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Social functioning in euthymic bipolar disorder

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Abstract

Background: The relationship between residual depressive symptoms, cognition, and functioning in euthymic patients with bipolar disorders (BD) is a subject of debate.

Aims: Our objective was to assess whether cognition mediates the association between residual depressive symptoms and functioning in euthymic patients with BD.

Methods: We included 241 adults with euthymic BD in a multicenter cross-sectional study. We used a battery of tests to assess six cognition domains. A path analysis was then used to perform a mediation analysis of the relationship between residual depressive symptoms, cognitive components, and functioning.

Results: Only verbal and working memory were significantly associated with better functioning. Residual depressive symptoms were associated with poorer functioning. No significant relationship was found between residual depressive symptoms and any cognitive component.

Conclusions: Cognition and residual depressive symptoms appear to be two independent sources of variation in the functioning of euthymic patients with BD.

Declaration of interest: None.

Keywords: bipolar disorders; cognition; verbal memory; euthymia; attention; social functioning; executive functions; speed processing; working memory; principal component analysis, path analysis, mediation analysis

INTRODUCTION

Bipolar disorders (BD) are highly disabling (1) and prevalent (2). More than half the individuals with BD experience significant functional impairment in several domains, such as family and social life and work, outside the acute phases of the illness (3). In the last decade, the focus of research in BD has changed from clinical remission to functional recovery (3). However, the sources of high variation observed in the psychosocial functioning of individuals with BD are still poorly understood. Cognitive impairment is an important determinant of functional impairment in BD (4). Because the strength of association between poor social functioning and cognitive impairment in BD is similar to that seen in schizophrenia (5), it seems crucial to characterize the underlying architecture of cognitive performance in BD.

Previous studies investigating multiple cognitive areas in BD have usually focused on domains *a priori* that were subjectively defined and selected. However, the validity of these domains is questionable, as it relies on the assumption that the latent organization of human cognition is similar in persons with BD and healthy controls. This crucial assumption has received few experimental evidence (6). It thus remains possible that the same neuropsychological tests might evaluate different cognitive competencies in these two groups of participants if there is a discrepancy in how cognitive measures relate to one another between individuals with and without BD. This lack of equivalence between the constructs could lead to artifacts in the observed differences in cognitive test performances. A few studies have explored the latent cognitive structure in BD and found that cognitive functioning was best described by multi-factorial models (6-8). However, some of these studies included symptomatic patients (7, 8). Here, we have measured performance for a broad range of cognitive domains in euthymic BD using a comprehensive battery of neuropsychological tests. We have examined the component structure of BD cognitive

processes using a Principal Component Analysis, which allows the data-driven reduction of multiple cognitive measures, avoids arbitrary and *a priori* categorization of several tests into domains, and results in a reliable estimate of underlying cognitive constructs in BD.

Among clinical factors, residual depressive symptoms have been reported to be the strongest predictor of functional impairment (9) and quality of life (10) in euthymic BD. They are also associated with lower adherence to medication in BD (11). In contrast, residual hypomanic symptoms have no impact on functioning in euthymic BD (4, 9, 12-14). Whereas residual hypomanic symptoms are not related to cognition (15), it is less clear whether subthreshold depressive symptoms negatively affect neuropsychological performance in euthymic BD or not. The relationship between residual depressive symptoms and cognition is mixed, showing a small impact of subthreshold depression on only a few cognitive components, such as verbal memory, speed, and executive function, but not for others (16). A few studies have explored the role of cognition in mediating the relationship between depressive symptoms and functioning in euthymic BD, leading to inconsistent results. One study showed that verbal memory partially mediated the relationship between subthreshold depressive symptoms and functional outcome in euthymic people with BD (17). However, the sample size was not large enough to include other cognitive moderators in the model. In contrast, another study reported that cognition did not mediate the relationship between depressive symptoms and social competencies in BD (18). Again, only one global neurocognitive composite score was included as the cognitive moderator in the model, due to the limited sample size. There have been no studies, to date, that have investigated simultaneous mediation between sub-depressive symptoms and functioning by multiple cognitive components in BD. In this study, the cognitive domains obtained with PCA were entered in a path analysis model, as potential mediators between residual depressive symptoms and functioning.

METHODS

Study design and recruiting network characteristics

This multicenter, cross-sectional study included patients recruited into the FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders) cohort by a French national network of nine BD Expert Centers (Bordeaux, Créteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris and Versailles). This network was set up by the FondaMental Foundation (www.fondation-fondamental.org) and funded by the French Ministry of Research and the French Ministry of Health to build an infrastructure and provide resources to follow clinical cohorts and comparative-effectiveness research on a representative patient population.

Participants

BD was diagnosed based on a structured clinical interview that assessed the DSM-IV-R criteria. Outpatients of 18 to 65 years of age with type I, II, or not otherwise specified (NOS, including cyclothymia) BD were eligible. All patients were euthymic when they were tested according to the DSM-IV-R criteria, with a Montgomery Åsberg Depression Rating Scale (19) (MADRS) of less than 10 and a Young Mania Rating Scale (20) (YMRS) of less than 10. Exclusion criteria were a history of neurological or sensory disorders, dyslexia, dysorthographia, dyscalculia, dysphasia, dyspraxia, language delay, substance-related disorders in the previous month, and electroconvulsive therapy in the past year. The ethics committee (Comité de Protection des Personnes Ile de France IX) approved the study protocol on January 18, 2010. Although the committee waived the requirement for written informed consent, the patients received a letter informing them of the study and asking whether they agreed to participate.

Assessment tools

Clinical assessments

The age at onset; number of previous mixed, hypomanic, manic, and major depressive episodes; subtype of BD; and history of psychotic symptoms were recorded. We used the yes/no format for recording whether the patient was taking lithium carbonate, anticonvulsants, antipsychotics, antidepressants, or anxiolytics at the time of the evaluation. Finally, three socio-demographic characteristics were collected: sex, age, and educational level.

Psychosocial functioning was measured using the Functioning Assessment Short Test (FAST), which covers six functioning domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time (21). The higher the score, the greater the disability. FAST has good internal consistency (Cronbach alpha between 0.87 and 0.96) and test-retest reliability (Pearson correlation coefficient between 0.90 and 0.97; intraclass correlation coefficient between 0.90 and 0.98, see Supplemental References S1 for a bibliography of FAST psychometrical properties).

Battery of cognitive tests

Experienced psychologists administered the tests in a fixed order. Testing lasted a total of 120 minutes, including a 5 to 10-minute break. The standardized test battery complied with the recommendations issued by the International Society for Bipolar Disorders (22). It included 11 tests and evaluated the following six cognitive domains:

- motor speed with the digit symbol coding and symbol search subtests from the Wechsler Adult Intelligence Scale (WAIS) version III;
- attention with the Conners' Continuous Performance Test II (CPT-II) (23) and the Trail Making Test (TMT) (24);

- executive functions with the Stroop color and word test and verbal fluency (25) ;
- verbal memory with the California Verbal Learning Test (CVLT) (26);
- working memory with the digit span subtest from the WAIS III and the spatial span subtest from the Wechsler Memory Scale version III; and
- intellectual functioning with the vocabulary and matrix reasoning subtests from the WAIS-III

Some of the current cognitive data obtained with this battery have been published previously (27).

Statistical analyses

Principal Component Analysis (PCA)

PCA is a powerful statistical method for identifying the underlying organization of multiple variables like cognitive measures and allows data reduction necessary to avoid Type I errors from multiple comparisons. The data set for the PCA included 22 raw cognitive variables: number of correct answers for the digit symbol coding and symbol search tests, percentages of omissions and commission errors for the CPT, reaction time (ms) for hits in the CPT, time (s) to complete the TMT-A & B, number of responses in the color, word, and color-word conditions of the Stroop test, number of correct words for phonemic and semantic verbal fluency, number of recalled words in the immediate recall, short, and long delay free recall of the CVLT, number of total correct recognized words for the CVLT, span lengths for the forward and backward conditions of the spatial and digit span tests, number of correct answers for matrix reasoning, and total score for vocabulary.

Sampling adequacy was evaluated using the Kaiser-Meyer-Olkin (KMO) measure (28) for the overall cognitive data set and Bartlett's test of sphericity (29). The number of components to

be extracted in the PCA was determined by Horn's parallel analysis (30). This method contrasts eigenvalues produced through a parallel PCA on 1000 random datasets, with the same number of variables and observations as the observational dataset, to generate eigenvalues for components that are adjusted for sample error-induced inflation. Adjusted eigenvalues > 1 indicate dimensions to retain.

We ran a PCA on cognitive variables followed by an Oblimin rotation. The rotation was performed to simplify the component structure. We used an oblique rotation because the cognitive components were believed to be correlated with each other. In PCA, the usual standard for sample size is a participant-to-variable ratio > 5 (31), and therefore required 110 participants for the current study.

Path and mediation analysis

Zero-order correlations between MADRS, cognitive components, FAST scores, age, sex, and education were calculated using Pearson correlation coefficients. A path analysis was performed using MADRS, cognitive components, and FAST scores to test whether cognitive components mediated the relationship between residual depressive symptoms and functioning. The model tested in the path analysis did not include the YRMS score, as we expected it to correlate with neither cognition nor functioning. The model allowed the residual variances of the cognitive components scores to be correlated. Age, sex, and education were used as covariates in the model.

Analyses were performed using the *lavaan* package of *R* statistical software version 3.3 with the Maximum Likelihood estimation method. Linear regression analyses were conducted to evaluate the relationships among the variables and were indexed using standardized path coefficients. Because the FAST total score is usually not normally distributed in euthymic BD

(32), we used a nonparametric bootstrapping of the standard errors with 2000 iterations for the correlation and SEM analyses.

The fit between the model and the data was assessed using four indices: the chi-square goodness-of-fit statistic (χ^2), comparative fit index (CFI), root-mean-squared error of approximation (RMSEA), and standardized root mean square residual (SRMR).

RESULTS

Participants

We included 241 patients. Table 1 reports their sociodemographic and clinical characteristics and Table 2 the results of the battery of cognitive tests. No patient had more than 5% missing cognitive data; the missing cognitive data were estimated using a multivariate imputation by chained equations in the *mice* package of *R*.

PCA

The KMO measure for the overall cognitive data set was 0.85 and Bartlett's test of sphericity was significant ($X^2(231) = 2295$, $p < 0.001$), both indicating good factorability of the cognitive data. Horn's parallel analysis showed that five components should be retained, as their adjusted eigenvalue was above 1 (see Supplemental Table S2). The 5-component structure explained 61% of the variance (see Supplemental Table S3). All component loadings were greater than 0.4, and all communalities were higher than 0.3 (see Table 3). The first component consisted of all measures of the CVLT and was designated "verbal memory." The second component bundled TMT, CPT omissions, symbol search, vocabulary, symbol coding and semantic verbal fluency and was designated "speed of processing and verbal knowledge." The third component included all measures of spatial and digit spans, with matrix reasoning, and was designated "working memory and problem-solving." The fourth component consisted

of all measures of the Stroop test, with phonemic verbal fluency, and was designated “verbal fluency and inhibition.” The final component included CPT reaction time and commission and was designated “visual sustained attention.”

Path and mediation analyses

Supplemental Table S4 reports the zero-order correlations between the variables included in the model. The path analysis model allowed correlations between the residual variances of all cognitive components, except “visual sustained attention” which was not correlated with any other cognitive components.

The path analysis model is shown in Figure 1. We represent neither covariances between cognitive components, nor the regressions on covariates, to enhance readability.

Path analysis requires at least 15 participants for each variable (33). We included ten variables in the model and therefore required at least 150 participants. There were 0.8% missing data, which were handled using the full information maximum likelihood estimation. The four patterns of missingness are reported in Supplemental Table S5 and the covariance coverage matrix of missing data in Supplemental Table S6.

The model provided a good fit for the data, as suggested by the nonsignificant chi-square goodness-of-fit statistic ($X^2(4) = 7.5$, $p = 0.113$), a CFI greater than 0.95 (0.989), an RMSEA not significantly larger than 0.05 (RMSEA = 0.06, one-sided *P* value of the test of the null hypothesis RMSEA = 0.05, 0. 329), and SRMR lower than 0.08 (0.017).

The model explained 30% of the variance in functioning. Altogether, the analysis revealed the following relationships between the variables (Figure 1): a significant positive association between MADRS and FAST, a significant negative association between “verbal memory” cognitive component and FAST, and a significant negative association between the “verbal fluency and inhibition” cognitive component and FAST. We found no other significant associations, and in particular, MADRS was not significantly associated with any

cognitive component, thus showing that cognitive component scores did not mediate the relationship between MADRS and FAST. Estimated standardized path coefficients for all variables included in the path analysis model (including covariates) and residual correlation coefficients between cognitive components are reported in Supplemental Table S7.

DISCUSSION

Here, we first used a PCA to identify the underlying architecture of cognitive processing in euthymic patients with BD. We then used a path analysis to evaluate whether cognition mediated the relationship between residual depressive symptoms and functioning.

We found five underlying components involved in cognition in euthymic BD. Two components were derived from individual variables that were relatively homogeneous and specific regarding modality: the “verbal memory” component was derived only from CVLT measures and the “visual sustained attention” only from CPT measures. The remaining three components were more heterogeneous. The “verbal fluency and inhibition” component consisted of verbal responses sometimes involving inhibition (phonemic verbal fluency and color/word condition of the Stroop test) and sometimes not (color and word condition of the Stroop test). The “speed of processing and verbal knowledge” component contained a combination of visuospatial and verbal variables. The “working memory and problem solving” component bundled non-verbal reasoning and working memory measures. Greater variability within cognitive components has already been reported in BD and was interpreted as a decrease in the differentiation of previously discrete cognitive processes through a decline in neural connectivity (8). The number of extracted cognitive components is similar to that of previous studies which found five (6) or six underlying dimensions in cognition for BD (7). The labels used in these previous studies to describe the cognitive dimensions were similar to those applied in the current study, consisting of verbal memory, speed of

processing, working memory, executive functions, verbal knowledge, and attention dimensions. This suggests a relative stability and reliability of the method we used to uncover the underlying cognitive components in BD.

There was a negative association between residual depressive symptoms and functioning: individuals with more pronounced depressive symptoms had a poorer social functioning, which was not explained by age, sex, lower education, or poorer cognition. This finding is in accordance with previous cross-sectional (13, 17, 18, 32) and longitudinal studies (9, 14), showing that subclinical depressive symptoms in bipolar disorders are the main predictors of poor functional outcome, particularly work functioning (34). The present study included only euthymic patients, based on stringent criteria: the mean score for depression was very low but similar to previous studies exploring social functioning in euthymic BD (9, 13, 17, 32). However, the data show that functional impairment may be associated with even very low residual depressive symptoms, measured with a scale that was not specifically designed to assess subsyndromal depressive symptoms.

Among the five cognitive components found in this study, only two were positively associated with functioning: “verbal memory” and “verbal fluency and inhibition.” Patients with better verbal memory, verbal fluency and inhibition also had a better social functioning. These results are consistent with several prior reports indicating that verbal memory (14) and inhibitory control (Stroop Colour Word Test) (35) were more highly associated with functioning than other cognitive functions. That functioning was more highly related to residual depressive symptoms than cognition could be explained by the auto evaluation method we used to measure everyday functioning. Self-reported measures of social functioning may be influenced less by objective cognitive performance and more by depressive symptomatology, due to a pessimistic subjective appraisal of oneself and one's environment. This influence might be particularly important for low FAST scores (better

functioning), like in our sample, where the distribution of FAST scores was skewed on the right. In contrast, the reverse may be true for performance-based measures of functioning and real-world functional milestones in BD, which may be influenced more by objective cognitive performance and less by depression (5, 12).

No associations between residual depressive symptoms and cognitive components were significant, showing that cognition does not mediate the relationship between subclinical residual depressive symptoms and functioning. This result is in accordance with a previous study reporting that perceived cognitive impairment and subclinical residual depressive symptoms are two independent sources of variation in the functioning of individuals with BD (36). However, this mediation might occur for higher levels of depressive symptoms, as the impact of depressive symptoms on cognition varied according to the clinical response after treatment (37).

Our model explained only 30% of the variance in functioning, supporting a role for other factors that were not measured here. Previous studies have suggested that functioning may be impaired when sleep is persistently disrupted (38), when social cognition is impaired (13), and when episode density is high (35). The mean level of functioning in participants recruited in this study corresponds to moderate functional difficulties (3). It is in the range (from 6 to 29) of those found in studies exploring the relationship between cognition and functioning in euthymic BD (13, 32, 36). This consistency supports the general applicability of our findings to patients with euthymic BD, provided the same assessment tools are used.

Limitations of our study include the cross-sectional design, which precludes the assessment of causality and the direction of potential causal links. Another limitation is the lack of inclusion of social cognitive tasks in the assessment. We did not compare the cognitive architecture found in the current sample of BD patients to a control group. Finally,

the sample size was not large enough to test a more complex model that includes other variables of the illness (type of BD, number of previous episodes, age at onset, and history of psychosis) and medication. The time since the last mood episode might also be an important factor lacking in the present study. These variables might have also had an effect on functioning in euthymic BD.

Our findings have important implications for future clinical studies. Individuals with BD who respond to treatment may nevertheless continue to experience residual depressive and cognitive symptoms, leading to difficulties in functioning. First, it seems crucial to improving the assessment and the characterization of residual depressive symptoms, with for example specific scales. Treatment approaches should possibly include the cognitive performance improvement and the full residual depressive symptoms remission as important targets to obtain functional recovery in BD. The optimal method to treat residual depressive symptoms is not clear, but they may be targeted by the use of mood stabilizers effective in the treatment of depressive polarity. Evidence for the efficacy of pharmacological and psychological interventions that target cognitive deficits in BD is still preliminary, despite promising avenues such as functional remediation (39). Among cognitive dimensions for cognitive remediation in euthymic BD, our data suggest that verbal memory and fluency, and inhibition may be choice targets.

In summary, this study provides further evidence that cognitive impairments in specific dimensions are a core feature of BD. This study also suggests that cognition is a separable dimension from depressive symptoms that persist during the inter-episodic period of BD. Verbal memory and fluency and Stroop test performance were particularly associated with functioning in our sample of euthymic BD and should be assessed in future studies focusing on functional outcome in BD.

Declaration of interest: none

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Figure Legends

Figure 1. Mediation Model. Rectangles represent the observed measured variables. Arrows showing the free regression weight are drawn between variables. Values are the standardized path coefficients. The squared multiple correlation (R^2) value for the dependent variable appears in the upper right corner of each rectangle. Covariates and covariation between the cognitive components are not drawn to increase readability but were indeed included in the model.

**0.01 > p > 0.001, ***p < 0.001.

MADRS: Montgomery Åsberg Depression Rating Scale

FAST: Functioning Assessment Short Test

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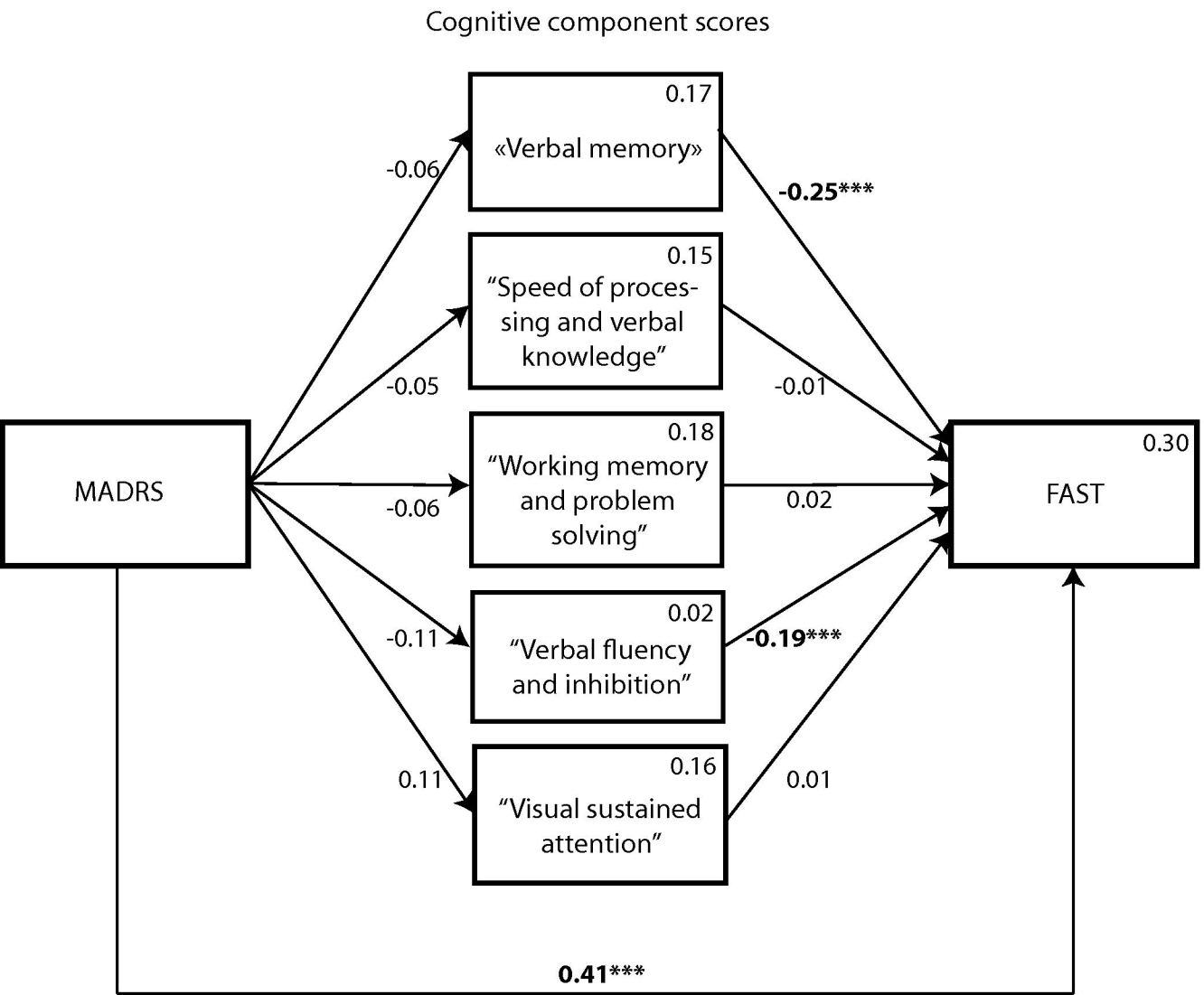
Cognitive component scores
0.17
«Verbal memory»
0.15
"Speed of proces-sing and verbal knowledge"
0.18
"Working memory and problem solving"
0.02
"Verbal fluency and inhibition"
0.16
"Visual sustained attention"
MADRS
FAST
0.30
-0.06
-0.05
-0.06
-0.11
0.11
-0.25***
-0.01
0.02
-0.19***
0.01
0.41***

Table 1. Participant socio-demographical and clinical characteristics:

Variable	**Mean**	**SD**	**Range**
Age (years)	41	11.3	19-65
Educational level (years)	14.5	2.7	7-22
Age at onset (years)	25	9.5	12-60
Number of mixed episodes	0.2	0.7	0-8
Number of hypomanic episodes	2.8	5.3	0-30
Number of manic episodes	1.4	1.9	0-10
Number of major depressive episodes	5.2	5.4	0-30
MADRS [0-60]	4	3.4	0-10
YMRS [0-60]	1.1	2	0-10
FAST [0-72]	16.8	13.2	0-64
		Percentage	
Sex (percentage of males)	40.2		
Diagnosis	55.6 (Type 1)	29.5 (Type 2)	14.9 (NOS)
History of psychosis	43.6		
Antidepressant	26		
Lithium Carbonate	25		
Anticonvulsant	32.7		
Antipsychotic	28.4		

MADRS: Montgomery Åsberg Depression Rating Scale

YMRS: Young Mania Rating Scale

FAST: Functioning Assessment Short Test

NOS: Not Otherwise Specified

Table 2. Participant neuropsychological performance:

Function	Test	Variable	Mean (percentile)	SD (percentile)	Mean (raw)	SD (raw)
Motor speed	Digit / Symbol Coding		43.1	25.8	70.2	15.2
	Symbol Search		56.2	28	33.7	7.5
Attention	Continuous Performance Test	Omissions	43.1	27.9	2.2%	4.6%
		Commissions	53.6	30.1	30.8%	20.2%
		Reaction Time	52	32.6	402.5 ms	84.2 ms
	Trail Making Test	Part A	49.6	25.7	35 s	13 s
		Part B	45.5	28.3	104.1 s	15.9 s
Executive functions	Stroop Test	Word	45.8	22.8	104.1	15.9
		Color	37.4	25.2	73	12.9
		Color/Word	47	29.8	43.1	11.1
	Verbal Fluency	Phonemic	48.2	31.3	24.1	7.3
		Semantic	39.9	27.9	31.7	8
Verbal memory	California Verbal Learning Test	Immediate Recall	46.8	32.5	56.4	9.9
		Short Delay Free Recall	46.9	30	11.9	2.9
		Long Delay Free Recall	44.8	30.3	12.2	2.7
		Total Recognition	52.8	26.3	15.1	1.2
Working memory	Spatial Span	Forward	46.1	26.5	8.3	1.9
		Backward	43.9	26	7.4	1.8
	Digit Span	Total	43.6	25.9		
		Forward			9.4	2
		Backward			6.4	2.3
Intellectual functioning	Matrix Reasoning		45.8	29	18.3	4.5
	Vocabulary		61.9	28	42.9	10.2

Table 3. Component loadings and communalities for the cognitive variables

Variable	Component loadings					Communality
	1	2	3	4	5	
CVLT Long Delay Free Recall	**0.94**	0.03	-0.06	0.04	0.02	0.88
CVLT Short Delay Free Recall	**0.92**	0.03	-0.03	0.01	0.01	0.85
CVLT Immediate Recall	**0.84**	0.02	0.05	0.09	-0.05	0.78
CVLT Total Recognition	**0.73**	-0.15	0.06	-0.23	0.07	0.55
TMT B	-0.13	**-0.69**	-0.16	0.03	-0.08	0.66
CPT Omissions	0.26	**-0.65**	0.17	0.04	0.02	0.37
Symbol Search	0.1	**0.65**	0.06	0.17	-0.1	0.62
Vocabulary	-0.03	**0.62**	0.04	0	0.25	0.44
Symbol Coding	0.17	**0.61**	0.05	0.21	-0.15	0.65
TMT A	-0.07	**-0.52**	-0.2	-0.03	0.16	0.46
Verbal Fluency Semantic	0.03	**0.46**	0.13	0.24	0	0.41
Spatial Span Backward	-0.02	0.16	**0.74**	-0.09	-0.03	0.61
Spatial Span Forward	0.01	0.04	**0.73**	-0.02	-0.06	0.55
Digit Span Backward	0.08	-0.04	**0.69**	0.21	0.06	0.62
Digit Span Forward	-0.08	-0.14	**0.65**	0.35	0.17	0.57
Matrix Reasoning	0.18	0.3	**0.56**	-0.35	0.01	0.62
Stroop Word	-0.04	0.08	0.01	**0.77**	0.02	0.63
Stroop Color	0.13	0.08	0.1	**0.69**	-0.06	0.62
Stroop Word/Color	0.11	0.09	0.18	**0.56**	-0.16	0.5
Verbal Fluency Phonemic	0.09	0.27	-0.18	**0.41**	0.34	0.39
CPT Reaction Time	-0.03	-0.13	0	-0.09	**0.86**	0.78
CPT Comissions	-0.07	-0.14	-0.05	-0.06	**-0.83**	0.74