The trajectory of emotional and non-emotional cognitive function in newly diagnosed patients with bipolar disorder and their unaffected relatives: A 16-month follow-up study

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Received 12 August 2022; received in revised form 3 November 2022; accepted 6 November 2022

Abstract
Cognitive impairments are evident in remitted patients with bipolar disorder (BD) and their unaffected relatives (UR) compared to healthy controls (HC). However, the temporal course of cognition, and whether cognition is marked by neuroprogressive changes, remain unclear. In a large prospective study of newly diagnosed patients with BD, we assessed patients with BD (n = 266), UR (n = 105) and HC (n = 190) using an extensive cognitive battery of non-emotional and emotional cognition at baseline and 16-months follow-up. Cognitive change across groups was examined with linear mixed-model analyses. Results showed no evidence of trajectory differences between patients with BD, UR, and HC in neurocognition and emotional cognition (ps≥.10). Patients with BD showed stable impairments in global neurocognitive functioning over time, as well as within the domains of ‘working memory and executive function’ and ‘attention and psychomotor speed’, compared to HC. Patients who relapsed during the follow-up

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https://doi.org/10.1016/j.euroneuro.2022.11.004
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1. Introduction

Bipolar disorder (BD) is a disabling mental illness characterized by recurrent mood episodes of (hypomanic and depression (World Health Organization, 1992). Approximately 50-70% of remitted patients with BD experience cognitive impairments (Green et al., 2020; Miskowiak et al., 2018), which are associated with impaired functioning and poorer illness prognosis (Keramatian et al., 2021; Pascual-Sanchez et al., 2019). Further, BD is often initially misdiagnosed and the average delay in diagnosis is between five and 10 years (Baldessarini et al., 2007; Keramatian et al., 2022). Indeed, traditional, phenotypic-based psychiatry is partially based on descriptive behaviors and there is generally a lack of objective markers to confirm diagnosis, thus hampering patients from receiving correct treatment and early intervention. This points to a need for objective illness biomarkers to inform diagnostic evaluations and predict the course of illness.

Endophenotypes are stable, heritable disease-associated traits that are independent of clinical states and present in unaffected family members relative to the general population (Gottesman and Gould, 2003). Indeed, cross-sectional studies have shown that euthymic patients with BD and their unaffected first-degree relatives (UR) exhibit impairments in both non-emotional and emotional cognition compared to healthy controls (HC) (Kessing and Miskowiak, 2018; Miskowiak et al., 2017b). Specifically, remitted patients with BD and - to a lesser extent - their UR show broad non-emotional neurocognitive impairments spanning the domains of memory, executive functioning, attention, and processing speed, as well as within emotional cognitive domains tapping into facial expression recognition, abnormal reactivity to- and regulation of emotional information, and heightened attentional interference by emotional stimuli (e.g., Bora et al., 2009; Gillissie et al., 2022; Miskowiak et al., 2017b, 2019).

Bipolar disorder has frequently been conceptualized as a progressive illness associated with increased risk of recurrence following mood episodes and worsening of cognitive impairments during the course of the illness (Kessing and Andersen, 2017). This is in line with the staging model of BD, stating that cognitive dysfunction is more pronounced in later stages of the illness as compared to earlier stages (Berk, 2009; Kapczinski et al., 2009). Evidence for neuroprogression in BD has mainly come from cross-sectional studies that link features of illness progression to poorer cognitive function (Cardoso et al., 2015) exempt from studies on the long-term risk of developing dementia (Velosa et al., 2020). Extant longitudinal studies of the cognitive trajectory in BD have generally found limited evidence for neuroprogression with patients’ neurocognitive functioning remaining stable over both short (mean duration 1.5 years) (Bora and Özerdem, 2017) and long (mean duration 5.5 years) (Bora and Özerdem, 2017; Samamé et al., 2022) follow-up periods, even in newly diagnosed and late-life BD patients (Szmulewicz et al., 2020). Longitudinal studies to date are generally hampered by limitations, including (i) small sample sizes (n < 100), (ii) the majority not investigating patients in the early courses of BD, (iii) not including unaffected relatives, and (iv) lacking measures of emotional cognition. Long-term prospective studies of non-emotional and emotional cognitive functions in BD across the various illness stages and in first-degree relatives are thus critically needed to clarify whether BD is marked by ‘neuroprogression’ (Cardoso et al., 2015).

As part of the cross-sectional part of the Bipolar Illness Onset (BIO) study, we previously compared cognitive performance in fully or partially remitted patients with newly diagnosed BD, their UR, and HC at baseline (Kjaerstad et al., 2020). Here, we found that patients with BD exhibit broad neurocognitive impairments, as well as reduced emotional reactivity and impaired downregulation of emotions in positive scenarios relative to HC. Further, UR exhibited impaired discrimination accuracy for surprised faces, performing intermediate between patients and HC, suggesting a candidate familial marker for BD (Kjaerstad et al., 2020). In the present report, we investigated the trajectory of the cognitive deficits within 16 months prospective follow-up of the BIO cohort (Kessing et al., 2017). Specifically, we aimed to investigate (i) the trajectory of emotional and non-emotional cognition in newly diagnosed patients with BD and their UR relative to HC; (ii) whether episode relapse during the 16-month follow-up period is associated with cognitive decline. In accordance with previous longitudinal studies of cognition in BD, we hypothesized that (i) emotional and non-emotional cognition remains stable over a 16-month period in patients with BD, their UR, and HC, and that, in accordance with the neuroprogression model, (ii) patients experiencing mood episodes during the follow-up period exhibit a worsening of cognitive decline over time compared to patients who remained in remission and HC.
2. Experimental procedures

2.1. Study design

The present study is a longitudinal assessment of baseline and follow-up data across an average of 16 months from the Bipolar Illness Onset study (Kessing et al., 2017). This report includes data from participants recruited from September 2015 to January 2021, with data from follow-up assessments collected between February 2017 and February 2021. Informed consent was provided by all participants prior to onset of the study. Study approval was granted by The Committee on Health Research Ethics, Capital Region of Denmark (protocol no: H-7-2014-007) and the Danish Data Protection Agency, Capital Region of Copenhagen (protocol no: RHP-2015-023).

2.2. Participants

Patients newly diagnosed with BD within two years prior to study inclusion, between 15 and 70 years of age, were recruited from the Copenhagen Affective Disorder Clinic at the Psychiatric center Copenhagen, Denmark. Patients were referred by their treating psychiatrist and received treatment as usual irrespective of participation in the study. The semi-structured interview Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) was used to confirm the ICD-10 diagnosis of BD (World Health Organization, 1992) and to ascertain whether patients had comorbid anxiety disorders (ICD-10 F40–42). The SCAN was conducted by a PhD student in medicine or psychology. Full or partial remission of mood symptoms (HDRS-17 and YMRS-scores ≤14) was evaluated using the Hamilton Depression Rating Scale-17 (Hamilton, 1967) and the Young Mania Rating Scale (Young et al., 1978).

Patients’ unaffected first-degree relatives (siblings and/or offspring) between the ages of 15 and 40 years were invited to participate with consent from their affected relative. Relatives were excluded from participation if they had a treatment-required psychiatric disorder and/or substance abuse.

Recruitment of age- and sex-matched HC took place from the University Hospital Blood Bank, Rigshospitalet, Copenhagen. Healthy controls were excluded from participation if they had a personal or up to first-degree familial history of treatment-required psychiatric disorder or substance abuse. Relatives and HC were screened using the SCAN interview to confirm the absence of psychiatric disorder. Predicted full-scale IQ was estimated using the Danish version of the National Adult Reading Task (DART) (Nelson and O’Connell, 1978). General exclusion criteria for all participants included severe somatic illness, pregnancy, current substance abuse and a history of brain injury.

2.3. Assessment of emotional cognition

Participants were administered an extensive neuropsychological test battery comprising the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1958), Trail Making Test-A and B (TRMT-A/TRMT-B) (Army Individual Test Battery, 1944), Coding and Digit Span Forward from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), the Rapid Visual Information Processing (RVP) and the Spatial Working Memory (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Letter-Number-Sequence subtest from Wechsler’s Adult Intelligence Scale 3rd edition (WAIS-III) (Wechsler, 1997), and verbal fluency letters S and D (Borkowski et al., 1967). Different versions of the RAVLT (list AB, GeAB, and Cr-AB) and RBANS coding (version A and B) were counterbalanced at baseline and follow-up to reduce the risk of practice effects.

2.4. Assessment of emotional cognition

Emotion reactivity and regulation in response to social scenarios was assessed with the Social Scenarios Task (Kjaerstad et al., 2016), while facial emotion processing was measured using the Facial Expression Recognition Task and the Faces Dot-Probe Task (The Emotional Test Battery; P1vital® Oxford Emotion Test Battery, 2017).

2.4.1. Social scenarios task

Participants were presented with written descriptions on a computer monitor describing various social situations and related self-belief statements. Presented scenarios were either overwhelmingly negative or positive with accompanying self-belief statements. Participants were asked to either naturally react or dampen their emotional response prior to the presentation of each scenario. No specific emotion regulation strategies were provided, to ensure the most natural response was elicited. Each block of scenarios consisted of 11 sentences describing the situation and 10 accompanying self-belief statements, which were visible for 3 s each. Participants were asked to rate their level of discomfort or pleasure on a scale from 0 to 100 following each presented self-belief statement, with a total of 10 emotion ratings. A total of nine social scenarios were presented, including an initial neutral condition followed by two negative conditions, followed by two positive conditions and so on. Each pair of negative or positive conditions included an instruction to dampen the emotional response in one condition, while participants were asked to react naturally in the other condition. Prior to commencement of the task, participants’ sexual orientation was determined, and the respective version of the task was administered.

2.4.2. The facial expression recognition task

Participants were presented with depictions of faces expressing one of six basic emotions: disgust, anger, fear, sadness, happiness and surprise which were morphed at stages of 10% intensity ranging from neutral (0%) to full emotion (100%) and presented in random order. A total of 250 faces, including four depictions of each emotion at each intensity (240 trials) as well as a neutral expression (10 trials) were presented during the task. Each face was visible for 500 ms after which a blank screen followed immediately, and participants were asked to indicate the correct facial expression by pressing the corresponding key. Participants were instructed to be as fast and accurate as possible, and accuracy and reaction time were both recorded.

2.4.3. The faces dot-probe task

Participants were presented with horizontal pairs of faces displaying either happy-neutral, fearful-neutral or neutral-neutral expressions, after which one of the displayed faces was immediately replaced by either two vertical (•) or two horizontal (–) dots. (Murphy et al., 2008). In the unmasked emotion condition face pairs were shown for 100 ms, and in the masked condition the emotional faces were shown for 17 ms immediately followed by a neutral mask. The task included a total of 192 trials with each block comprising 12 trials including an alternating presentation of eight blocks of masked trials followed by eight blocks of unmasked trials. Participants were asked to indicate the direction of the dots as quickly and accurately as possible by pressing the respective key on the computer.

2.5. Assessment of functioning

Overall functioning was assessed using the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) measuring domains of autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationship, leisure time, including a total
functioning score, with a score of >11 indicating a degree of functional impairment (Bonin et al., 2018).

2.6. Statistical methods

2.6.1. Non-emotional cognition

The raw scores of the neuropsychological tests were converted into standardized z-scores (i.e., mean = 0, SD = 1) using HC’s scores ((test score - HC test M)/ HC test SD). Outlying z-scores ±4 SD from the mean were truncated at z = ±4.0. Considering the differences in direction of the scales, z-scores for TMT-A, TMT-B, SWM (between errors and strategy), and RVP (mean latency) were reversed so that lower scores reflect worse performance. Four non-emotional cognitive domains were derived from averaging z-scores of their respective tests: (i) Sustained attention and psychomotor speed: TMT-A, Coding, Digit Span Forward, RVP (mean latency and accuracy), (ii) Verbal learning: RAVLT trail 1-V correct, trial VI correct, delayed recall, and recognition, (iii) Working memory and executive function: TMT-B, Letter-Number Sequencing, SWM (between errors and strategy) and (iv) Verbal fluency: Verbal fluency letters S and D. Given that the tests of ‘attention’ and ‘psychomotor speed’ as well as ‘working memory’ and ‘executive function’, overlap, we collapsed these domains to two. Finally, the z-score average of the non-emotional cognitive domains composed a global non-emotional cognitive composite score.

2.6.2. Emotional cognition

For the social scenarios task, raw values were arcsine transformed and measures of positive and negative emotion regulation were obtained by subtracting the emotional ratings of the dampen conditions from the react conditions. For the facial expression recognition task, discrimination accuracy for facial expressions (d) was obtained for every facial expression, using the formula: 

\[
\text{d} = \frac{(\text{number of hits} + 0.5)}{(\text{number of targets} + 1)} - \frac{(\text{number of false alarms} + 0.5)}{(\text{number of distractors} + 1)}
\]

(Corwin, 1994). Reaction time (RT) was log-transformed. Responses to all facial expressions were averaged to obtain a measure of general facial expression recognition accuracy (d’) and RT. Also, faces displaying happy and surprise were averaged to obtain a measure of discrimination accuracy (d’) and RT to positive faces, and faces displaying sad, fear, disgust and anger were averaged to obtain measures of discrimination accuracy (d’) and RT to negative faces. For the faces dot-probe task, vigilance scores were calculated by subtracting the response time (in ms) for the probes following neutral faces from the emotional faces. A positive value would correspond to vigilance (i.e., an attentional bias towards emotional faces), whereas a negative value would correspond avoidance (i.e., attention away from emotional face).

2.6.3. Group comparisons

To analyze demographic, clinical, and cognitive variables at baseline and follow-up, respectively, linear mixed models were conducted with group as fixed factor and familial relationship as random factor. For change in demographic, clinical, or cognitive variables between baseline and follow-up, we conducted mixed models analyses with group (BD, UR, HC) and time as fixed factors, familial relationship as random factor, and days between baseline and follow-up as a covariate. Significant group-by-time interactions were followed up with pairwise mixed-models analyses. To assess our secondary aim (i.e., the effects of mood episodes on cognition over time), we differentiated between patients who had experienced at least one mood episode (BD+) and those who remained in remission (BD-) between the two timepoints. We then repeated the mixed models analyses above, but with group (BD+, BD-, HC) and time as fixed factors and days between baseline and follow-up as covariate. Given a possible effect of subsyndromal symptoms on cognition, analyses revealing significant group-by-time interactions or main effect of group were repeated but additionally adjusting for subsyndromal depression and mania symptoms (HDRS and YMRS total scores). We additionally adjusted for IQ in analyses revealing significant group-by-time interactions or main effect of group when investigating difference between BD, UR, and HC. Sidak correction was applied to account of multiple comparisons in all analyses of cognition.

2.6.4. Associations between aberrant cognition, subsyndromal symptoms, functioning, and illness characteristics

Across all participants, we conducted exploratory Pearson correlation analyses to investigate the associations between aberrant cognition, subsyndromal depression (HDRS) and mania (YMRS) symptoms, functioning (total FAST) across baseline and follow-up. We also conducted exploratory Pearson correlation analyses between deficits in non-emotional and emotional cognition for variables where we found significant group differences in the main analysis. For patients with BD, we additionally explored the association between aberrant cognition and psychotropic medication use (the use of antidepressants, antipsychotics, anticonvulsants, and lithium) and illness characteristics (total mood symptoms, age of onset, illness duration, and hospitalizations). All statistical analyses were conducted using SPSS version 25.

3. Results

3.1. Participants

The baseline data were composed of 561 participants including 266 patients with BD, 105 of their UR and 190 HC. A total of 348 participants were assessed at follow-up: 152 patients with BD, 61 UR and 135 HC. Follow up was conducted mean 16 (±6; median=14; interquartile range=12-18) months after baseline. There was no significant difference in follow-up times between the three groups (p = .25). Information regarding episodes at follow-up was unavailable for four patients with BD. Two UR and one HC developed a major depressive episode between baseline and follow-up and were excluded from the analyses.

3.1.1. Baseline demographic and clinical variables

Patients with BD, their UR and HC were comparable for age and sex at baseline (p>.053) (Table 1). Significant group difference was found for years of education (p=.001), which was driven by BD and UR having fewer years of education compared to HC (p<.001), with no significant difference between BD and UR (p=.47). There was also a significant group difference for predicted full-scale IQ (p=.02): UR presented with lower IQ than patients with BD and HC (p≤.03). As anticipated, the three groups significantly differed in subsyndromal mood symptoms (p<.001): patients with BD experienced more subsyndromal depressive and manic symptoms compared to both UR and HC (p<.001), with no significant difference between UR and HC (p≥.09). There was a significant effect of group for functioning (p<.001): patients with BD presented with more functional impairments compared to HC and UR on all domains of FAST (p≤.001) and UR presenting with more overall functional impairments as well as within the domain of leisure compared to HC (p<.009). Finally, 12% (n = 31) of patients met criteria for comorbid anxiety disorder (ICD-10 F40-42); including n = 9 agoraphobia, n = 3 social phobia, n = 9
Table 1  Demographic and clinical variables for newly diagnosed patients with bipolar disorder, their unaffected first-degree relatives, and healthy controls at baseline and follow-up.

|                        | Baseline                  | Follow-up                  | Group-by-time interaction P-value |
|------------------------|---------------------------|----------------------------|-----------------------------------|
|                        | Bipolar disorder          | Unaffected relatives      | Healthy controls                  | F/χ² | P-value | Pairwise comparison | Bipolar disorder | Unaffected relatives | Healthy controls | F/χ² | P-value | Pairwise comparison |
|                        | (n = 266)                 | (n = 105)                  | (n = 190)                         |      |         |                  | (n = 152)       | (n = 61)                  | (n = 135)         |      |         |                  |
| Demographic variables  |                           |                            |                                  |      |         |                  |      |                           |                      |      |         |                  |
| Sex, n (% female)      | 173 (65%)                 | 54 (51%)                   | 117 (62%)                        | 5.89 | 0.053   |                   | 15.48 (3.23)    | 15.48 (2.99)              | 16.24 (2.00)      | 3.02 | 0.05   |                   |
| Age, years             | 31.16 (9.00)              | 29.39 (10.05)              | 31.43 (11.16)                    | 2.20 | 0.11    |                   |                   |                           |                      |      |         |                  |
| Education, years       | 15.02 (3.46)              | 14.75 (2.63)               | 16.08 (3.05)                     | 7.61 | 0.001   | BD & UR < HC     | 5.05 (3.84)      | 2.75 (3.80)               | 0.97 (1.46)       | 60.98 | <0.001 | BD > UR 0.02 |
| Predicted full-scale IQ| 111.91 (5.55)             | 110.89 (5.93)              | 112.64 (5.60)                    | 4.26 | 0.02    | UR < HC          | 5.05 (3.84)      | 2.75 (3.80)               | 0.97 (1.46)       | 60.98 | <0.001 | BD > UR 0.02 |
| HDRS                   | 5.37 (3.88)               | 1.61 (2.20)                | 1.00 (1.48)                      | <0.001 | BD > HC & HC & BD |                   |                   |                           |                      |      |         |                  |
| YMRS                   | 2.67 (3.09)               | 0.92 (1.45)                | 0.69 (1.39)                      | <0.001 | BD > HC & HC & BD |                   |                   |                           |                      |      |         |                  |
| Functioning            |                           |                            |                                  |      |         |                  |      |                           |                      |      |         |                  |
| FAST total             | 17.91 (12.28)             | 4.28 (7.23)                | 1.34 (2.16)                      | <0.001 | BD > UR (10.70) |                   | 12.95 (10.70)    | 3.71 (5.83)               | 1.70 (3.41)       | 79.82 | <0.001 | BD > UR <0.001 |
| FAST autonomy          | 1.81 (2.19)               | 0.38 (0.91)                | 0.13 (0.47)                      | <0.001 | BD > HC (1.92) |                   | 1.34 (1.92)      | 0.44 (1.02)               | 0.12 (0.43)       | 29.89 | <0.001 | BD > UR 0.04 |
| FAST occupation        | 6.20 (6.76)               | 1.09 (3.30)                | 0.17 (0.53)                      | <0.001 | BD > HC & HC & UC |                   | 4.23 (5.70)      | 0.97 (2.98)               | 0.62 (0.43)       | 28.14 | <0.001 | BD > UR 0.001 |
| FAST cognition         | 4.31 (3.41)               | 1.00 (1.58)                | 0.41 (0.77)                      | <0.001 | BD > HC & UC & UR |                   | 3.53 (2.72)      | 0.93 (1.24)               | 0.41 (0.76)       | 99.76 | <0.001 | BD > UR 0.01 |
| FAST financial         | 1.19 (1.68)               | 0.25 (0.65)                | 0.10 (0.39)                      | <0.001 | BD > HC & UC & UR |                   | 0.70 (1.21)      | 0.19 (0.54)               | 0.06 (0.30)       | 21.67 | <0.001 | BD > UR 0.06 |
| FAST relationships     | 3.14 (3.09)               | 0.90 (2.10)                | 0.35 (0.88)                      | <0.001 | BD > HC & UC & UR |                   | 2.33 (2.64)      | 0.64 (1.24)               | 0.32 (0.74)       | 44.00 | <0.001 | BD > UR 0.02 |
| FAST leisure           | 1.26 (1.56)               | 0.65 (1.16)                | 0.19 (0.48)                      | <0.001 | BD > UR > HC     |                   | 0.83 (1.17)      | 0.56 (1.04)               | 0.17 (0.56)       | 16.45 | <0.001 | BD > UR 0.02 |

(continued on next page)
|                          | Baseline |                          | Follow-up |                          | Group-by-time interaction |
|--------------------------|----------|--------------------------|----------|--------------------------|---------------------------|
|                          | Bipolar disorder (n = 266) | Unaffected relatives (n = 105) | Healthy controls (n = 190) | F/χ² | P-value | Pairwise comparison |
|                          | Bipolar disorder (n = 152) | Unaffected relatives (n = 61) | Healthy controls (n = 135) | F/χ² | P-value | Pairwise comparison |
| **Clinical variables**   |          |                          |          |                          |                           |
| BD Type II, N (%)        | 181 (68%) |                          |          |                          |                           |
| Comorbid anxiety disorder (F40-F42), N (%) | 31 (12%) |                          |          |                          |                           |
| Illness duration, years  | 8.05 (7.58) |                          |          |                          |                           |
| Untreated illness, years | 6.83 (7.52) |                          |          |                          |                           |
| Age of onset, years      | 22.55 (8.24) |                          |          |                          |                           |
| Suicide attempts         | 0.16 (6.46) |                          |          |                          |                           |
| Hospitalizations         | 0.87 (1.52) |                          |          |                          | 0.91 (1.32)               |
| Lithium, N (%)           | 122 (46%) |                          |          |                          | 62 (41%)                  |
| Anticonvulsants, N (%)   | 108 (41%) |                          |          |                          | 101 (67%)                 |
| Antidepressants, N (%)   | 52 (20%) |                          |          |                          | 15 (10%)                  |
| Antipsychotic, N (%)     | 94 (35%) |                          |          |                          | 56 (37%)                  |
| No of depressive episodes| 11.45    |                          |          |                          | 12.45                     |
| No of hypomanic episodes | 9.53 (16.34)|                        |          |                          | 10.73                     |
| No of manic episodes     | 1.00 (3.60) |                        |          |                          | 0.88 (3.46)               |
| No of mixed episodes     | 0.58 (2.87) |                        |          |                          | 0.40 (1.53)               |

Values are presented as means (standard deviations), unless otherwise noted. Bold values indicate significant values.

Abbreviations: HDRS=Hamilton Depression Rating Scale; YMRS=Young Mania Rating Scale; FAST=Functioning Assessment Short Test.

* Illness duration calculated as time between first manic, hypomanic or mixed episode and time of cognitive testing.

* Untreated illness calculated as time between first manic, hypomanic or mixed episode and diagnosis.

* Age of onset calculated as time between date of birth and first manic, hypomanic or mixed episode.

* Suicide attempts at time of study inclusion; follow-up data was not collected.
specific phobia, \( n = 8 \) panic disorder, \( n = 2 \) generalized anxiety disorder, and \( n = 4 \) obsessive-compulsive disorder.

3.2. Assessing differential change in subsyndromal symptoms, functioning, and cognition over time between patients with bipolar disorder, their unaffected relatives, and healthy controls

3.2.1. Change in subsyndromal symptoms and functioning
Analyses of changes in symptoms of depression and mania over time revealed a significant group-by-time interaction effect for subsyndromal depression symptoms (\( p < .02 \); BD vs. UR: \( F(1, 211.0) = 5.32, \ p = .02 \); UR vs. HC: \( F(1, 194.0) = 4.86, \ p = .03 \)). This was driven by a non-significant trend-level increase in subsyndromal depression symptoms in UR from baseline to follow-up (\( p = .06 \)), whereas subsyndromal depression in BD and HC remained stable (\( ps > .12 \)). There was no interaction effect for subsyndromal mania symptoms (\( p = .35 \)).

Analysis of FAST revealed a significant group-by-time interaction for general functioning (\( F(2344.8) = 12.09, \ p < .001 \)), as well as the subdomains of autonomy (\( F(2, 342.3) = 3.19, \ p = .04 \)), occupational (\( F(2, 344.2) = 7.38, \ p = .001 \)), cognitive (\( F(2, 344.3) = 4.29, \ p = .01 \)), and inter-personal (\( F(2, 345.9) = 4.06, \ p = .02 \)) functioning. These interactions were driven by significantly improved functioning in patients with BD during the 16-month follow-up time (\( p < .02 \)), whereas HC and UR remained stable (\( ps > .08 \) and 0.26, respectively).

3.2.2. Non-emotional cognition
Performance in non-emotional cognition at baseline and follow-up are summarized in Table 2. There were no significant trajectory differences between groups (group-by-time interactions) for global cognitive performance (\( p = .60 \)) or the individual cognitive domains (\( ps > .10 \)).

A significant main effect of group was found for global cognition (\( F(2, 345.00) = 11.69, \ p = .001 \)), with patients with BD generally underperformed HC at both time points (\( p < .001 \)) and showed a trend towards poorer performance than UR (\( p = .07 \)), with no significant difference between UR and HC (\( p = .38 \)) (Fig. 1A). There was also a significant main effect of group for the domain 'working memory and executive function' (\( F(2, 289.54) = 20.06, \ p < .001 \)); driven by patients generally performing poorer than HC (\( p < .001 \)), with UR intermediate in between patients with BD (\( p = .03 \)) and HC (\( p = .045 \)) (Fig. 1B). Results also revealed a significant main effect of group for 'attention and psychomotor speed' (\( F(2, 318.84) = 15.17, \ p < .001 \)), driven by patients with BD performing worse than HC and UR (\( ps < .002 \)). There was no significant difference between UR and HC (\( p = .85 \)) (Fig. 1C). All significant main effects of group prevailed after adjusting for subsyndromal depression and mania symptoms and IQ, respectively (\( ps < .001 \)). In contrast, there were no significant group differences for verbal learning or verbal fluency (\( p = .07 \) and \( p = .22 \), respectively; Fig. 1D-E).

Notably, participants generally exhibited increase in cognition over time exhibited by main effects of time (global cognition: \( F(1, 345.00) = 61.08, \ p < .001 \), average improvement \( z = 0.17 \)), likely reflecting normative improvement due to practice or test-retest effects.

3.2.3. Emotional cognition
Emotional cognitive performance for both timepoints (i.e., baseline and follow-up) is summarized in Table 2.

3.2.3.1. Emotional reactivity and down-regulation of emotion in social scenarios.
We found no significant trajectory differences between groups (group-by-time interaction) for neither emotion reactivity nor ability to down-regulate emotions in negative or positive social scenarios (\( ps > .18 \)).

There was a significant effect of group for emotional reactivity in negative social scenarios (\( F(2, 325.26) = 6.17, \ p = .002 \)), which was driven by BD patients exhibiting higher emotional reactivity in negative scenarios compared to HC (\( p = .003 \)) and a non-significant trend towards a difference between BD and UR (\( p = .08 \)), with no differences between UR and HC (\( p = .97 \)). This significant group difference prevailed after adjusting for IQ (\( p = .004 \)) but rendered non-significant after adjusting for subsyndromal depression and mania symptoms (\( p = .27 \)). Results revealed a significant group effect for ability to down-regulate emotions in pleasant social scenarios (\( F(2, 313.54) = 7.13, \ p = .001 \)): patients with BD were less successful at down-regulating their emotions in pleasant scenarios compared to HC (\( p = .002 \)) and UR (\( p = .03 \)), with no significant difference between HC and UR (\( p = 1.00 \)). This main effect of group prevailed after adjusting for subsyndromal symptoms and IQ, respectively (\( p > .008 \)). There were no differences between groups in emotional reactivity in pleasant social scenarios or ability to down-regulate emotions in negative social scenarios (\( ps > .21 \)).

Significant main effects of time were found for both emotional reactivity in positive and negative scenarios (\( F(1, 329.25) = 7.38, \ p < .007 \) and \( F(1, 326.11) = 11.49, \ p < .001 \), respectively), driven by emotional reactivity generally being lower at follow-up compared to baseline.

3.2.3.2. Facial expression recognition.
For discrimination accuracy and speed during facial expression recognition of all faces, and for positive and negative faces, respectively, we found no significant trajectory differences between groups (\( ps > .32 \)) nor significant main effects of group (\( ps > .31 \)). As anticipated, significant effects of time were found for discrimination accuracy and speed at which participants correctly recognised faces (\( d' \) accuracy: \( F(1, 209.77) = 52.86, \ p < .001 \); speed: \( F(1, 246.57) = 8.06, \ p < .005 \)), positive faces (\( d' \) accuracy: \( F(1, 242.79) = 5.56, \ p = .02 \); speed: \( F(1, 255.15) = 14.57, \ p < .001 \)), and negative faces (\( d' \) accuracy: \( F(1, 206.15) = 59.01, \ p < .001 \); speed: \( F(1, 248.74) = 4.66, \ p = .03 \)), with participants generally performing better (i.e., more accurate), but slower at follow-up.

3.2.3.3. Attentional vigilance and avoidance of fearful and happy faces.
No significant group-by-time interactions were found for vigilance towards masked/unmasked fearful/happy faces (\( ps > .11 \)). There was a non-significant trend towards a main effect of group on vigilance to masked fear (\( F(2, 332.77) = 2.51, \ p = .08 \)). Follow-up pairwise comparison revealed, however, no signifi-
Table 2  Cognitive performance in patients with bipolar disorder (BD), their unaffected relatives (UR) and healthy controls (HC) at baseline and follow-up.

| Neurocognition                         | Baseline F-value | Baseline P-value | Baseline Pairwise comparison | Follow-up F-value | Follow-up P-value | Follow-up Pairwise comparison | Group-by-time interaction P-value |
|----------------------------------------|------------------|------------------|-------------------------------|-------------------|------------------|-------------------------------|-----------------------------------|
| Global cognition                       | −0.30 (0.62)     | 15.39            | <0.001                        | −0.07 (0.58)      | 10.14            | <0.001                        | 0.60                              |
| Working memory and executive function  | −0.43 (0.78)     | 20.19            | <0.001                        | −0.25 (0.77)      | 19.19            | <0.001                        | 0.22                              |
| Attention and psychomotor speed        | −0.42 (0.69)     | 27.06            | <0.001                        | −0.09 (0.63)      | 10.64            | <0.001                        | 0.10                              |
| Verbal learning                        | −0.18 (0.93)     | 2.74             | 0.003                         | −0.01 (0.92)      | 1.12             | 0.33                          | 0.47                              |
| Verbal fluency                         | −0.15 (1.00)     | 5.82             | 0.003                        | −0.06 (0.95)      | 1.54             | 0.22                          | 0.50                              |
| Emotional cognition                    |                  |                  |                               |                   |                  |                               |                                   |
| Positive emotion                       | 1.03 (0.23)      | 0.80             | 0.45                          | 0.99 (0.21)       | 1.02             | 0.53                          | 0.94                              |
| Negative emotion                       | .97 (0.24)       | 7.06             | 0.001                        | .95 (0.24)        | 5.63             | 0.004                        | 0.18                              |
| Positive downregulation                | .20 (0.19)       | 4.16             | 0.02                          | .21 (0.21)        | 1.12             | 0.33                          | 0.72                              |
| Negative downregulation                | .27 (0.22)       | 0.62             | 0.54                          | .28 (0.22)        | 1.63             | 0.20                          | 0.66                              |
| Dot Probe Task                         |                  |                  |                               |                   |                  |                               |                                   |
| Masked fear                            | −22.36 (68.16)   | 0.1              | 0.90                          | −30.14 (66.72)    | 2.86             | 0.06                          | 0.47                              |
| Masked happy                           | 12.16 (90.56)    | 1.04             | 0.36                          | 32.70 (64.79)     | 1.67             | 0.19                          | 0.22                              |
| Unmasked fear                          | −32.48 (76.55)   | 3.6              | 0.03                          | −15.19 (94.77)    | 1.87             | 0.16                          | 0.11                              |
| Unmasked happy                         | −4.25 (106.37)   | 1.66             | 0.19                          | 24.63 (113.13)    | 1.01             | 0.37                          | 0.16                              |

(continued on next page)
| Table 2  (continued) | Baseline | | | Follow-up | | | | Group-by-time interaction |
|---|---|---|---|---|---|---|---|---|
| | BD | UR | HC | F-value | P-value | Pairwise comparison | BD | UR | HC | F-value | P-value | Pairwise comparison |
| Facial Recognition Task Discrimination Accuracy (d’): All emotions | .47 (0.08) | .45 (0.09) | .48 (0.08) | 3.16 | 0.04 | UR < HC | .49 (0.09) | .47 (0.07) | .49 (0.07) | 0.68 | 0.51 | .32 |
| Positive emotions | .55 (0.08) | .55 (0.08) | .57 (0.08) | 2.75 | 0.07 | | .55 (0.08) | .56 (0.06) | .56 (0.07) | 0.85 | 0.43 | .46 |
| Negative emotions | .42 (0.10) | .40 (0.11) | .44 (0.09) | 2.81 | 0.06 | | .46 (0.10) | .43 (0.09) | .46 (0.09) | 1.61 | 0.20 | .35 |
| Reaction time (log-transformed): All emotions | 3.16 (0.12) | 3.18 (0.11) | 3.16 (0.12) | 0.94 | 0.39 | | 3.19 (0.12) | 3.19 (0.13) | 3.20 (0.12) | 0.53 | 0.59 | .65 |
| Positive emotions | 3.10 (0.13) | 3.12 (0.12) | 3.09 (0.14) | 1.14 | 0.32 | | 3.14 (0.13) | 3.14 (0.14) | 3.15 (0.13) | 0.38 | 0.69 | .66 |
| Negative emotions | 3.19 (0.12) | 3.22 (0.12) | 3.20 (0.12) | 1.52 | 0.22 | | 3.22 (0.12) | 3.22 (0.13) | 3.23 (0.13) | 0.48 | 0.62 | .56 |

Note. Scores refers to mean (standard deviations). Bold values indicate significant values.
significant differences between BD patients, UR or HC (ps ≥ 0.17). All other effects of group were non-significant (ps≥ .51). There were no significant main effect of time (ps ≥ 0.18).

3.3. Assessing the differential change in subsyndromal symptoms, functioning, and cognition between relapers, non-relapers, and healthy controls

3.3.1. Change in subsyndromal symptoms and functioning

Of the 152 patients at follow-up, 103 (70%) patients experienced at least one mood episode between baseline and follow-up (BD+), whereas 45 (30%) patients remained in remission (BD-) (Table 3).

Analyses of changes in subsyndromal symptoms over time revealed significant main effects of group (HDRS: F(2,278.99)=150.46, p<.001; YMRS: F(2,279.01)=61.14, p<.001; but no significant group-by-time interactions; ps≥.21): BD+ patients generally had more subsyndromal depression and mania symptoms over time compared to HC (ps<0.001) and BD- (ps<0.010), with BD- presenting with intermediate symptoms that were significantly lower than BD+ and higher than HC (ps<.02).

Analyses of overall functioning revealed a significant group-by-time interaction (F(2, 278.89)=9.80, p<.001). This was driven by significantly improved functioning in BD+ and BD- (ps<0.001) whereas HC remained stable (p=.26), with no significant differential change in functioning over time between patients who relapsed and patients who remained in remission during the follow-up time (p=.65).

3.3.2. Non-emotional cognition

Analyses comparing BD+, BD- and HC showed no significant trajectory differences between groups (i.e., group-by-time interactions) (ps≥.16). Significant main effects of group were observed for global cognition (F(2,279.00)=9.94, p<.001) and the subdomains of ‘working memory and executive function’ (F(2,279.03)=18.45, p<.001) and ‘attention and psychomotor speed’ (F(2,279.09)=13.10, p<.001), all of which were driven by significantly poorer cognitive performance in both BD groups compared to HC (ps<.01) with no significant difference between BD+ and BD- patients (ps≥.50). The significant main effects of group prevailed after adjusting for subsyndromal symptoms (ps<0.001).

3.3.3. Emotional cognition

3.3.3.1. Emotional reactivity and down-regulation of emotion in social scenarios. There were no significant trajectory differences nor significant main effect of group be-
Table 3  Baseline and follow-up demographic and clinical variables in patients with bipolar disorder who relapsed (BD+), patients who remained in remission (BD-), and healthy controls (HC) at baseline and 16-months follow-up.

| Demographic variables | Baseline | Follow-up | Group-by-time interaction p-value |
|-----------------------|----------|-----------|----------------------------------|
|                       | BD+ (n = 103) | BD- (n = 45) | HC (n = 190) | F/t/U/ \chi^2 | P-value | Pairwise comparison | BD+ (n = 103) | BD- (n = 45) | HC (n = 135) | F/t/U/ \chi^2 | P-value | Pairwise comparison |
| Gender, n (% female)  | 72 (70%) | 24 (53%) | 117 (62%) | 4.08 | 0.13 |                    | BD+ < HC | 15.29 (3.03) | 15.98 (3.69) | 16.24 (2.00) | 3.54 | 0.03 | BD+ < HC |
| Age                   | 30.25 (8.44) | 33.40 (9.26) | 31.16 (11.16) | 1.52 | 0.22 |                    |                    |                    |                    |                    |     |     |        |
| Education, years      | 14.85 (3.06) | 15.70 (3.03) | 16.08 (3.05) | 5.44 | 0.005 | BD+ < HC | 5.82 (3.85) | 3.29 (1.38) | 0.97 (1.46) | 83.65 | <0.001 | BD+ < HC |
| Predicted full-scale IQ | 117.94 (5.62) | 113.37 (4.69) | 112.64 (5.60) | 1.15 | 0.32 |                    |                    |                    |                    |                    |     |     |        |
| HDRS                  | 6.49 (3.77) | 3.44 (3.80) | 1.00 (1.48) | 135.74 | <0.001 | HC < BD- < BD+ | 5.82 (3.85) | 3.29 (1.38) | 0.97 (1.46) | 83.65 | <0.001 | BD+ < HC |
| YMRS                  | 3.46 (3.45) | 1.36 (1.96) | 0.69 (1.39) | 49.22 | <0.001 | HC < BD+ & BD- < BD+ | 2.58 (3.22) | 1.20 (1.84) | 0.49 (1.03) | 26.79 | <0.001 | HC < BD+ & BD- < BD+ |
| FAST, total score     | 18.62 (12.27) | 14.82 (13.18) | 1.34 (2.16) | 152.39 | <0.001 | HC < BD- < BD+ | 14.36 (10.66) | 9.51 (10.30) | 1.70 (3.41) | 74.23 | <0.001 | HC < BD- < BD+ |
| Clinical characteristics |        |            |                  | 1379.50 | <0.001 | HC < BD+ < BD- | 74.23 (14.36) | 9.51 (10.30) | 1.70 (3.41) | 74.23 | <0.001 | HC < BD+ < BD- |
| Bipolar type, n (% type II) | 76 (74%) | 29 (64%) | 1.32 | 0.25 | |                    |                    |                    |                    |                    |     |     |        |
| Illness duration, years a | 8.35 (7.28) | 6.61 (7.15) | 1719.50 | 0.03 | BD- < BD+ | |                    |                    |                    |                    |     |     |        |
| Untreated illness, years b | 7.31 (7.32) | 5.43 (6.76) | 1701.50 | 0.02 | BD- < BD+ | |                    |                    |                    |                    |     |     |        |
| Age of onset, years c | 21.39 (7.38) | 26.09 (8.52) | 1384.00 | <0.001 | BD+ < BD- | |                    |                    |                    |                    |     |     |        |
| Suicide attempts d | 0.65 (2.62) | 0.20 (0.51) | 2110.00 | 0.41 | | | | | | | | |
| Hospitalizations | 0.73 (1.17) | 0.98 (1.27) | 2124.50 | 0.17 | | | | | | | | |

(continued on next page)
|                                    | Baseline |          | F/t/U | P-value | Pairwise comparison | Follow-up |          | F/t/U | P-value | Group-by-time interaction p-value |
|------------------------------------|----------|----------|--------|---------|---------------------|-----------|----------|--------|---------|----------------------------------|
|                                    | BD+      | BD-      | HC     |         |                     | BD+       | BD-      | HC     |         |                                 |
|                                    | (n = 103)| (n = 45) | (n = 190)|         |                     | (n = 103) | (n = 45) | (n = 135)|         |                                 |
| Antidepressants, n (% yes)         | 23 (22%) | 4 (9%)   | 3.79   | 0.051   |                     | 12 (12%)  | 2 (4%)   | 1.90   | 0.17    |                                 |
| Antipsychotics, n (% yes)          | 25 (24%) | 19 (42%) | 4.83   | 0.03    | BD+ < BD-           | 41 (40%)  | 14 (31%) | 1.01   | 0.31    |                                 |
| Anticonvulsants, n (% yes)         | 34 (33%) | 22 (49%) | 3.36   | 0.07    |                     | 74 (72%)  | 25 (56%) | 3.75   | 0.053   |                                 |
| Lithium, n (% yes)                 | 52 (51%) | 26 (58%) | 0.67   | 0.41    |                     | 41 (40%)  | 20 (44%) | 0.28   | 0.60    |                                 |
| Mood episodes between baseline and follow-up |          |          |        |         |                     |           |          |        |         |                                 |
| Mean follow-up period, months      |          |          |        |         |                     |           |          |        |         |                                 |
| Total no. of mood episodes         |          |          |        |         |                     |           |          |        |         |                                 |
| No. of depressive episodes         |          |          |        |         |                     |           |          |        |         |                                 |
| No. of hypomanic episodes          |          |          |        |         |                     |           |          |        |         |                                 |
| No. of manic episodes              |          |          |        |         |                     |           |          |        |         |                                 |
| No. of mixed episodes              |          |          |        |         |                     |           |          |        |         |                                 |

Values are presented as means (standard deviations), unless otherwise noted. Bold values indicate significant values.

Abbreviations: HDRS=Hamilton Depression Rating Scale; YMRS=Young Mania Rating Scale; FAST=Functioning Assessment Short Test.

a Illness duration calculated as time between first manic, hypomanic or mixed episode and time of cognitive testing.
b Untreated illness calculated as time between first manic, hypomanic or mixed episode and diagnosis.
c Age of onset calculated as time between date of birth and first manic, hypomanic or mixed episode.
d Suicide attempts at time of study inclusion; follow-up data was not collected.
between BD+, BD- and HC during emotion reactivity or down-regulation of emotion in social scenarios (ps≥.11). There was a significant difference between groups for emotional reactivity in aversive social scenarios (F(2279.48)=6.41, p=.002), driven by BD+ patients exhibiting significantly greater emotional reactivity than HC (p=.001) with no difference between BD- and HC (p=.38) or the two BD groups (p=.54). However, this significant main effect of group rendered non-significant after adjusting for subsyndromal symptoms (p=.28). Results also revealed a significant main effect of group for emotion down-regulation in positive social scenarios (F(2, 279.08)=5.10, p=.007): BD+ patients were less successful at down-regulating their emotions in positive scenarios compared to HC (p=.01), with BD- patients displaying intermediate levels with a non-significant trend towards a difference between HC (p=.07) but no significant difference with BD+ (p = 1.00). This significant main effect of group remained after adjusting for subsyndromal depression and mania symptoms (p=.02).

3.3.3.2. Facial expression recognition. Accuracy and speed during facial expression recognition showed no significant time-by-group interactions or group differences between BD+, BD- and HC (ps≥.10).

3.3.3.3. Attentional vigilance and avoidance of fearful and happy faces. Analyses revealed no significant trajectory differences or group differences between BD+, BD- and HC (ps≥.30).

3.4. Associations between aberrant cognition, subsyndromal symptoms, functioning, medication use, and illness characteristics

For all participants across both timepoints, lower global non-emotional cognitive performance was significantly associated with more subsyndromal depression (r=-.11, p=.001) and mania symptoms (r=-.12, p<.001), as well as more general functional impairments (r=-.24, p<.001). Greater difficulty with down-regulating emotions in positive scenarios was significantly associated with more subsyndromal depression (r=-.07, p=.04) but not manic: p=.51) symptoms and more functional impairments (r=-.12, p<.001). Deficit in global neurocognitive functioning correlated with difficulty with down-regulating emotions in positive social scenarios across all participants at both timepoints (r = 0.15, p<.001). For patients with BD, lower global non-emotional cognition was associated with antipsychotic use (r=-.17, p<.001) and older age of onset (r=-.20, p<.001), but did not correlate with antidepressant, anticonvulsant or lithium use (ps≥.10) or other illness characteristics (ps≥.06). Finally, difficulties with down-regulating emotions in positive social scenarios was associated with more prior mood episodes (r=-.12, p=.02), longer illness duration (r=-.13, p=.009), and more hospitalizations (r=-.12, p=.03), but not with age of onset (p=.19) or medication use (ps≥.14).

4. Discussion

We investigated the trajectory of non-emotional and emotional cognitive functioning in recently diagnosed remitted patients with BD, of their unaffected first-degree relatives, and HC at baseline and 16 months follow-up. In accordance with our first hypothesis, we found no evidence of trajectory differences between patients, UR and HC in non-emotional or emotional cognitive domains. Patients with BD showed stable deficits in global neurocognitive function and subdomains of ‘working memory and executive function’ and ‘sustained attention and psychomotor speed’ relative to HC over the 16-month follow-up period. Unaffected relatives of BD patients also showed stable impairments in ‘working memory and executive function’, that was intermediate between patients with BD and HC over both timepoints. Patients with BD were less successful at down-regulating emotions in positive social scenarios compared to both UR and HC. There were no significant differences between the groups in attention to- or recognition of- positive and negative faces. Contradictory to our second hypothesis, we found no evidence of differential cognitive changes in patients who relapsed, patients who remained in remission, and HC over the 16-month follow-up. However, only patients who had relapsed displayed greater difficulties down-regulating emotions in positive scenarios relative to HC. Finally, both lower non-emotional cognitive functioning and difficulties down-regulating emotions in positive scenarios were significantly associated with more functional impairments and subsyndromal symptoms. While global non-emotional cognitive function was associated with antipsychotic medication use and older age of onset, difficulties with positive down-regulation was associated with longer illness duration, more prior mood episodes, and hospitalizations.

4.1. Stable non-emotional cognitive trajectory in newly diagnosed patients with bipolar disorder and their unaffected relatives: no evidence of neuroprogression

The stable trajectory of widespread cognitive deficits over the 16-month follow-up in remitted, recently diagnosed patient with BD and UR is in accordance with a majority of previous longitudinal studies of neurocognition in BD (Van Rheezen et al., 2020) and UR (Correa-Ghisays et al., 2017, 2019; Luperdi et al., 2021). Meta-analyses and systematic reviews found no trajectory differences between patients with BD and HC both in recently diagnosed patients with BD (Szmulewicz et al., 2020) and patients with longer illness duration (Bora and Özderem, 2017; Cardoso et al., 2015; Samamé et al., 2022, 2014; Szmulewicz et al., 2020). Nevertheless, a few longitudinal studies reported decline in cognition over time in BD within measures of verbal memory and executive function, respectively (Santos et al., 2014; Torrent et al., 2012). In contrast to our study, these studies had (i) longer follow-up period (five and nine years, respectively), (ii) a different neuropsychological test battery, and (iii) smaller patient sample with longer illness duration. These findings are in accordance with results from longitudinal studies with dementia as the outcome measure (Velosa et al., 2020). The few longitudinal studies that have previously investigated neurocognition at multiple timepoints in adult UR have also demonstrated stable deficits in visual memory and attention and psychomo-
tor speed over two- and five-year follow-ups in UR vs. HC (Correa-Ghisays et al., 2017, 2019; Luperdi et al., 2021).

Cognitive heterogeneity in BD has been suggested to explain some of the inconsistent findings regarding neurocognitive trajectories in published studies (Van Rheenen et al., 2020). Indeed, data-driven studies found that remitted patients with BD can be categorized into distinct neurocognitive subgroups spanning intact non-emotional cognitive functioning to significant global impairments (Green et al., 2020; Kjærstad et al., 2019; Lima et al., 2019; Rabelo-da-Ponte et al., 2022). Recently, longitudinal investigations of these distinct neurocognitive subgroups in BD have shown differential cognitive trajectories between subgroups over 5-year and 16-months follow-up, respectively (Ehrlich et al., 2022; Kjærstad et al., 2022). However, these studies yielded no evidence of cognitive decline over time in patients categorized as globally impaired, further providing support for BD not being inherently a neuroprogressive disorder.

Taken together, our findings do not provide evidence for non-emotional cognitive deficits in BD having a neuroprogressive origin in the newly diagnosed stages of illness. Importantly, this could be due to the relatively short follow-up period of 16-months not being sufficient to capture neuroprogressive changes in cognition. Moreover, a majority of the present sample of newly diagnosed patients comprised of BD-II patients (68%). Also, only a few patients (n = 5) developed manic episodes during follow-up. This may explain the absence of evidence for neuroprogression because neuroprogression may be specifically associated with the neurotoxic effect of manic episodes on cognition (Samamé et al., 2022; Streijilevich et al., 2015). As such, manic episodes and/or symptoms are linked with greater cognitive decline (Sanchez-Morla et al., 2019; Schouws et al., 2016) and decreased gray matter volume and cortical volume in the bilateral dorsolateral prefrontal cortex (Abe et al., 2015; Ekman et al., 2010) - a brain region consistently implicated in cognitive dysfunction in BD (Miskowiak et al., 2016; Zarp Petersen et al., 2022). On the contrary, in the cross-sectional part of the study, we found no differences in cognition between BD-I and BD-II patients (Jensen et al., 2021), which speaks against the view that neuroprogression is particularly associated with the neurotoxic effect of manic episodes. Our results showing an association between antipsychotic use and poorer cognition is in line with previous literature suggesting a deleterious effect of antipsychotics on cognition (Xu et al., 2020). However, it is also possible that the subset of patients who use antipsychotic medication have greater cognitive difficulties and patients were rarely treated with antipsychotics alone, hindering the investigation into the direct effect of antipsychotic monotherapy on cognition. Additionally, the beneficial effects of specialized treatment as provided in a specialized clinic as the Copenhagen Affective disorder clinic may counteract accentuated neuroprogressive changes over time. Indeed, patients with BD presented with substantial functional impairments at baseline, which improved over time despite stable cognitive performance, likely due to the beneficial impact of treatment on functioning. Finally, behavioral measures of cognition may lack the required sensitivity to detect subtle trajectory differences that are otherwise detectable using more sensitive assays of brain-based changes, such as neuroimaging techniques (Kurtz et al., 2021).

4.2. Working memory and executive function as a stable marker of familial risk?

Both recently diagnosed remitted patients with BD and -to a lesser extent- their UR showed stable impairments in working memory and executive function. Across both time-points, patients with BD presented with moderate impairments in working memory and executive function (average z = −0.46), whereas their UR presented with more subtle, mild impairments (average z = −0.24). Indeed, impairments in working memory and executive functioning have consistently been reported in UR (Bora et al., 2009; Gillissie et al., 2022; Miskowiak et al., 2017b). In a recent meta-analysis of neurocognitive functioning in UR, executive functioning was found to be the neurocognitive domain most affected in UR (Gillissie et al., 2022), suggesting a promising endophenotype for BD. There is currently a lack of consensus on what constitutes ‘clinically relevant’ cognitive impairment. Small to medium effect sizes in BD and UR may nevertheless reflect clinically relevant impairments, particularly given the association between poorer cognition and more functional impairments and subsyndromal symptoms in the present study (Miskowiak et al., 2017a). Taken together, impairments in this domain may reflect a trait-related marker of BD associated with familial risk. As such, impairments in working memory and executive function in UR may signify a prodromal symptom of BD, rendering the UR exhibiting impairments in this domain a population at particularly high risk of illness onset. Indeed, impairments in measures of working memory and executive functioning have been found to predict subsequent illness onset (mainly BD, but also MDD and anxiety) in individuals at heritable risk of BD (Meyer et al., 2004; Vinberg et al., 2013).

4.3. Emotional cognition: emotion down-regulation of positive emotion associated with illness progression?

The observed stable impairments in emotion down-regulation in positive social scenarios in BD over the 16-month follow-up period are in line with cross-sectional studies showing positive emotion regulation deficits in patients with BD at early (Kjærstad et al., 2020) and more progressed stages of the disorder (Kurtz et al., 2021). Notably, even though deficits in both positive emotion regulation and global non-emotional cognition do not significantly change over time, these stable deficits in BD significantly correlate, in which more impairments in non-emotional cognition function are associated with more emotion regulation difficulties. Moreover, the stable difficulties with down-regulating emotion in positive social scenarios in BD was particularly prominent in patients who had relapsed during 16-month follow-up. This, coupled with the finding that emotion regulation abilities in UR were on par with HC, suggests that the deficient emotion regulation in positive scenarios observed in BD patients may reflect disease-related scarring of experienced mood episodes. In line with this, lower ability to
down-regulate emotion in positive scenarios correlated with features of illness progression, including longer illness duration and more prior mood episodes. The group of patients who had relapsed in the 16-month follow-up period may reflect the existence of a more severely impaired subgroup of patients experiencing more recurrent mood episodes. This further highlights the importance of early treatment and targeted prophylactic strategies for newly diagnosed individuals to counteract the onset of new mood episodes and, consequently, the effects of illness progression on emotion regulation abilities.

The lack of trajectory differences between groups or group differences in attention to or recognition of emotional facial expressions is in contrast with previous observations of attentional interference by emotional stimuli and impairments in facial expression recognition in remitted patients with BD (Miskowiak et al., 2019) of which the latter seems to prevail for up to seven years (Martino et al., 2016). The lack of group differences in the present study may be due to differences in the employed paradigms or statistical methods. Moreover, this is the first study to assess emotional cognition longitudinally in UR. More studies using various measures of emotional cognition are warranted to further investigate potential markers of BD associated with familial risk, given that impairments in emotional cognition has been suggested to represent a putative marker of BD that is more specific to BD compared to more transdiagnostic impairments in non-emotional cognitive functioning (Guglielmo et al., 2021; Kessing and Miskowiak, 2018).

4.4. Strengths and limitations

Strengths of the study include the longitudinal design, the inclusion of an extensive cognitive battery assessing both non-emotional and emotional cognition, and the large sample of recently diagnosed patients, unaffected first-degree relatives, and HC, which enables the assessment of cognition at various illness stages. Nevertheless, it should be noted that even though patients were recently diagnosed within two years prior to study inclusion, they had a median delay in diagnosis of BD (i.e., time difference between first mood episode and diagnosis of BD) of four years. This diagnostic delay is characteristic of BD and impedes research into the early stages of the disorder (Berk, 2009).

Thus, it is plausible that illness progression (e.g., number of mood episodes) prior to study inclusion have contributed to the cognitive deficits observed in the sample of BD patients. Nevertheless, the main limitation of the study is the short follow-up period of 16-months. Previous studies with longer follow-up of five to nine years have previously found evidence of neuroprogressive decline in cognition (Santos et al., 2014; Torrent et al., 2012). Thus, it is likely that the 16-month follow-up period in the current study is too short a period for potential neuroprogression to take place. We continue to prospectively follow-up the BIO cohort and will replicate analyses at a later stage. Moreover, it is possible that neuroprogressive cognitive decline over time is more pronounced in patients who opt not to participate in the study or are lost at follow-up. A limitation was the number of participants with cognitive data at both timepoints (62%; baseline n = 561; follow-up n = 348).

This decrease in participants with follow-up data may reflect a selection bias common in longitudinal research. In fact, the current follow-up sample is consistent with previous longitudinal studies of cognition during the early stages of the illness, which have generally included a follow-up sample of approximately 53–67% of the original baseline sample (Daglas et al., 2016; Demno et al., 2017; Lee et al., 2015; Torres et al., 2020). Notably, those who were lost to follow-up did not differ on age, sex, years of education, or subsyndromal depression or mania symptoms. An additional limitation was that most patients received pharmacological treatment, which has been associated with both neuroprotective and neurodegenerative effects (Dias et al., 2012). Unhealthy lifestyle factors prevalent in BD - such as high sedentary behavior and low levels of physical activity coupled with poor diet quality - may partially explain cognitive symptoms that persist over time (Van Rheenen and O’Neill, 2022). However, investigating the potential confounding effects of unhealthy lifestyle factors is beyond the scope of this study.

4.5. Conclusion

In conclusion, this longitudinal assessment of a large sample of newly diagnosed patients with BD, UR, and HC revealed no trajectory differences between groups over a 16-month follow-up time, thus providing no evidence for neuroprogressive changes. Further, remitted patients with BD exhibited stable trait-related impairments in global non-emotional cognition, as well as in the domains of ‘working memory and executive function’ and ‘attention and psychomotor speed’. Both patients and UR showed stable impairments in ‘working memory and executive function’, highlighting this domain as a putative marker of familial risk. Stable impairments in down-regulation of emotions in positive social scenarios was particularly prominent in patients who relapsed during the follow-up time and was associated with longer illness duration and more prior mood episodes, suggesting a, possibly bidirectional, link with illness progression.

Contributors

KWM, LVK and MV were principle investigators of the BIO study. KWM was responsible for the original BIO-3 study design and draft of protocol. HLK was responsible for participant recruitment and conducting diagnostic interviews. HLK were responsible for rating of mood symptoms, neuropsychological testing and data collection, under the supervision of KWM. KS wrote the initial manuscript draft and conducted the statistical analyses in collaboration with HLK and KWM. All authors contributed to interpretation of the data. All authors have approved the final manuscript.

Role of funding source

The BIO study is funded by grants from the Mental Health Services, Capital Region of Denmark, The Danish Council for Independent Research, Medical Sciences
Declarations of Conflicts of Interest

MV has received consultancy fees from Lundbeck and Janssen Cilag the past three years. LVK has within the preceding three years been a consultant for Lundbeck and Teva. KWM has received consultancy fees from Lundbeck and Janssen-Cilag in the past three years. The remaining authors declare no conflicts of interest.

Acknowledgements

The Research Fund of the Mental Health Services - Capital Region of Denmark has provided HLK’s post-doctorate salary. KWM holds a five-year Lundbeck Foundation Fellowship (grant no. R215-2015-4121).

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