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Long-term course of cognitive functioning in bipolar disorder: A ten-year follow-up study

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Abstract

Introduction: Cognitive impairments are common in bipolar disorder (BD), but the long-term course remains understudied. Longitudinal data on cognitive functioning from the start of the first treatment could help clarify pathophysiological processes that shape the illness outcome. We here aim to investigate the 10-year cognitive course in BD compared to healthy controls (HC) and the effects of clinical symptoms on cognitive trajectories.

Methods: Fifty-six BD participants recruited within their first year of treatment and 108 HC completed clinical and cognitive assessments at baseline and 10-year follow-up. We derived eight cognitive domain scores and a cognitive composite score, which were further investigated using linear mixed model analyses. Correlation analyses were used to assess associations between the composite score and depressive, manic and psychotic symptoms.

Results: BD participants performed poorer than HCs in all domains except mental speed and verbal fluency. Verbal learning and memory, verbal fluency and the composite score improved over time in both BD participants and HC, while short-term memory, mental speed, psychomotor speed and working memory were stable. We found no significant correlations between cognition and symptom level at either time point in BD participants.

Conclusions: We found evidence of long-term cognitive stability or improvement in BD participants from first treatment to 10-year follow-up. Though the BD group was impaired in all domains except mental speed and verbal fluency, the change in cognitive functioning was parallel to that of HCs. These findings are not consistent with the notion of neuroprogression in BD.

KEYWORDS
bipolar disorder, cognition, cognitive function, longitudinal studies, long-term effects

1 | INTRODUCTION

Bipolar disorder (BD) is a severe mental disorder with recurrent episodes of (hypo)mania and depression. It was initially perceived as an episodic illness with relatively minor inter-episode cognitive impairments.[1] However, cognitive impairments are also evident in euthymia and substantially impact functional outcome.[2] It is well-documented that certain cognitive domains are particularly impacted in BD, notably attention, processing speed, memory and executive functioning.[3] Impairments in processing speed have even been suggested as a possible endophenotype for BD.[4] There are no apparent signs of marked premorbid cognitive deficits in BD[5] as seen in schizophrenia, but cognition appears to be impaired at illness onset.[6]

It remains unclear whether the observed impairments are neurodevelopmental, develop around the first illness episode with subsequent stability or increase over time due to neuroprogressive processes.[7] According to the latter hypothesis, cognitive decline would be observed, resulting from illness-related brain changes, which are exacerbated as the illness progresses. The notion of potential neuroprogression is currently debated.[8,9] Cross-sectional studies link more severe cognitive impairments to more severe clinical illness, and findings from neuroimaging and neurophysiological studies have lent some support to the neuroprogression hypothesis. Models have posited neurosensitization and stress-related as well as illness-related, accumulated damage to neuronal networks.[10,11] At the present time, though, longitudinal neuroimaging and neurophysiological studies are lacking. Moreover, cross-sectional studies show better cognitive performance in first-treatment samples than in chronic samples, consistent with cumulative negative effects of further illness episodes on cognition.[12]

However, these findings could also result from selection bias as chronic samples could be enriched for more clinically ill and cognitively compromised patients.[13] To resolve ambiguities regarding the course of cognitive functioning in BD, there is a need for longitudinal studies following a representative group of participants from the start of their first treatment. Half of the patients with BD have a depressive presenting polarity, and some patients may also experience short manic or hypomanic episodes without seeking treatment. A manic episode that brings the patient in contact with mental health services is the first time it is possible to identify the disorder as BD. Accordingly, first-treatment samples are recruited as early as achievable and likely to consist of individuals within the entire range of clinical outcomes. The findings of studies on such samples will have implications for our understanding of the psychopathological processes involved in shaping the post-onset cognitive trajectory of BD.

However, the relatively few existing longitudinal studies of cognitive functioning in BD have primarily included multi-episode patients. The follow-up periods are relatively short, with only a few studies reporting on longer-term follow-up data up to 9 years and often without healthy control (HC) samples. These studies have provided little evidence of overall progressive cognitive decline.[14,15] On the contrary, two meta-analyses of multi-episode participants report stability in most functions and evidence of gains in verbal and visual memory and working memory.[15,16] A recent meta-analysis of longitudinal studies with a follow-up period of 5 years or more, also found evidence of cognitive stability.[17] Some long-term follow-up studies have, however, found indications of decline. One study with a mean follow-up of 6.5 years found indices of deterioration for a subgroup with marked IQ deficits at baseline,[18] and a 9-year follow-up study of attention and executive functioning found signs of deterioration in executive functioning.[19]

Studies of cognitive trajectories in representative first-treatment bipolar samples are rare. Some long-term studies of cognition in first-episode psychosis comprise a proportion of patients with psychotic affective/BD but either include only psychotic BD and/or do not report specific findings for BD.[20,21] A meta-analysis that identified six longitudinal studies of recent-onset BD (i.e. with less than 2 years of treatment) with a maximum follow-up period of 2 years, mainly reported stability as well as improvements in verbal memory.[15] However, apparent stability in the early phases of treatment does not rule out cognitive deterioration in the longer term. The only longitudinal study of cognition in first-treatment mania with a longer follow-up period than 1 year found favourable cognitive outcomes during the first year of the 3-year follow-up.[22] To our knowledge, no studies have reported the long-term course of cognitive functioning in first-treatment BD.

Notably, both normal developmental factors and illness-specific factors should be considered in the investigation of long-term cognitive trajectories in BD. Cognitive functions do not develop in concert. In point of fact, recent re-analysis of the 10-year AESOP first-episode study reports case–control differences in specific cognitive domains at specific ages, finding increasing group differences with increasing age for two measures of verbal abilities. Younger participants in the clinical sample performed better than controls, with evident deficits only in patients that were over the age of 30. Deficits for verbal learning and memory, psychomotor processing speed, cognitive control and category fluency appeared static across participants of different ages. This study underlines the need for HC groups to investigate deviations from expected age-related changes. Further, group-level analyses may mask significant inter-individual differences in the degree and extent of impairment. The fluctuations in symptoms that characterize BD raise additional challenges since both depressive, manic and psychotic symptoms have been linked to cognitive performance.[12,19,23] Consequently, studies of cognitive trajectories in BD need to account for the effect of symptom levels.

This study's overall aim is thus to investigate the long-term course of cognitive functioning in first-treatment BD, including a HC group and structured assessments of clinical symptoms. The present study reports data from a representative group of participants with psychotic and non-psychotic BD recruited in their first year of treatment and followed up after 7–10 years. Randomly drawn HC from the same geographical area were also included. A comprehensive neuropsychological battery was used to measure cognition at both time points. Our first aim was to investigate the 10-year course of cognitive functioning in BD compared to HC, both in global cognition and on the domain level. Our second aim was to examine

associations between clinical symptoms and cognitive performance and change in the BD group. Symptom load, especially depressive symptomatology, was expected to negatively impact cognitive performance and improvement in symptom levels were expected to be associated with improvement in cognition.

2 | MATERIALS AND METHODS

2.1 | Participants

This study is part of the prospective study of first-treatment patients in the Thematically Organized Psychosis (TOP) study. Patients were recruited from outpatient and inpatient departments at hospitals in the larger Oslo area and Innlandet Hospital within the first 12 months after starting their first adequate treatment for a manic episode (i.e. receiving a therapeutic dose of antipsychotic medication or mood stabilizers). A representative sample of HCs was also recruited from the same areas of Oslo based on statistical records. Baseline assessments ran consecutively from 2005 to 2012 and follow-up assessments from 2015 to 2021. The overall mean time to follow-up was 9.78 (SD = 1.63) years for the whole sample, 10.32 (SD = 0.84) for Oslo and 7.08 (SD = 0.33) for Innlandet Hospital.

Inclusion criteria for the patient group were a DSM-IV diagnosis of Bipolar I, no previous adequate treatment, an estimated IQ >70, adequate Norwegian language proficiency for neuropsychological testing and no history of clinically significant brain injury or neurological disorder. Additional exclusion criteria for the HCs were a history of severe mental illness or severe mental illness in close relatives. A total of 115 participants diagnosed with BD type 1, and 121 HC, were eligible for the study at baseline. A total of 56 BD participants and 108 HC investigated at baseline participated in cognitive assessments at follow-up, 10 HC were here excluded due to having been treated for psychiatric disorders during the follow-up period and three were excluded due to acquired brain injury. Participant flow in the BD and HC groups is shown in Figure 1. The overall retention rate of the BD sample was 55%, calculated excluding participants who died during follow-up but including participants that moved out of the area or abroad. The prevalence of psychosis (lifetime) in the BD group was 73%.

There were no significant differences between study completers and non-completers in clinical characteristics, IQ or baseline cognition and no considerable differences in cognitive variability (Tables S2 and S3). One-year data were available for a subset ($N = 21$) of the BD sample, and change scores from baseline to follow-up did not significantly differ between completers and non-completers. Running *t*-tests to compare the change scores of individuals recruited in Oslo (10-year follow-up) and Innlandet hospital (SIHF, 7-year follow-up) found no significant differences except for short-term memory where the participants at SIHF had poorer performance at follow-up (−1.01), while the participants in Oslo had improved (0.22), $t = 4.63$, $p < 0.001$.

2.2 | Clinical assessment

Clinical psychologists and medical doctors that had completed a training course to achieve inter-rater reliability administered the

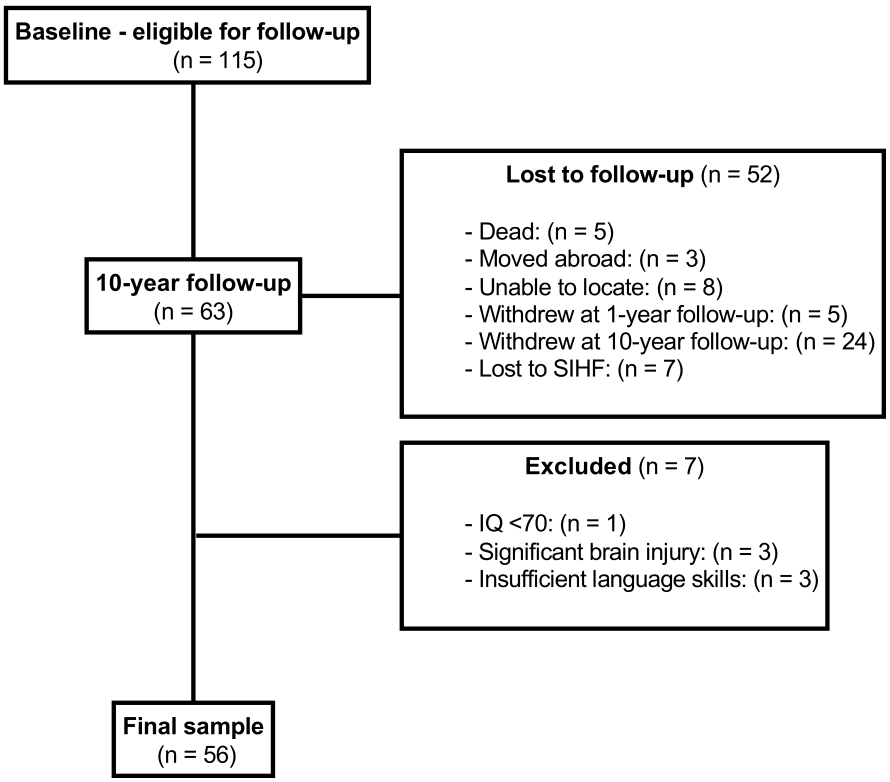

FIGURE 1 Participant flow in the BD group. Bipolar participants lost to follow-up, excluded and included. BD, bipolar disorder; SIHF, sample recruited at Innlandet Hospital.

SCID-1 for DSM-IV[24] and reviewed medical records to arrive at baseline diagnoses. Diagnostic assessments were then discussed in consensus meetings with experienced specialists in clinical psychology and psychiatry. Depressive symptoms were assessed using the Inventory of Depressive Symptomatology—Clinician rating (IDS-C),[25] the Young Mania Rating Scale (YMRS)[26] was used to measure symptoms of mania, and the Positive and Negative Syndrome Scale (PANSS)[27] was used to measure psychotic symptoms. PANSS scores are reported using the Wallwork five-factor model.[28] General symptom level and functioning were measured with the Global Functioning Scale (GFS), split version, GFS-S and GFS-F.[29] The Alcohol Use Disorders Identification Test (AUDIT) and Drug Use Disorders Identification Test (DUDIT) were used to measure alcohol and substance use. The use of antipsychotics, antidepressants and mood stabilizers (lithium and antiepileptics) was measured as equivalent daily doses at baseline and follow-up.

2.3 | Cognitive assessment

Clinical psychologists and trained personnel administered neuropsychological testing of the BD group and HCs, respectively. Testers were trained and supervised by a neuropsychologist and calibrated on measures of premorbid IQ and verbal abilities (vocabulary and similarities) to verify inter-rater reliability. To reduce the effect of tiredness on test performance, assessments typically started at 9 am. Participants were screened for recent substance use on the day of assessment.

The test battery used for both baseline and follow-up assessment consisted of the California Verbal Learning Test (CVLT-II),[30] logical memory from the WMS (LM),[31] color-word interference test (CWIT) and verbal fluency (VF) from the D-KEFS,[32] and digit span, letter-number sequencing and digit-symbol coding from the WAIS.[33] Premorbid IQ was estimated using the Norwegian version of the National Adult Reading Test (NART).[34] Current IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI).[35]

This extensive neuropsychological battery enabled us to tease apart domain-level effects of cognitive change. When feasible, subtest scores tapping similar cognitive functions were combined to increase reliability. However, the choice was made to divide processing speed measures into two domains, mental- and psychomotor processing speed, as psychomotor speed specifically has been proposed as an endophenotype in BD.[36] Raw cognitive scores were converted to *z*-scores centred on baseline HC scores. Domain scores were calculated from mean *z*-scores. The following theory-based cognitive domains were constructed:

1. Verbal learning: CVLT-II list A total recall, LM sum trial 1(immediate recall).
2. Verbal memory: CVLT-II long-delay free recall, LM sum trial 2 (delayed recall).
3. Short-term memory: Digit span.
4. Psychomotor processing speed: Digit-symbol coding.
5. Mental processing speed: CWIT Color naming and reading.
6. Working memory: Letter-number sequencing.
7. Verbal fluency: VF FAS, Categories and Switching.
8. Cognitive control: CWIT interference and switching.

To obtain a measure of global cognition, a cognitive composite score was calculated, as the mean of all domain scores.

2.4 | Statistical analyses

TSD (services for sensitive data) facilities, developed and operated by the IT Department (USIT) at the University of Oslo, were used for data storage and analysis. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 27. The ggplot2, dplyr and Raincloudplots packages were used to create Raincloudplots in RStudio version 1.3.1093.[37–40]

We used linear mixed models to analyse group-level changes in each domain and the composite score. As scores were not age-corrected, age was entered as a covariate. Models with random slopes did not converge, but a random intercept was included in the model, with a covariance structure set as identity. Estimates were based on maximum likelihood. The formula for the group model was:

$$Y_{ij} = (\beta_1 + b_{1j}) + \beta_2 \times \text{time} + \beta_3 \times \text{group} + \beta_4 \times \text{age} + \beta_5 \times \text{time} \times \text{group} + \beta_6 \times \text{time} \times \text{age} + e_{ij}.$$

Where Y_{ij} is the domain score for person $i = 1...164$ at year $j = 0$, 10, β signifies fixed effects, b signifies random effects, and e is the error term. Alpha was set to 0.05 two-sided, and we applied Holm-Bonferroni correction for multiple comparisons, as the model was run for all domains and for the cognitive composite score.

Spearman's rho correlation analyses were used to assess the association between the PANSS positive, IDS-C and YMRS scores and the cognitive composite score to evaluate the possible effect of psychotic, depressive and manic symptomatology on cognitive functioning at either time point. Additionally, change scores from symptom measures and the cognitive composite were used to investigate associations between symptom level and cognitive course. Scatter plots were used to identify significant outliers, and the analyses were repeated after their removal.

3 | RESULTS

Demographic and clinical characteristics are presented in Table 1. There were no significant differences in age or gender between the two groups, but the HC sample had significantly more years of education than the BD sample. Baseline mood scores ranged from 0 to 28 on YMRS and 0 to 50 on IDS-C, indicating a high degree of variation in symptom levels for both manic and depressive polarities. At follow-up, BD participants had significantly improved on depressive and manic symptoms, as well as on global symptom level

and functioning. There was no difference between PANSS positive scores at baseline and follow-up.

BD participants had significantly poorer performance than HCs on all domains except mental processing speed and verbal fluency, as well as on the cognitive composite score ($p<0.01$), with scores approximately 0.5 SD below the HC across domains at both time points. Improvements were found in verbal learning and memory, verbal fluency and the composite score in both groups, with no time×group interactions. Stability for both groups was found for short-term memory, psychomotor processing speed, mental processing speed, working memory and cognitive control. All estimates from mixed model analyses are shown in Table 2. Means and standard deviations of domain scores and the cognitive composite score are shown in Table S1.

The statistical effect of age indicated poorer performance with increasing age in psychomotor processing speed and a time*age interaction for verbal fluency showing decreases in gains as baseline age increased in both groups. Estimated marginal means from the models are shown in Figure 2.

Figure 3 illustrates inter-individual variability in cognitive trajectories and differences in variability between the BD group and HCs. Visual inspection indicates higher variability in the level of cognition in BD participants compared to HCs. A high degree of heterogeneity in the cognitive course was also apparent in the Raincloudplots.

No significant correlations were found between symptom measures and the cognitive composite score at baseline. At follow-up, the cognitive composite score was statistically significantly correlated with the IDS-C score ($r_s=-0.294$, $p=0.045$), but not with YMRS or PANSS positive (psychosis) scores. After visual inspection of scatterplots to identify outliers, one outlier was removed, and the correlation was not significant after this. Correlations between change scores for PANSS positive, YMRS and IDS-C and for the cognitive composite did not show any significant effects. See Table 3 for all correlation coefficients.

Post-hoc correlation analyses with Spearman's rho correlation coefficients showed a dose-dependent relationship between the amount of antipsychotic medication and the cognitive composite score at baseline: $r_s=-0.374$, $p<0.006$, but no associations with the level of antidepressants, antiepileptics or lithium. After visual inspection to identify outliers, one outlier with high antipsychotic dosage and low cognitive performance was identified, and the correlation was no longer significant after this. There were no significant correlations between medication dosages at follow-up and no statistically significant associations between medication dosages

TABLE 1 Demographics and clinical characteristics.

			Group comparisons	
Mean (SD)	**Bipolar ($N=56$)**	**HC ($N=108$)**	**t/χ^2**	***p*-value**
Demographics				
Age	30.05 (9.57)	30.92 (7.42)	0.71	ns
Gender M (%)	25 (43.1)	61 (57.5)	3.10	ns
Education	13.38 (2.26)	14.29 (2.13)	−2.65	0.009
Premorbid IQ	111.79 (7.59)	113.46 (5.98)	1.43	ns
Baseline IQ	108.09 (12.84)	114.90 (8.57)	3.80	0.001
Follow-up IQ	113.08 (10.97)	117.82 (8.96)	2.97	0.003
Clinical characteristics	**Baseline**	**Follow-up**		
GFS-S	54.41 (13.51)	66.27 (13.54)	−5.85	<0.001
GFS-F	50.52 (13.41)	67.66 (17.12)	−7.00	<0.001
PANSS positive	6.39 (3.50)	5.38 (2.40)	1.99	ns
YMRS	4.55 (5.92)	2.35 (3.07)	2.22	0.031
IDS-C	16.27 (11.08)	8.80 (10.39)	4.00	<0.001
AUDIT	9.25 (7.11)	4.86 (4.82)	3.58	0.001
DUDIT	2.46 (6.81)	0.76 (3.49)	1.30	ns
Antipsychotic use %	61.7	31.7		
Antidepressant use %	33.3	10.0		
Antiepileptic use %	31.7	30.0		
Lithium use *n* %	18.3	20.0		
Duration of illness	3.55 (6.49)			

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test, use of antipsychotics, antidepressants, antiepileptics and lithium: equivalent daily doses, duration of illness: years since onset of mania; GFS-F, Global Functioning Scale-functioning; GFS-S Global Functioning Scale-symptoms; IDS-C, Inventory of Depressive Symptomatology-Clinician rating; NART, National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale, positive score according to the Wallwork five-factor model; YMRS, Young Mania Rating Scale; WASI, Wechsler Abbreviated Intelligence Scale.

Note: Baseline and follow-up IQ is WASI full-scale IQ, Premorbid IQ is derived from the NART.

TABLE 2 Estimates from mixed model analyses.

Domain	Parameter	Estimate	SE	*t*	*p*-Value	95% CI	
						Lower	Upper
Verbal learning	Intercept	1.06	0.28	3.79	0.000	0.51	1.62
	Time	1.02	0.22	−4.56	0.000	0.58	1.46
	Group	−0.56	0.15	−3.62	0.000	−0.86	−0.25
	Age	−0.02	0.01	−2.29	0.023	−0.04	0.00
	Time × group	−0.23	0.12	1.83	0.069	−0.47	0.02
	Time × age	−0.02	0.01	2.70	0.008	−0.03	0.00
Verbal memory	Intercept	1.24	0.29	4.22	0.000	0.66	1.81
	Time	0.80	0.23	−3.50	0.001	0.35	1.25
	Group	−0.58	0.16	−3.66	0.000	−0.90	−0.27
	Age	−0.03	0.01	−3.16	0.002	−0.05	−0.01
	Time × group	−0.22	0.13	1.73	0.086	−0.47	0.03
	Time × age	−0.01	0.01	2.07	0.040	−0.03	0.00
Short-term memory	Intercept	0.32	0.35	0.93	0.354	−0.36	1.01
	Time	0.04	0.28	−0.15	0.877	−0.51	0.60
	Group	−0.71	0.19	−3.73	0.000	−1.08	−0.33
	Age	0.00	0.01	−0.24	0.808	−0.02	0.02
	Time × group	−0.26	0.16	1.64	0.104	−0.56	0.05
	Time × age	−0.01	0.01	−0.66	0.513	−0.01	0.02
Psychomotor speed	Intercept	1.44	0.33	4.39	0.000	0.79	2.08
	Time	0.75	0.25	−3.04	0.003	0.26	1.23
	Group	−0.87	0.18	−4.88	0.000	−1.21	−0.52
	Age	−0.04	0.01	−3.98	0.000	−0.06	−0.02
	Time × group	−0.16	0.14	1.19	0.237	−0.43	0.11
	Time × age	−0.02	0.01	2.37	0.019	−0.03	0.00
Mental speed	Intercept	0.44	0.30	1.45	0.149	−0.16	1.03
	Time	0.35	0.22	−1.61	0.109	−0.08	0.78
	Group	−0.44	0.16	−2.68	0.008	−0.76	−0.12
	Age	−0.01	0.01	−1.48	0.140	−0.03	0.00
	Time × group	−0.02	0.12	−0.15	0.885	−0.22	0.26
	Time × age	−0.01	0.01	1.64	0.103	−0.02	0.00
Working memory	Intercept	0.59	0.31	1.89	0.060	−0.03	1.20
	Time	0.29	0.30	−0.98	0.329	−0.30	0.88
	Group	−0.85	0.17	−4.98	0.000	−1.19	−0.52
	Age	−0.01	0.01	−1.20	0.233	−0.03	0.01
	Time × group	0.02	0.17	−0.12	0.903	−0.31	0.35
	Time × age	−0.00	0.01	0.24	0.813	−0.02	0.02
Verbal fluency	Intercept	1.22	0.30	4.02	0.000	0.62	1.81
	Time	1.12	0.23	−4.83	0.000	0.66	1.58
	Group	−0.44	0.17	−2.68	0.008	−0.77	−0.12
	Age	−0.03	0.01	−3.06	0.003	−0.05	−0.01
	Time × group	−0.01	0.13	0.07	0.946	−0.26	0.25
	Time × age	−0.03	0.01	3.60	0.000	−0.04	−0.01

TABLE 2 (Continued)

Domain	Parameter	Estimate	SE	*t*	*p*-Value	95% CI	
						Lower	Upper
Cognitive control	Intercept	0.91	0.33	2.75	0.006	0.26	1.57
	Time	0.83	0.27	−3.14	0.002	0.31	1.36
	Group	−0.76	0.18	−4.15	0.000	−1.11	−0.40
	Age	−0.02	0.01	−1.81	0.072	−0.04	0.00
	Time × group	−0.10	0.15	0.66	0.508	−0.39	0.19
	Time × age	−0.02	0.01	1.94	0.054	−0.03	0.00
Composite score	Intercept	0.91	0.21	4.29	0.000	0.49	1.33
	Time	0.63	0.13	−4.85	0.000	0.37	0.89
	Group	−0.66	0.12	−5.73	0.000	−0.89	−0.43
	Age	−0.02	0.01	−3.18	0.002	−0.03	−0.01
	Time × group	−0.12	0.07	1.60	0.112	−0.27	0.03
	Time × age	−0.01	0.00	2.97	0.004	−0.02	0.00

Abbreviations: BD, bipolar disorder; HC, Health control.

Note: Model estimates from linear mixed models of each cognitive domain and the composite score comparing participants with BD and HC. Controls are coded as group 1 and BD participants as group 2, with this estimate showing the effect for the BD group.

and cognitive change scores. In our sample, 17 participants discontinued antipsychotics, 12 did not use at either time point, nine used at both time points and three initiated treatment with antipsychotics during follow-up. Comparing the change scores of the cognitive composite, we found no significant differences between those who discontinued antipsychotics and those who did not use at either time point. We did, however, observe a small, nominal difference between the three who started antipsychotic medication during the follow-up (composite change = 0.26) and the 17 who stopped using them (composite change = −0.65). However, the group starting medication was far too small for the findings to be interpreted in any meaningful way or to allow for correction for possible clinical factors that could confound the associations.

4 | DISCUSSION

The main finding of the current study was a pattern of long-term stability or improvements across all cognitive domains in first-treatment BD participants. The performance was poorer than in HC at baseline and follow-up for most domains with no interaction effects. These findings align with previous reports from more chronic BD samples. They do not support the notion of a post-onset progressive cognitive decline.[14,15,17,41,42]

In addition to improvement in the cognitive composite score, there were improvements in verbal learning and memory and verbal fluency. There were no significant interaction effects between group and time, indicating parallel trajectories in BD participants and HCs.

The trajectories are consistent with those expected from normal development. During early to middle adulthood, cognition is expected to be relatively stable, although some decline in processing speed and working memory is expected over time. In contrast, verbal abilities show stability or even increase into late adulthood.[43] In concordance with this, improvements were observed for measures relying on verbal abilities. Meta-analysis of existing long-term studies have mainly found stability in verbal memory, though one study on an euthymic BD sample reported decline.[17] Even so, there are some previous reports of better verbal memory in BD samples with a longer duration of illness.[15,16] Deterioration has also previously been reported in executive functioning, though this has not been replicated in other long-term studies.[17] As this domain is not fully developed until early adulthood, increases might be due to continued maturation as our sample is on average quite young.

No indications of cognitive deterioration were detected, a finding with clear implications for our understanding of the long-term cognitive trajectories of BD. A prevailing hypothesis has been that BD is a progressive disorder with increasing severity of neurobiological indices, clinical symptoms and functional impairment over time.[13] Longitudinal studies of multi-episode samples are not sufficient for addressing the question of neurodegeneration. The observed general longer-term stability in cognitive functioning in these chronic samples could be based on participants already having reached a plateau of cognitive decline at the start of the study and accordingly, further changes are unlikely. The findings from the current study add to the results of recent shorter longitudinal studies of first-treatment and recent-onset patients, challenging the notion of neuroprogression.[44,45] Our results do not suggest to what extent the cognitive disturbances are neurodevelopmental or caused by processes associated with the onset of the disorder. Also, even with a 10-year follow-up, we cannot rule out the possibility of a more prominent age-related cognitive loss in BD in old age.[46] Group-by-time interactions were furthermore found to approach the threshold of significance for verbal learning and memory. This

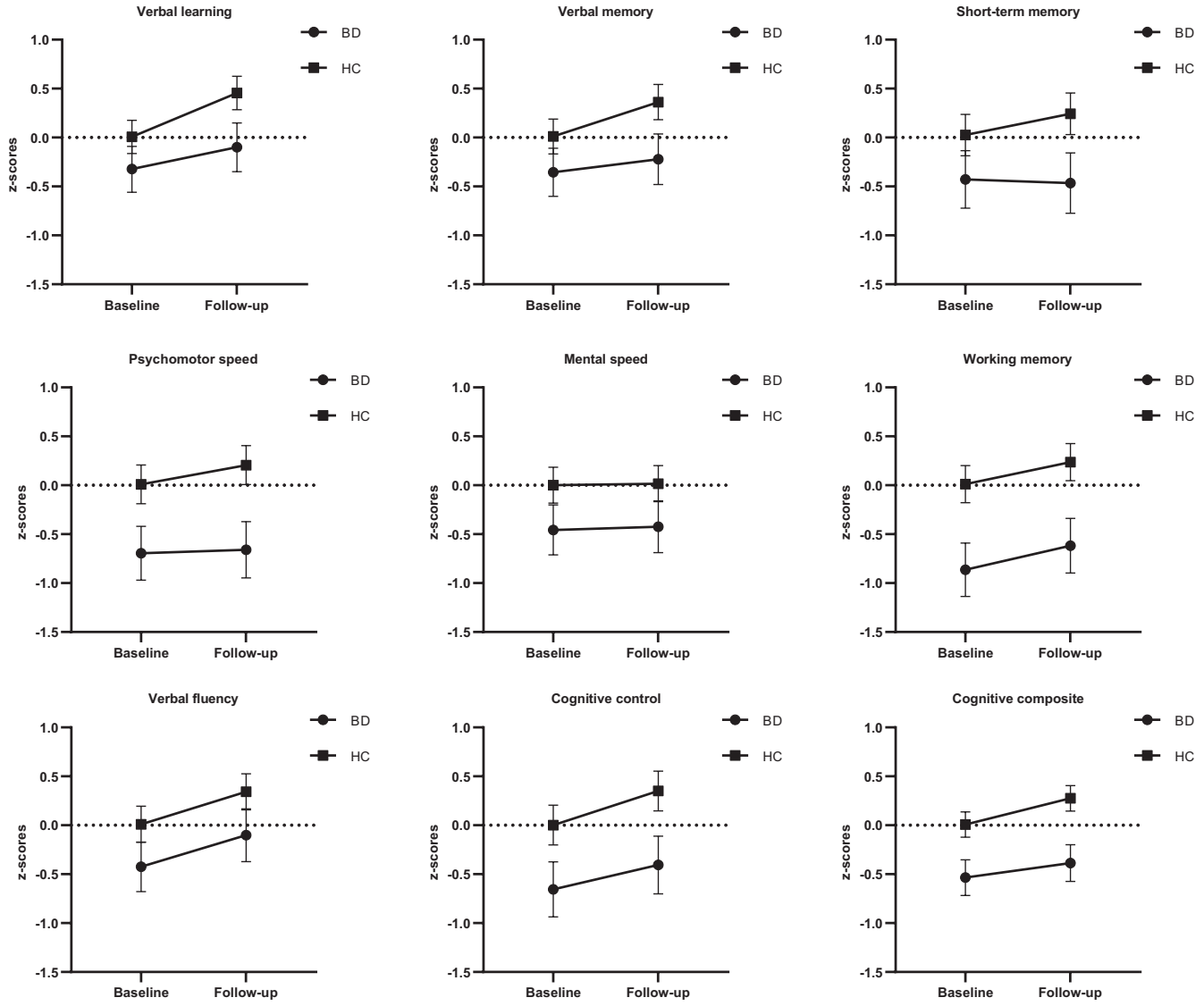

FIGURE 2 Group-level cognitive course. Line graphs showing group-level changes in each domain from baseline to follow-up. Estimated marginal means were evaluated at age ≈ 30.8, error bars show the 95% CI of the estimate. BD, bipolar disorder; HC, healthy controls.

could conceivably indicate a lag relative to HC, which was not detected due to insufficient statistical power. Studies with even longer follow-up and larger samples are accordingly needed to further elucidate cognitive trajectories in BD.

Cross-sectionally, more pronounced group differences in working memory, psychomotor speed, and cognitive control were observed. The latter two are speeded measures, and our findings thus align with the hypothesis that psychomotor speed decrements are a key cognitive deficit in BD.[4,36] We detected no group differences in mental speed, indicating that the psychomotor component of processing speed is specifically impaired. An alternative interpretation is that slow processing disturbs the performance of complex tasks more than simple tasks. Our measure of psychomotor speed, that is symbol coding, requires both speed, psychomotor coordination and working memory capacity. The basic cognitive functions of working memory and psychomotor speed could thus impede performance on more complex tasks.

Raincloudplots were used to visualize individual trajectories and variability in cognition at both time points. The sizeable observed variability in both the level and course of cognition within the BD sample underlines the importance of going beyond case–control mean differences in future studies. Neither manic, depressive, nor psychotic symptom load was, however, found to be associated with cognition. Also, there were no correlations with psychotic symptoms, in contrast to some,[23] but not all previous studies.[47] As clinical factors are shown to influence cognitive trajectories,[48,49] symptom remission could underlie the observed improvements in the BD group, masking an increasing cognitive gap relative to controls. However, no associations between change in symptom level and change in cognitive performance were found, rendering this less likely.

Previous findings on medication effects are also mixed. Most studies of antipsychotics and cognitive function in psychotic disorders, where antipsychotics is the first drug of choice, show minor cognitive effects. Detrimental effects of antipsychotics on

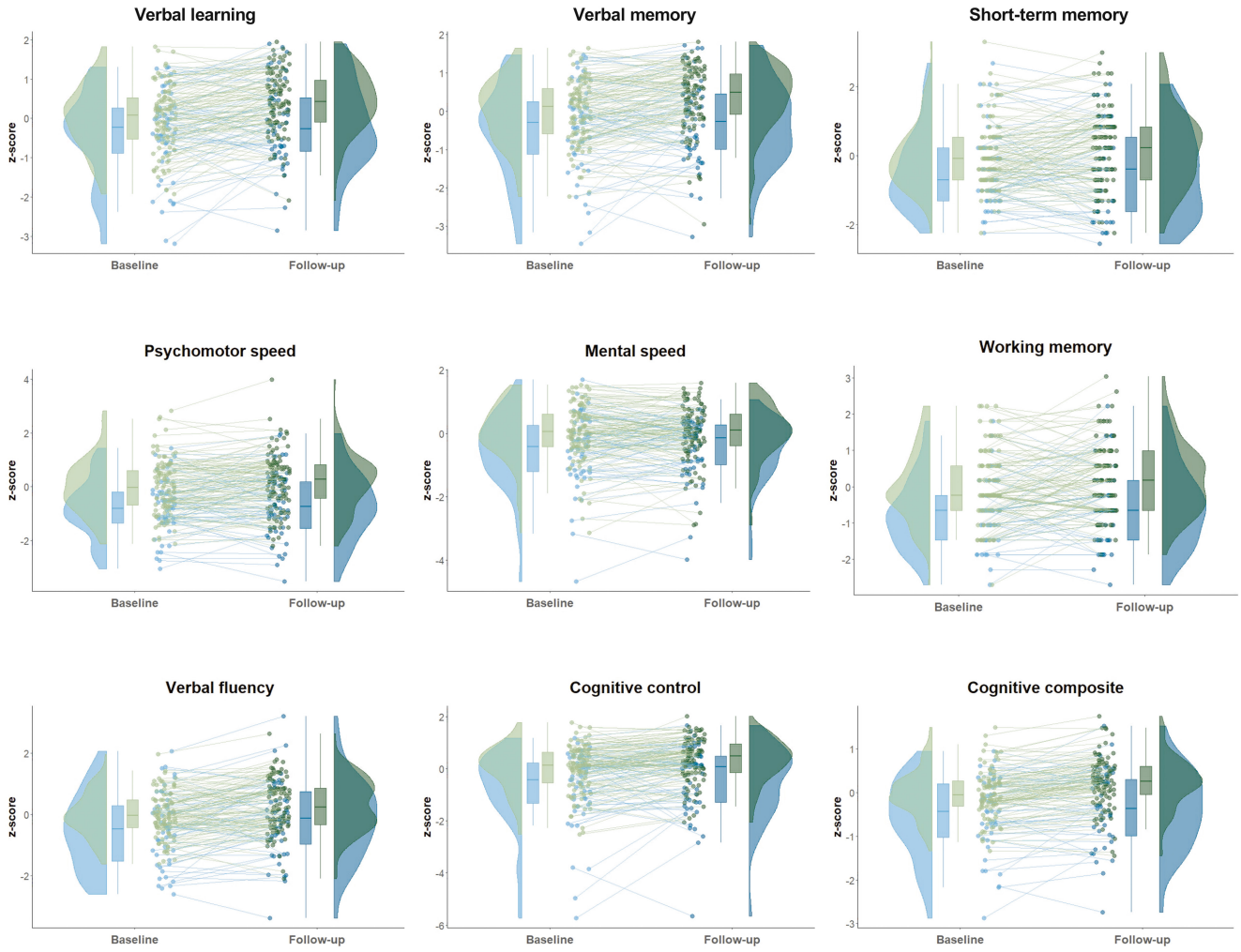

FIGURE 3 Distribution and individual-level cognitive course. Distribution of scores from baseline to follow-up are presented in Raincloudplots, showing dispersion, box plots and individual trajectories. The bipolar group is shown in blue, and healthy controls are shown in green.

cognition have, however, been found, with memory gains after antipsychotic discontinuation.[15] Based on previous reports, lithium may, on the other hand, have beneficial effects on cognitive performance in BD.[50] However, no associations between medication use and cognition were found, barring an effect of antipsychotic dosage and cognitive performance at baseline that appeared to be based on one outlier. Few participants were on antipsychotic medication at follow-up, and few were on lithium at either time point, accordingly, the present study may lack statistical power to detect any effect at this point of time. Nevertheless, the results indicate that medication use was not a confounding variable in our main analyses.

The models did not correct for years of education or IQ. Illness onset in BD is usually during early adulthood and often interrupts educational attainment. Fewer years of education can thus be attributed to the disruptive effect of the illness per se. Looking at estimates of the impact of education on IQ, our group difference was only half of what would be expected from education alone[51] and the impact on basic cognitive functions would be assumed to be even lower.[52] A slightly lower group-level IQ post-onset is also a key feature of the illness. By covarying for educational attainment or IQ, we are, to some extent entering illness-related factors twice and have thus chosen not to correct. Still, IQ and educational level are indicative of cognitive reserve, and this topic could be an interesting avenue for further research on long-term cognitive trajectories.

4.1 | Strengths and limitations

This study presents data from a well-described sample of BD participants and HCs followed over 10 years in the first study of long-term cognitive trajectories in first-treatment BD. Long-term data are rare, but essential to illuminating illness factors as well as cognitive trajectories. Nonetheless, several limitations should be noted.

Considerable attrition in the BD group could have consequences for interpretation and generalizability of findings. Since this study was

TABLE 3 Correlations between symptoms and cognitive composite score.

	Baseline		Follow-up	
	r_s	*p*-Value	r_s	*p*-Value
Cognitive composite				
PANSS positive score	−0.100	0.481	−0.199	0.180
YMRS total score	−0.056	0.695	−0.174	0.243
IDS-C total score	0.117	0.484	−0.262	0.075
Antipsychotics	−0.282	0.077	−0.119	0.424
Antidepressants	−0.109	0.503	−0.031	0.838
Antiepileptics	−0.109	0.504	−0.033	0.825
Lithium	−0.140	0.389	−0.049	0.745
Cognitive composite change- score[a]				
PANSS positive change-score	−0.201	0.209		
YMRS change-score	−0.175	0.273		
IDS-C change-score	−0.132	0.423		

Abbreviations: PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale; IDS-C: Inventory of Depressive Symptomatology-Clinician rating. Medication dosage was measured as equivalent daily dose.

Note: Spearman's rho (r_s) correlations between symptom level and medication dosage and the cognitive composite score at baseline and 10-year follow-up. For correlations with IDS-C scores and antipsychotic dosage, one outlier was removed.

[a]Change scores were calculated subtracting baseline total scores from follow-up total scores.

conducted as part of a larger multi-disciplinary study, it involved an extensive research protocol, which might have contributed to our low retention rate. Retention is, however, at the same level as other long-term follow-up studies, reporting retention rates down to 32%[20,42] this reflects the significant problems with re-engaging this patient group in longitudinal studies. Even so, analyses of differences between completers and non-completers did not show signs of biased attrition.

However, high attrition could also affect statistical power. Mixed models are sensitive to attrition at follow-up, and for this reason, we chose to only include completers in the analyses. Given the possibility of underpowered tests due to reduction in sample size, the risk of false positives was mitigated by correction for multiple comparisons. To maximize power, age was entered as the only covariate and associations with other factors were explored in correlation analyses.

Longitudinal studies on cognition run the risk of conflating true increase in performance with practice effects. Practice effects are evident with short test–retest intervals, but not expected to be substantial in long-term follow-up.[53] One-year data were available for a subset of the BD sample ($N = 21$), and no indications were found of higher increases due to higher exposure to the tests. There were also no indications of better performance for participants recruited from SIHF, who had shorter test–retest intervals.

5 | CONCLUSION

Participants with BD and HCs exhibited parallel cognitive trajectories of either improvement or stability for all cognitive domains over the 10-year follow-up period. Improvements were found in verbal learning and memory, and verbal fluency and stability were found in short-term memory, mental- and psychomotor processing speed and cognitive control. BD participants, however, scored approximately 0.5 SDs below HCs, with the largest deficits in psychomotor speed, working memory and cognitive control. Our findings on the long-term cognitive course in BD extend the current literature and add to the cumulative evidence against the hypothesis of progressive neurodegeneration after illness onset. In closing, the findings provide grounds for optimism regarding the long-term course of cognition. This is of clinical relevance as hope is an important aspect of personal recovery. The observed stable deficits also indicate that individuals with poor cognitive functioning at illness onset may have a less favourable long-term cognitive, and hence functional, outcome. Future research should explore the potential of early interventions, such as cognitive remediation.

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CONFLICT OF INTEREST STATEMENT

We have no competing interests to declare.

DATA AVAILABILITY STATEMENT

The dataset used for the current study is not available to the public due to containing information that could compromise research participants' privacy and consent.

ETHICS STATEMENT

This study is approved by the Regional Ethics Committee of South-Eastern Norway. All participants gave informed consent by signing a written consent form. Consent could be withdrawn at any time.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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