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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. 

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,

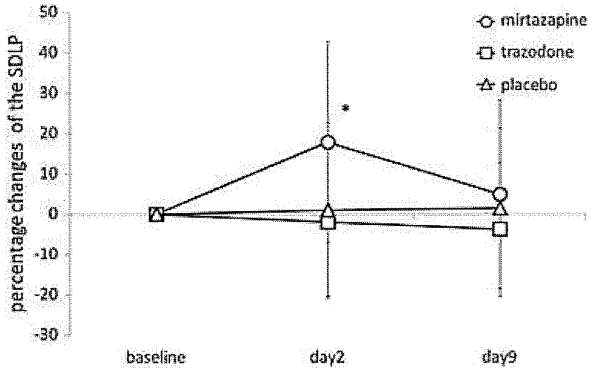


Figure 1. Mean (standard deviation) standard deviation of lateral position (SDLP) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N=17$). Differences in SDLP were examined by a two-way repeated-measures analysis of variance. Differences in SDLP at each 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 ($p=0.001$).

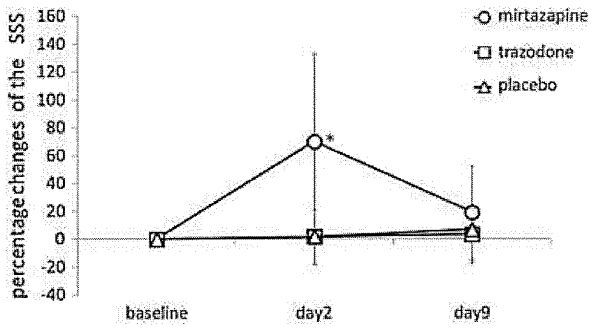


Figure 2. Mean (standard deviation) Stanford Sleepiness Scale (SSS) after 2 and 9 days of crossover treatment with 15-mg mirtazapine, 25-mg trazodone, and placebo ($N=19$). Differences in SSS were examined by a two-way repeated-measures analysis of variance. Differences in SSS at each evaluation point 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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# Poor sleep quality impairs cognitive performance in older adults

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**Keywords**
memory performance, sleep duration, sleep efficiency

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**SUMMARY**

The prevalence of insomnia increases with age. Short sleep duration is associated with deficits in cognitive performance. We hypothesized that short sleep duration and sleep quality influence cognitive performance in older adults. The study included 78 adults aged 60 years and over (72.2 ± 5.9 years). Total sleep time and sleep efficiency (total sleep time/time in bed × 100) were calculated using actigraphy. We evaluated cognitive performance with the continuous performance test-identical pairs and the number-back test. Sleep apnea was evaluated overnight with a portable home monitoring system. The accuracy of the 0-back test significantly decreased in participants with total sleep time less than 5 h compared with those with total sleep time greater than 7 h, but there was no significant difference in continuous performance test-identical pairs between the two groups. Participants with sleep efficiency <85% showed a significant decrease in 0- and 1-back test accuracy compared with those with sleep efficiency ≥85%. There were no significant differences in the accuracy of number-back tests and continuous performance test-identical pairs between apnea–hypopnea index ≥15 $h^{-1}$ and apnea–hypopnea index <15 $h^{-1}$ groups, or among lowest $SpO_2$ ≥ 90%, lowest 80–90%, and lowest $SpO_2$ < 80% groups. Age, total sleep time and sleep efficiency were significantly correlated with accuracy on the 0-back test. Age and sleep efficiency were significantly correlated with accuracy on the 1-back test. Multiple regression analysis revealed that total sleep time was independently correlated with accuracy on the 0-back test, while age was independently correlated with accuracy on the 1-back test. Our findings suggest that sleep duration and sleep quality may play a role in cognitive performance in older adults.

## INTRODUCTION

Poor sleep is associated with health problems, such as obesity, diabetes mellitus, hypertension and decreased cognitive performance (Calhoun and Harding, 2010; Tworoger *et al.*, 2006; Van Cauter and Knutson, 2008). Sleep complaints increase with age, with older adults most often complaining of difficulty initiating or maintaining sleep (Ancoli-Israel, 2009). Late-life insomnia is often attributed to medical and psychiatric disorders, as well as age-related physiological changes in sleep–wake regulation (Neikrug and Ancoli-Israel, 2010). It is important to diagnose and treat insomnia in older adults properly because poor sleep can have serious consequences, including decreased health-related quality of life (LeBlanc *et al.*, 2007) and impaired cognitive performance (Tworoger *et al.*, 2006).

Short sleep duration impacts health in various ways, and manifests as higher general mortality compared with people getting 7–8 h of sleep per night. Previously, we demonstrated that short sleep duration (<4 h) was associated with deficits in cognitive performance, even in young adults (Miyata *et al.*, 2010). Cognitive performance declines with age in a part of domains, such as memory, reasoning and spatial visualization (Salthouse, 2010), but there is substantial individual variability in the magnitude of these changes (Reuter-Lorenz and Lustig, 2005). In one epidemiological study, both short (3–4 h) and long (>10 h) self-reported sleep duration were independently related to memory impairment

evaluated with a delayed word recall test in older Chinese adults (Xu *et al.*, 2011). Given that perceived sleep duration may differ from objectively measured sleep duration under the influence of personal characteristics, relying solely on self-reported measures may introduce bias (Fichten *et al.*, 2005).

In this study, we aimed to investigate whether objective sleep duration and sleep quality are associated with cognitive performance in community-dwelling older adults.

## MATERIALS AND METHODS

### Study participants

A letter containing a description of the study and a request for participation were sent to community-dwelling older adults. The study enrolled 78 consecutive volunteers aged 60 years and over (72.2 ± 5.9 years). None of the participants reported recent reductions in memory or cognitive performance, and none had any impairment in basic or instrumental activities of daily living. Study participants underwent actigraphy, as well as cognitive performance and sleep apnea screening tests, and completed questionnaires. The Chubu University Ethics Review Committee approved all procedures associated with this study. All participants were informed of the study objectives and conditions, and provided written informed consent prior to beginning the study.

### Actigraphy

Actigraphy was performed for seven consecutive days for all participants as previously described (Otake *et al.*, 2011). The actigraph (Ambulatory Monitoring, New York, NY, USA) was worn around the wrist of a non-dominant hand and was set to store data in 1-min increments. We analysed actigraphic data using the algorithm supplied by the ActionW-2 clinical sleep analysis software package for Windows (Ambulatory Monitoring). Sleep and activity were scored according to the Cole–Kripke formula. We measured total sleep time (TST), sleep efficiency (calculated as TST/time in bed × 100), sleep latency and wake after sleep onset (WASO).

### Cognitive performance tests

*Continuous performance test (CPT)*

The CPT measures sustained attention and vigilance. We used the CPT-identical pairs version (CPT-IP) software (Biobehavioral Technologies, Inc., NY, USA), as described previously (Cornblatt *et al.*, 1988). A series of four-digit stimuli were presented for a period of 50 ms, with an interstimulus interval (ISI) of 950 ms. Each complete task consisted of 150 trials, of which 30 were target trials requiring a response. In this study, we measured performance by the ratio of correct responses (accuracy).

*Number (n)-back test*

We used the *n*-back test to measure working memory capacity using software that requires participants to update their mental set continually while responding to a previously seen stimulus or stimuli (i.e. numbers) using the numeric keypad of the PC, as described previously (Callicott *et al.*, 2003). The stimulus duration was 0.4 s, and the ISI was 1.4 s; each test included 14 trials. We used 0- and 1-back conditions, and measured performance as the percentage of correct responses (accuracy, %).

### Questionnaires

*Pittsburgh Sleep Quality Index (PSQI)*

We evaluated sleep quality using the PSQI, a questionnaire that assesses sleep quality and quantity over a 1-month period (Buysse *et al.*, 1989). The PSQI contains 19 items in seven component domains: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleep medication; and daytime dysfunction. The questionnaire requires the patient to describe sleep patterns, such as typical bedtime and wake time, length of time taken to fall asleep, and actual sleep duration. The patient then answers a series of questions relating to sleep habits and quality. Component scores are based on a four-point Likert scale that ranges from Very Good (0) to Very Bad (3). The component scores are combined to produce the Global Sleep Quality Score ranging from 0 to 27. We considered participants with scores of 6 or greater to be poor sleepers.

*Epworth Sleepiness Scale (ESS)*

In this test, the participant rates, on a four-point scale, his/her chances of dozing in each of eight different situations that are often encountered in daily life (Johns, 1991). The total ESS score is the sum of all responses, and ranges from 0 to 24. A score of 11 or greater reflects excessive daytime sleepiness.

### Sleep apnea screening

We screened for sleep apnea using the portable Apnomonitor 3 (Chest, Tokyo, Japan) with an oronasal thermistor sensor to record airflow, a pulse oximeter to record both oxygen saturation and heart rate, and a snoring sensor. For home recording, participants were instructed on how to wear the equipment and start recording. We calculated the sleep apnea–hypopnea index (AHI) as the total number of apneas and hypopneas divided by the number of hours of artifact-free

recording. The lowest oxygen saturation ($SpO_2$) value was also evaluated.

### Statistical analysis

All results are presented as mean ± standard deviation (SD). We divided participants into groups based on sleep efficiency, sleep latency, WASO (Blackwell *et al.*, 2011; Otake *et al.*, 2011), and clinical guidelines for the use of unattended portable monitors by the Portable Monitoring Task Force of the American Academy of Sleep Medicine (Collop *et al.*, 2007). Results of cognitive performance tests for TST, sleep latency, WASO and lowest $SpO_2$ groups were compared using one-way analysis of variance (ANOVA) with Bonferroni's test. We compared sleep latency and AHI between the two groups with the non-paired *t*-test. We performed Pearson's [age, TST, sleep latency, WASO, AHI and 3% desaturation index (DSI)] and Spearman's (sleep efficiency, lowest $SpO_2$, ESS and PSQI) correlation analyses followed by multiple regression analysis to determine the independent parameters correlated with the CPT-IP, 0- or 1-back test. A value of $P < 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics version 19 (IBM, Chicago, IL, USA).

## RESULTS

Baseline characteristics of participants are shown in Table 1. The accuracy of the 0-back test significantly decreased in participants with TST < 5 h compared with those with TST > 7 h (90.6 ± 12.0% versus 97.9 ± 4.5%, $P = 0.024$), but there was no significant difference in the accuracy of the 1-back test between the two groups (Table 2). Participants with <85% sleep efficiency showed a significant decrease in accuracy compared with those with ≥85% sleep efficiency on both the 0-back (90.0 ± 11.9% versus 97.3 ± 7.7%, $P = 0.003$) and 1-back (51.4 ± 22.3% versus 64.6 ± 25.0%, $P = 0.017$) tests. There was no significant difference in accuracy between the two groups on the CPT-IP (Table 3). Participants with sleep latency ≥30 min showed decreased accuracy on the 0- and 1-back tests compared with participants with <15 min or 15–30 min sleep latency, but this difference was not significant. These groups showed no significant difference in accuracy on the CPT-IP (Table 3). Participants with WASO longer than 30 min tended to have lower accuracy on the 0- and 1-back tests than those with WASO ≤ 5 min or 5–30 min, but these differences were also not significant. There was no significant difference in accuracy on the CPT-IP among the three groups (Table 3).

There were no significant differences in accuracy on the CPT-IP, 0- and 1-back tests between the two AHI groups. The lowest $SpO_2$ ≥ 90% group tended to have greater accuracy on the CPT-IP than the <80% or 80–90% groups. The lowest $SpO_2$ groups had no significant differences in accuracy on the 0- and 1-back tests (Table 4).

**Table 1** The characteristics, actigraphy and sleep apnea screening data, cognitive performance tests, PSQI and ESS of all subjects

| | |
|---|---|
| Age (years) | 72.2 ± 5.9 |
| Sex: male (%) | 16 (20.5) |
| Body mass index (kg $m^{-2}$) | 22.4 ± 2.4 |
| Dyslipidemia (*n*, %) | 39 (50.0) |
| Hypertension (*n*, %) | 52 (66.7) |
| Diabetes mellitus (*n*, %) | 13 (16.7) |
| Cardiovascular diseases (*n*, %) | 17 (21.8) |
| Orthopedic problems (*n*, %) | 21 (26.9) |
| Insomnia (*n*, %) | 2 (2.6) |
| Medication (*n*, %) | 56 (70.9) |
| Sleep drugs (*n*, %) | 21 (26.6) |
| Current smoker (*n*, %) | 14 (17.7) |
| Current drinker (*n*, %) | 26 (33.3) |
| TST (min) | 317.2 ± 105.8 |
| Sleep efficiency (%) | 83.4 ± 13.0 |
| Sleep latency (min) | 24.2 ± 35.6 |
| WASO (min) | 27.6 ± 30.5 |
| AHI ($h^{-1}$) | 13.1 ± 11.6 |
| DSI ($h^{-1}$) | 3.8 ± 4.1 |
| Lowest $SpO_2$ (%) | 84.6 ± 5.8 |
| CPT-IP: accuracy | 0.685 ± 0.221 |
| 0-back test: accuracy (%) | 94.0 ± 10.4 |
| 1-back test: accuracy (%) | 58.5 ± 24.6 |
| PSQI | 5.9 ± 3.0 |
| ESS | 5.8 ± 4.2 |

AHI, apnea–hypopnea index; CPT-IP, continuous performance test-identical pairs; DSI, 3% desaturation index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; $SpO_2$, oxygen saturation; TST, total sleep time; WASO, wake after sleep onset.

**Table 2** Results of cognitive performance tests and questionnaires in each TST group

| | *TST* | | |
|---|---|---|---|
| | *<5 h* | *5–7 h* | *>7 h* |
| *n* | 26 | 21 | 31 |
| CPT-IP: accuracy | 0.639 ± 0.225 | 0.677 ± 0.212 | 0.729 ± 0.221 |
| 0-back test: accuracy (%) | 90.6 ± 12.0* | 92.1 ± 12.7 | 97.9 ± 4.5 |
| 1-back test: accuracy (%) | 54.9 ± 22.8 | 60.8 ± 26.4 | 59.8 ± 25.0 |

CPT-IP, continuous performance test-identical pairs; TST, total sleep time.
*$P < 0.05$, versus >7 h.

Single correlation analysis revealed that age was significantly related to CPT-IP accuracy ($r = -0.276$, $P = 0.015$). Age, TST and sleep efficiency were significantly correlated with accuracy on the 0-back test (age, $r = -0.324$, $P < 0.001$; TST, $r = 0.270$, $P = 0.017$; sleep efficiency, $r = 0.354$, $P = 0.001$). Age and sleep efficiency were significantly correlated with accuracy on the 1-back test (age,

**Table 3** Results of cognitive performance tests and questionnaires in each sleep efficiency, sleep latency and WASO group

| | *Sleep efficiency* | | *Sleep latency* | | | *WASO* | | |
|---|---|---|---|---|---|---|---|---|
| | *≥ 85%* | *<85%* | *<15 min* | *<30 min* | *≥ 30 min* | *≤ 5 min* | *≤ 30 min* | *>30 min* |
| *N* | 42 | 36 | 46 | 14 | 15 | 16 | 26 | 22 |
| CPT-IP: accuracy | 0.687 ± 0.205 | 0.683 ± 0.242 | 0.690 ± 0.214 | 0.655 ± 0.234 | 0.660 ± 0.245 | 0.671 ± 0.261 | 0.671 ± 0.175 | 0.692 ± 0.235 |
| 0-back test: accuracy (%) | 97.3 ± 7.7 | 90.0 ± 11.9* | 94.8 ± 10.7 | 93.8 ± 12.2 | 91.9 ± 8.0 | 93.8 ± 12.5 | 95.9 ± 8.6 | 92.9 ± 10.3 |
| 1-back test: accuracy (%) | 64.6 ± 25.0 | 51.4 ± 22.3* | 57.0 ± 23.6 | 63.3 ± 26.1 | 52.9 ± 25.0 | 54.5 ± 23.7 | 66.2 ± 25.0 | 47.7 ± 23.1 |

CPT-IP, continuous performance test-identical pairs version; WASO, wake after sleep onset.
*$P < 0.05$.

**Table 4** Results of cognitive performance tests and questionnaires in AHI and lowest $SpO_2$ groups

| | *AHI* | | *Lowest $SpO_2$* | | |
|---|---|---|---|---|---|
| | *<15 $h^{-1}$* | *≥ 15 $h^{-1}$* | *<80%* | *<90%* | *≥ 90%* |
| *n* | 48 | 30 | 14 | 51 | 10 |
| CPT-IP: accuracy | 0.657 ± 0.247 | 0.731 ± 0.167 | 0.633 ± 0.244 | 0.665 ± 0.224 | 0.837 ± 0.096 |
| 0-back test: accuracy (%) | 93.0 ± 11.9 | 95.5 ± 7.4 | 96.4 ± 6.1 | 93.0 ± 11.8 | 95.7 ± 6.9 |
| 1-back test: accuracy (%) | 59.8 ± 25.1 | 56.4 ± 23.9 | 57.6 ± 28.4 | 57.6 ± 24.6 | 57.1 ± 17.7 |

AHI, apnea–hypopnea index; CPT-IP, continuous performance test-identical pairs; $SpO_2$, oxygen saturation.

**Table 5** Simple and multiple regression analysis

| | *CPT-IP* | | | | *0-back test* | | | | *1-back test* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Simple* | | *Multiple* | | *Simple* | | *Multiple* | | *Simple* | | *Multiple* | |
| | *r* | *P* | *β* | *P* | *r* | *P* | *β* | *P* | *r* | *P* | *β* | *P* |
| Age | −0.276 | 0.015 | −0.274 | 0.058 | −0.324 | <0.001 | −0.093 | 0.499 | −0.556 | <0.001 | −0.468 | <0.001 |
| TST | 0.152 | 0.185 | 0.210 | 0.157 | 0.270 | 0.017 | 0.267 | 0.033 | 0.107 | 0.352 | 0.018 | 0.885 |
| Sleep efficiency | 0.004 | 0.972 | −0.260 | 0.144 | 0.354 | 0.001 | 0.001 | 0.994 | 0.240 | 0.035 | 0.293 | 0.052 |
| Sleep latency | 0.062 | 0.597 | −0.088 | 0.586 | −0.073 | 0.534 | −0.072 | 0.643 | 0.118 | 0.313 | 0.252 | 0.067 |
| WASO | 0.012 | 0.925 | −0.109 | 0.513 | −0.132 | 0.298 | −0.076 | 0.639 | −0.168 | 0.184 | 0.049 | 0.728 |
| AHI | 0.137 | 0.231 | 0.075 | 0.644 | 0.094 | 0.413 | 0.186 | 0.240 | −0.071 | 0.537 | 0.091 | 0.505 |
| DSI | 0.115 | 0.326 | 0.152 | 0.427 | −0.143 | 0.221 | −0.348 | 0.064 | −0.202 | 0.082 | −0.206 | 0.205 |
| Lowest $SpO_2$ | −0.116 | 0.321 | −0.093 | 0.606 | −0.029 | 0.805 | −0.126 | 0.470 | 0.016 | 0.895 | −0.076 | 0.619 |
| ESS | 0.022 | 0.851 | −0.006 | 0.968 | −0.050 | 0.662 | −0.061 | 0.638 | 0.248 | 0.029 | −0.085 | 0.454 |
| PSQI | 0.093 | 0.418 | 0.066 | 0.624 | 0.085 | 0.460 | 0.172 | 0.202 | −0.012 | 0.919 | 0.151 | 0.197 |

AHI, apnea–hypopnea index; CPT-IP, continuous performance test-identical pairs; DSI, 3% desaturation index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; $SpO_2$, oxygen saturation; TST, total sleep time; WASO, wake after sleep onset.

$r = -0.556$, $P < 0.001$; sleep efficiency, $r = 0.240$, $P = 0.035$). Multiple regression analysis showed that TST was independently correlated with accuracy on the 0-back test ($\beta = 0.267$, $P = 0.033$), while age was independently correlated with accuracy on the 1-back test ($\beta = -0.468$, $P < 0.001$). None of the other factors, such as sleep efficiency, sleep latency, WASO, AHI, DSI, lowest $SpO_2$, ESS and PSQI, showed significant correlations with 0- or 1-back test accuracy (Table 5).

## DISCUSSION

We found that short sleep duration and diminished sleep efficiency decreased memory capacity, while AHI and lowest $SpO_2$ did not influence memory-back performances in our participants. Sleep duration was independently associated with memory. Short sleep duration and poor sleep quality might have adverse effects on neural bases of memory in older adults.

### Sleep duration, aging and memory

Total sleep time was correlated with 0-back test accuracy, while age was correlated with 1-back test accuracy in this study. This difference could be interpreted as a task characteristic: the 0-back test reflects simple attention and short-term memory; and the 1-back test reflects working memory capacity, in particular, executive function (Callicott *et al.*, 2003; Craik, 2002). In general, working memory tasks significantly decline with normal aging (Dobbs and Rule, 1989). Middle-aged and older adults perform more poorly than younger adults on working memory tests (Reuter-Lorenz and Lustig, 2005), and there are load-dependent age effects (Jaeggi *et al.*, 2009). The 1-back test requires a heavier mental workload of working memory than the 0-back test. According to increase in mental workload of the *n*-back test, age may have a stronger effect on the cognitive state (0-back test: accuracy 94.0 ± 10.4% versus 1-back test: accuracy 58.5 ± 24.6%; Table 1). Further evaluation is needed to clarify these points.

### Sleep quality and cognitive performance

We showed that objective sleep duration and sleep efficiency were related to cognitive performance decline in older adults. Sleep quality was significantly associated with poor cognitive performance as measured using the Mini-Mental State Examination and Trail Making Test part B in older women (Blackwell *et al.*, 2006). Sleep problems are related to quality of life in older adults, and sleep quantity and quality tend to decrease with age (Cirelli, 2012). In older women, good (PSQI < 6) and poor (PSQI ≥ 6) sleepers significantly differ on tests of working memory, attentional set shifting and abstract problem solving (Nebes *et al.*, 2009). Motor-sequence learning, but not verbal declarative memory, displays loss of sleep-dependent consolidation with aging. Improving sleep through behavioral or pharmacological treatments may enhance cognition and performance in older adults (Pace-Schott and Spencer, 2011). Our findings suggest that poor sleep quality may be a marker for memory impairment. Sleep evaluation using actigraphy in older adults provides important information for the early detection and prevention of sleep-related cognitive impairment.

### Sleep and sustained attention

We did not observe a relationship between sleep duration or sleep quality and sustained attention. Sustained attention is impaired by excessive daytime sleepiness in sleep disorders and sleep-disordered breathing (SDB) with hypersomnia (Van Schie *et al.*, 2012). In our study, the ESS of most participants was within normal limits (mean ESS, 5.8 ± 4.2).

Further studies involving older adults with moderate to severe SDB with hypersomnia will help clarify the relation between sleep and sustained attention.

### Sleep apnea and cognitive performance

Reports on the relationship between SDB and cognitive performance have been inconsistent. Indeed, SDB impaired cognitive performance in older adults in some studies (Yaffe *et al.*, 2011), while it did not in others (Sforza *et al.*, 2010). One prospective study showed that older women with SDB were more likely to develop mild cognitive impairment or dementia (Yaffe *et al.*, 2011). However, a cross-sectional study found that the impact of undiagnosed SDB on cognitive performance was limited in generally healthy older adults, and only slightly affected severe cases (Sforza *et al.*, 2010). In our study, SDB was not independently correlated with cognitive performance. Older adults with AHI $\geq$ 15 $h^{-1}$ or lowest $SpO_2$ < 90% did not show significant differences in cognitive performance compared with those with AHI < 15 $h^{-1}$ or lowest $SpO_2$ $\geq$ 90%. SDB included both patients with middle-age- and elderly-onset SDB. These two patient types show different clinical characteristics. Elderly-onset obstructive sleep apnea syndrome (OSAS) may have a smaller impact on physiological changes associated with OSAS than middle-age-onset OSAS (Bliwise, 2011). In a previous study, we observed differences in electroencephalographic and cardiac arousal, and the pattern of SDB between middle-aged and older patients with SDB (Noda *et al.*, 1995, 2000). Age-dependent increases in the incidence of SDB may not directly influence the hemodynamics leading to severe cardiovascular complications or cognitive dysfunction (Noda *et al.*, 1998). We evaluated sleep apnea with portable home monitoring systems in this study. Polysomnographic measurements may provide a pathophysiological explanation for the connection between sleep parameters, including arousal and cognitive performance, in older adults.

## LIMITATIONS

Although our results suggest that short sleep duration impairs memory, our study included a high percentage of female participants. In aged populations, the prevalence of mild cognitive impairment is higher in men than women (Petersen *et al.*, 2010). We showed that TST independently impaired short-term memory, but it remains unclear why TST did not affect working memory. More complex information processing that includes short-term memory may explain the differences in working *n*-back task results. Given the cross-sectional design, future studies will be needed to confirm the causal relationship between sleep-related factors and cognitive impairment, and include an adequate number of male participants in prospective cohorts.

In conclusion, our findings suggest that short sleep duration is associated with decreased memory performance. Sleep might play an important role in individual differences in cognitive performance in older adults.

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## CONFLICT OF INTEREST

No conflicts of interest declared.

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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

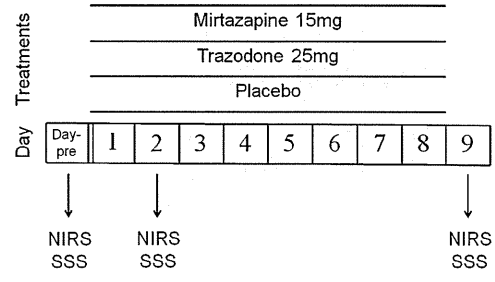


**Fig. 1** Study design. Subjects were to be measured more than a week prior to receiving the first medication (day-pre), on days 2 (three times during the study) and 9 (three times during the study). *NIRS* NIRS measurement, *SSS* Stanford Sleepiness Scale

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 $\rho$. Values of $p<0.05$ were considered statistically significant for all analyses.

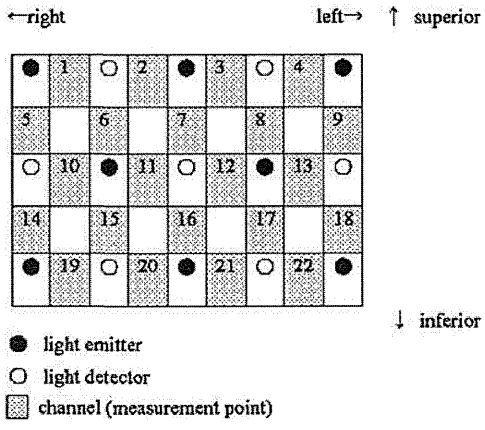


**Fig. 2** Placement of NIRS shells

## 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

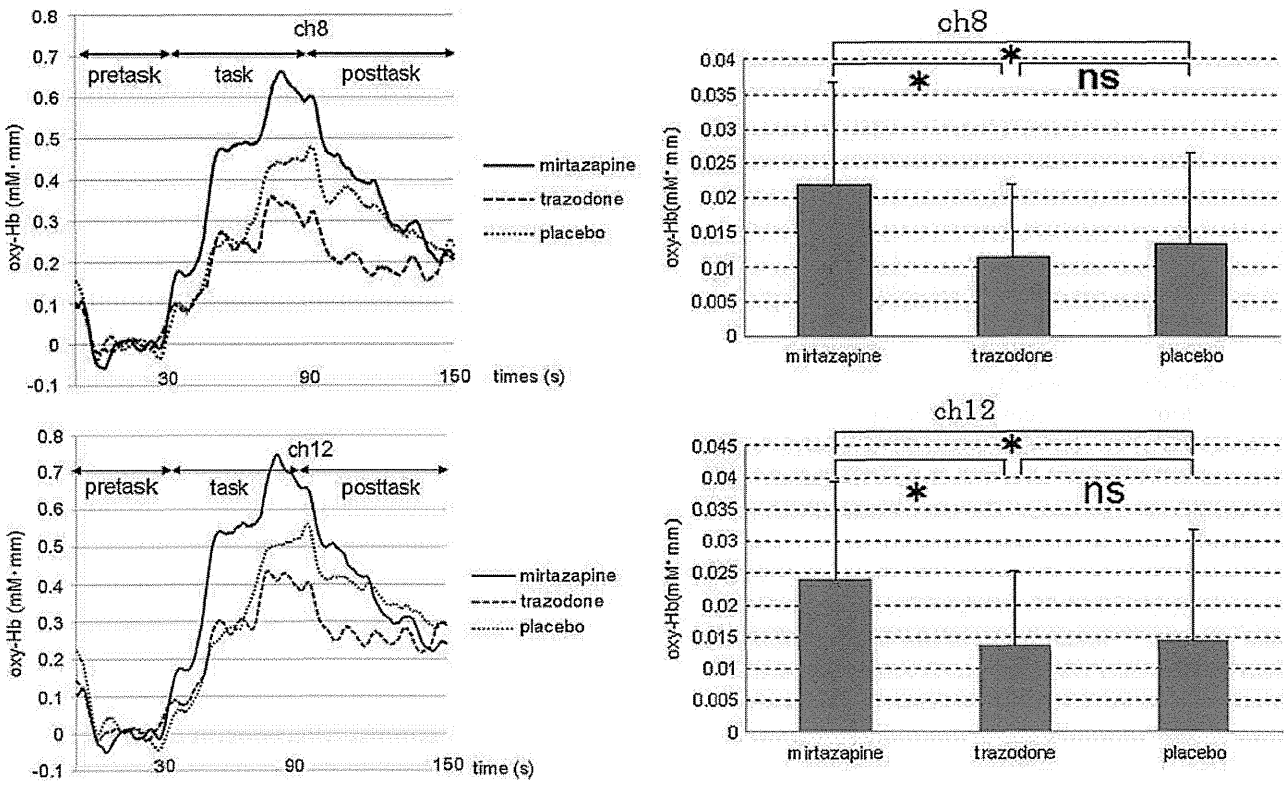


**Fig. 3** Oxy-Hb concentration change during the whole 150-s period on day9 s (*left*) and averaged oxy-Hb concentration change during the 60-s task period on day9 s (*right*). The *asterisk* indicates $p$<0.05 (post hoc test; protected least significant difference)

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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