Cognitive function, treatment response to lithium, and social functioning in Japanese patients with bipolar disorder

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Abstract

Objectives. Patients with bipolar disorder often suffer from cognitive impairment that significantly influences their functional outcome. However, it remains unknown whether lithium exerts a central role in cognition and functional outcome. We examined whether cognitive performance and functional outcome were predicted by demographic and clinical variables including the response to lithium in lithium-treated euthymic patients with bipolar disorder.

Methods. We evaluated 96 lithium-treated patients with bipolar disorder and 196 age- and sex-matched healthy controls, using the Brief Assessment of Cognition in Schizophrenia (BACS). The patients were also assessed by the Social Functioning Scale (SFS) and "The Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" scale (Alda scale), which was evaluated as either continuous measure of the total scale or dichotomous definition of the response to lithium.

Results. Multiple regression analysis revealed that premorbid intelligent quotient, age and number of mood episode were predictors of BACS composite score, and that the BACS composite score, negative symptom and continuous measure of the total Alda scale, but not its dichotomy, predicts total SFS score. Structural Equation Modeling (SEM) confirmed these findings, and revealed additionally that the Alda scale was significantly associated with negative symptoms and the number of mood episodes, regardless of whether it was evaluated alternatively.

Conclusions. SEM delineated how demographic and clinical variables, cognitive performance, and response to lithium treatment were causally associated with, and converges on, social function. The putative role of Alda scale for social function warrants further study.

Keywords.

Bipolar disorder,

Cognitive function,

Social function,

Lithium responder,

BACS,

SFS,

Alda scale

Introduction

Evidence is cumulating to suggest that cognitive impairment is a cardinal feature of psychosis in schizophrenia and bipolar disorder. A number of meta-analyses have revealed that cognitive impairment exists in a substantial number of patients with bipolar disorder even when they recover from acute mood episodes (1-4), which suggests that it may be a trait marker rather than mood-dependent state marker. This contention is supported by other lines of evidence, such as the finding that first-degree relatives of patients with bipolar disorder show similar, but moderate forms of cognitive impairment (1, 5-7). Thus, cognitive impairment in bipolar disorder may be inherent in the genetic predisposition to the disease (1, 8).

Early studies in this area have reported that specific cognitive domains, such as verbal learning memory and executive function, are impaired in patients with bipolar disorder (9, 10). By contrast, other studies have reported that patients with bipolar disorder experience generalized cognitive impairment across multiple cognitive domains, which is moderated relative to schizophrenia (11-13). Overall, patients with bipolar disorder present with cognitive impairments that are milder, but qualitatively similar to those for schizophrenia (12, 14-16), and that fall within the range of medium effect size compared with the norm derived from healthy controls (3, 12, 17).

Lithium is widely prescribed as the first-line prophylactic treatment for bipolar disorder. Accumulating evidence suggests that lithium has neuroprotective effects by acting on molecular mechanisms involved in cellular signal transduction (18, 19). For example, the neuroprotective effect of lithium is evident by studies showing that it increases the plasma concentration of brain derived neurotrophic factor (20, 21) and the hippocampal volume (22) in patients with bipolar disorder. However, previous studies showed that lithium exerts small negative effects on some cognitive domains (23-25), whereas others have reported no such

effects (26, 27). More recent studies showed that patients on lithium treatment showed better spatial reasoning (28), and better short-term auditory memory, long-term memory and attention as compared to those on anticonvulsants (29), and that patients with first episode mania who were treated with lithium monotherapy for one year showed greater improvement in performance in verbal fluency relative to quetiapine-treated patients (30). Regarding the relationship between the response to lithium and cognition, a few studies have investigated the effect of lithium treatment on cognitive function when it is weighed against its prophylactic efficacy (21, 31). Only recently has the trade-off between the effect of lithium on cognition and the benefit of prophylaxis been acknowledged (32). This is relevant to studies showing an inverse correlation between cognitive performance and the number of manic or depressive episodes in patients with bipolar disorder (33-36). To measure the response to lithium treatment retrospectively, we adopted the "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" scale, which is also referred to as the "Alda scale" (37-41) . We believe that the Alda scale can be used to explore whether a relationship exists between cognitive performance and response to lithium treatment in patients with bipolar disorder.

Previous conflicting findings on the influence of lithium on cognition may be attributable, at least in part, to the difficulty of disentangling the direct effect of lithium on cognition from highly variable confounders associated with the disease. Therefore, the evaluation of cognition of lithium-treated patients should be adjusted for confounders such as the status of affective symptoms (2, 42-44), lifetime occurrence of psychotic symptoms (45-50), number of lifetime manic and depressive episodes (33-36), all of which has been shown to contribute to the severity of cognitive impairment in patients with bipolar disorder. Another likely factor that may influence cognition is negative symptoms; some studies showed that there is a significant

correlation between cognitive impairment and negative symptoms in a cross-diagnostic samples of patients with schizophrenia and bipolar disorder (17, 51, 52).

Emphasis has been placed on the relationship between cognition and functional outcome in schizophrenia research. Studies on bipolar disorder also suggest that cognitive impairment (14, 53-59), residual depressive symptoms (44, 60, 61) and negative symptoms (54) can negatively affect the functional outcome. Given that cognition predicts social function, the use of traditional multiple regression analysis is challenging because so many variables require adjustment. Recently, Structural Equation Modeling (SEM) has been proposed as a statistical method to help delineate causality among potential predictors. Using SEM, Bowie et al (54) reported that cognitive impairment and negative symptoms predict everyday activities in real world in patients with bipolar disorder. We hypothesize that response to lithium warrants consideration for inclusion in SEM, and that the analysis may be pertinent to the understanding of whether lithium treatment is related to cognitive performance, clinical variables, and functional outcome.

Neuropsychological batteries initially developed to measure cognitive performance in patients with schizophrenia have recently been used to evaluate cognitive performance in patients with affective disorders. For example, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (62) and the Brief Assessment of Cognition in Schizophrenia (BACS) (15, 63, 64) have been validated for use in bipolar disorder.

The primary aim of this study was to explore whether the response to lithium would be associated with cognitive performance of patients with bipolar disorder using assessment with BACS and adjustment for clinical variables. The secondary aim was to perform SEM to delineate how demographic variables, clinical variables, cognitive performance, and response to

lithium treatment are causally associated and converge on social function, as assessed by the Japanese version of the Social Functioning Scale (SFS) (65, 66).

Materials and methods

Participants

The demographic features of the participants from the Kanto area of Japan are shown in Table 1. These comprised 96 patients with bipolar disorder (55 males and 41 females) aged 53.06 ± 11.22 years (mean ± standard deviation [SD]), and 196 unrelated controls (112 males and 84 females) aged 52.80 ± 10.61 years.

Patients with bipolar disorder, diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5, APA 2013), were recruited from Dokkyo Medical University School of Medicine Hospital and affiliated hospitals. All patients were administered lithium at the time of cognitive assessment, and acknowledged to be eligible for the assessment of the Alda scale. When electroconvulsive therapy had been used, cognitive performance was assessed no sooner than 24 weeks after the course of electroconvulsive therapy. Patients were excluded if they had substance-related and addictive disorders, intellectual disabilities, personality disorders, or “organic brain disorders”.

The healthy controls were volunteers from a sample of nonprofessional university/hospital staff, and were free of diagnosed psychiatric disorders. The controls were derived from those who participated in our previous study (67), and were matched to patients by age and gender.

The objective of the present study was explained to all participants, and written informed consent was obtained in accordance with the Declaration of Helsinki (http://www.wma.net). The study was formally approved by the Institutional Review Board of the Ethical Committees of Dokkyo Medical University School of Medicine and of affiliated hospitals.

Assessment

Japanese version of the BACS. All participants were administered Version A of the Japanese version of the BACS, per a previous report (68). This included a brief assessment of verbal memory (list learning), a digit sequencing task, a token motor task, a verbal fluency test (category instances and controlled oral word association test), a symbol coding, and a Tower of London (TOL) task.

Premorbid intelligent quotient (IQ) assessment. All participants were assessed by the Japanese Adult Reading Test (JART) (69, 70) to obtain a surrogate of premorbid IQ.

Positive and Negative Symptom Scale. Patients were assessed by the Positive and Negative Symptom Scale (PANSS), a 30-item scale designed by Kay et al (71), using the associated rating manual (72). Positive symptoms (items P1 to P7), negative (items N1 to N7) symptoms, and general psychopathology (items G1 to G16) were evaluated with the summed scores of each category used as separate variables (subscales).

Japanese version of the SFS. Patients were also assessed by Japanese version (65) of the SFS, a self-reported questionnaire. This included the following items: withdrawal, interpersonal communication, independence performance, recreational activities, pro-social performance, independence competence, employment (66).

Assessment of euthymia. To ensure that we only selected patients with moods within the euthymic range, we primarily recruited patients who had scores of 10 points or less on the 17-item Hamilton Depression Rating Scale (HAM-D) and scores of 10 points or less on the Young Mania Rating Scale (YMRS), based on the findings of a previous meta-analysis (4).

The Alda scale for response to lithium treatment. We retrospectively assessed the response to lithium treatment using the Alda scale. This scale rated the number of episodes before lithium

(criterion B1), the frequency of episodes before lithium (B2), the duration of lithium treatment (B3), compliance during treatment (B4), and the use of additional medication (B5) subtracted from the degree of lithium-associated stabilization of mood fluctuation (criterion A) (38). Scoring of the Alda scale was accomplished by thorough discussion among two researchers (SS and KA) who had been trained to score two-stage case vignettes. Patients were dichotomized into two groups by the Alda scale, as follows: those with a score of 7 points or more and those with a score of 6 points or less, according to the criteria of a previous report (39). These two groups were referred to as lithium responders and non-responders, respectively. Continuous measure of total Alda scale was also used for statistical analyses.

Other variables. The lifetime number of mood episodes, lifetime occurrence of mood-incongruent psychotic features, age of onset, and medication status were obtained from retrospective chart reviews. Individual depressive episodes were defined as those separated by a euthymic state and persisting for at least two months. The cumulative number of manic and depressive episodes since disease onset was defined as the lifetime number of mood episodes. Lifetime occurrence of mood-incongruent psychotic features was treated as a categorical variable. Antipsychotics were grouped into first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). Olanzapine, risperidone, quetiapine, aripiprazole, perospirone, blonanserin, and zotepine were categorized as SGAs, and all other included antipsychotics were regarded as FGAs, per our previous results (67). The statuses of individual medications (lithium, carbamazepine, valproate, FGA, and SGA) were treated as categorical variables.

Statistical analyses

The difference in sex between patients and the controls was assessed using the chi-square

test. Continuous variables were assessed for normal distribution by the Shapiro-Wilk test, and those without a normal distribution were standardized across all subjects by Blom transformation (73) for use in the multiple regression analyses. Z-scores were derived from primary scores of cognitive subdomains of BACS for patients relative to the norm, defined by setting the mean and SD of primary measures of BACS subdomains per healthy control to 0 and 1, respectively. The composite score for global cognition was generated by transforming the mean of all six BACS z-scores to re-standardized values for controls, according to a normative mean of 0 and an SD of 1. P values for the difference in continuous demographic variables between the controls and patients with bipolar disorder were determined using either the Mann–Whitney *U* or Student *t* test.

The following analyses were conducted in the 96 lithium-treated patients. Demographic and clinical variables were compared between the lithium responders and non-responders using appropriate tests (chi-square, Student *t*, and Mann–Whitney *U* tests). Correlation coefficients between BACS performance (z-scores of subdomains and the composite score) and demographic/clinical variables were determined using Spearman's rank correlation coefficient. Alda scale was one of such variables eligible for the assessment for the correlation with BACS indices, and handled as either continuous measure of total scores or dichotomous definition of the response to lithium. Subsequently, the variables that met a criteria of entry ($P<0.05$) were used as independent variables for multiple regression analysis to identify variables that predicted BACS indices, and also used as covariates for an analysis of covariance (ANCOVA) to determine whether BACS indices differed between the lithium responders and non-responders adjusted for them. The P value was conservatively set at $p < 0.0071$ for the threshold of significance in the multiple regression analyses and ANCOVA for the BACS z-scores and composite scores, because there were six BACS subdomains plus the composite

score (i.e., P = 0.05/7).

Analyses were performed to identify predictors of functional outcome, as assessed by SFS, in a stepwise manner. In the first step, demographic and clinical variables that met a criteria for entry (P<0.05) according to correlations with total SFS score in Spearman's rank correlation coefficient and the BACS composite scores were entered as predictor variables of the total SFS in the multiple regression analysis. As the second step, SEM was implemented by including the PANSS negative symptoms, BACS composite score, explanatory variables of BACS composite score (premorbid IQ, age and number of mood episodes), and either continuous measure of total scores or dichotomous definition of the Alda scale to delineate a causative relationship between these variables and SFS. The best-fitting model was judged according to three goodness-of-fit of the statistics; non-significant chi-square tests, the comparative fit index (CFI) greater than 0.90, and the root mean square error of approximation (RMSEA) less than 0.08. The P value for the threshold of significance for total SFS scores was set at $p < 0.05$ for the first and second steps. All statistics were implemented in IBM SPSS, Version 23 and IBM SPSS Amos, Campus Edition (IBM Japan, Tokyo, Japan).

Results

Comparison of the demographic features and BACS z-scores between patients and controls are shown in **Table 1**. There were no significant differences in age, duration of education, premorbid IQ, or the male-to-female ratio between patients and controls. Patients did have BACS z-scores that were significantly lower than controls, with z-scores for patients being －0.60 to －1.04 below the mean for controls. The mean of the Alda scale in patients were 4.50.

When comparing the response to lithium therapy among patients, the lithium responders had significantly lower HAM-D scores, lower PANSS negative symptoms, fewer lifetime mood episodes, significantly lower prescribing frequency of SGA (**Table 2**). By definition, the

lithium-responders and non-responders differed significantly in the Alda scale with average scale score being 7.58 and 3.36, respectively. When adjusted for covariates, there was no significant difference in BACS z-scores or composite score between the lithium responder and non-responders (supplementary table 1).

Both types of the Alda scale assessment met a criteria of entry into the multiple regression analysis to predict token motor task, symbol coding and total SFS score. Accordingly, multiple regression analyses were performed to identify predictors of BACS z-scores and total SFS scores, with two types of Alda scale assessments being separately included if necessary. The results showed the following (**Table 3**); that premorbid IQ was a significant predictor of better z-scores for verbal memory, digit sequence task, verbal fluency, TOL task, and composite scores; that age was a significant predictor of lower z-scores for verbal memory, symbol coding, and composite scores; that PANSS negative symptoms significantly predicted lower z-scores for the token motor task (for the dichotomy of Alda scale only), and symbol coding; that number of previous mood episodes was a significant predictor of lower z-scores for the token motor task (for the dichotomized groups of Alda scale only), symbol coding and composite score; the continuous measure of total Alda scale, but not dichotomous definition of Alda scale, was a significant predictor of token motor task. Neither of continuous measure nor dichotomous definition of Alda scale was a predictor of symbol coding. Hig**h**er total SFS scores were predicted by lower PANSS negative symptom scores, higher BACS composite score and higher continuous measure of Alda scale.

SEM was implemented with either continuous measure of total scores or dichotomy in the response to lithium, and the other explanatory variables of total SFS. Three goodness-of-fit of the statistics (chi-square tests, CFI, RMSEA) were comparable between these alternatives. The SEM analysis confirmed that PANSS negative symptoms, BACS composite score and

continuous measure of the total Alda scale predicted total SFS scores (**Fig 1.a,b**). The Alda scale was significantly associated with negative symptoms and the number of lifetime mood episodes, regardless of whether it was assessed as continuous or dichotomous measure of Alda scale

Discussion

In the present study, we used BACS for the cognitive assessments. Although this was originally developed to assess cognition in patients with schizophrenia (74), it has more recently been developed to assess cognition in patients with bipolar disorder (15, 63, 64). The assessments were confined to patients with bipolar disorder who were receiving lithium, together with their age- and sex-matched controls for simple comparison. Our primary aim of this study was to examine whether the response to lithium, which was evaluated by the Alda scale, would be associated with cognitive performance and functional outcome of patients with bipolar disorder. The secondary aim of this study was to delineate how combined contribution of clinical variables, cognitive performance, and the response to lithium treatment are causally associated and converge on the functional outcomes. SEM was used to analyze this complex relationships among variables, because it has been validated as the best algorithm for predicting the contributions of cognitive performance and clinical symptoms for the functional outcome of patients with bipolar disorder or schizophrenia (54). To our knowledge, this is the first study of using SEM with the satisfactory goodness-of-fit statistics to investigate the relative contributions of demographic variables, clinical variables, cognitive performance, and lithium response as the predictor variables of functional outcome in patients with bipolar disorder (**Fig.1**).

We identified six main findings, which we will discuss next. First, the lithium responders

showed significantly lower PANSS negative symptoms and HAM-D scores, and fewer lifetime mood episodes, and had significantly lower frequency of SGA administration when compared with lithium non-responders (**Table 2**). Two previous studies (75, 76) have shown that an age at onset and a family history of bipolar disorder were clinical predictors of a favorable lithium response, but neither of these was confirmed in this study (**Table 2**). The mean of total scores of the Alda scale for 96 patients in the present study was 4.50, which is close to that as was previously reported by Manchia et al (39). The rate of favorable response in lithium-treated patients ranged between 21% and 35% in earlier studies depending on the clinical variables included (37, 77-79). Manchia et al (39) reported that the distribution of the Alda scale was best fitted to a dichotomous model, with 33% of patients scoring seven or more being definable as lithium responders. Using the same criteria as reported by Manchia et al (39), we showed that 27.1% of patients were lithium responders. Overlapping clinical factors were reported to be associated with both the continuous measure and dichotomous definition of the Alda scale (37, 41). We found that its continuous measure, but not its dichotomy, yields a predictive value for token motor task z-scores and total SFS score (**Table 3**). However, there was no direct association between the Alda scale and BACS composite score (**Fig 1**), suggesting that the response to lithium may not have a robust effect on cognition. Our results are in agreement with the contention that previously reported adverse effects of lithium on cognition should be weighed against the benefits of prophylaxis against a fluctuant disease trajectory (32).

Second, SEM revealed that both assessments of the Alda scale had an inverse correlation with the numbers of lifetime mood episodes since disease onset and negative symptoms. The inverse relationship between negative symptoms and lithium response has not been reported so far. Despite the general tendency for studies on bipolar disorder to overlook negative symptoms, a longitudinal assessment did report that these symptoms exist to a similar extent

and in severity in patients with bipolar disorder and other psychotic disorders as well as schizophrenia (80). More recent studies have reported that, contrary to patients with schizophrenia manifesting a wide range of negative symptoms, patients with bipolar disorder showed mainly avolition and anhedonia among subdomains of negative symptoms (52, 81). Animal experiment suggests that lithium may counteract chronic stress-induced disruption of appetitive behavior reflecting anhedonia (82). Although difficult to reconcile with animal studies, the assessment of the relative strength of subdomains of negative symptoms in a future study may help predict a core lithium-responsive subpopulation. Meta-analysis showed that the number of distinct episode sequences (mania-depression-free interval vs depression-mania-free interval) would be a more precise predictor of the response to lithium than the number of lifetime mood episodes (75). A strict assessment distinguishing such episode sequences (75) is difficult with retrospective chart review, which limit conclusions about the degree to which the numbers of lifetime mood episodes influences the response to lithium.

Third, we found that the number of lifetime mood episodes (i.e., total episodes of mania plus depression) have negative effects on cognitive performance (i.e., z-scores of the token motor speed and symbol coding and the composite score) (Table 3). While some studies have emphasized an inverse correlation between only the number of manic episodes solely and cognitive performance in patients with bipolar disorder (34, 36), other studies have implicated roles for both manic and depressive episodes (33, 35). A plausible explanation for this discrepancy in the roles of manic and depressive episodes is that the report implicating the number of manic episodes in cognition recruited only patients with bipolar disorder type Ⅰ (36). By contrast, we recruited patients with both bipolar type I and bipolar type II, and it is known that this latter group experience more depressive episodes than hypomanic episodes. Fig 1

delineates a likely pattern that cognitive function mediates between the number of lifetime mood episodes and functional outcome, which is congruent with early studies touching this correlation (57, 59).

Fourth, evidence now shows that cognitive performance is a predictor of functional outcome in patients with bipolar disorder (14, 53-59). Cognitive impairments endure in a large proportion of patients with bipolar disorder and limit their daily functioning, personal communication and occupational outcomes to a greater extent than are generally considered (14, 55, 59). A critical issue in assessing functional outcome is that self-reported or subjective assessments of functional status which have been used in early studies in this area should be interpreted with caution, because this method has been shown to correlate poorly with performance-based objective evaluation of functional capacity (14, 56, 59). Using SEM, Bowie et al (54) reported that neurocognitive impairment, negative symptoms and lower performance-based functional capacity predicts decline of real-world activities in patients with either bipolar disorder or schizophrenia. Although our SEM was implemented without objective evaluation of functional capacity, we found that BACS composite score and negative symptoms were predictor of total SFS (**Fig 1**), which is consistent, in part, with the report by Bowie et al (54). We also found that the continuous measure of total Alda scale provides a weak, but significant predictive value for functional outcome (**Fig 1b**). A few studies have examined the relationship between the response to lithium and functional outcome. Kessing et al (83) reported that patients who started on lithium therapy at the early stage of disease had a significantly lower rate of premature retirement from employment. Together, exploration of the performance based-evaluation of functional capacity in lithium-treated patients with bipolar disorder is encouraged in future study.

Fifth, we found that FGAs had a trend for negative effects on the verbal memory z-scores

and total SFS, while SGAs had no such effects (**Fig 3**). The main FGA administered in the present study was low-dose phenothiazine (mean chlorpromazine equivalent dose = 79 mg). In our previous study of patients with schizophrenia, we showed that FGAs, but not SGAs, caused deleterious effects on token motor tasks, TOL tasks, and composite scores, indicating the importance of discriminating between FGAs and SGAs (67). By contraries, most of the SGAs were administered as alternative mood stabilizers (mean chlorpromazine equivalent dose = 361 mg). This explains why SGAs are more frequently prescribed in lithium non-responders than responders (**Table 2**). Although previous studies have shown that SGAs have adverse effects on cognition in patients with bipolar disorder (24, 84), the multiple regression analysis in the present study revealed that SGAs did not remain as a contributory factor to worsening of any of BACS domains. Detailed analyses of the effects of SGAs on cognition are challenging due to the heterogeneity of pharmacological actions in this class, but a study exists reporting differential effect of several SGAs on cognition in euthymic bipolar patients (85). Due to the limited number of participants, we treated the administration status of SGA as a categorical variable in this study, leaving the effect of individual SGAs on cognition in patients with bipolar disorder to be examined in a further study.

Sixth, we did not observe a significant effect of the presence of previous episodes of mood-incongruent psychotic features on any of BACS z-score (**Table 3**). This is consistent with the three research studies reporting that patients with and without previous psychotic features did not differ in any of the cognitive subdomains (86-88). Although other studies have showed that a lifetime history of psychosis is associated a worse degree of cognitive impairment in patients with bipolar disorder, the cognitive subdomains that were reported to be impaired in these patients varied among those studies (45-47, 49, 50). In fact, we did not use a battery including Stroop word/color interference, spatial memory task or Wisconsin Card

Sorting Test, for which patients with bipolar disorder and psychotic episodes performed worse than those without psychosis episodes (45, 46, 49). Further, in a meta-analysis by Bora et al (48), the effect sizes of the differences in cognitive impairment between groups with and without psychotic features were considered modest. Performance of our patients without previous episodes of mood-incongruent psychotic features is estimated to be worse, as evident by composite scores = - 1.13 in comparison to control, than that of participants discriminated by this category in previous literature (46, 47), which could reflect a ceiling effect for our patients. The administration of SGA ($P = 0.007$, χ^2 test), but not FGA ($P = 0.900$, χ^2 test), had high degree of association with previous episodes of psychotic feature. However, given the administration of SGA did not contribute to worsening of cognition, at least in our study, it is difficult to interpret our finding as reflective of the use of SGA as a confounder.

Seventh, using the JART to assess premorbid IQ, we confirmed our previous finding (67) that JART-estimated premorbid IQ and age significantly affected performance on BACS subdomains. However, the premorbid IQ did not differ between patients with bipolar disorder and controls, which contrasts with the significant reduction seen in patients with schizophrenia when compared with controls (67). The finding that premorbid IQ was unaltered in our patients is consistent with a review indicating that bipolar disorder was associated with fewer premorbid IQ deficits compared with schizophrenia (89).

The limitations of the present study include the recruitment of patients with chronic diseases and its cross-sectional design for cognitive assessment. However, bipolar disorder is difficult to diagnose unless a manic episode is identified during the clinical course, and clinical features like response to lithium and number of episodes may not be evident until early to middle adulthood (83). These limitations were somewhat mitigated by matching cases and controls by age and sex. Another issue concerns the limited number of clinical factors employed as

independent variables. For example, neither benzodiazepines nor anticholinergics were included as independent variables because the prescribing frequency was low in this cohort. In addition, although it is increasingly prescribed as a mood stabilizer, lamotrigine was not included as an independent variable because recent evidence has shown that it has no apparent adverse effect on cognition (23).

In conclusion, using the Japanese version of BACS, we investigated the effects of confounding variables on cognition among patients with bipolar disorder. By combining multiple regression analyses and SEM, our data help to provide a better understanding of how several factors, specifically cognition, converge on the functional outcome. We found that BACS composite score, and negative symptoms exert direct effects on functional outcomes. Moreover, the Alda scale scores were associated with negative symptoms and number of mood episodes only when assessed with the SEM analysis. The continuous measure of the total Alda scale score may yield a more predictive value for functional outcome than what is assessed as the dichotomized group. Given that patients with bipolar disorder may benefit from functional remediation (90), longitudinal clinical study that incorporates cognitive or functional remediation programs, assessment of cognition and of a range of symptoms including subdomains of negative symptoms as well as mood symptoms in a larger number of lithium-treated patients with bipolar disorder is warranted to better understand the complex correlation among cognition, clinical features, response to lithium, and functional outcomes.

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Conflict of interests

K Akiyama has received consulting honoraria from Taisho Toyama Pharmaceutical Co., Ltd. This consultancy had no role in the study design; the collection, analysis, and interpretation of data, the writing of the report; or the decision to submit the paper for publication. K Shimoda has received research support from Shionogi & Co., Ltd., Eli Lilly Japan, K.K., Yoshitomi Pharmaceutical Industries, Ltd., Meiji Seika Pharma Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Daiichi Sankyo Co., and honoraria from Takeda Pharmaceutical Co., Ltd., Kracie Pharmaceutical, Ltd., Pfizer Inc., MSD K.K., Janssen Pharmaceutical K.K., Sumitomo Dainippon Pharma Co., Ltd., Eisai Co., Ltd., Meiji Seika Pharma Co., and Otsuka Pharmaceutical Co., Ltd.

None of the remaining authors declare any conflicts of interest.

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Legends to Figures

Figure 1

The final best-fitting model with paths from demographic and clinical variables to cognitive performance and functional outcome in lithium-treated euthymic patients with bipolar disorder. Figures 1a and 1b are the best-fitting models with the assessment of Alda scale being treated as either the dichotomous definition of the response to lithium (Fig 1a) or continuous measure of total score (Fig 1b). Values for the chi-square tests, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA) were shown.

Values associated with bidirectional arrows represent correlational coefficients, while those associated with unidirectional arrows represent regression coefficients.