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Comparative study of cognitive impairment between medicated and medication-free patients with remitted major depression: Class-specific influence by tricyclic antidepressants and newer antidepressants

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ABSTRACT

Patients with major depressive disorder (MDD) are known to present with cognitive deficits; however, the presence of these deficits in the remitted state have been inconsistent. One of the most important factors potentially contributing to inconsistencies between studies may be the influence of medications. To explore the influence of antidepressants on cognitive performance in remitted MDD, we evaluated memory and executive functions using Wechsler Memory Scale-Revised and Stroop Color and Word Test, and compared performance among 50 medicated (29 treated with tricyclic antidepressants [TCA], 21 treated with selective serotonin reuptake inhibitors or serotonin noradrenalin reuptake inhibitors) and 19 medication-free MDD patients and 31 controls. The results showed that all 3 MDD groups had significantly lower performance for verbal memory compared with controls. Both medicated groups showed significantly lower performance for visual memory compared with controls; however, the medication-free group did not differ from controls. For the executive function, only the TCA group showed a significantly lower performance compared with controls. These results suggest that cognitive impairment remained even in remitted patients with MDD, however, part of this impairment may be influenced by class-specific antidepressant side effects.

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1. Introduction

Patients with major depressive disorder (MDD) are known to present with cognitive deficits (*e.g.* verbal and visual memory, verbal fluency, attentional set-shifting, motor speed, inhibitory control and working memory) (Austin et al., 2001). These cognitive deficits, including memory and executive dysfunctions, have also been reported in medication-free depressed patients (Porter et al., 2003; Vythilingam et al., 2004; Gallassi et al., 2006). Recent studies have indicated that cognitive dysfunction may change during the course of depression (Wagner et al., 2012) and, at least in part, remain unresolved even after remission from depressive episodes (Paelecke-Habermann et al., 2005; Gallassi et al., 2006; Nakano et al., 2008; Baba et al., 2010). However, results have varied among remitted patients with MDD, and findings remain controversial (Vythilingam et al., 2004; Halvorsen et al., 2011). In most cases, remitted patients with MDD were treated with antidepressants. Thus, one of the most important factors potentially contributing to the inconsistencies among these studies may be the influence of different psychotropic medications. Weiland-Fiedler et al. (2004) evaluated cognitive function in remitted, medication-free patients with a history of MDD and described the presence of deficits in sustained attention, intact visual memory, and learning function in these patients. However, few studies have compared cognitive function between medicated and medication-free patients with remitted MDD.

To explore the influence of antidepressants on cognitive impairment in remitted patients with MDD, we performed neuropsychological tests on remitted patients and healthy controls,

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and compared performance among medicated remitted patients, medication-free remitted patients, and controls. Furthermore, medicated patients were subdivided according to the class of antidepressant used. This study is a part of the Juntendo University Mood Disorder Project (JUMP).

2. Methods and materials

2.1. Subjects

Sixty-nine patients with MDD (28 males and 41 females) were recruited from Juntendo Koshigaya Hospital, Minami-Saitama Hospital, and Izumi Clinic. All patients had previously met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria for MDD. At the time of the study, however, all patients were considered to be in remission, which was confirmed by the fact that they no longer met the DSM-IV criteria for MDD. In addition, scores for the 21-item Hamilton Rating Scale for Depression were below 7 points (Hamilton, 1960). Patients were excluded if they had a history of other psychiatric disorders, including delusions; severe or acute medical illnesses; neurological disorders; and/or the use of drugs that may cause depression. Patients who had clinical evidence of dementia or a Mini-Mental State Examination (MMSE) score <24 were excluded. Fifty patients were on antidepressant medications, and 19 patients had discontinued medication at the time of the study. Of the antidepressant-medicated patients, 29 were receiving tricyclic antidepressants (TCAs) and 21 were receiving selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenalin reuptake inhibitors (SNRIs). Patients were divided into 3 groups according to medication status (TCA group: mean $\pm$ standard deviation age, 49.2 ± 12.1 years; SSRI/SNRI group: 48.4 ± 13.5 years; medication-free group: 48.7 ± 16.4 years). The doses of antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006). Four patients in the TCA group and 6 patients in the SSRI/SNRI group were taking lithium, 7 patients in the TCA group and 4 patients in the SSRI/SNRI group were taking anticonvulsants, and 18 patients in the TCA group and 14 patients in the SSRI/SNRI group were taking benzodiazepines.

Thirty-one healthy controls (10 males and 21 females) who were matched for age and education were recruited (control group: 47.2 ± 15.5 years). Exclusion criteria for controls included a history of depression and the same exclusion criteria used for patients. All controls were working at least part-time. Detailed demographic and clinical features of participants are shown in Table 1.

The study was approved by the Medical Ethics Committee of Juntendo University and was performed in accordance with the regulations outlined by Juntendo University. All participants provided written informed consent.

2.2. Neuropsychological tests

Memory functions were measured using 3 subtests of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). The WMS-R is a well-known battery of tests used to evaluate anterograde memory; its detailed characteristics are reported in the test manual. Logical memory (LM) and verbal paired associates (VPA) subtests were used to measure verbal memory, and the visual reproduction (VR) subtest was used to measure visual memory (Maeshima et al., 2012).

To evaluate executive function, we used the modified Japanese version of Golden's Stroop Color and Word Test (Nakano et al., 2008). In Part I of the Stroop test, the participant read aloud color words that were printed in different-colored ink (congruent condition). Part II required the participant to name the incongruent printed color of the color words (incongruent condition). Time differences between Parts I and II (Part II–Part I) were evaluated (Golden, 1978; Nakano et al., 2008).

2.3. Data analysis

Age, education, MMSE score, WMS-R scores, and Stroop test score were compared among the 4 groups (TCA group, SSRI/SNRI group, medication-free group, and control group), and the number of depressive episodes and total duration of depressive episodes were compared among the 3 MDD groups using the Kruskal–Wallis test. A *post hoc* analysis was performed using the two-tailed

Table 1
Demographic and clinical features of participants.

	Control ($N=31$)	MDD ($N=69$)		
	Mean (S.D.)	Medication-free ($N=19$) Mean (S.D.)	SSRI/SNRI ($N=21$) Mean (S.D.)	TCA ($N=29$) Mean (S.D.)
Age (years)	47.2 (15.5)	48.7 (16.4)	48.4 (13.5)	49.2 (12.1)
Gender (M/F)	10/21	6/13	7/14	15/14
Education (years)	13.1 (3.6)	14.4 (1.9)	14.2 (2.2)	13.6 (2.0)
MMSE score	27.2 (2.4)	29.0 (1.4)	27.1 (2.2)	27.3 (2.0)
Number of depressive episodes	–	1.0 (0.0)[a]	2.1 (1.5)	1.5 (0.7)
Total duration of illness (mos)	–	18.3 (7.4)	16.7 (14.7)	18.2 (12.0)
Daily dose of antidepressant (mg)[b]	–	–	113.0 (44.9)	115.6 (42.3)

MDD, major depressive disorder; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin noradrenalin reuptake inhibitors; S.D., standard deviation; MMSE, Mini-Mental State Examination.

[a] The medication-free group had significantly fewer depressive episodes than the TCA and SSRI/SNRI groups ($p=0.014$).

[b] Doses of antidepressants were converted to an equivalent dose of imipramine.

Table 2
Results of executive function and memory function tests.

Cognitive test	Control ($N=31$)	MDD ($N=69$)			
	Mean (S.D.)	Medication-free Mean (S.D.)	SSRI/SNRI ($N=21$) Mean (S.D.)	TCA ($N=29$) Mean (S.D.)	K–**W** test
Logical memory (LM)	27.0 (7.5)	21.1 (7.3)[*,a]	19.3 (7.9) [**,a]	16.9 (7.1)[**,a]	$p<0.001$
Verbal paired associates (VPA)	19.3 (3.5)	15.6 (4.3)[**,b]	15.9 (5.0)[*,b]	14.3 (4.1)[**,b]	$p<0.001$
Visual reproduction (VR)	37.6 (3.8)	37.4 (3.9)	34.3 (5.9)[*,c]	34.2 (6.2)[*,c]	$p=0.011$
Stroop test	55.5 (15.1)	61.6 (38.3)	61.6 (18.5)	89.1 (39.3)[**,d]	$p=0.001$

Mann–Whitney test; control group vs. depression groups; MDD, major depressive disorder; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin noradrenalin reuptake inhibitors; S.D., standard deviation; K–W test, Kruskal–Wallis test.

[a–d] *Post hoc* analysis comparing MDD groups and controls (Mann–Whitney *U* test).

* $p<0.05$.

** $p<0.01$

[a] Medication-free group ($p=0.014$), SSRI/SNRI group ($p=0.001$), and TCA group ($p<0.001$) showed lower LM scores compared with controls.

[b] Medication-free group ($p=0.004$), SSRI/SNRI group ($p=0.011$) and TCA group ($p<0.001$) showed lower VPA scores compared with controls.

[c] SSRI/SNRI group ($p=0.014$) and TCA group ($p=0.012$) showed lower VR scores compared with controls.

[d] TCA group showed lower performance in stroop test compared with controls ($p<0.001$).

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