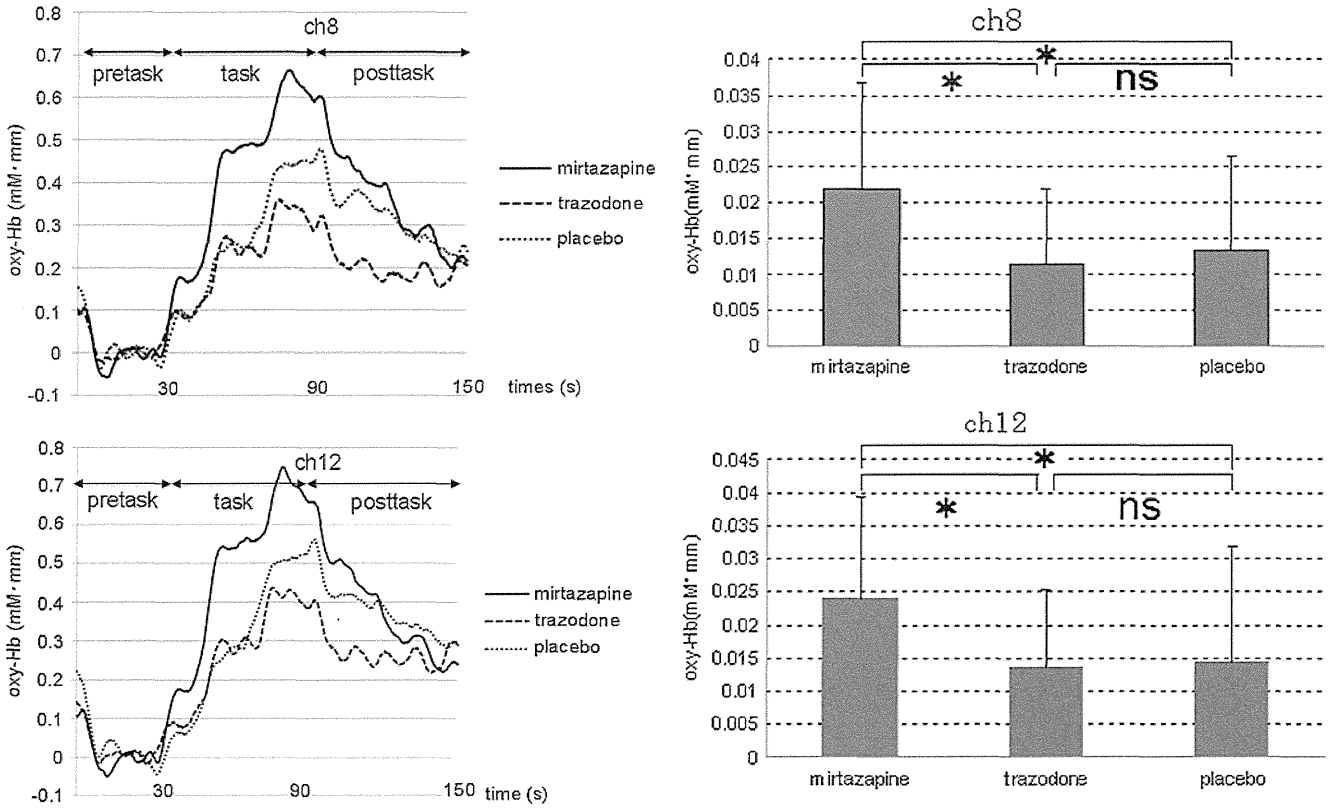

Fig. 3 Oxy-Hb concentration change during the whole 150-s period on day9 s (*left*) and averaged oxy-Hb concentration change during the 60-s task period on day9 s (*right*). The *asterisk* indicates p<0.05 (post hoc test; protected least significant difference)

measured by NIRS (Tsuzuki et al. 2007). A previous study revealed that activation in the left prefrontal cortex and right premotor cortex was decreased with paroxetine, as measured by fMRI during a linguistic task, similar to our task (Peran et al. 2008). To the best of our knowledge, no previous studies have examined the effects of antidepressants on brain blood flow during verbal fluency tasks. However, we did identify several studies that examined the effects of antidepressants on brain activity (frontal lobe function) during cognitive tasks. In a study using the Go/No-Go task during fMRI, activity in bilateral prefrontal cortices was increased with mitrazapine compared to placebo (Vollm et al. 2006). Another fMRI study revealed that activity in the frontal area was decreased with escitalopram during the Mackworth Clock Test (Wingen et al. 2008).

According to these studies, brain response during cognitive tasks (which measure frontal lobe function) differs according to the type of drug used. This suggests that activity in the frontal area is decreased in a cognitive task with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and escitalopram, whereas activity in the area can be increased with mirtazapine, which was also examined in this study. SSRI is known to have serotonergic effect. By contrast, mirtazapine has adrenergic and dopaminergic in addition to serotonergic effect (Millan et al. 2000; Nakayama et al. 2004). As for antihistamines, NIRS studies revealed that ketotifen significantly decreased cortical activation in the lateral prefrontal cortex (Tsujii et al. 2009; 2007). Studies using PET also clarified that D-chlorpheniramine decreased regional cerebral blood flow in the frontal area (Mochizuki et al. 2002; Okamura et al. 2000). In the present study, antihistaminic effect of mirtazapine significantly increased sleepiness on day 2 as is the case in antihistamines. The increase of oxy-Hb concentration change in the frontal cortex with mirtazapine may attribute to other pharmacological effects such as adrenergic, dopaminergic, and serotonergic effects in addition to antihistaminic effect. Differences in pharmacological properties can thus influence brain activity, manifesting as different responses (i.e., blood flow as measured by NIRS). Moreover, outcomes can change with the dose and duration of drug administration. Further examination of the effects of different factors that may influence brain activity is thus needed using other neuroimaging techniques (e.g., fMRI).

According to some previous studies, the increased oxy-Hb concentration change during cognitive tasks implies that mirtazapine can intensify brain activity (Hock et al. 1997; Kleinschmidt et al. 1996; Mehagnoul-Schipper et al. 2002; Toronov et al. 2001). Oxy-Hb change is reportedly decreased in patients with major depressive disorder, suggesting reduced brain activity (Suto et al. 2004; Herrmann et al. 2004). We therefore speculate that mirtazapine may have some potential to restore deteriorated function of brain activity in depression. On the other hand, continuous administration of mirtazapine did not change the scores for behavioral performance. We can therefore also assume that increased brain activation might be needed to achieve the same performance during mirtazapine administration, which was indicated in the study of Alzheimer's disease using NIRS (Tomioka et al. 2009).

Several limitations must be considered when interpreting the results of this study. First of all, NIRS measurement has been suggested to have insufficient spatial resolution, although the temporal resolution is high (Kameyama et al. 2006). NIRS probes in this study could measure limited cerebral regions. We had a considerable area that was not measured between the probes and outside of the NIRS shell. In addition, we had to exclude 8 of 22 channels from detailed analysis because of low S/N ratios. Second, initial doses for both mirtazapine and trazodone were applied to the subjects to carefully examine drug effects, side effects, and influences on brain function at a low dose. Nevertheless, we have to acknowledge that these doses hold a methodological problem because the initial doses may not be sufficient to influence brain activity. Third, we have not measured oxy-Hb concentration changes after the previous drug was washed out. This might interfere with assessment of the exact difference between the pretreatment baseline and the periods treated with the second and the third drugs. However, we assume that this problem could be resolved to some extent because the order of the drugs administered was randomized and counterbalanced. Fourth, the validity of NIRS measurement should be considered. Further investigations are needed to determine whether the results of NIRS measurement are consistent with the results of other neuroimaging methods such as fMRI. Finally, all subjects in this study were healthy men who were not taking any medications. In general, most patients are taking other pharmacotherapies, and extracting exact responses to a single specific administered drug in such patients would be difficult. Hormonal changes resulting from the menstrual cycle might also affect cognitive function, thus influencing the results of cognitive tasks (Hampson 1990; Maki et al. 2002; Phillips and Sherwin 1992). Changes to brain function in a patient could differ from those in a healthy man, and sensitivity and response to a drug might not be the same in women and the elderly. The results from healthy subjects in this study thus might not be fully applicable to patients.

Conclusion

We observed that continuous administration of an antidepressant would affect brain function in this study by examining using a NIRS recorder for functional brain imaging. In addition, influences on brain function differed between the

drugs used in our experimental protocol. Medication and the type of antidepressant a subject takes appear to represent factors affecting Hb concentration change in NIRS, along with age, sex, and sleepiness; all of which should be considered when assessing brain activity in a patient with a psychiatric disorder. In addition, differences between each antidepressant in terms of the response of the brain need to be determined to allow easy evaluation of whether a drug will be effective for a patient. These techniques are expected to prove beneficial in future personalization of therapy.

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Conflict of interest None of the authors have any conflicts of interest directly relevant to the content of this study.

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SHORT COMMUNICATION

Effects of low-dose mirtazapine on driving performance in healthy volunteers

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Objective This study aimed to assess whether a lower initial dose of mirtazapine can lessen the harmful effect on driving performance or not in a double-blinded, placebo-controlled crossover trial.
Methods Thirteen healthy men received 8 days of continuous nocturnal doses of mirtazapine at 7.5 mg or 15 mg, or placebo. At baseline and on days 2 and 9, subjects performed three driving tasks (road-tracking, car-following, and harsh-braking tasks) using a driving simulator and a Continuous Performance Test. Stanford Sleepiness Scale (SSS) scores were also assessed. In the mirtazapine 7.5 mg series, 15 mg of mirtazapine was additionally administered on day 9, followed by all the same assessments on day 10.
Results Mirtazapine 7.5 mg had no significant effects on any tasks except for SSS compared with placebo. Mirtazapine 15 mg impaired road-tracking task and SSS. The increase in mirtazapine dose also had no significant effects on any tasks compared with those before dose increase.
Conclusions Mirtazapine 7.5 mg did not cause driving impairment compared with mirtazapine 15 mg, while both doses of mirtazapine produced subjective somnolence. The increase in mirtazapine had no detrimental effects on psychomotor performance. Initial low-dose mirtazapine may be safer for automobile driving than the normal starting dose. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—mirtazapine; sedation; driving performance; cognitive function; starting dose

INTRODUCTION

Mirtazapine is a noradrenergic and specific serotonergic antidepressant with a unique pharmacologic profile that differs from currently available antidepressants. The therapeutic effects are derived by blockade of the alpha$_2$-adrenoreceptors and by indirect stimulation of serotonin (5-HT)$_1$ receptors, via blockade of 5-HT$_2$ and 5-HT$_3$ receptors (de Boer, 1995). Efficacy of mirtazapine has been established in a systematic review and meta-analysis of randomized controlled trials (Cipriani *et al.*, 2009; Watanabe *et al.*, 2008). Mirtazapine is also one of the most commonly used drugs for chronic insomnia in the US because of safety and lower dependence.

Despite the efficacy of mirtazapine, a key clinical problem is tolerability, and the most commonly reported adverse event is somnolence (Watanabe *et al.*, 2010). Sedation and somnolence are considered as the most important causes of driving impairment in patients being treated with antidepressants (Ramaekers, 2003). In fact, previous studies have suggested that acute administration of mirtazapine could impair road-tracking performance (Ramaekers *et al.*, 1998; Ridout *et al.*, 2003; Wingen *et al.*, 2005). Therefore, administration methods that can reduce driving impairment of mirtazapine are needed for patients' social lives and public safety.

It is considered that a lower initial dose of mirtazapine provides potent histaminergic blockade inducing prominent somnolence, whereas a higher initial dose of mirtazapine is associated with reduced

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sedating antihistaminergic activity through increased noradrenergic transmission (Stahl *et al.*, 1997; Stimmel *et al.*, 1997). Generally, dose reduction may be used to relieve antidepressants' detrimental effects, but little is known regarding the effects of mirtazapine, especially at lower doses, on driving performance. The aim of the present study was thus to evaluate the effects of a lower initial dose of mirtazapine on driving performance and cognitive function. By measuring the effects of different low doses of mirtazapine on driving performance, we evaluated the driving safety of an initial low dose of mirtazapine.

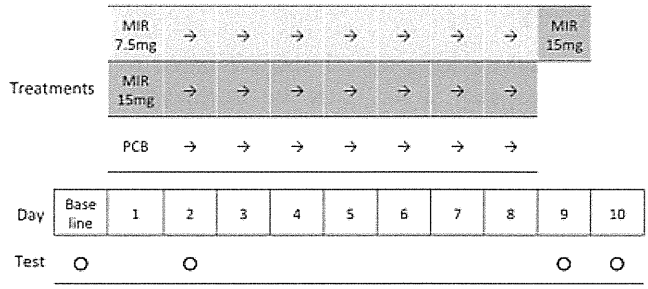

Figure 1. Summary of treatments and schedules in this study. Each subject received nocturnal dosing with mirtazapine (MIR) 7.5 mg, MIR 15 mg, or matched placebo (PCB) for 8 days in a double-blind, crossover design. In the MIR 7.5 mg series, MIR 15 mg was also administered on day 9. A washout period of ≥7 days was provided between each treatment session. Assessments were performed at baseline (once before treatment) and on days 2, 9, and 10 (only in the MIR 7.5 mg series) of each treatment series

MATERIAL AND METHODS

Thirteen healthy male volunteers (32–49 years old, mean ± SD, 39.2 ± 6.2 years) were included through health interviews and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. All applicants had had a driving license for ≥10 years and had been driving a car daily (minimum 5000 km/year). The study was approved by the ethics review committees of the Nagoya University Graduate School of Medicine and Nagoya University Hospital, and written informed consent was obtained from each subject before participation.

The present study used a double-blind, placebo-controlled, three-way crossover design. Each subject received 8 days of continuous bedtime dosing with either 7.5 or 15 mg of mirtazapine, or matched placebo in identical capsules across three different treatment series. Under the mirtazapine 7.5 mg series, 15 mg of mirtazapine was additionally administered on day 9. Dosing started at bedtime on day 1, preceding the first test day (day 2). A washout period of ≥7 days was provided between each treatment series. All subjects received substantial training in both driving and cognitive tests 1–2 weeks before the first testing until reaching a plateau level. After baseline assessments without treatment, subsequent assessments were performed on days 2 and 9 at 0930 for each treatment series. In addition, the same assessments were performed on day 10 (dose increase from 7.5 to 15 mg) only for the mirtazapine 7.5 mg series. The study schedule is shown in Figure 1.

A driving simulator (DS) (Toyota Central R&D Labs, Nagakute, Japan) was used to examine three driving skills that have been associated with traffic accidents. The details of DS configuration and tasks have been described previously (Iwamoto *et al.*, 2008). The road-tracking test measures standard deviation of lateral position (SDLP) on a gently winding road at a constant speed of 100 km/h. The car-following test measures coefficient of variation of the distance between preceding car and subject's own (Uchiyama *et al.*, 2003). Subject was required to maintain a constant distance between cars. The harsh-braking test measures mean brake reaction time in seven braking trials to avoid crashing into the humanoid models that randomly ran into the road. Each test was recorded every 20 ms and lasted for 5 min. As for the cognitive test, the Continuous Performance Test—Identical Pairs version (Cornblatt *et al.*, 1988) was used to measure sustained attention. A series of four-digit stimuli was used, and performance was measured by the signal detection index d-prime, a measure of discriminability computed from "hits" and "false alarms". The Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) is also used to examine the level of alertness at the beginning of each test day.

To compare the conditions following the administration of the three drugs, the differences between the baseline values and each evaluation point values were analyzed. Two-way repeated-measures analysis of variance with time and drug as factors was used to analyze the outcome variables over 8 days. Post-hoc tests were examined with one-way repeated-measures analysis of variance followed by the Bonferroni test at each evaluation point. Outcome variables on day 10 in the mirtazapine 7.5 mg series were compared with those on day 9 in the same series using paired *t*-tests. All tests were two-tailed, with the alpha level set at 0.05.

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RESULTS

In the road-tracking test, 1 subject failed to complete the test on day 2 for both the mirtazapine 7.5 and 15 mg series, as he was sliding off the track. No other subjects were stopped prematurely and crashed during driving test. Because of technical malfunctions, road-tracking test, harsh-braking test, and Continuous Performance Test data were incomplete for 1 subject. Only complete data sets were included in analyses.

A summary of the results is shown in Table 1. There is a significant *main drug effect* in the road-tracking test ($F=10.2$, $df=1$, 13, $p=0.004$). SDLP in the mirtazapine 15 mg series was significantly greater than that observed in the mirtazapine 7.5 mg or placebo series on day 2 ($p=0.004$, both). There is no significant drug × time interaction or *main drug effect* in other driving and cognitive tests. There is a significant drug × time interaction in sleepiness ($F=6.46$, $df=2$, 24, $p=0.006$). SSS scores in the mirtazapine 7.5 and 15 mg series were significantly greater than that observed in the placebo series on day 2 ($p=0.028$ and $p=0.027$, respectively). The results for SDLP and SSS on days 2 and 9 are presented in Figure 2. With regard to increased mirtazapine on day 9, any variables on day 10 did not significantly changed compared with those on day 9.

DISCUSSION

The present results indicate that mirtazapine 7.5 mg did not significantly affect driving performances and sustained attention, although mirtazapine 15 mg had a significantly deleterious effect on road-tracking performance. However, mirtazapine 7.5 mg, like 15 mg, significantly increased subjective sleepiness compared with placebo in acute dosing. Mirtazapine-induced sleepiness decreased over time and was no longer clinically relevant after repeated dosing. Furthermore, the increase in mirtazapine from 7.5 to 15 mg did not impair any performance. This study examines the effects of an initial lower dose of mirtazapine on both driving performance and cognitive function.

Mirtazapine-induced sedation is considered attributable in large part to potent blockade of histamine$_1$ receptors. Antihistamine activity is thought to be offset by increased noradrenergic transmission at higher doses (Stahl *et al.*, 1997; Stimmel *et al.*, 1997). Radhakishun *et al.* (2000) showed that initial mirtazapine doses of 15 and 30 mg had similar impacts on subjective alertness, but few data have been accumulated to confirm this theory, particularly at lower doses. In the case of antihistamines, dose-dependent effects on psychomotor performance including driving performance (Theunissen *et al.*, 2004) and brain

Table 1. Summary of the results of driving tests, cognitive test, and subjective measurement in healthy subjects enrolled in a crossover trial of mirtazapine 7.5 mg, mirtazapine 15 mg and placebo ($N=13$)

Measure	Test time	Mean (SD)		
		Placebo	Mirtazapine 7.5 mg	Mirtazapine 15 mg
Driving test	Baseline		42.9 (12.6)	
SDLP* (cm)	Day 2	40.7 (10.6)	41.3 (9.8)	48.3 (11.2)
	Day 9	42.5 (11.5)	40.3 (10.6)	44.8 (12.3)
	Day 10	...	40.8 (10.5)	...
DCV	Baseline		37.4 (25.0)	
	Day 2	39.3 (40.4)	57.3 (85.7)	67.0 (86.2)
	Day 9	27.9 (18.5)	24.5 (21.1)	27.1 (24.8)
	Day 10	...	26.3 (21.8)	...
BRT** (ms)	Baseline		542.3 (43.9)	
	Day 2	533.3 (70.8)	521.2 (41.1)	538.6 (44.7)
	Day 9	525.2 (43.5)	526.8 (41.0)	538.9 (52.9)
	Day 10	...	527.0 (38.8)	...
Cognitive test	Baseline		3.0 (0.8)	
CPT (d')**	Day 2	3.4 (0.7)	3.4 (0.5)	3.1 (0.8)
	Day 9	3.4 (0.7)	3.6 (0.5)	3.4 (0.7)
	Day 10	...	3.6 (0.6)	...
Subjective measurement	Baseline		2.4 (0.5)	
SSS	Day 2	2.5 (0.7)	3.3 (0.9)	3.8 (1.3)
	Day 9	2.5 (0.6)	2.3 (0.5)	2.6 (0.6)
	Day 10	...	2.5 (0.6)	...

SDLP, standard deviation of lateral position; DCV, distance coefficient of variation; BRT, brake reaction time; CPT, Continuous Performance Test; SSS, Stanford Sleepiness Scale.
Baseline data were assessed once before treatment.
*$N=11$, **$N=12$,

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