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A 2-year naturalistic study on cognitive functioning in bipolar disorder

Arts B, Jabben N, Krabbendam L, van Os J. A 2-year naturalistic study on cognitive functioning in bipolar disorder.

Objective: Cognitive alterations in bipolar disorder may reflect genetic influence. However, to what degree mood, medication, thyroid function and other factors impact on longitudinal cognitive functioning remains unclear.
Method: A group of patients with bipolar (spectrum) disorder ($n = 76$) underwent two monthly cognitive assessments over a 2-year period in a prospective, repeated measures design. Regression models were used to investigate associations with predictors, corrected for multiple testing.
Results: Patients with bipolar disorder performed worse than healthy controls ($n = 61$) on all cognitive domains tested. Effect sizes were small, with a maximum of −0.36 for sustained attention. However, cognitive performance varied substantially over the 2- year follow-up, co-varying with subjective cognitive complaints and impacting on functioning. Alterations in sustained attention and motor speed were the only impairments that were invariant over time. Predictors had very limited explanatory power on temporal variation in cognition. Use of second-generation antipsychotics was associated with the largest negative effects on cognition, which were evident in the areas of motor speed and basic information processing ($-0.35 < \beta < -0.5$).
Conclusion: Cognitive function in bipolar disorder varies significantly over time, largely independent of clinical factors. The temporal stability of sustained attention is the exception, suggesting it may represent a possible candidate intermediary phenotype.

B. Arts[1], N. Jabben[1], L. Krabbendam[2], J. van Os[1,3]

[1]Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, the Netherlands, [2]Centre Brain and Learning, Faculty of Psychology and Education, VU University, Amsterdam, the Netherlands and [3]Division of Psychological Medicine, Institute of Psychiatry, London, UK

Key words: cognition; disease characteristics; mood; medication; bipolar disorder

Baer Arts, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, PO Box 616 (KAP2), 6200 MD Maastricht, the Netherlands.
E-mail: b.arts@np.unimaas.nl

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Significant outcomes

- Cognitive function in patients with bipolar disorder varies over time with a modest role for mood and medication.
- Subjective cognitive complaints predict cognitive performance.
- Gene × environment interactions merit further investigation as a cause of cognitive dysfunction in bipolar disorder.

Limitations

- Data reflect a naturalistic study without systematic control for confounding factors.
- Substantial attrition over time occurred.

Introduction

Cognitive dysfunction in patients with bipolar disorder in part may reflect the expression of genetic risk for bipolar disorder (1). Evidence for an association between cognitive dysfunction and genetic liability in healthy twins discordant for bipolar disorder (2), presence of premorbid cognitive alterations in at risk populations (3) and cognitive alterations in children with bipolar

disorder , independent of mood and medication (4), support this hypothesis. Furthermore, there is evidence that certain cognitive dysfunctions are stable over time (5, 6) and persist during euthymia, as shown in several recent meta-analyses (7, 8). To the degree that cognitive alterations reflect genetic risk for the disorder, values outside the control range would also be expected in the unaffected family members of patients with bipolar disorder. Studies using this paradigm display heterogeneous results, suggesting that response inhibition (7, 8) as well as verbal learning and working memory (9) may represent so-called intermediary phenotypes of bipolar disorder. The heterogeneity in results is possibly attributed to multiple familial cognitive risk factors (10) and further illustrated by two recent studies finding comparable cognitive functioning in relatives and controls in one (11), and worse verbal learning in relatives in the other (12). Cognitive dysfunctions in relatives are subtle and not as widespread as in patients with bipolar disorder, suggesting that the greatest part of cognitive dysfunction in patients is associated with disease-related factors (9). Examples of these factors suggested in the literature are number of episodes (13), age of onset (8) and (antipsychotic) medication (8, 14). Another potential moderator of cognition is thyroid function, given the association between bipolar disorder and thyroid dysregulation (15) and the possible negative cognitive effects of thyroid dysfunction (16). Furthermore, the antithyroid effects of lithium (17) may contribute to the cognitive deficits seen in lithium-treated bipolar patients (18).

There are conflicting reports as to whether neurocognitive impairments in patients with bipolar disorder are associated with the subjective cognitive complaints that many patients present with (19, 20). This question is of major importance for longitudinal treatment trajectories, given the fact that changes in subjective cognitive complaints over time may reflect underlying changes in neurocognition. There have been no previous studies attempting to link longitudinal changes in neurocognition with subjective cognitive complaints over time, and how these relate to functioning.

Aims of the study

The aim of the present explorative and naturalistic study was to analyse multiple time point, longitudinal associations between neurocognition on the one hand and disease characteristics, symptoms, global functioning and medication on the other in a cohort of patients with bipolar disorder followed up for 2 years and assessed at two monthly intervals.

Material and methods

Subjects

Individuals were participants in the BIPOLCOG (BIPOLar and COGnition) study (11), a study on cognitive functioning in bipolar disorder (BD) in which three groups were investigated: i) patients with bipolar disorder, ii) healthy first-degree relatives of patients with bipolar disorder, and iii) healthy control participants. All subjects were between the ages of 18 and 60 , fluent in Dutch, had an IQ > 70 and were without a history of neurological disorders such as epilepsy and concussion with loss of consciousness.

Cross-sectional baseline data were reported elsewhere (11); in the current longitudinal study, healthy controls, tested twice at two monthly intervals, were used as reference group only.

Patients with a diagnosis of bipolar spectrum disorder according to DSM-IV (21) were recruited through in-patient and out-patient mental health facilities in South Limburg, and through the local association of bipolar patients and their families. The computer program OPCRIT was used to confirm DSM-IV diagnoses based on current and lifetime recorded symptomatology listed in the Operational Criteria Checklist for Psychotic Illness, scored by the clinical researcher based on all interview and historical case note data (OCCPI) (22).

Control subjects were recruited from the general population using random mailing methodology. Controls were clinically interviewed with The Comprehensive Assessment of Symptoms and History (CASH) (23) to rate OPCRIT criteria, yielding DSM-IV diagnoses, allowing exclusion of those presenting with a diagnosis of BD or psychotic disorder. Healthy controls were additionally interviewed with the FIGS (24) to confirm the absence of a family history of psychotic or bipolar disorder.

The initial sample consisted of 81 patients and 61 healthy control subjects. Three patients were excluded because data on diagnosis were missing. Data on neuropsychological performance were missing for two patients. As a consequence, the risk set for the current study consisted of 76 patients and 61 controls.

There were 57 patients with a diagnosis of bipolar I disorder, 17 patients with a diagnosis of bipolar II disorder and 2 patients were diagnosed with schizoaffective disorder bipolar type. Three

controls had a history of major depression – these were not excluded so as to not bias the findings by selection of 'supernormal' controls.

Procedure

Patients were examined at two monthly intervals over a period of 2 years, yielding a maximum of 12 assessments. At all time points, neuropsychological testing and psychiatric interviewing took place, and questionnaires were completed (regarding social functioning, medication, use of drugs, etc.). Blood samples were collected at each time point to determine mood stabilizer plasma level, TSH and free T4. During the baseline interview, basic demographic information was collected and information on illness characteristics was obtained. Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects. Neuropsychological tests and psychiatric interviews were conducted by trained psychologists, each interview occasion taking approximately 2 h to complete. Recent use of drugs prior to neuropsychological interview was checked by asking the patient at every two monthly visit prior to testing. Recent drug use, assessed this way, was non-existent in our sample.

Psychopathology

At each interview occasion, current depressive and manic psychopathology was assessed using the 21-item Hamilton Rating Scale for Depression (25) and the Young Mania Rating Scale (26) respectively. To assess the domains of psychopathology at the time of testing, the extended Brief Psychiatric Rating Scale (BPRS-E) (27) was administered by the clinical investigator. This scale assesses a wider range of current psychopathology, including symptoms of depression, mania, psychosis, anxiety and withdrawal in the past 2 weeks.

Presence of a history of positive psychotic symptoms in patients based on current and lifetime recorded symptomatology as listed in the OCCPI (22) was used to define a measure of psychotic symptoms at baseline. Information was obtained from patient interviews and case notes. Subjective mood was assessed by the self-report version of the Life-Chart (LCM) (28). Psychosocial functioning was assessed using the Global Assessment of Functioning scale (GAF) (21).

Subjective cognitive complaints

Patients' subjective cognitive complaints were measured using the Cognitive Failure Questionnaire (CFQ) (29), higher scores indicating less cognitive failures.

Neurocognitive assessment

Neurocognitive tests were administered by computer, using E-prime for Windows on a 15-inch monitor Toshiba Tecra laptop. The test battery included tasks measuring various neurocognitive domains, guided by previous evidence of impaired performance in these domains in patients with bipolar disorder (7, 8).

Overall intellectual functioning was estimated at baseline using three Groningen Intelligence Test (GIT) subtests (Mental Rotation, Word Analogies and Mental Arithmetic) (30), yielding results that are comparable with those of the Wechsler Adult Intelligence Scale III (31).

Verbal learning and memory was assessed with the standardized Dutch version of the Visual Verbal Learning Test (32). In three consecutive trials, 15 monosyllabic non-related words had to be memorized and reproduced. The total number of words recalled over the three trials was used as a measure of immediate recall. Delayed recall was measured after a 20-min delay. Parallel versions of this test were used to avoid test–retest effects.

Sustained attention was measured with a continuous performance test, the CPT-HQ version, a variant of the CPT-AX. Subjects were instructed to respond as quickly as possible by pressing the spacebar of the PC keyboard whenever target stimulus 'Q' was preceded by an 'H' on the screen. In the CPT-HQ, 300 stimuli (i.e. letters) were presented in a randomized sequence at a rate of one per second. Each letter was presented for 150 ms, after which an empty screen was presented for 850 ms. Presentation of an H-Q target-pair had a probability of 0.18 ($n = 28$) among the 150 sequential letter-pairs. In a similar number of sequential letter-pairs, the letter Q was presented following another letter than H (I, L, J or T). In another 28 pairs, the letter H was presented followed by another letter than Q (I, L, J or T). Outcome measures were expressed as the proportion correct detections and the reaction time of correct detections (33, 34).

The Flanker CPT (Cogtest plc, London, UK) (35) is a measure of selective visual control of attention. Subjects are instructed to respond by pressing the right or left mouse button depending on whether the middle element in a display of five lines has an arrowhead pointing to the right or left. There are three trial types: i) neutral trials in which the flankers are just horizontal lines without arrowheads, ii) congruent trials in which all

flankers have an arrowhead pointing in the same direction as the target and iii) incongruent trials, in which flankers are pointing in the opposite direction from the target. The incongruent condition involves more cognitive effort, because the flankers are associated with a response that needs to be suppressed (measure of response inhibition). One-half of the trials were presented with the stimuli above the fixation cross and the other half were presented below fixation to prevent the subjects from keeping their gaze fixed in one position. The test consisted of 144 trials of neutral, congruent and incongruent flankers, which were presented randomly. Outcome measures were the mean reaction time for correct responses (RT) and the sum of correct trials in each condition.

The Tapping Speed test (Cogtest plc) is a finger tapping test alternating between the right and left hand, used as a simple measure of motor speed and manual dexterity. The Cogtest version is similar to the Finger Tapping Test or the Finger Oscillation Test of the Halstead Reitan Neuropsychological Battery (36). Subjects were asked to tap a key on the keyboard with their index finger as fast as they could for 8 s in five trials for each hand. Outcome measures were the total number of taps with the index finger of each hand and the latency to each and every response, generating an index of the variance in tapping speed.

Finally, Digit Span Forward and Digit Span Backward of the Wechsler intelligence Scale III (37) were used as measures of attention and working memory respectively.

All 14 cognitive measures were standardized, higher scores reflecting better performance. The 14 cognitive measures reflect the following higher-order cognitive domains: verbal learning (immediate recall Visual Verbal Learning Test), verbal memory (delayed recall Visual Verbal learning Test), sustained attention (Continuous Performance Test), basic information processing (neutral and congruent condition of Flanker CPT), selective attention and response inhibition (incongruent condition of Flanker CPT), motor speed (Tapping Speed Test), attentional span (Digit Span, forward condition) and working memory (Digit Span, backward condition).

Statistical analyses

Regression analyses were carried out using the statistical software program STATA (38) (version 10.1). The Simes modification of the Bonferroni correction for multiple testing (39) was applied, given the large number of statistical tests ($n = 476$), yielding a corrected P-value for significance of $P < 0.014$.

Data were hierarchical with multiple observations (interview occasion or time; level 1) clustered within subjects (level 2). Unless stated otherwise, data were analysed using the STATA XTREG multilevel random regression routine with time as a random factor.

Standardized beta scores (β) are reported. To assess whether multiple time point associations between predictor variables and neurocognition varied over time, interactions with interview occasion were fitted for variables significantly associated with neurocognition in the multilevel random regression models.

TSH had a high proportion of missing values. Under the assumption that data generally are missing at random (40), meaning that missingness is probabilistic and thus can be predicted by variables observed, missing values can be imputed using multiple imputation (41). Thus, for TSH, 20 data sets were imputed using the ICE routine (42) in STATA. This increased the (maximum) number of observations from 463 to 530.

Multiple time point associations between cognition and time-varying and fixed exposures. Multiple time point associations between cognition on the one hand and time-varying as well as fixed demographic, psychopathology, medication, global functioning and illness-related factors on the other were assessed in two stages in the multilevel random regression models. In the first stage, the effect of groups of variables was assessed by comparing models with and without the group in question by likelihood ratio test (STATA LRTEST routine). This strategy tests the broad hypothesis whether certain types of variables (medication, psychopathology) impact on cognition. In the second stage, the separate effect of specific variables within these groups was assessed.

The analyses of the effects of medication and psychopathology were *a priori* adjusted for the possible confounding effects of demographic (age, sex, education) and disease characteristics (number of episodes, alcohol use) by entering them into the equations. In addition, effects of medication on cognitive functions were tested adjusting *a priori* for the possible confounding effect of symptoms (BPRS) in all cases, and for thyroid function in the case of lithium. Dummies were constructed for all medication variables with value 1 for using a certain type of medication and value 0 for not using this medication.

Finally, the specific effects of thyroid function (TSH) and subjective mood (LCM), both were not

included in the models described previously, owing to the large number of missing data (TSH) and the small number of observations (LCM), were determined separately.

Variability of cognitive measures over time. To assess variability of cognitive measures over time, time was modelled as the $k-1$ dummy variables of the number of interview occasions (i.e. maximum of 11 dummies for individuals with 12 interviews) and assessed using a Wald test with 11 degrees of freedom, testing that the parameters of all dummies equalled zero using the STATA TEST command. The effect of time, thus tested, reflects both practice effects (i.e. new learning) associated with repeated administration of neurocognitive tests and remaining variation in cognition associated with changes in medication and mental state over time. To quantify new learning, time was modelled as a linear variable, the β thus reflecting the summary change in cognition with each subsequent follow-up.

Can variability over time be reduced to clinical and other variables? To assess to what degree variability over time could be reduced to the effects of demographics (age, sex, education), psychopathology (BPRS, HDRS, YMRS, CFQ, psychotic symptoms in past), medication [lithium, second-generation antipsychotics, anticonvulsants, antidepressants, benzodiazepines, polypharmacy (0 for using no medication, 1 for using one type of medication and 2 for using two or more different types of medication)], global functioning (GAF) and illness-related factors (number of episodes, age first onset, units alcohol use in last 2 months), the previously described analysis of variability over time, testing that the parameters of all dummies of time equalled zero, was compared between models without other independent variables and models with variable groups representing demographics, mood, medication, global functioning and other clinical factors.

Directional changes over time: cognitive improvement and cognitive deterioration. To assess the rate of significant improvement and deterioration of cognitive function over time, the rate of 0.5 SD improvement, compared with baseline (hereafter: cognitive improvement) or 0.5 SD deterioration, compared with baseline (hereafter: cognitive deterioration) was calculated using survival analysis in multiple-record-per-subject survival data. Although cognitive improvement partly will reflect non-declarative learning, the rate of such non-declarative learning will also be subject to variation between persons (i.e. one person will have more or less increases over time than another) that may in part be attributable to, for example, illness characteristics or changes in mood and medication.

Predictors of cognitive improvement and cognitive deterioration. To assess the impact of selected time-varying as well as fixed variables on rate of cognitive improvement and cognitive deterioration over time as defined earlier, Cox proportional hazard models were fitted to multiple-record-per-subject survival data, yielding measures of relative risk (hazard ratio; HR). Exposure variables selected for these analyses were those with significant main effects in the multiple time point analyses using multilevel random regression as earlier. Kaplan–Meier survivor functions were graphed for key findings.

Impact on functioning. To prospectively assess the impact of cognitive measures on functioning, the rate of 1.0 SD deterioration in functioning, compared with baseline, was calculated using survival analysis and modelled with Cox proportional hazard models as described previously.

Results

Demographic data, disease characteristics, medication, symptom scores and neurocognitive test results are presented in Table 1.

Patients with bipolar disorder were adequately frequency matched with healthy controls, moderately ill and relatively asymptomatic.

Attrition

The study started with 76 patients with bipolar disorder at baseline; 23 patients had left the study after the second interview occasion. Of the 53 remaining patients, 14 dropped out over the 2-year follow-up, with 39 patients remaining at interview occasion 12.

Patients staying longer in the study did not perform better on any of the cognitive measures, with the exception of basic information processing (correct number of neutral flankers in the Flanker CPT) ($\beta = 0.2$; P: 0.008). At baseline, there was only a single significant difference in sustained attention between patients who dropped out and patients who remained, patients remaining in the study performing faster ($\beta = 0.27$; P: 0.007). These data suggest that there was little in terms of selective attrition.

Group differences

Patients with bipolar disorder performed worse on all tasks, significantly so ($P < 0.014$) for five of the

Table 1. Demographics, symptom scores and neurocognitive test results at baseline

	Patients with bipolar disorder(n = 76)		Controls (n = 61)	
	Mean	SD	Mean	SD
Gender M/F	35/41		23/38	
Age range	27–60		25–56	
Age	44.7	7.9	45.3	8.7
Educational level	5.5	2.2	5.8	1.7
GIT_IQ	113.2	11.8	119.7	9.5
Age first episode	27.7	8.8		
Illness duration	6.1	5.2		
Number of episodes	8.5	6.1		
Number of hospitalizations	2.3	2.3		
Medication (cases)				
Lithium	29			
Anticonvulsants	25			
Antipsychotics	21			
Antidepressants	14			
Benzodiazepines	10			
Polypharmacy	34			
Medication (blood level)				
Lithium	0.76	0.23		
Valproic acid	76.7	14.5		
Carbamazepine	9.0			
Lamotrigine	2.7	1.5		
TSH	1.8	0.9		
BPRS	34.8	6.6	26.0	1.8
HDRS	4.0	4.3	1.1	1.6
YMRS	1.6	2.4	0.4	0.7
Verbal learning and memory				
Immediate recall	23.0	5.3	26.0	4.5
Delayed recall	7.1	2.9	8.6	2.5
Sustained attention				
% correct detections	0.95	0.07	0.99	0.02
RT correct detections	482.1	95.5	473.1	78.0
Information processing				
Correct-neutral	43.1	6.1	44.9	4.0
Correct-congruent	43.2	6.4	45.7	3.3
RT-neutral	673.4	89.1	647.2	65.1
RT-congruent	673.5	87.0	644.2	55.8
Selective attention				
Correct-incongruent	38.8	8.8	42.1	5.1
RT-incongruent	725.1	83.9	706.3	64.6
Motor speed				
Rate	187.0	36.3	180.8	22.2
Hits	272.2	44.3	278.1	34.1
Attentional span				
Forward condition	8.5	1.9	9.0	1.9
Working memory				
Backward condition	5.7	1.9	6.6	1.9

seven cognitive domains, using controls as a reference group (Table 2). Effect sizes were small, with a maximum of −0.36 for sustained attention, and even smaller differences in verbal learning and memory, basic information processing, selective attention and working memory.

Multiple time point associations with (groups of) time-varying and fixed exposures

The main effects of groups of variables on cognitive domains are presented in Table 3.

Table 2 Associations between group status (BD) and neurocognition (controls as reference)

	Patients with bipolar disorder	
	β*	P
Verbal learning and memory		
Immediate recall	−0.22	**0.002**
Delayed recall	−0.23	**0.004**
Sustained attention		
% correct detections	−0.36	**0**
RT correct detections	−0.05	0.55
Information processing		
Correct-neutral	−0.2	0.035
Correct-congruent	−0.26	**0.005**
RT-neutral	−0.18	0.045
RT-congruent	−0.21	0.017
Selective attention		
Correct-incongruent	−0.23	**0.006**
RT-incongruent	−0.13	0.14
Motor speed		
Rate	−0.13	0.16
Hits	−0.1	0.29
Attentional span		
Forward condition	−0.13	0.13
Working memory		
Backward condition	−0.23	**0.003**

*β standardized beta scores.
All analyses adjusted for age, sex and education.
For all cognitive variables: higher values indicate better performance.
Bold value indicate significant levels $P < 0.014$.

Contribution of demographic variables. When introduced simultaneously as a group, demographic variables had a significant effect on verbal learning and memory ($0.0026 < P < 0.0004$), sustained attention (percentage correct detections; $P = 0.0009$), basic information processing ($0.0052 < P < 0.0001$), selective attention ($0.0085 < P < 0.0001$) and attentional span ($P = 0.0097$). In healthy controls, this group of variables had a significant effect on verbal learning only ($P = 0.0004$).

Testing the contribution of individual variables revealed that *Age* overall displayed small negative effects, but a significant effect was apparent only for basic information processing (correct response condition), with effect sizes between −0.35 and −0.38 ($P = 0.001$), and for selective attention ($\beta = -0.4$; $P = 0.000$). *Sex* displayed no significant effects. Higher *Education* had a significant positive effect on verbal learning ($\beta = 0.26$; $P = 0.002$), sustained attention (percentage correct detections: $\beta = 0.25$; $P < 0.0001$), basic information processing ($0.25 < \beta < 0.28$; $0.008 < P < 0.004$), selective attention ($\beta = 0.26$; $P = 0.007$), attentional span ($\beta = 0.28$; $P = 0.003$) and working memory ($\beta = 0.22$; $P = 0.013$).

Contribution of disease characteristics. Tested as a group, the only significant main effects were on

Table 3. Effect of demographics, disease characteristics, psychopathology, medication and global function on cognition

	No. of observations	Demographics*		Disease characteristics		Psychopathology		Medication		Global function	
		χ^2 (df)	*P*	χ^2 (df)	*P*	χ^2 (df)	*P*	χ^2 (df)	*P*	χ^2 (df)	*P*
Verbal learning and memory											
Immediate recall	545	18.1 (3)	**0.0004**	12.5 (3)	**0.0057**	29.1 (5)	**0.0000**	2.8 (6)	0.8325	3.5 (1)	0.0601
Delayed recall	545	14.2 (3)	**0.0026**	13.1 (3)	**0.0043**	14.3 (5)	0.0140	5.8 (6)	0.4412	6.4 (1)	**0.0117**
Sustained attention											
% correct detections	548	16.5 (3)	**0.0009**	3.2 (3)	0.3695	11.8 (5)	0.0384	6.6 (6)	0.3600	0.1 (1)	0.7551
RT correct detections	548	0.5 (3)	0.9224	1.2 (3)	0.7457	10.9 (5)	0.0529	12.3 (6)	0.0560	1.1 (1)	0.3032
Information processing											
Correct-neutral	500	30.5 (3)	**0.0000**	1.8 (3)	0.6181	8.9 (5)	0.1095	2.2 (6)	0.9029	0.2 (1)	0.6632
Correct-congruent	500	26.6 (3)	**0.0000**	0.4 (3)	0.9414	10.5 (5)	0.0620	3.6 (6)	0.7278	6.1 (1)	**0.0136**
RT-neutral	500	14.1 (3)	**0.0028**	3.8 (3)	0.2875	10.9 (5)	0.0527	14.9 (6)	0.0214	1.2 (1)	0.2844
RT-congruent	500	12.8 (3)	**0.0052**	3.3 (3)	0.3503	13.0 (5)	0.0234	15.3 (6)	0.0182	0.6 (1)	0.4543
Selective attention											
Correct-incongruent	500	33.4 (3)	**0.0000**	0.1 (3)	0.9897	8.8 (5)	0.1188	4.1 (6)	0.6627	0.5 (1)	0.5009
RT-incongruent	500	11.7 (3)	**0.0085**	5.8 (3)	0.1215	12.4 (5)	0.0301	14.2 (6)	0.0279	0.6 (1)	0.4245
Motor speed											
Rate	485	6.6 (3)	0.0861	1.3 (3)	0.7283	24.3 (5)	**0.0002**	20.3 (6)	**0.0024**	0.5 (1)	0.4779
Hits	485	7.0 (3)	0.0715	1.2 (3)	0.7470	23.8 (5)	**0.0002**	15.1 (6)	0.0198	1.4 (1)	0.2359
Attentional span											
Forward condition	544	11.4 (3)	**0.0097**	7.6 (3)	0.0548	11.9 (5)	0.0356	5.5 (6)	0.4824	0.1 (1)	0.8072
Working memory											
Backward condition	544	5.3 (3)	0.1504	10.9 (3)	**0.0124**	14.6 (5)	**0.0123**	5.8 (60)	0.4432	0.1 (1)	0.8042

*Demographics: age, sex, education.

Disease characteristics: number of episodes, age of onset, alcohol use.

Psychopathology: BPRS, HDRS, YMRS, psychotic symptoms.

Medication: lithium, anticonvulsants, antipsychotics, antidepressants, benzodiazepines, polypharmacy.

Global function: GAF.

Bold value indicate significant levels $P < 0.014$.

verbal learning and memory ($0.0057 < P < 0.0043$) and working memory ($P = 0.0124$).

Testing the contribution of individual variables revealed that a higher *Number of episodes* influenced working memory negatively ($\beta = -0.3$; $P = 0.002$). Later *Age of onset* had a significant negative effect on verbal learning and memory, with an effect size between −0.3 and −0.34 ($0.005 < P < 0.002$). *Alcohol* use in the last 2 months had no significant effects on any of the cognitive variables.

Contribution of psychopathology variables. Tested as a group, psychopathology variables had significant effects on verbal learning ($P < 0.0001$), motor speed ($P = 0.0002$) and working memory ($P = 0.0123$).

In healthy controls, symptoms (BPRS, CFQ) influenced only basic information processing (number correct; $P = 0.009$) and selective attention (number correct; $P = 0.0026$).

Testing the contribution of individual variables revealed that higher *BPRS* score had small negative effects on all the cognitive domains with significant effects on verbal learning and memory ($-0.11 < \beta < -0.16$; $0.002 < P < 0.0001$), basic information processing (correct response: $\beta = -0.19$; $P = 0$), selective attention ($\beta = -0.12$; $P = 0$) and motor speed ($-0.11 < \beta < -0.12$; $0.003 < P < 0.002$). Higher *HDRS* scores impacted negatively on verbal learning (β; −0.13; $P < 0.0001$), motor speed ($-0.11 < \beta < -0.13$; $0.001 < P < 0.0001$) and basic information processing (correct response, congruent condition; $\beta = -0.19$; $P < 0.0001$). *YMRS* scores were not associated with cognitive measures. *Psychotic symptoms* in the past had no significant effect on cognitive functioning. Higher CFQ scores negatively influenced all the cognitive domains, with effect sizes between −0.14 and −0.24 ($0.011 < P < 0.0001$), with the largest effects on selective attention and verbal learning.

Contribution of medication variables. Tested as a group, as shown in Table 3, effects of medication variables were significant only for motor speed (tapping rate; $P = 0.0002$).

Testing individual medications revealed that *Lithium* was used by 33 patients at any given moment during the study (number of observations: 314). The use of lithium was not associated with significant effects on cognitive functioning. Lithium use at baseline displayed a significant positive association with motor speed (tapping rate; $\beta = 0.6$; $P = 0.013$), and longer duration of lithium use

was also positively associated with motor speed ($0.19 < \beta < 0.24$; $0.003 < P < 0.0001$). Negative effects of lithium were found for use in the last 2 months before interview occasion on basic information processing (reaction time; $-0.32 < \beta < -0.37$; $0.019 < P < 0.005$). *Anticonvulsants* were used by 36 patients with a total number of observations of 255. The use of these medications was not associated with any significant effect on cognitive measures. *Second-generation antipsychotics* were taken by 24 patients (number of observations: 93). Their use had a significant negative effect on motor speed ($-0.36 < \beta < -0.5$; $0.003 < P < 0.0001$) and basic information processing (reaction time, congruent condition; $\beta = -0.35$; $P = 0.011$). *Antidepressants* were used by 21 patients with bipolar disorder in our study with a total number of observations of 140. No associations with cognitive measures were observed. *Benzodiazepines* were taken by only 16 patients (number of observations: 80). No associations with cognition were apparent. *Polypharmacy* was observed in 48 patients (number of observations: 250). It was negatively associated with motor speed ($-0.18 < \beta < -0.21$; $P = 0.0001$).

Associations with global functioning. In the analyses testing effects of groups of variables, associations between cognitive measures and GAF score are shown in Table 3 and concern verbal memory ($P = 0.0117$) and basic information processing (number correct, congruent condition; $P = 0.0136$). Tested as individual variable, higher *GAF* scores were positively associated with verbal learning and memory ($\beta = 0.16$; $P = 0.001$), basic information processing (number correct; $0.15 < \beta < 0.25$; $0.02 < P < 0.0001$) and motor speed ($0.13 < \beta < 0.14$; $0.017 < P < 0.011$).

Thyroid function. For partly imputed TSH values, effect sizes were small but significant for basic information processing ($\beta = -0.2$; $P = 0$), selective attention ($-0.13 < \beta < -0.17$; $0.004 < P < 0.001$) and motor speed ($-0.11 < \beta < -0.13$; $0.011 < P < 0.004$).

Life-charts. A varying number of patients, between 17 and 29, had reliable life-chart data on subjective mood over the period 7 days before the interview, yielding a varying number of observations (between 215 and 261) for depressive mood and between 62 and 78 for (hypo-)manic symptoms.

Life-chart depressive mood had a significant negative effect on motor speed ($-0.31 < \beta < -0.42$; $P < 0.0001$). Life-chart manic symptoms negatively impacted on basic information processing (reaction time; $\beta = -0.27$; $P = 0.001$) and selective attention (number correct; $\beta = -0.24$; $P = 0.003$).

Interactions with interview occasion. For the previously reported effects, there were no significant interactions with interview occasion, except for symptomatology (HDRS) in the motor speed task (tapping rate; $\beta = 0.13$; $P = 0.01$). This interaction indicated decreased effects of HDRS on cognition at later interview occasions. Of note was the fact that associations between CFQ and neurocognition were constant over time, as indicated by non-significant interactions with interview occasion.

Variability of cognitive measures over time and new learning

Analysis of variability over time, testing that the parameters of all dummies of time equalled zero, revealed effects of time that were large and highly significant for most of the cognitive domains (five of seven), with the exception of sustained attention and motor performance (Table 4).

Inspection of the parameters for the dummy variables indicated increasingly better cognitive performance over time from baseline to the end of the study for most of the variables, suggestive of new learning. Follow-up modelling of time as a linear variable quantified new learning effects in five of seven cognitive domains (verbal learning and memory, basic information processing, selective attention, attentional span and working memory). Sustained attention and tapping showed no improvement over time; selective attention displayed the largest increases ($\beta = 0.37$).

Can variability of cognitive measures over time be reduced to other factors?

Introducing groups of independent variables (demographics, psychopathology, medication, GAF, illness-related factors) in the model generally did not or only minimally impact on the effect of time (testing that the parameters of all dummies of time equalled zero) (Table 4), indicating that most of the variance over time was related to other factors.

Directional changes over time

The rate of cognitive improvement and cognitive deterioration was high for all cognitive domains. The mean monthly rate of cognitive improvement was around 5% and around 3% for cognitive deterioration. The 2-year cumulative incidence rate

Table 4. Variability of cognitive measures over time

	No. of observations	Time		Time*	
		χ^2 (df)	*P*	χ^2 (df)	*P*
Verbal learning and memory					
Immediate recall	545	**161.4 (11)**	**0.0000**	130.4 (11)	**0.0000**
Delayed recall	545	**140.1 (11)**	**0.0000**	119.8 (11)	**0.0000**
Sustained attention					
% correct detections	548	**18.2 (11)**	0.0767	19.7 (11)	0.0502
RT correct detections	548	**9.7 (11)**	0.5564	10.6 (11)	0.4805
Information processing					
Correct-neutral	500	**78.9 (11)**	**0.0000**	61.0 (11)	**0.0000**
Correct-congruent	500	**100.3 (11)**	**0.0000**	64.6 (11)	**0.0000**
RT-neutral	500	**155.8 (11)**	**0.0000**	140.5 (11)	**0.0000**
RT-congruent	500	**140.7 (11)**	**0.0000**	129.4 (11)	**0.0000**
Selective attention					
Correct-incongruent	500	**72.9 (11)**	**0.0000**	58.9 (11)	**0.0000**
RT-incongruent	500	**175.9 (11)**	**0.0000**	164.8 (11)	**0.0000**
Motor speed					
Rate	485	**14.4 (11)**	0.2100	12.7 (11)	0.3162
Hits	485	**16.4 (11)**	0.1267	14.6 (11)	0.2021
Attentional span					
Forward condition	544	**45.4 (11)**	**0.0000**	33.7 (11)	**0.0004**
Working memory					
Backward condition	544	**120.7 (11)**	**0.0000**	106.1 (11)	**0.0000**

Time: Effect of time without any of the other groups of independent variables included in the model.
*Time: Effect of time with all of the other groups of independent variables included in the model.
Bold value indicate significant levels $P < 0.014$.

of cognitive improvement was 48% and around 31% for cognitive deterioration, i.e. a net improvement over time for all cognitive domains, with the exception of sustained attention (net decrement of 5%).

Of the variables signalling associations in the multiple time point analyses, lithium use positively predicted cognitive improvement in verbal learning (HR = 2.3; $P = 0.009$) and negatively predicted cognitive deterioration in verbal memory (HR = 0.4; $P = 0.036$), although the latter was just below the set significance level. The first effect is illustrated in Fig. 1.

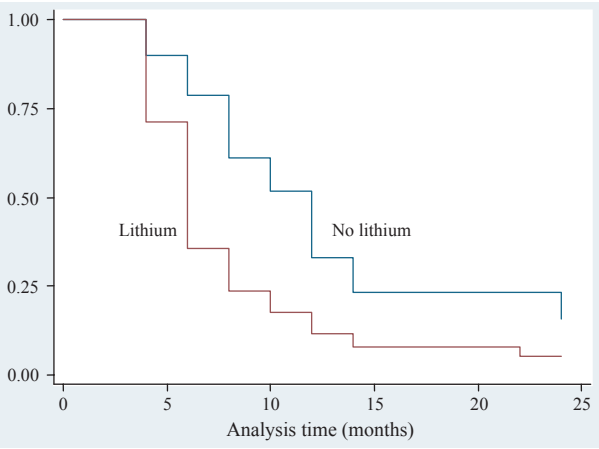

Fig. 1. Kaplan–Meier survival estimates of the effect of lithium time to cognitive improvement in verbal learning.

Higher CFQ scores negatively impacted on cognitive improvement in the area of basic information processing (HR = 0.37, $P = 0.005$) and in the area of selective attention (HR = 0.47, $P = 0.003$). Higher BPRS scores predicted cognitive deterioration in verbal learning (HR = 5.9: $P = 0.008$).

Prediction of functioning

Cox proportional hazard models of deterioration of functioning, corrected for age, sex and education, revealed protective effects for 11 of 14 cognitive variables that were statistically significant for higher verbal learning (HR = 0.42, $P = 0.009$), higher verbal memory (HR = 0.38, $P = 0.010$) and higher sustained attention (HR = 0.42, $P = 0.001$). A similar protective effect size was apparent for better subjective cognition measured with the CFQ, albeit below the corrected significance level (HR = 0.42, $P = 0.036$).

Discussion

Summary of findings

Patients with bipolar disorder displayed small impairments in the cognitive domains studied, with the largest significant effect size for sustained attention. Smaller effect sizes were found for verbal learning and memory, basic information process-

ing, selective attention and working memory with no significant differences for motor speed and attentional span. Cognitive impairment co-varied with subjective cognitive complaints and both predicted deterioration in functioning. The effects of the groups of independent variables studied (demographic and disease characteristics, psychopathology, medication, global function) were generally small and discrete, influencing different cognitive domains in different ways. The largest, but still small, significant effect sizes were found for age on selective attention, for number of episodes on working memory, for age of onset on verbal learning and memory, for subjective depressive mood (life-charts) on motor speed, and, finally, for antipsychotic medication on basic information processing and motor speed.

Cognitive functioning improved over time, particularly selective attention. Most likely, this improvement through practice reflected non-declarative learning (i.e. via implicit processes), although performance on some other tasks may also have benefitted from explicit formulating of more efficient strategies (i.e. declarative learning) (43). Sustained attention and motor speed showed no improvement, and cognitive performance also deteriorated at some stage during the follow-up in more than a third of the sample. Time explained most of the variance in the observed cognitive areas, with the exception of sustained attention and motor speed.

Directional changes in improvement and deterioration over time was considerable for verbal learning and memory and attentional span. Lithium use, symptoms and subjective cognitive complaints influenced this variability in several ways, especially in the case of verbal learning and memory as well as basic information processing.

Effects of time

Given observed practice effects for most of the cognitive domains studied, non-declarative learning may, at least in part, be intact in patients with bipolar disorder, in line with a number of previous studies (44, 45). A dissociation between declarative and non-declarative learning has been described for other disorders as well and is in accordance with different brain networks underlying both forms of memory (43). However, we did not formally test whether the practice effects were based on non-declarative processes, and, in addition, high rates of cognitive deterioration and other sources of variation over time were apparent. The true rate of non-declarative learning, therefore, may be approximated by considering the difference between the 50% cumulative rate of 2-year cognitive improvement vs. the 30% cumulative rate of cognitive deterioration. The difference between these two percentages reflects the bias towards cognitive improvement induced by repeated exposure to cognitive tasks. Regardless of whether non-declarative or declarative processes form the basis for this effect, the results clearly show that there is room for cognitive improvement in bipolar disorder, a finding that has hitherto not been exploited (44, 45).

The findings of widespread variability are in contrast to the sparse literature on the longitudinal course of cognitive functioning in bipolar disorder in three studies with repeated measurement after 2, 3 and 6 years, respectively, which revealed stability over time for, respectively, executive functioning and processing speed (46), fluency, verbal memory, Stroop-interference tasks (5) and verbal memory (47). The current study, with more frequent assessments, yielded a much more detailed and heterogeneous picture. Of note was the fact that a range of disease and treatment variables failed to have a large impact on variation of cognition over time, suggesting that unknown person-specific factors explain such longitudinal variation.

Subjective and objective measures of cognition

The CFQ reliably assesses multiple dimensions of cognitive failures (48) and is weakly associated with neuroticism, but more strongly with psychopathology (29). In the current study, CFQ was associated, in a stable fashion, with cognitive functioning in all domains in the multiple time point analyses, in contrast to earlier work (19). An association between subjective complaints and cognitive dysfunctions was reported, however, in another study (20). Number of episodes and mood symptoms influenced subjective cognitive complaints negatively and subjective cognitive complaints predicted deterioration in functioning with a similar effect size as measures of neurocognition. Medication did not impact on cognitive complaints in their study (20). However, *post-hoc* analysis in our sample yielded significant negative associations between medication (lithium and anticonvulsants) and subjective cognitive complaints.

The results therefore suggest that in bipolar disorder, subjective cognitive complaints correspond, in part, to objective measures of neurocognition. This observation may be important, as it would allow for a sensitive clinical assessment of variation over time and the impact of changes in medication, mood and other time-varying vari-

ables. The findings also suggest that subjective cognitive complaints may be relevant predicting the outcome of rehabilitation efforts, particularly in the area of work.

Also of note was the fact not only that CFQ was associated with current cognitive assessment in the multiple time point analyses but also that CFQ negatively predicted future cognitive improvement in the areas of basic information processing and selective attention. This suggests that the apparent negative interference with current cognition of CFQ also indexes a longer-term vulnerability interfering with new learning.

Intermediary cognition phenotypes in bipolar disorder

In the current sample of patients with bipolar disorder, sustained attention was the most stable cognitive function over the 2-year period. Thus, sustained attention may be a candidate intermediary phenotype for bipolar disorder. In a recent meta-analysis on cognitive intermediary phenotypes in bipolar disorder, it was concluded that response inhibition deficit is the most prominent intermediary phenotype, as well as sustained attention (8). This corresponds to the finding that attention (in general), as an early cognitive process, represents the most stable deficit in patients with bipolar disorder over time, while later cognitive processes, such as verbal learning and memory, may be subject to greater levels of variation (49). A similar tendency for greater level of variation over time was found in the current study for verbal learning and attentional span; these cognitive domains may thus be more related to the clinical expression of bipolar disorder (8, 46). A recent study challenges the position of response inhibition deficit as a candidate intermediary phenotype by finding intact inhibitory control in first-degree relatives of patients with bipolar disorder (50). Furthermore, sustained attention deficits, independent of working memory, have been reported in euthymic bipolar patients and described as a reduced inherent capacity, which remained apparent in a study of patients not taking medication (51). Another study found that only sustained attention deficit survived controlling for mild affective symptoms, suggesting that sustained attention indeed represents a vulnerability marker for bipolar disorder (52). Finally, sustained attention may be considered as an endophenotype of the illness (53).

Factors impacting on cognition

Disease characteristics. In our study, *number of episodes* had a negative effect on all cognitive domains but only significantly influenced working memory. This is in line with the literature on its negative effects on various cognitive domains, like verbal memory and response inhibition (13, 54).

Later *age of onset* had a significant negative effect on verbal learning and memory. Cognitive dysfunction in bipolar patients with late onset has been described earlier (55, 56); however, both positive and negative associations between (early) age of onset and cognitive functions have also been reported (57).

Post-hoc analysis did not reveal any significant effects of *length of illness* and *number of hospitalizations*, which correspond to equivocal findings in the literature (13, 58). In general, the direction of causality of these associations cannot be determined. In this respect, there is an interesting possibility that bipolar patients with neurocognitive impairments are more prone to a severe and recurrent form of illness (57).

Alcohol use during the last 2 months did not significantly influence cognitive functioning, in contrast to the finding of worse executive functioning in bipolar patients with alcohol dependence in the past (58). A likely factor explaining the difference was that use of alcohol was moderate in the current sample.

Psychopathology. Overall, the effects of symptoms were rather small, perhaps owing to the subclinical level of psychopathology in our study. *Post-hoc* analysis revealed no evidence for a non-linear relationship between mood symptoms and cognition.

Furthermore, the tasks used in our study may not be specific or 'warm' enough to find effects of (subclinical) symptoms on cognitive dysfunction (59). This is illustrated by a study, finding only differences between unmedicated depressed bipolar patients and controls on specific tasks regarding reward processing and sensitivity to negative feedback, and no differences on conventional, 'cold' tests (60).

A remarkable finding, however, is the relatively large effects of subjective mood, as measured by the life-chart, on motor speed and selective attention. The importance of (residual) mood symptoms on cognitive functioning in patients with bipolar disorder is emphasized by others (52). Finally, *psychotic symptoms* did not impact on cognitive functions, with the remarkable exception of a near significant positive effect on verbal memory ($\beta = 0.4$; $P = 0.024$). Interestingly, another study found a positive association between schizotypal personality scores and visual memory performance in patients with bipolar disorder (61). Negative

effects of psychotic symptoms on cognition are described in the literature (61, 62), as well as absence of any effect (63). Others, however, found better cognitive performance in first-degree relatives of bipolar patients with (positive) psychotic symptoms, indicative of a relative protective effect of the absence of liability to neurodevelopmental impairment (11).

Medication. Overall, the effects of medication were small and different for the various cognitive domains studied. This is in accordance with the equivocal, sparse literature in this area (64), showing deficits in affective processing (65), attention (51, 66) and memory (56, 67) in medicated bipolar patients. Neurocognitive performance in drug-free and medicated euthymic bipolar patients was studied (67). The only significant difference was on delayed verbal recall, drug-free patients performing better. This difference became non-significant, however, after controlling for residual mood symptoms, and effect sizes were modest (67, 68).

Lithium had positive and negative effects on cognitive functioning, which corresponds to the ongoing discussion in the literature on the neuroprotective vs. neurotoxic effects of this drug (69). Negative (short-term) effects of lithium, in the current study on processing speed, are described in the literature regarding verbal memory, speed of processing and executive functioning (14, 70, 71). Long-term use of lithium, in the current study, was positively associated with motor speed. Long-term positive effects of lithium are illustrated by several studies (46, 47, 72). Furthermore, lithium may induce neuroplastic changes in amygdala and hippocampus, by increasing grey matter volume of these core regions of emotional and cognitive processing (73).

Anticonvulsants were not associated with any significant effect on cognitive functioning. This is in accordance with the literature, showing none, or only modestly negative, effects of valproic acid (65, 74, 75), and none, or only positive, effects on cognition of lamotrigine (76, 77).

Antipsychotics had the most prominent negative effects on cognition. In several studies, this negative association is described in patients with bipolar disorder (14, 71, 78). Euthymic bipolar patients with and without use of antipsychotics were studied, finding no differences between patients without antipsychotics and healthy controls on any neuropsychological measure, whereas a significant underperformance was apparent in the domains of verbal learning and executive functioning in the group using antipsychotics (71).

It has been suggested that second-generation antipsychotics may improve cognitive functioning in the treatment of schizophrenia (79, 80). These cognitive improvements may be (partly) attributed to non-declarative learning in the sense of practice effects (81). Another interesting hypothesis, however, is that the effect of antipsychotics depends on hyperdopaminergia in selected brain areas, causing beneficial effects in hyperdopaminergic states, as in schizophrenia, and inducing suboptimal cognitive functioning in bipolar patients without such increased dopaminergic alterations (71).

Polypharmacy was negatively associated with motor speed in our study, comparable with another study (20). On the other hand, better working memory performance has been observed in bipolar patients on combination treatment, compared with monotherapy (82).

Thyroid function. Elevated TSH values, possibly indicating (sub)clinical hypothyroidism, had only very small negative effects on some of the investigated cognitive domains. This could be due in part to a threshold effect, the levels of TSH in our sample being too low to influence cognition in a significant way. The hypothesis that the antithyroid effects of lithium may contribute to the cognitive deficits of lithium-treated bipolar patients could not be confirmed (18).

Associations with global functioning

Cognitive measures were positively associated with *GAF* scores and survival analyses indicated better neurocognition, and indeed less subjective cognitive complaints, protected against deterioration in functioning, particularly verbal learning and memory and sustained attention. Several studies are in agreement with these results, describing negative effects on functional outcome of deficits in verbal memory, attention and executive functioning in patients with bipolar disorder (83, 84). Negative effects of (subclinical) mood symptoms on daily functioning are illustrated in another study (85). In the current study, *post-hoc* analysis revealed negative associations between functional outcome on the one hand and psychopathology and use of antipsychotic medication on the other. Finally, impairment in theory of mind (86) may be important as well in daily functioning.

Methodological considerations

The prospective repeated measures design, increasing power and making it possible to disentangle the differential effects of various independent variables

on (change in) cognitive functioning, is a strong point of this naturalistic study. The large number of observations in the repeated measures design increases reliability of significant, albeit small, effects, decreasing the risk of type I errors. In our opinion, we adequately controlled for confounding variables and for multiple tests of significance. Furthermore, the naturalistic character of our study in a heterogeneous group of patients increases the external validity of our findings.

A drawback of our study is the loss of almost half of the patients over the 2- year follow-up for unknown reasons; selective attrition, however, was shown to be unlikely. Furthermore, partly owing to the naturalistic character of our study, we did not control for other factors possibly influencing cognitive functioning, like medical and psychiatric comorbidity, somatic (anticholinergic) medication, past drug use, traumatic events in the past, motivational factors and intrusive thoughts. Our sample of bipolar spectrum patients was moderately ill, which, perhaps, plays a role in the small effect sizes found. Finally, the tests we used may be too 'cold' to detect effects of (subclinical) mood and medication on cognitive functioning (57, 59, 60, 87). The proportion of bipolar patients with cognitive impairments can vary substantially dependent on the particular task employed (57).

In conclusion, Cognitive functioning in patients with bipolar disorder is likely the result of the dynamic interplay of multiple factors, in which a variable genetic vulnerability is influenced by various external, possibly interacting, unknown factors with a modest role for mood and medication. Several cognitive domains are influenced differently by these factors, with sustained attention as a possible candidate intermediary phenotype and verbal memory and selective attention being more related to the clinical expression of bipolar disorder. Multiple time point measures of subjective mood symptoms and subjective cognitive complaints predict cognitive performance in a stable fashion over time. As cognitive performance in turn is associated with functioning in daily life, these data suggest that subjective complaints have relevance for the potential of societal participation in patients with bipolar illness. Cognitive functioning changes and, sometimes, improves over time, which gives opportunities for cognitive rehabilitation (88).

The results of our study agree with a model of neuropsychological dysfunction in patients with bipolar disorder, which describes the emotional and cognitive abnormalities of the disorder as the product of durable functional alterations of dynamic neural, fronto-striatal networks involved in mood and cognition with a potential role for residual symptomatology and long-term medication (89).

This model indicates the importance of gene × environment interactions in the causation of cognitive dysfunctions in patients with bipolar disorder. An illustrative example of this interaction is the positive effect of antipsychotics on working memory only in patients with schizophrenia homozygous for the COMT (108/158) met allele (90). Similar interactions between medication and gene polymorphisms may apply to patients with bipolar disorder (91). Candidate genes, in this respect, are LIS1 (92), DISC1 (93), DAOA (94), AKT1 (95), GSK3b (96), BCL-2/BAG-1 (97), COMT (98) and BDNF (99).

In our view, further research in this direction may be interesting and relevant, as illustrated by studies of the effects of lithium and valproic acid on BDNF (100).

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