Validity and reliability of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) in Japanese patients with bipolar disorder

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Ethical Approval

The local ethics committee from Hokkaido University approved this study. After a complete study explanation, patients provided their written informed consent to participate.

Highlights

- The psychometric properties of the COBRA in Japanese bipolar patients are unknown.
- Test-retest reliability of the COBRA was confirmed in this patient population.
- The COBRA is valid and reliable for assessing subjective cognitive impairment.

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Abstract

In Japan, there are currently no reliable rating scales for the evaluation of subjective cognitive impairment in patients with bipolar disorder. We studied the relationship between the Japanese version of the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) and objective cognitive assessments in patients with bipolar disorder. We further assessed the reliability and validity of the COBRA. Forty-one patients, aged 16-64, in a remission period of bipolar disorder were recruited from Hokkaido University Hospital in Sapporo, Japan. The COBRA (Japanese version) and Frankfurt Complaint Questionnaire (FCQ), the gold standard in subjective cognitive assessment, were administered. A battery of neuropsychological tests was employed to measure objective cognitive impairment. Correlations among the COBRA, FCQ, and neuropsychological tests were determined using Spearman's correlation coefficient. The Japanese version of the COBRA had high internal consistency, good retest reliability, and concurrent validity—as indicated by a strong correlation with the FCQ. A significant correlation was also observed between the COBRA and objective cognitive measurements of processing speed. These findings are the first to demonstrate that the Japanese version of the COBRA may be clinically useful as a subjective

cognitive impairment rating scale in Japanese patients with bipolar disorder.

Keywords: Subjective cognitive impairment, Japan, neuropsychological tests, cognition, COBRA, bipolar disorder.

1. Introduction[1]

Bipolar disorder is a chronic mental illness that can cause periods of depression as well as periods of elevated mood. Lifetime prevalence rates vary worldwide but range from 4.4% in the United States to 0.7% in Japan (Merikangas et al., 2011). Cognitive impairment is a core feature of both schizophrenia and bipolar disorder (Kurtz and Gerraty, 2009; Stefanopoulou et al., 2009). In particular, verbal memory and executive functions are significantly impaired (Martinez-Aran et al., 2004; Torrent et al., 2006). Evidence suggests that patients with bipolar disorder experience cognitive deficits both in the acute stage of the illness and during remission (Martinez-Aran et al., 2004; Robinson et al., 2006). Cognitive impairment has a major effect on psychological and psychosocial function (Bonnin et al., 2014; Bonnin et al., 2010; Goldberg and Chengappa, 2009; Sole et al., 2012), treatment adherence (Lopez-Jaramillo et al, 2010), and results in increased allostatic load, commonly referred to as the

[1] Abbreviations:

COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment; FCQ: Frankfurt Complaint Questionnaire; CDS: Cognitive Difficulties Scale; CFQ: Cognitive Failures Questionnaire; PAOF: Patient's Assessment of Own Functioning; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HAM-D: Hamilton Rating Scale for Depression; YMRS: Young Mania Rating Scale; JART-25: Japanese Adult Reading Test-25; WCST: Wisconsin Card Sorting Test; WFT: Word Fluency Test; CPT: Continuous Performance Test; TMT: Trail Making Test; AVLT: Auditory Verbal Learning Test

"wear and tear" that stress exerts on the mind and body (Ogden, 2004; Vieta et al., 2013). A recent systematic review found a high prevalence of cognitive impairment among individuals with type I or II bipolar disorder and reported that cognitive dysfunction remained even when patients were in remission (Cullen et al, 2016).

At present, opinion is divided regarding the relationship between subjective and objective cognitive function among patients with affective disorders (Demant et al., 2015; Svendsen et al., 2012). Research has indicated that patients with bipolar disorder present with both objective and subjective cognitive impairment. However, few studies have investigated the relationship between subjective cognitive complaints and objective neuropsychological impairment (Burdick and Endick, 2005). In fact, patients with bipolar disorder frequently report difficulties relating to attention, concentration, memory, perception, thought, language, and emotion (Peralta and Cuesta, 1998).

A number of cognitive assessment tools exist to measure subjective levels of dysfunction in patients with mental disorders, including the Functional Cognitive Questionnaire (FCQ; Cuesta et al., 1996), the Cognitive Difficulties Scale (CDS; McNair et al., 1983), the Cognitive Failures Questionnaire (CFQ; Broadbent et al., 1982), and the Patient's Assessment of Own Functioning (PAOF; Chelune et al., 1986). However, these instruments are not specific to bipolar disorder. Recent reports have suggested that objective cognitive functions cannot be sufficiently assessed using subjective assessment tools (Miskowiak et al.,

2012; Svendsen et al., 2012). For example, Miskowiak and colleagues (2016) found that patients with high premorbid IQ had a tendency to underreport objective cognitive impairment. In contrast, a number of studies have reported a weak correlation between the two (Arts et al., 2011; Demant et al., 2015; Martinez-Aran et al., 2005; Rosa et al., 2013), with some researchers arguing that subjective assessment reflects mood symptoms rather than objective dysfunction (Miskowiak et al., 2012).

The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) is a self-reporting rating scale developed by the Bipolar Disorder Program at the Hospital Clinic of Barcelona (Vieta, 2011) that assesses subjective cognitive impairment in daily life activities experienced by patients with bipolar disorder. It has been shown to be partially correlated with objective assessment of memory and executive functions (Rosa et al., 2013). In Japan, there is currently no rating scale that has been shown to be reliable and valid for evaluating subjective cognitive impairment in patients with bipolar disorder. We therefore aimed to investigate the relationship between the Japanese version of the COBRA and objective cognitive assessment in patients with bipolar disorder, and to examine the psychometric properties of the COBRA.

2. Methods

2.1. Patients

A total of 41 patients participated in this study; 13 were diagnosed with bipolar disorder type I and 28 with bipolar disorder type II, in accordance with criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Patients eligible for this study were those who satisfied the remission criteria at least 8 weeks prior to the assessment (≤7 points on the (HAM-D) and the Young Mania Rating Scale (YMRS), respectively). All included patients were between 18–64 years of age and had consulted with the Department of Psychiatry at Hokkaido University Hospital on an outpatient basis.

2.2. Clinical and sociodemographic assessment

In addition to the sociodemographic and clinical data collected from the patient records, the 17-HAM-D and YMRS were administered to each patient to assess depressive and manic symptoms, respectively.

2.3. Subjective cognitive measures

After translating the Spanish version of the COBRA to Japanese, a back translation was performed, and approval was obtained from the original author. The COBRA includes 16 items that allow patients to report assessments of subjective cognitive dysfunction related to executive function, processing speed, working memory, verbal learning and memory, attention and concentration, and mental tracking. All items are rated using a 4-point scale:

0=never, 1=sometimes, 2=often, and 3=always (see English version in Appendix A, Japanese Version in Appendix B). A total COBRA score was calculated by adding the scores of each item, with higher scores reflecting higher levels of subjective complaints.

The FCQ is a validated and reliable instrument used to assess cognitive difficulties and subjective cognitive impairment in patients with mental disorders (Cuesta et al., 1996; Musha, 1991). This instrument has been used widely in Europe and, with the permission of the original author, was translated into Japanese by Musha and colleagues (1991), who reported a high Cronbach's α coefficient of 0.9576. The FCQ contains 103 items across 12 subscales that aim to examine the following categories of impairment: loss of control, simple perception, complex perception, cognition and thought, language, memory, loss of automatisms, anhedonia, motor skills, and sensory overstimulation. Items are rated 0 (no) or 1 (yes), with a total score ranging from 0–103.

2.4. Objective cognitive measures

Premorbid IQ was estimated using the Japanese Adult Reading Test-25 (JART25; Matsuoka and Kim, 2006). The following neuropsychological tests were also administered to all participants to measure objective cognitive impairment: executive function, Wisconsin Card Sorting Test (WCST); verbal fluency, Word Fluency Test (WFT); sustained attention and motor speed, Continuous Performance Test (CPT); visual-motor processing, motor speed, and

executive function, Trail Making Test (TMT); verbal learning and immediate and recent memory, Auditory Verbal Learning Test (AVLT); and selective attention, Stroop Test. This battery of neuropsychological tests required 60–90 minutes to administer by a neuropsychologist, and patients took a break midway if required.

2.5. Validity and reliability assessment

We examined the reliability (e.g., internal consistency) of the COBRA using the Cronbach's alpha and examining item-total correlations. We also examined the concurrent validity of the COBRA as follows: (1) by assessing the relationship between the COBRA and the FCQ, and (2) by examining the association between the COBRA and objective cognitive measures via the battery of neuropsychological tests. In order to assess the test-retest reliability of the COBRA, patients underwent the same test 2–4 weeks after the initial assessment. Feasibility was defined as the percentage of patients who responded to the questionnaire in its entirety. The local ethics committee from the appropriate university approved this study. After a complete study explanation, patients provided their written informed consent to participate.

2.6. Statistical analysis

Internal consistency was assessed by calculating the Cronbach's alpha coefficient. The Spearman's correlation coefficient was determined to assess a possible relationship between

the COBRA and FCQ, and between the neuropsychological tests and the clinical course of the disease. Test-retest reliability was examined by comparing the COBRA scores acquired at baseline and at the 2–4week follow-up. Exploratory factor analysis was conducted using principal axis factoring and the rotation was examined using the Quartimax method. All statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS Version 23.0, IBM Analytics, Chicago, Illinois, US) software. The level of significance was set at $p<0.05$.

3. Results

Forty-one patients were recruited, with a mean age of 43.34±10.51 years. Sociodemographic and clinical characteristics of the patients are shown in Table 1. Eighteen (43.9%) patients were male, and 23 (56.1%) were female. Thirteen patients (31.7%) were diagnosed with bipolar I disorder and 28 (68.3%) with bipolar II disorder. The mean duration of education for this patient sample was 14.27±2.27 years, and the mean premorbid IQ score as assessed by the JART was 106.51 (SD 10.63). Almost all patients (39, 95.1%) exhibited objectively measured cognitive impairment, and nearly half of the patients scored ≥13 on the COBRA (20, 48.8%). Among these 20 patients, 19 (95.0%) exhibited objectively measured cognitive impairment, similar to those who scored <13 on the COBRA (20, 95.2%). There was no significant difference between patients with bipolar I and bipolar II disorder with regard to the total COBRA score (Mann-Whitney U = 143.0, p=0.274).

3.1. Internal consistency

The Japanese version of the COBRA had very high internal consistency (Cronbach's alpha=0.887) for the total score, suggesting that each individual item was sufficiently reliable. All individual items were also significantly correlated with the COBRA total score: Assessment of the total score minus the item of interest resulted in a Cronbach's alpha range of 0.872-0.887, indicating that all items contributed to the overall COBRA score. Factor analyses revealed that only one component exhibited positive factor loadings for all items (Table 2). We were unable to perform further confirmatory factor analyses due to the low number of patients.

3.2. Test-retest reliability

Test-retest reliability of the COBRA was examined in only 35 patients in remission. Data could not be collected for the remaining six patients, as they were lost to follow-up and did not complete the second round of testing. The results revealed acceptable reliability of the COBRA (rho=0.721, $p<0.001$). A significant correlation was also observed between COBRA and FCQ scores, indicating concurrent validity of the COBRA (rho=0.668, $p<0.001$; Fig 1).

3.3. Associations between subjective and objective cognitive measures and clinical features

of bipolar disorder

Spearman's correlation coefficients were calculated to assess the relationship between subjective and objective cognitive measures (Table 3, Appendix C). A weak yet significant correlation was observed between the COBRA and TMT-A (processing speed, rho=0.356, p=0.022). However, we observed no significant correlation between the COBRA and clinical features of bipolar disorder (data not shown), or between estimates of IQ and the COBRA (rho=-0.132; p=0.412). In addition, although we observed a significant association between the COBRA and HAMD-17 (rho=0.351, p=0.024), no such association was observed between the COBRA and the YMRS (rho=0.112, p=0.487).

3.4. Feasibility

The COBRA exhibited high feasibility, with missing values representing less than 1% of the data for each of the 16 items contained in this instrument.

4. Discussion

The results of the present study indicate that the Japanese version of the COBRA possesses high internal consistency and concurrent validity via significant correlation with the FCQ, supporting previous validation research on the COBRA (Rosa et al., 2013). Furthermore, the COBRA also exhibited sufficient psychometric characteristics. We observed a significant

correlation between the COBRA and TMT-A, which assesses processing speed.

Significant correlations have been previously reported between the COBRA and several other neuropsychological tests, particularly single scale ratings for executive function, working memory, language, and visual memory (Jensen et al., 2015; Rosa et al., 2013). The results of this study did not largely deviate from those of previous studies detailing the correlation between the COBRA and cognitive function. Subjective cognitive function was predicted by affective symptoms, suggesting that these symptoms do not reflect objective deficits, but are rather associated with alterations in mood (Miskowiak et al., 2012). Subjective cognitive measures were partially correlated with the results of some objective cognitive assessments (e.g. executive function and memory tasks) and with poor patient outcomes. Although self-reports may be biased, the patient's assessment of his or her own cognitive problems via an instrument specifically designed to address commonly reported difficulties is nonetheless important in both clinical practice and investigation. However, subjective cognitive complaints do not always correspond to objective cognitive impairment, and a neuropsychological battery administered by a trained neuropsychologist is required to confirm cognitive deficits. A longitudinal study including both objective and subjective assessments (e.g., COBRA) may greatly contribute to our understanding of the clinical relevance of and outcomes associated with specific cognitive complaints in patients with bipolar disorder (Rosa et al., 2013).

A correlation between subjective cognitive impairment and processing speed was not found in a previous study (Rosa et al., 2013). Therefore, the fact that a correlation was observed between the COBRA and TMT-A is novel in itself. A study using the CFQ to determine the relationship between subjective and objective assessment of cognitive function in patients with bipolar disorder indicated that there was no significant relationship between the CFQ and objective neurocognitive measures, except for the relationship between "memory for names" and information processing speed (van der Werf-Eldering et al., 2011). A high total CFQ score indicates a significant correlation between low scores and selective attention areas during basic information processing (Arts et al., 2011). However, reports have also indicated the absence of a relationship between total CFQ score and objective cognitive function scales (Burdick and Endick, 2005).

Previous work has suggested that some subjective cognitive measures reflect symptoms of depression rather than objective cognitive dysfunction (Svendsen et al., 2012), and that processing speed may be influenced by the adverse effects of medications. However, a recent review paper by Tsitsipa and Fountoulakis (2015) suggests that neurocognitive dysfunction is a core feature of bipolar disorder, as opposed to a secondary outcome of mood symptoms or medication. For example, one study found levels of neurocognitive impairment in patients prior to receiving pharmacological treatment that were similar to those in chronically medicated patients (Nehra et al, 2006). In the present study, post-hoc analysis revealed no

association between the COBRA and type of medication (anti-psychotics, anti-depressants, anti-anxiety). Post-hoc partial correlation analysis using the HAMD-17 as a control variable, however, revealed that the COBRA was significantly correlated with both executive functioning via the WCST-PEM ($p=0.003$) and processing speed ($p=0.027$), in accordance with the findings of previous European studies on the relationship between the COBRA and executive functioning (Rosa et al., 2013).

4.1. Limitations

The Japanese version of the COBRA does not solely assess subjective cognitive function in patients with bipolar disorder; its correlation with objective cognitive function measurements is also useful from a clinical and research perspective. However, our study has a number of limitations that should be considered. This cross-sectional study was unable to control for the influence of medication on subjective and objective cognitive measures since all participants were receiving drug therapies at the time of the study. Furthermore, this study was conducted at a single institution, a tertiary hospital environment wherein patients tend to have severe symptoms. Our sample was limited to those in remission who had a long history of illness, and our proportion of patients with bipolar II disorder was higher than that of previous studies (Rosa et al., 2013). Therefore, it may not be appropriate to use the findings of this study to make generalized conclusions relevant to a wider population of patients with bipolar

disorder. However, in accordance with the World Mental Health Japan (WMHJ) survey, we also found a higher proportion of patients with bipolar II disorder than bipolar I, suggesting that our sample is representative of bipolar patients in Japan. Further, the present study did not include a control group of healthy individuals. Future studies should include such participants in order to measure the sensitivity of the COBRA and its discriminant validity. In addition, future researchers should examine whether the correlation between the COBRA and processing speed remains after adjusting for medications that may affect cognitive functioning.

In conclusion, the Japanese version of the COBRA shows high internal consistency and concurrent validity through its significant correlation with the FCQ. It also exhibits good psychometric properties and may be a valid and reliable instrument for assessing cognitive complaints in Japanese patients with bipolar disorder. The association between subjective and objective cognitive impairment among patients in remission is less clear and warrants further investigation.

Conflict of Interest

None.

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Table 1: Clinical and sociodemographic characteristics of Japanese patients with bipolar disorder

Characteristic of patients (n=41)	**Mean (SD) or number (%)**
Age, mean years (SD)	43.34 (10.51)
Age at illness onset, mean (SD)	27.78 (8.94)
Gender, male, no. (%)	18 (43.9)
Years of education, mean (SD)	14.27 (2.27)
Currently employed, no. (%)	17 (41.5)
Married, no. (%)	21 (51.2)
Living alone, no. (%)	12 (29.3)
Depressive onset, mean years (SD)	27.15 (10.44)
Bipolar Ⅰ disorder, no. (%)	13 (31.7)
Number of hospitalizations, mean (SD)	1.80 (2.18)
Number of total episodes, mean (SD)	5.73 (3.74)
Number of hypomanic episodes, mean (SD)	1.56 (1.90)
Number of manic episodes, mean (SD)	0.76 (1.41)
Number of depressive episodes, mean (SD)	3.12 (1.68)
Number of mixed episodes, mean (SD)	0.29 (0.56)
Number of suicidal attempts, mean (SD)	0.54 (0.98)
JART-25 pre-morbid IQ score, mean (SD)	106.51 (10.63)

HAMD-17 score, mean (SD)	2.34 (2.21)
YMRS score, mean (SD)	0.32 (0.99)
COBRA score, mean (SD)	13.63 (7.946)

SD: Standard deviation; JART-25: Japanese Adult Reading Test-25; HAMD: Hamilton Rating Scale for Depression; YMRS: Young Mania Rating Scale; COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment

Table 2: Factorial loading on the COBRA

	Factor				
	1	2	3	4	5
Item 1	.289	.438	-.448	.226	.273
2	.179	.421	.007	.183	.427
3	.324	.548	.442	.404	-.122
4	.284	-.024	.016	.759	.117
5	.596	.314	.067	.136	-.234
6	.729	-.131	.214	.323	.060
7	.273	.776	.154	-.109	.077
8	.660	.052	-.055	-.386	.268
9	.414	.590	-.037	-.207	-.003
10	.249	.230	.583	.096	.058
11	.495	-.089	.360	.331	.221
12	.809	.238	-.036	.135	-.075
13	.463	.102	.158	.064	.721
14	.557	.014	.587	-.097	.303
15	.830	.031	.139	.053	.043
16	.781	.263	-.303	-.144	.095

Extraction method: principal axis factoring (Quartimax rotation). COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment

Table 3: Associations between subjective and objective cognitive measures among patients with bipolar disorder

Measure	**COBRA *rho (p)****
WCST-CA	-0.126 (0.433)
WCST-PEM	0.219 (0.169)
CPT number of errors	0.223 (0.161)
CPT reaction time	0.034 (0.833)
WFT	-0.119 (0.460)
ST reaction time	0.217 (0.173)
ST number of errors	-0.082 (0.611)
TMT-A	0.356 (0.022)
TMT-B	0.205 (0.198)
AVLT immediate memory	-0.118 (0.461)
AVLT recent memory	-0.065 (0.685)

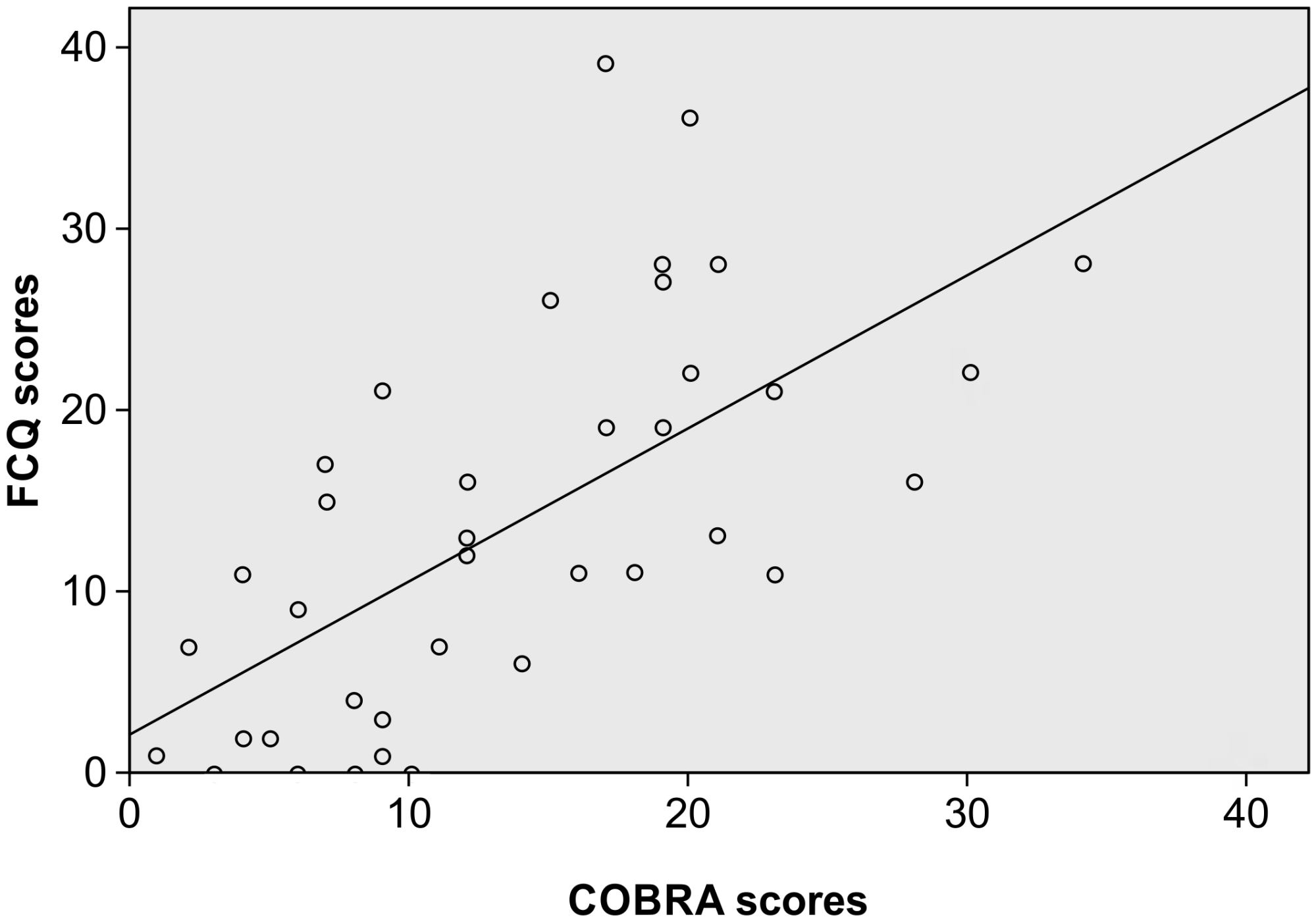
*Spearman's correlation (rho). WCST: Wisconsin Card Sorting Test; CA: category of achievement; PEM: Milner perseverative errors; CPT: Continuous Performance Test; WFT: Word Fluency Test; ST: Stroop Test; TMT: Trail Making Test (TMT-A = processing speed; TMT-B = executive function); AVLT: Auditory Verbal Learning Test

Figure legend

Fig 1. Concurrent validity of the COBRA. Spearman's correlation between the COBRA and Frankfurt Complaints Questionnaire (FCQ) scores (rho=0.668, p<0.001). COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment

Supplementary Material

Appendix A, B, and C


FCQ scores
COBRA scores
0
10
20
30
40