

Performance on the Wechsler Adult Intelligence Scale (WAIS) in Japanese patients with bipolar and major depressive disorders in euthymic and depressed states

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Aim: This study aimed to examine the cognitive performance of patients with bipolar disorder (BD) stratified by illness phase compared to that of patients with major depressive disorder (MDD) and healthy controls.

Methods: Participants were 139 patients with BD (55 euthymic and 84 depressed), 311 patients with MDD (88 euthymic and 223 depressed), and 386 healthy controls who underwent the Wechsler Adult Intelligence Scale-Revised or the Third Edition. They were non-elderly Japanese individuals with normal estimated premorbid intelligence quotient (IQ; >90), group-matched for age, sex, and premorbid IQ.

Results: The depressed BD group showed significantly lower scores on verbal IQ, performance IQ, full-scale IQ, and three group indexes of perceptual organization, working memory, and processing speed when compared with healthy controls (all $P < 0.001$). All IQs and working memory index were also significantly lower than those of the

depressed MDD group. The depressed MDD group scored significantly lower than controls in performance IQ ($P < 0.001$), full-scale IQ, and only in the index of processing speed ($P < 0.001$). The euthymic BD group scored significantly lower than controls in performance IQ ($P = 0.004$), whereas the euthymic MDD group scored significantly lower than controls only in processing speed ($P = 0.030$).

Conclusion: Patients with BD appear to have global and more intense cognitive impairments in depressed states compared with those with MDD whose impairments seem to be apparent only in processing speed in the Wechsler Adult Intelligence Scale. Attenuated impairments appear to exist in euthymic states of both patients.

Keywords: bipolar disorder, major depressive disorder, perceptual organization, premorbid IQ, Wechsler Adult Intelligence Scale.

<http://onlinelibrary.wiley.com/doi/10.1111/pcn.13191/full>

Cognitive deficits are widespread across a broad range of psychiatric disorders from psychosis through depression to personality and substance use disorders.^{1,2} Among these, cognitive deficits in schizophrenia have been examined in various domains, such as attention, working memory, verbal and visual memory, processing speed, reasoning and problem solving, executive function, and social cognition,³ and have been well replicated across ethnicity, including our own with a Japanese population.^{3,4} Previous reviews and a meta-analysis have pointed out similar, but smaller, cognitive deficits in patients with bipolar disorder (BD) compared with those with schizophrenia.^{3,5,6} It is becoming accepted that differences in cognition between patients with schizophrenia and BD are quantitative, but not qualitative. Most studies including systematic reviews and meta-analyses on cognitive performance in patients with major depressive disorder (MDD) have found moderate deficits in memory, attention, executive function, and processing speed, with some functions showing persistent impairment after symptomatic remission.^{7–12} Growing evidence suggests that cognitive deficits represent a core feature of the illness, and a principal determinant of social, occupational, and functional non-recovery not only in schizophrenia, but also in BD^{13–19} and MDD.^{20–24}

Several meta-analyses on studies comparing cognition between euthymic BD patients and controls found medium-to-large effect size deficits in euthymic BD in domains such as response inhibition; abstraction and set shifting; executive function (category fluency, mental manipulation); verbal memory/learning; and sustained attention; and small-to-medium effect size deficits in processing speed, visual memory, and letter fluency.^{25–29} These meta-analyses, however, observed heterogeneous distribution of effect sizes in many of the tests undertaken, as well as in education levels or premorbid IQ, which obscured the robustness of these findings.

Thus, researchers have focused on cognitive within-group heterogeneity in nosological categories of schizophrenia, BD, and MDD,^{14,30–34} Each diagnostic category has cognitive subgroups, including severe impairment, good functioning, and one or more selective or modest impairment clusters, and that good cognitive functioning cluster has a higher premorbid intelligence quotient (IQ) and higher psychosocial functioning. However, the prevalence of those belonging to the severe impairment and good functioning subgroups are significantly different between schizophrenia and BD.^{14,35} Premorbid and post-onset cognitive performance in schizophrenia is generally accepted as impaired, but premorbid deficits in BD, as a group, are not as robust as in

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schizophrenia.³ A Swedish cohort study reported that those with both excellent and poor school grades at age 16 years had increased risk of later BD,³⁶ which might explain why post-onset cognitive performance in BD is heterogeneous.^{32,37} Previous studies on BD included mixed samples of different premorbid IQ levels. To date, normative data of the Wechsler Memory Scale (WAIS) profile in BD and MDD patients is lacking. If participants are limited to patients without premorbid intellectual impairment, negative impact due to depression and its prognosis could be identified more precisely.

Patients with BD are frequently misdiagnosed as having MDD, especially those presenting depression at the onset and no clear history of mania, which leads to inadequate treatment and poor prognosis.³⁸ Yet, direct comparisons of cognition between BD and MDD patients within a single study remain limited.³⁹ As cognitive impairments have been traditionally accepted as state-dependent,^{40,41} most studies including a meta-analysis by Samamé *et al.* compared the patients in the same phase of illness.^{38,42–44} However, most primary studies were conducted with small samples, and sample characteristics were different from study-to-study. The meta-analysis by Samamé *et al.* observed heterogeneity in many of the tasks performed. Although BD patients mostly performed numerically worse compared with MDD patients in either euthymic or depressed state, the meta-analysis by Samamé *et al.* found a significant overall effect size favoring MDD exclusively for list learning during euthymia ($ES = 0.65$, $P < 0.001$), and no significant difference was identified during depressed state. A study by Bearden *et al.*, which was not included in the Samamé *et al.* meta-analysis, also found qualitatively similar patterns of deficits in declarative memory (verbal recall and recognition) in both patients group-matched for depression severity.⁴⁵

Previously, we examined the executive function and memory⁴⁶ and manual dexterity⁴⁷ in BD and MDD patients with a relatively large sample. We found a significant difference favoring the depressed MDD group in executive function (Wisconsin Card Sorting Test) and episodic memory (logical memory I + II of the WAIS-Revised [WAIS-R] converged) compared with the depressed BD II group, and also in dexterity (Purdue pegboard test) compared with the depressed and euthymic BD group.

To date, large studies on IQ and cognitive profile of mood disorder patients using a full version of the WAIS-R or WAIS Third Edition (WAIS-III)^{48,49} are scant, although the WAIS covers most of the cognitive domains, except memory, and has been most commonly used in clinical settings. The advantage of using the WAIS-III is to generate group index scores from converged age-adjusted subtest scores, enabling us to evaluate each cognitive domain comprehensively.

This study aimed to: (i) clarify the WAIS profiles of patients with BD and MDD with normal premorbid IQ (>90) in depressed and euthymic states; (ii) identify specific cognitive domains that might differ between BD and MDD patients in the same phase of illness; and (iii) examine how current depression severity and psychotropic medication are associated with cognitive performance in these disorders. As previous studies reported inconsistent findings on the effects of depression severity and medication to cognition, we would like to clarify these points. To minimize the effects of aging and premorbid cognitive functioning, the five clinical groups (i.e. depressed and euthymic patients with BD and MDD and healthy controls) were matched for age, sex, and premorbid IQ. To our knowledge, this is the first large study on the WAIS profile of mood disorder patients in a well-matched sample, and would provide normative data of BD and MDD patients in the Japanese population. Based on previous literatures^{39, 42} and the findings of our own,^{46,47} we hypothesized that depressed BD patients would show severer cognitive impairments compared with depressed MDD, euthymic BD, and euthymic MDD patients.

Methods

Participants

Participants were 139 patients with BD (55 euthymic, 84 depressed), 311 patients with MDD (88 euthymic, 223 depressed), and 386 healthy

controls matched for age, sex, ethnicity (Japanese), and premorbid IQ (Table 1), who volunteered to participate in neurocognitive research studies at the Department of Mental Disorder Research, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan, from 2003 to 2020 through our website announcements, notices posted in the NCNP hospital, or advertisements in local free magazines. Participants' ages ranged from 18 to 59 years. Approximately 7% of the patients were inpatients at the NCNP hospital, and the rest were outpatients regularly attending either the NCNP hospital or a nearby hospital/clinic. Approximately half of the participants overlapped with our previous study.⁴⁶

Consensus diagnosis was made for each patient by at least two experienced research psychiatrists based on the Japanese version of the Mini-International Neuropsychiatric Interview,^{50,51} detailed interviews and medical records, if available, according to the DSM-IV⁵² criteria. For controls, we ruled out the possibility of current or past Axis I psychiatric disorders using the Mini-International Neuropsychiatric Interview, and confirmed they had no contact with psychiatric services; psychiatric medications; exposure to severe trauma; or family history of schizophrenia, BD and/or autism spectrum disorder within their second-degree relatives through a non-structured interview by a research psychiatrist. Individuals with a current or past history of substance abuse/dependence, severe head injury, central nervous system disease, or ongoing severe medical illness (such as thyroid deficiency) were excluded. People with a concurrent diagnosis of intellectual disability or borderline intelligence, or those with premorbid IQ <90 estimated by the Japanese version of the National Adult Reading Test (JART)^{53,54} (3 BD, 2 MDD, and 2 healthy controls; $<1\%$ of the total participants) were also excluded.

Depression severity was assessed using the 17-item version of the Hamilton Depression Rating Scale (HAM-D-17),⁵⁵ and manic symptoms were assessed using the Young Mania Rating Scale⁵⁶ for BD patients. According to the criteria for mania recommended by the International Society for Bipolar Disorders Task Force,⁵⁷ participants with Young Mania Rating Scale score ≥ 8 were regarded as hypomanic/manic and were excluded. Each patient group was divided into two groups (HAM-D-17 score ≤ 7 : euthymic; HAM-D-17 >7 : depressed), according to the International Society for Bipolar Disorders Task Force criteria for subsyndromal depression.

This study was approved by the Ethics Committee at NCNP, and was conducted in accordance with the Declaration of Helsinki. After the nature of the study procedures had been explained, written informed consent was obtained from all participants.

Cognitive assessment

Each participant underwent a neurocognitive test battery, comprising the JART, and a full Japanese version of the WAIS-R^{48,58} or the WAIS-III.^{49,59} The JART is a reading test of 100 Japanese ideographic script (Kanji) compound words that are difficult to read, and premorbid IQ was estimated using the validated regression equation from the JART score to the full-scale IQ (FSIQ).⁴⁷ Verbal IQ (VIQ), performance IQ (PIQ), FSIQ of the WAIS-R ($n = 123$) or the WAIS-III ($n = 219$), four group indexes of the WAIS-III [i.e. verbal comprehension (VC), perceptual organization (PO), working memory (WM), and processing speed (PS)], as well as 14 age-adjusted subtest scores of the WAIS-III were used for group comparison.

Statistical analysis

Differences in demographics and cognitive performance across the five groups were examined through one-way ANOVA; post-hoc between-group differences were examined using a pairwise multiple comparison test with Bonferroni correction. A χ^2 -test was used for categorical variables. After that, effects of depression severity and psychotropic medication on each IQ and group index were examined by Spearman's rank correlation, as well as an ANCOVA on cognitive performance of medicated and unmedicated patients for

Table 1. Demographics and clinical data of the participants.

	BD (n = 139)		MDD (n = 311)		HC E (n = 386)	Statistics	P	
	Depressed A (n = 84)	Euthymic B (n = 55)	Depressed C (n = 223)	Euthymic D (n = 88)				
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD			
<i>Demographics</i>								
Male, n (%)	36 (43%)	24 (44%)	105 (47%)	39 (44%)	172 (45%)	$\chi^2(4) = 0.636$	0.959	
Age (years)	37.4 ± 8.7	40.8 ± 10.3	39.0 ± 10.3	40.6 ± 9.8	40.1 ± 10.7	F (4, 831) = 2.260	0.061	
Education (years)	15.2 ± 2.2	14.9 ± 2.3	14.9 ± 2.0	14.9 ± 2.2	15.0 ± 2.0	F (4, 831) = 0.431	0.786	
Estimated premorbid IQ [†]	111.6 ± 7.7	112.5 ± 8.2	111.8 ± 7.9	112.9 ± 6.6	112.1 ± 7.3	F (4, 831) = 0.447	0.774	
<i>Clinical variables</i>								
Age of onset [‡]	28.1 ± 7.8	29.6 ± 10.8	31.2 ± 10.9	32.3 ± 10.2	—	F (3, 443) = 2.809	0.039	<i>post-hoc</i> (corrected)
Duration of medication (years)	10.1 ± 6.7	11.4 ± 8.4	6.9 ± 5.8	7.8 ± 6.7	—	F (3, 443) = 9.698	<0.001	B>D (P = 0.011), A,B>C (P < 0.001)
Outpatients, n (%)	73 (89%)	47 (96%)	189 (94%)	79 (96%)	—	$\chi^2(3) = 4.261$	0.235	
History of hospitalization, n (%)	22 (27%)	19 (37%)	41 (20%)	21 (25%)	—	$\chi^2(3) = 7.234$	0.065	B>C (P = 0.008)
Past suicide attempts, n (%)	20 (24%)	17 (32%)	35 (16%)	8 (9%)	—	$\chi^2(3) = 14.123$	0.003	B>D (P = 0.001), B>C (P = 0.008)
Recurrent episode, n (%)	N/A	N/A	120 (54%)	61 (69%)	—	$\chi^2(1) = 5.851$	0.016	D>C (P = 0.016)
HAMD-17 total	15.1 ± 5.5	4.0 ± 2.3	14.8 ± 5.4	4.4 ± 2.2	—	F (3, 443) = 166.428	<0.001	A,C>B,D (P < 0.001)
YMRS total	1.5 ± 1.9	1.5 ± 1.9	N/A	N/A	—	$\chi^2(1) = 0.002$	0.961	
<i>Medication dose</i>								
AP, if any	204.6 ± 303.9	250.8 ± 326.6	153.9 ± 232.4	133.2 ± 116.2	—	F (3, 132) = 1.171	0.323	
AP, typical, if any	27.6 ± 26.1	17.2 ± 18.8	155.8 ± 340.0	70.1 ± 51.4	—	F (3, 39) = 0.833	0.484	
AP, atypical, if any	230.6 ± 317.6	282.5 ± 336.9	141.8 ± 147.7	152.9 ± 118.2	—	F (3, 100) = 1889	0.136	
AD, if any	189.5 ± 141.7	126.1 ± 87.8	192.6 ± 152.8	139.8 ± 124.1	—	F (3, 192) = 2.211	0.088	—
<i>Medication use, n (%)</i>								
Antipsychotics	32 (38%)	24 (44%)	59 (27%)	24 (28%)	—	$\chi^2(3) = 8.896$	0.031	
Antidepressants	36 (43%)	17 (31%)	129 (58%)	54 (61%)	—	$\chi^2(3) = 18.987$	<0.001	C,D>B (P < 0.001)
Lithium	29 (35%)	15 (27%)	13 (6%)	6 (7%)	—	$\chi^2(3) = 53.335$	<0.001	A,B>C,D (P < 0.001)
Other mood stabilizers	35 (42%)	27 (50%)	21 (11%)	7 (9%)	—	$\chi^2(3) = 67.506$	<0.001	A,B>C,D (P < 0.001)
Benzodiazepines	53 (63%)	24 (44%)	124 (56%)	41 (47%)	—	$\chi^2(3) = 7.424$	0.060	

[†]Estimated premorbid intelligence quotient (IQ) was calculated based on the score of the Japanese version of the National Adult Reading Test (JART).

[‡]Age at first contact at psychiatric services.

Bold figures represent statistical significance (P < 0.05).

A, depressed bipolar disorder; AD, imipramine equivalent dose of antidepressants; AP, chlorpromazine equivalent dose of antipsychotics; B, euthymic bipolar disorder; C, depressed major depressive disorder; D, euthymic major depressive disorder; E, healthy control (HC); HAMD-17, 17-item version of the Hamilton Depression Rating Scale; N/A, not available; SD, standard deviation; YMRS, Young Mania Rating Scale.

each medication covarying for age, sex, premorbid IQ, and HAMD-17 total score. Statistical significance was set at a two-tailed P < 0.05. Statistical analyses were performed using SPSS version 22.0 (SPSS Japan, Tokyo, Japan).

Results

Demographic and clinical characteristics

Demographic and clinical data of the participants are shown in Table 1. Patients were divided between euthymic and depressed

Table 2. Comparison of cognitive performance across the five clinical groups

	Depressed BD A	Euthymic BD B	Depressed MDD C	Euthymic MDD D	HC E	Total		
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	one-way ANOVA	<i>P</i>	Post-hoc (Bonferroni)
JART								
<i>n</i>	84	55	223	88	386	836		
Raw score	79.3 ± 10.6	80.5 ± 11.4	79.6 ± 10.9	81.1 ± 9.1	80.0 ± 10.1			
Estimated premorbid IQ [†]	111.6 ± 7.7	112.5 ± 8.2	111.8 ± 7.9	112.9 ± 6.6	112.1 ± 7.3	F(4, 831) = 0.447	0.774	—
WAIS-R/III								
<i>n</i>	84	55	223	88	386	836		
FSIQ	102.1 ± 13.8	109.2 ± 13.0	108.4 ± 13.1	110.0 ± 11.0	111.6 ± 11.5	F(4, 831) = 11.031	0.001	A<B,D,E; A<C<E
VIQ	105.1 ± 13.4	111.6 ± 11.6	109.9 ± 13.4	110.7 ± 11.5	111.2 ± 11.5	F(4, 831) = 4.519	<0.001	A<B,C,D,E
PIQ	98.0 ± 14.5	102.9 ± 15.8	104.4 ± 13.6	106.8 ± 12.2	109.8 ± 13.0	F(4, 831) = 16.639	<0.001	A<D,E; B,C<E; A<C
VIQ - PIQ	7.1 ± 11.2	8.7 ± 13.6	5.5 ± 13.1	3.8 ± 12.6	1.4 ± 12.5	F(4, 831) = 8.149	<0.001	A,B,C<E
WAIS-III group index:								
<i>n</i>	64	44	170	62	262	602		
Verbal comprehension	106.9 ± 13.7	112.1 ± 11.1	109.7 ± 14.0	110.3 ± 10.6	109.1 ± 11.3	F(4, 597) = 1.326	0.259	—
Perceptual organization	98.1 ± 15.1	102.8 ± 13.1	103.5 ± 14.7	104.9 ± 14.3	106.3 ± 13.6	F(4, 597) = 4.679	0.001	A<E
Working memory	96.0 ± 14.3	102.5 ± 14.8	101.9 ± 14.1	103.5 ± 15.8	104.4 ± 13.7	F(4, 597) = 4.661	0.001	A<C,D,E
Processing speed	96.3 ± 14.5	102.2 ± 16.0	100.2 ± 14.6	102.2 ± 12.7	108.2 ± 13.8	F(4, 597) = 13.825	<0.001	A,C,D<E

[†]Premorbid intelligence quotient (IQ) was estimated by the Japanese version of the National Adult Reading Test (JART) score.

Bold figures represent statistical significance (*P* < 0.05) with Bonferroni correction.

A, depressed bipolar disorder; B, euthymic bipolar disorder; C, depressed major depressive disorder; D, euthymic MDD; E, healthy control (HC); SD, standard deviation.

groups. There was no significant difference in the male-to-female ratio, age, years of education, or estimated premorbid IQ across the five groups. The HAMD-17 total scores did not significantly differ between BD and MDD patients either in the euthymic or depressed phase. Among the BD patients, 16 euthymic and 21 depressed patients were diagnosed with BD I, which comprised 29% and 25% of each patient group, respectively. The remaining BD patients were diagnosed with BD II.

Comparison of cognitive performance across the five clinical groups

Comparisons of the JART score, WAIS-R/III IQ, and WAIS-III group indices across the five clinical groups are shown in Tables 2 and 3 and Fig. 1. The depressed BD group had the lowest performance followed by the depressed MDD and euthymic BD groups, scoring approximately the same level, the euthymic MDD group, and healthy controls, in this order. The depressed BD group showed significantly lower scores on all IQs and three group indexes (except for VC, which was similar across the five groups) compared with healthy controls (all *P* < 0.001), and significantly lower in all IQs and WM compared with the depressed MDD group. The depressed MDD group scored significantly lower than controls in PIQ (*P* < 0.001), FSIQ (*P* = 0.016), and processing speed index (*P* < 0.001). The euthymic BD group scored significantly lower than controls in PIQ (*P* = 0.004) and tended to score lower in processing speed (*P* = 0.092), while the euthymic MDD group scored significantly lower than controls only in processing speed (*P* = 0.030). No significant differences were found across euthymic patient groups. VIQ/PIQ

discrepancy was significant in depressed and euthymic BD, and depressed MDD groups compared with controls.

To see differences across the five groups in more detail, subtest scores of each patient group were compared against those of the control group (Table 4). The depressed BD group scored significantly lower on eight of the 14 subtests, whereas the depressed MDD group scored significantly lower only on timed tasks. The euthymic BD group scored significantly lower only in picture arrangement, whereas the euthymic MDD group scored significantly lower only in digit symbol-coding. Furthermore, component analysis of the digit symbol-coding revealed that visual memory was significantly impaired in the depressed BD, and depressed and euthymic MDD groups, whereas copy speed was significantly impaired only in the depressed MDD group. No significant difference was found in any subtest between the euthymic and depressed BD groups or between the euthymic and depressed MDD groups. These subtest results almost coincided with the results of group index scores.

Effects of depression severity and psychotropic medication on cognitive performances in each patient group

Relationships of depression severity and medication with cognitive performance are shown in Table 5. Overall, correlations between HAMD-17 total score and cognition were minimal in both patient groups; modest correlations were found only in PO (Spearman's ρ = -0.222) and FSIQ (ρ = -0.219) in BD patients. As to the medication dosage, both WS and PS were modestly negatively correlated with lithium dosage in patients with BD, and with atypical antipsychotics dosage in patients with MDD. Effects of medication use were

Table 3. Post-hoc analyses of cognitive performance across the five clinical groups.

	P value (Cohen's d)								
	A vs E	A vs D	A vs C	A vs B	C vs E	B vs E	D vs E	B vs D	C vs D
WAIS-R/III									
FSIQ	<0.001 (0.80)	<0.001 (0.63)	0.001 (0.47)	0.009 (0.53)	0.016 (0.26)	1.000 (0.21)	1.000 (0.14)	1.000 (0.07)	1.000 (0.13)
VIQ	<0.001 (0.51)	0.029 (0.45)	0.021 (0.36)	0.022 (0.51)	1.000 (0.11)	1.000 (0.03)	1.000 (0.04)	1.000 (0.08)	1.000 (0.06)
PIQ	<0.001 (0.89)	<0.001 (0.66)	0.002 (0.46)	0.336 (0.33)	<0.001 (0.41)	0.004 (0.52)	0.612 (0.23)	0.908 (0.28)	1.000 (0.18)
VIQ - PIQ	0.002 (0.46)	0.864 (0.28)	1.000 (0.13)	1.000 (0.13)	0.001 (0.32)	0.001 (0.58)	0.974 (0.19)	0.259 (0.38)	1.000 (0.13)
WAIS-III group index:									
Verbal comprehension									
Perceptual organization	<0.001 (0.59)	0.069 (0.46)	0.091 (0.36)	0.906 (0.33)	0.463 (0.20)	1.000 (0.26)	1.000 (0.10)	1.000 (0.15)	1.000 (0.10)
Working memory									
Processing speed	<0.001 (0.85)	0.182 (0.43)	0.552 (0.27)	0.336 (0.39)	<0.001 (0.57)	0.092 (0.42)	0.030 (0.44)	1.000 (0.00)	1.000 (0.14)

Bold figures represent statistical significance ($P < 0.05$) with Bonferroni correction.

A, depressed bipolar disorder; B, euthymic bipolar disorder; C, depressed major depressive disorder; D, euthymic major depressive disorder; E, healthy control (HC).

mainly found in PS and PIQ: PS was significantly lower in patients medicated with benzodiazepines than those unmedicated in both patient groups, and in MDD patients on atypical antipsychotics and antidepressants. Likewise, PIQ was significantly lower in BD patients medicated with benzodiazepines, and in MDD patients medicated with typical antipsychotics and antidepressants.

Discussion

Cognitive performance in depressed and euthymic patients

The present study aimed to clarify the WAIS profiles of patients with BD and MDD with normal premorbid IQ (>90) stratified by states,

and to examine how current depression severity and psychotropic medication are associated with cognitive performance in these disorders. To our knowledge, this is the first large study to compare cognitive performance of mood disorder patients in euthymic/depressed states using a full version of the WAIS, and to provide normative data of BD and MDD patients in the Japanese population. Our main findings are summarized as follows. The depressed BD group showed a wide array of impairments in the domains of WM, PO, and PS, whereas impairment in the depressed MDD group was limited to PS. The depressed BD group also scored significantly lower than the depressed MDD group in FSIQ, VIQ, PIQ, and WM, suggesting that cognitive impairments are global and more intense in depressed BD patients than in depressed MDD patients. The euthymic BD group

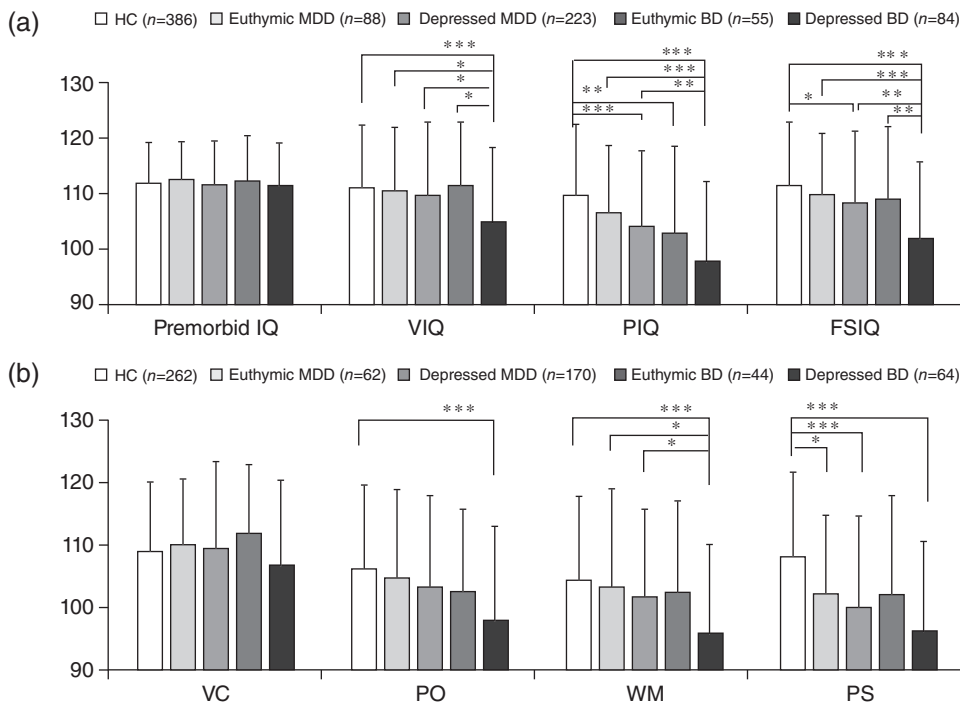


Fig. 1 Comparison of cognitive performance across the five clinical groups (mean + SD). (a) Comparison of estimated premorbid intelligence quotient (IQ) and current verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) of the Wechsler Adult Intelligence Scale-Revised or the Third Edition. (b) Comparison of group indices of the Wechsler Adult Intelligence Scale Third Edition. Tested by ANOVA, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; PO, Perceptual organization; PS, Processing speed; VC, Verbal comprehension; WM, Working memory.

Table 4. Comparison of the Wechsler Memory Scale Third Edition subtest scores against healthy controls ($n = 262$).

	Statistical comparison [†]	Depressed BD ($n = 64$)	Euthymic BD ($n = 44$)	Depressed MDD ($n = 170$)	Euthymic MDD ($n = 62$)
WAIS-III age-scaled score					
Vocabulary	$F(4, 596) = 1.918, P = 0.106$	→	→	→	→
Similarity	$F(4, 596) = 1.341, P = 0.253$	→	→	→	→
Information	$F(4, 596) = 1.263, P = 0.283$	→	→	→	→
Comprehension	$F(4, 596) = 1.619, P = 0.168$	→	→	→	→
Arithmetic	$F(4, 596) = 4.759, P = 0.001$	↓↓↓	→	→	→
Digit span	$F(4, 596) = 2.526, P = 0.040$	↓	→	→	→
Letter-number sequencing	$F(4, 596) = 1.852, P = 0.117$	→	→	→	→
Picture arrangement	$F(4, 596) = 4.546, P = 0.001$	↓	↓	→	→
Picture completion	$F(4, 596) = 1.205, P = 0.308$	→	→	→	→
Block design	$F(4, 596) = 5.148, P < 0.001$	↓↓	→	↓	→
Matrix reasoning	$F(4, 596) = 3.717, P = 0.005$	↓	→	→	→
Digit symbol-coding	$F(4, 596) = 13.231, P < 0.001$	↓↓↓	→	↓↓↓	↓
Symbol search	$F(4, 596) = 8.483, P < 0.001$	↓↓↓	→	↓↓↓	→
Object assembly	$F(4, 596) = 3.434, P = 0.009$	↓	→	→	→
Components of the digit symbol-coding subtests:					
Paired-associate recall	$F(4, 596) = 5.986, P < 0.001$	↓↓↓	→	↓	↓
Free recall	$F(4, 596) = 4.819, P = 0.001$	↓	→	↓	↓
Copy speed	$F(4, 596) = 3.847, P = 0.004$	↓	→	↓↓	→

[†]One-way ANOVA was performed to examine between-group differences; post-hoc analysis was made with Bonferroni correction. →, Non-significant; ↓, $P < 0.1$; ↓↓, $P < 0.05$; ↓↓↓, $P < 0.01$; ↓↓↓↓, $P < 0.001$ significance of difference against healthy controls. BD, bipolar disorder; MDD, major depressive disorder.

scored significantly lower than controls in PIQ and tended to score lower in PS, whereas the euthymic MDD group scored significantly lower than controls in PS, suggesting that attenuated impairments appear to exist in euthymic states of both patients.

Previous studies directly comparing cognitive performance between depressed BD and MDD patients yielded inconsistent results, and a recent meta-analysis on attention/processing speed, verbal memory, and executive function failed to find a significant difference between the two patient groups.⁴² We are the first to find a significant difference favoring depressed MDD in WM of the WAIS-III (combined data of digit span, arithmetic, and letter-number sequencing).

Just two studies have used the WAIS-III for comparing BD and MDD patients in a large sample to date. One is a study by Gorlyn *et al.*, which compared the performance of unmedicated depressed patients (a mixed sample of BD and MDD, $n = 121$) and controls ($n = 41$).⁶⁰ They found that the impairments in the depressed group were limited to PIQ, PS, and timed tasks, and that there was no significant difference between depressed BD and MDD patients. However, their findings were obtained from the relatively small number of BD patients ($n = 40$; 33% among patients), which might have led to overrepresentation of patients with MDD and lack of sample power of BD patients.

Another is a study by Xu *et al.*, a large, longitudinal study comparing cognitive performance of BD and MDD patients in euthymic and depressed states and controls, with a comprehensive test battery including two subtests from the WAIS (digit symbol-coding and digit span forward and backward).⁴³ In their study, both patients with BD and MDD were significantly impaired in digit symbol-coding either in depression and in remission, and in digit span backward in depression. Our findings are inconsistent with their study in that our euthymic BD patients only showed the tendency to score lower in digit symbol-coding ($P = 0.092$). This was probably due to insufficient sample power ($n = 44$), given that our euthymic BD patients scored numerically the same as our euthymic MDD patients, and the effect size between euthymic BD patients and controls was medium

($ES = 0.42$). Another difference from the study of Xu *et al.* is that we were unable to find impairments in digit span in our depressed MDD patients. They did not show impairments in WM, either. Depressed patients in the Xu *et al.* study might have had more difficulty in WM tasks, as they were all unmedicated and more depressed (mean HAM-D-17 total 27) than our patients. Yet, it is possible that depressed BD patients perform more poorly on WM tasks compared with depressed MDD patients, as is the case with our study, as there has been emerging evidence on more widespread abnormalities in white matter connectivity and white matter hyperintensities in BD than MDD depression,⁶¹ differential patterns of functional abnormalities in emotion regulation and attentional control circuitry between the two patient groups,⁶¹ distinct prefrontal activation difference between BD and MDD during a working memory task,⁶² along with a thinner dorsolateral prefrontal cortex in BD compared with MDD.⁶³ These findings from neuroimaging studies serve as supporting evidence for poor prefrontal processing in depressed BD patients, which might lead to failures in not only WM, but also in inductive reasoning and problem solving tasks (block design and matrix reasoning) in PO.

PO is derived from the combined data of picture completion, block design, and matrix reasoning, and it is one aspect of executive functions related to perceptual and conceptual information processing. A study by Dreben *et al.* on several organizational tasks reported that “[t]he schizophrenic group performed more poorly on tasks requiring either global analyses (counting lines when distracting circles were present) or top-down conceptual processing (rule learning) than they did on tasks requiring local analyses (counting heterogeneous lines) or bottom-up processing (attribute identification),” whereas “[n]ormal adults showed the reverse pattern,” and “[t]he depressive group performed similarly to the schizophrenic group on perceptual tasks but closer to the normal group on conceptual tasks.” They concluded that “[t]hese deficits in organizational strategy may be related to ... the allocation of attention”.⁶⁴ Depressed BD patients in the present study showed significant impairments in PO tasks requiring top-down conceptual processing and in WM tasks requiring divided attention,

Table 5. Effects of depression severity and psychotropic medication on cognitive performance in each patient group.

	N	WAIS-R/III IQ			N	WAIS-III group index			
		VIQ	PIQ	FSIQ		VC	PO	WM	PS
BD patients									
HAM-D17 total score [†]		-0.187*	-0.164§	-0.219**		-0.170§	-0.222*	-0.153	-0.193*
Core depressive symptoms		-0.150§	-0.12	-0.178*		-0.078	-0.146	-0.108	-0.178§
Sleep		-0.262**	-0.252**	-0.289**		-0.267**	-0.229*	-0.203*	-0.261**
Activity		-0.145§	-0.15§	-0.187*		-0.115	-0.128	-0.113	-0.263**
Psychic anxiety		-0.085	-0.1	-0.139		-0.053	-0.112	-0.101	-0.091
Somatic anxiety		-0.170*	-0.092	-0.152§		-0.256**	-0.156	-0.122	-0.129
Delusion		-0.175*	-0.079	-0.148§		-0.057	-0.105	-0.056	-0.044
<i>Medication dosage[‡]:</i>									
AP, if any		-0.212	-0.22	-0.249§		0.068	-0.200	-0.183	-0.105
AP, typical, if any		0.039	0.223	0.141		0.049	0.359	-0.275	0.085
AP, atypical, if any		-0.195	-0.23	-0.247§		0.033	-0.240	-0.322	-0.188
AD, if any		-0.013	-0.04	-0.026		0.096	-0.030	-0.162	-0.128
Lithium dosage, if any		-0.220	-0.07	-0.169		-0.327§	-0.010	-0.4*	-0.44*
Valproic acid dosage, if any		0.274	0.002	0.238		0.32	0.015	0.198	0.052
Lamictal dosage, if any		0.194	0.084	0.126		0.097	0.136	0.212	-0.042
<i>Medication use[‡]:</i>									
	NO / YES				NO / YES				
Typical antipsychotic use (F)	125 : 14	1.656	2.300	2.892	96 : 12	0.115	0.022	1.192	1.387
Atypical antipsychotic use (F)	91 : 48	0.034	1.564	0.875	74 : 34	1.357	0.867	0.172	2.857§
Antidepressant use (F)	86 : 53	0.000	0.399	0.056	71 : 37	0.027	1.960	0.587	0.006
Lithium use (F)	95 : 44	0.886	0.736	1.223	73 : 35	0.077	0.127	0.320	0.570
Valproic acid use (F)	102 : 29	2.357	3.740§	3.660§	79 : 22	0.137	0.522	0.286	3.583§
Lamictal dosage use (F)	98 : 35	0.005	2.524	0.916	70 : 33	0.011	1.498	1.133	0.232
Benzodiazepine use (F)	62 : 77	1.169	7.31**	4.992*	51 : 57	0.644	1.329	0.048	5.765*
MDD patients									
HAM-D17 total score [†]		-0.090	-0.134*	-0.124*		-0.109§	-0.105	-0.093	-0.139*
Core depressive symptoms		-0.035	-0.08	-0.063		-0.061	-0.044	-0.005	-0.106
Sleep		-0.075	-0.188**	-0.131*		-0.080	-0.131*	-0.043	-0.112§
Activity		-0.026	-0.06	-0.042		-0.019	-0.024	-0.069	-0.166*
Psychic anxiety		-0.063	-0.08	-0.080		-0.127§	-0.058	-0.012	0.071
Somatic anxiety		-0.125*	-0.08	-0.114*		-0.177**	-0.114§	-0.119§	-0.073
Delusion		-0.027	-0.08	-0.061		-0.098	-0.094	-0.053	-0.084
<i>Medication dosage[‡]:</i>									
AP, if any		0.012	-0.2§	-0.125		0.001	-0.254§	-0.200	-0.234§
AP, typical, if any		0.138	-0.22	0.009		-0.061	-0.295	-0.113	-0.097
AP, atypical, if any		-0.125	-0.2	-0.203		-0.010	-0.261§	-0.32*	-0.34*
AD, if any		-0.038	-0.06	-0.052		-0.023	0.028	-0.055	-0.059
<i>Medication use[‡]:</i>									
	NO / YES				NO / YES				
Typical antipsychotic use (F)	269 : 38	1.097	5.54*	3.998*	206 : 24	0.818	0.074	0.063	2.005
Atypical antipsychotic use (F)	250 : 57	1.073	2.688	2.524	189 : 41	0.003	0.659	0.609	4.959*
Antidepressant use (F)	125 : 182	0.089	5.09*	2.254	104 : 126	1.086	2.605	0.037	14.625***
Benzodiazepine use (F)	144 : 163	2.219	2.396	3.381§	116 : 114	0.243	0.110	1.539	6.621*

[†]Spearman's ρ was shown on the relationship of depression severity and medication dosage with cognitive performance.

[‡]Cognitive performance between medicated and unmedicated patients for each medication was compared using an ANCOVA covarying for age, sex, premorbid IQ, and HAM-D total score. F value was shown.

Bold figures represent correlation coefficient with significant p value (unmedicated > medicated).

§P < 0.1, *P < 0.05, **P < 0.01, ***P < 0.001.

AP: chlorpromazine equivalent dose of antipsychotics. AD: imipramine equivalent dose of antidepressants. HAM-D17: 17-item version of the Hamilton depression rating scale. YMRS: Young Mania Rating Scale. VIQ: verbal IQ; PIQ: performance IQ; FSIQ: full-scale IQ. VC: Verbal Comprehension; PO: Perceptual Organization; WM: Working Memory; PS: Processing Speed.

where depressed MDD patients showed little impairment in these domains. Taken together, the difference in PO and WM between depressed BD and MDD patients might be qualitative, whereas the difference in PS might be quantitative. The results of the present study might add evidence to the previous literature that cognition of depressed BD patients is qualitatively similar to that of schizophrenia.

Picture arrangement is a mentalization task that requires integration of contextual information and make inferences on others' mental states. Our euthymic and depressed BD groups showed significant impairment in picture arrangement, whereas the MDD group did not show impairment in either phase. These results are in line with a recent review and a meta-analysis that reported the theory of mind (ToM) impairment in BD patients across remitted and acute states, suggesting that mentalizing impairment might represent trait markers of BD.^{65,66} The present findings are also consistent with a recent systematic review reporting non-significant or minimal impairments in ToM in depressed MDD patients, except for those in acutely-depressed states.⁶⁷ There is also a meta-analysis that showed that ToM impairment in MDD was significantly related to depression severity.⁶⁸ Previously, we reported that almost half of the patients with BD in both euthymic and depressed states, and half of the patients with MDD in depressed states (but not in euthymic states) showed autistic-like traits at levels typical for subthreshold or threshold autism spectrum disorder, and that autistic-like traits in patients with MDD were dependent on depression severity.⁶⁹ As many of the social-interpersonal difficulties in autism spectrum disorder are considered to derive from the weakness of ToM, impairment in picture arrangement in BD patients irrespective of symptom severity suggests that mentalizing weakness is a deficit intrinsic to BD.

Relationship of depression severity and medication with cognitive performance

We found that PO was modestly correlated with HAMD-17 total score in BD patients (Spearman's $\rho = -0.222$), which suggests that mental manipulation, visuospatial ability, and inductive reasoning required for PO might be significantly impaired by depression in BD patients. Relationships between depression severity and other cognitive performances were minimal in both patient groups, but correlation coefficients were slightly larger in BD patients. These might suggest that cognition in patients with BD are more easily impaired in response to depression severity compared with patients with MDD. These results also corroborate the magnitude of effect size of euthymic-depressed between-group difference (Table 3), with modest effect size among BD patients (A vs B; Cohen's $d = 0.33-0.53$) and minimum effect size among MDD patients (C vs D; $d = 0.06-0.21$).

As to the effects of medication, moderate associations were found mostly on PS in both patient groups; a higher dosage of lithium or use of benzodiazepines were associated with lower PS in BD patients, and higher dosage of atypical antipsychotics, or use of either atypical antipsychotics, antidepressants, or benzodiazepines were associated with lower PS in MDD patients. Furthermore, higher dosage of lithium was also associated with lower WM in BD patients, and higher dosage of antipsychotics with lower WM in MDD patients. These findings were consistent with the results of a recent meta-analysis that found that either use of antipsychotics or antidepressants was associated with impairment in psychomotor speed or sustained attention on euthymic BD patients,²⁸ and also in line with the meta-analyses that reported negative associations of benzodiazepines^{70,71} and lithium⁷² on speeded tests, as well as a negative effect of lithium on verbal learning and memory,⁷³ whereas another meta-analysis reported some benefit of medication to cognition in MDD patients.⁷⁴ We detected a strong association between antidepressants and PS in MDD patients, whereas such an association was not observed in BD patients. This inconsistency could be explained by the facts that the ratio of BD patients on antidepressants was much smaller than that of MDD patients and that a substantial proportion of BD patients without antidepressants had taken other types of

medication, such as atypical antipsychotics and mood stabilizers, both of which were found to affect PS in our BD patients.

The strong sedative effect of benzodiazepines, antipsychotics, or tricyclic antidepressants might well cause psychomotor slowing. However, the findings that MDD patients on antidepressants had more impairments in PS than those unmedicated cannot be fully explained by tricyclic antidepressants alone, considering that most antidepressants used were either selective serotonin reuptake inhibitors or serotonin noradrenaline reuptake inhibitors. A previous study found that patients with psychomotor slowing have dopaminergic deficits and therefore do not respond to serotonin reuptake inhibitors.⁷⁵ As the authors suggested, alternative treatment might be required for such non-responders.

Limitations

The following are the limitations of this study. First, this was a cross-sectional study. A longitudinal study is required to ascertain the current findings on the differences between depressed and euthymic patients. Second, we used a mixed sample of BD I and BD II patients. It should be noted that BD II was overrepresented in our BD sample, although we found no significant difference between BD I and BD II patients in symptom severity or the WAIS profile in either euthymic or depressed state. Depressed BD I patients have been reported to show severer cognitive impairments than depressed BD II patients,^{43,76,77} although another study found no such difference.⁷⁸ Third, the number of euthymic BD patients who underwent the WAIS-III was relatively small ($n = 44$), which might have been insufficient to detect the subtle difference in PO and PS between euthymic BD patients and controls. Future studies should be made with larger samples. Fourth, most patients were prescribed mixed medication. The possibility of the confounding effects of medication could not be discounted. Fifth, we were unable to elucidate memory and executive function with the WAIS. These are the important domains that both BD and MDD patients are consistently reported to have impairments. Comprehensive test battery is required to evaluate all aspects of cognitive functions.

Conclusions

Patients with BD might have global and more intense cognitive impairments in depressed states compared with those with MDD, and attenuated impairments in overall non-verbal performance seem to remain in the euthymic states. Patients with MDD seem to have apparent impairments only in PS in the WAIS profile, which seem to remain in euthymic states in attenuated form.

Acknowledgments

This study was supported by the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development, AMED (18dm0107100h0003 and 18dk0307081h0001 for H.K.), and Intramural Research Grant for Neurological and Psychiatric Disorders at the National Center of Neurology and Psychiatry (27-1, and 30-1 for H.K.). These funding sources were only involved in financially supporting this study. This manuscript was proofread by a professional editor at Editage Co., Ltd. (Editage Japan, Tokyo, Japan). The authors thank the volunteers and their families for their participation.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Conception and design of the study: H.K.; acquisition of data: J.M., I.I., M.H., M.O., S.H., Y.Y., and H.H.; analysis of data: J.M.; drafting the manuscript or tables: J.M.; making suggestions on the manuscript: H.K. and H.H. All authors reviewed the manuscript and approved it for submission.

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