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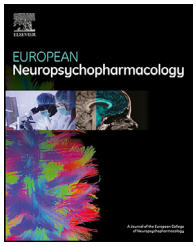

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The longitudinal trajectory of emotional cognition in subgroups of recently diagnosed patients with bipolar disorder

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Abstract
Although cross-sectional studies show heterogeneity in emotional cognition in bipolar disorder (BD), the temporal course within subgroups is unclear. In this prospective, longitudinal study we assessed the trajectories of emotional cognition subgroups within a 16-month follow-up period in recently diagnosed BD patients compared to healthy controls (HC). Recently diagnosed BD patients and HC underwent comprehensive emotional and non-emotional testing at baseline and again at follow-up. We employed hierarchical cluster analysis at baseline to identify homogenous emotional cognition subgroups of patients, and changes across the subgroups of BD and HC were assessed with linear mixed-model analyses. We found two emotional cognition subgroups: subgroup 1 (65%, $n = 179$), showing heightened negative emotional reactivity in neutral and negative social scenarios and faster recognition of emotional facial expressions than HC (ps$<$0.001, $n = 190$), and subgroup 2 (35%, $n = 96$) showing blunted reactivity in positive social scenarios, impaired emotion regulation, poorer recognition of positive and slower

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recognition of all facial expressions than HC (ps≤.03). Subgroup 1 exhibited normalization of the initial emotional cognition abnormalities in follow-up. In contrast, subgroup 2 showed a *lack of* improvement in reactivity positively-valenced emotional information. Patients in subgroup 2 presented more and longer mixed episodes during the follow-up time and were more often prescribed lithium. One third of patients display blunted emotional reactivity, impaired emotion regulation abilities and facial expression recognition difficulties also show persistent impairments and poorer course of illness. This subgroup may indicate a need for earlier and more targeted therapeutic interventions.

1. Introduction

Bipolar Disorder (BD) is associated with impairments in non-emotional and emotional cognitive functions, which persist during periods of remission (Bourne et al., 2013; Miskowiak et al., 2019a) and impacts functioning (Martinez-Aran et al., 2007; Ospina et al., 2018; Sanchez-Moreno et al., 2018) and quality of life (Michalak et al., 2005). Nonetheless, there is wide variability in cognitive functioning, as indicated by recent data-driven analyses that revealed subgroups of patients with distinct profiles of non-emotional and emotional cognitive functions (Bora et al., 2016; Burdick et al., 2014; Kjærstad et al., 2021; Russo et al., 2017; Varo et al., 2021, 2020). Current psychological treatments in BD aim to enhance medical adherence, stabilize mood symptoms, prevent relapse, and improve cognitive and overall functioning. However, a major caveat of all these interventions is that they use a "one fits all" strategy that neglects the heterogeneity of BD. There is a need for more targeted approaches to treatment and prevention. In line with this, personalized medicine proposes a more tailored therapy based on the patient's personal characteristics (Wium-Andersen et al., 2017). Thus, characterizing specific subgroup profiles and their trajectory can help re-think standard psychological treatments based on a more personalized approach towards the patient's needs.

Patients with BD exhibit trait-related impairments in emotional cognition, most consistently within the domains of facial emotion recognition and implicit emotion regulation, reward processing and affective decision making, although findings vary across studies (for systematic review, see Miskowiak et al., 2019a). This variability across studies is likely to reflect heterogeneity within emotional cognition in remitted patients with BD (Szmulewicz et al., 2020; Varo et al., 2021, 2020). In a large sample of fully or partially remitted patients with mood disorders, we found evidence for three distinct emotional cognition subgroups characterized as either 'emotionally preserved' (57%), 'emotionally blunted' (26%) or 'emotionally volatile' (17%), of which the two latter subgroups also displayed deficits in non-emotional cognition (Varo et al., 2021). Additionally, two studies of social cognition heterogeneity in patients with BD found evidence of two distinct profiles; one subgroup of patients showed normal performance (68% (Varo et al., 2020) and 71% (Szmulewicz et al., 2020), while the second subgroup displayed mild to moderate impairments in theory of mind, attributional bias (32%) (Varo et al., 2020) and emotional processing (29%) (Szmulewicz et al., 2020). Notably, these subgroups of patients with emotional cognition difficulties also showed more severe neurocognitive impairment, lower functioning, higher number of psychosis-like traits in one study (Szmulewicz et al., 2020), and higher subthreshold depressive symptoms, longer illness duration and poorer visual memory and attention in the other study (Varo et al., 2020). It has therefore been hypothesized that the deficits in emotional cognition, found in approximately 30% of patients, impact negatively on interpersonal relations and daily functioning and should therefore be directly targeted in future psychological interventions (Szmulewicz et al., 2020; Varo et al., 2020).

Nevertheless, studies to date have examined emotional cognition subgroups cross-sectionally (Szmulewicz et al., 2020; Varo et al., 2021, 2020). Longitudinal studies are needed to evaluate the trajectories in emotional cognition subgroups and elucidate the potential clinical prognostic implications of certain emotion cognitive profiles, which could be valuable for future treatment stratification. Further, longitudinal studies can provide insight into whether some - but not other - subgroups of patients are marked by 'neuroprogression', i.e., alteration of neurocognitive functions and brain structure and function due to ongoing illness-associated biochemical processes (Cardoso et al., 2015; Kessing and Andersen, 2017; Serafini et al., 2021). Therefore, the aim of this prospective, longitudinal study was to assess (i) the trajectory of emotional cognition subgroups within a 16-month follow-up period in recently diagnosed patients with BD compared to healthy control (HC) individuals; and (ii) whether potential trajectory differences are associated with illness characteristics, subsyndromal symptom severity, non-emotional cognition or functioning. We hypothesize that one or two emotional cognition subgroups of BD patients with deficits in emotion reactivity - and regulation and facial expression recognition will exhibit decline/ lack of improvement in emotional cognition over time and a poorer course of illness.

2. Methods

2.1. Study design

This study is part of the ongoing longitudinal Bipolar Illness Onset (BIO) cohort study (Kessing et al., 2017). The study protocol was approved by the Committee on Health Research Ethics of the Capital region of Denmark (proto-

col number: H-7-2014-007) and the Danish Data Protection Agency, Capital Region of Copenhagen (protocol number: RHP-2015-023). Informed consent was provided by all participants prior to inclusion in this study.

2.2. Participants

Recruitment took place between June 2015 and July 2022. At baseline, participants included 466 participants: 276 patients with BD diagnosis and 190 HC. Follow up data was collected in 321 participants: 175 patients with BD diagnosis and 146 HC. Patients, 18-65 years of age, were recruited from Copenhagen Affective Disorder Clinic, Psychiatric Centre Copenhagen, Denmark, where they were initially diagnosed with BD according to diagnostic criteria of the ICD-10 (World Health Organization, 1992) by specialists in psychiatry. Diagnosis of BD was made within two years prior to study inclusion. Patients received specialized treatment during study participation, including psychopharmacological treatment and psychoeducation (Kessing et al., 2013).Age- and sex-matched HC were recruited from the University Hospital Blood Bank, Rigshospitalet, Copenhagen. Exclusion criteria for HC were a personal or familial history of psychiatric disorder. All participants underwent diagnostic assessment using the semi-structured Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990) to confirm diagnosis of BD and lack of psychiatric illness in HC, respectively. The SCAN was conducted by a PhD-student in medicine or psychology. Exclusion criteria for all participants were total score >14 on the Hamilton Depression Rating Scale-17 (HDRS-17; Hamilton, 1967) or the Young Mania Rating Scale (YMRS; Young et al., 1978), severe somatic illness, a history of brain injury or neurological illnesses including dementia, and pregnancy. All participants were fluent in Danish.

2.3. Assessments

2.3.1. Emotional cognition measures

Participants were administered the Facial Expression Recognition Task (FERT) and Faces Dot-Probe Task from the Emotional Test Battery (P1vital® Oxford Emotional Test Battery, 2017) and the Social Scenarios Task to investigate processing of faces, emotional reactivity, and ability to downregulate emotions, respectively.

Facial Expression Recognition Task: This measure assessed discrimination accuracy and speed during facial expression recognition (Harmer et al., 2004; Kjærstad et al., 2020). Participants viewed pictures of faces depicting one of six emotions: fear, anger, disgust, sadness, happiness, and surprise. Faces were morphed at varying intensities in 10% increments, ranging from 0% (depicting a neutral face) to 100% (depicting full emotion). Two-hundred-and-fifty faces were presented in randomized order for 500 ms each. Four pictures of each emotion at each intensity level were shown, along with a neutral face for every emotion (in total 24 neutral faces). Participants indicated the emotion by pressing the corresponding key on a keyboard as quickly and accurately as possible. Facial expression recognition accuracy, misclassifications, and reaction times (RT) were recorded.

Faces Dot-Probe Task: This task involves the presentation of a pairs of happy-neutral, fearful-neutral, or neutral-neutral faces presented horizontally on a computer screen either masked (17 ms) or unmasked (100 ms) (Kjærstad et al., 2020; Murphy et al., 2008). One of the faces is then replaced by a probe depicted as either two vertical dots (:) or horizontal dots (..) and participants are instructed to indicate the orientation of the dots as quickly and accurately as possible. Reaction time to recognize the probe is calculated and used to infer attention markers. The faster the reaction for probes that replace emotional stimuli when compared to those that contain neutral stimuli indicate attentional vigilance and slower reaction times can be interpreted as attentional avoidance. The task comprised eight masked and eight unmasked blocks, in which each block included 12 alternately presented trials.

Social Scenarios Task: Participants read short text descriptions of positive or negative social situations and accompanying self-belief statements on a computer screen (Kjærstad et al., 2016). Participants were instructed to either react naturally or dampen their emotional response to the scenario before each block. The task comprised a total of nine blocks with each block comprising 11 sentences describing the scenario, 10 related self-belief statements (both blocks duration of 3 s) and 10 emotion ratings asking participants to rate their discomfort or pleasure on a visual analogue scale from 0 to 100. The opening block was a neutral condition followed by two negative scenarios with alternate react/dampen conditions. Participants received no specific instructions regarding which emotion regulation strategy to use during the 'dampen' conditions to elicit the strategy that participants would typically use in their daily life. The Social Scenarios Task was developed in-house, where, based on patient interviews, the scenarios with highest personal relevance and emotional salience were selected to produce a task with increased ecological validity that was specific for bipolar disorder (Kjærstad et al., 2016).

2.3.2. Non-emotional cognition measures

To assess non-emotional cognition, a neuropsychological test battery was used (Kjærstad et al., 2020), covering the cognitive domains: 'working memory and executive function', 'attention and psychomotor speed', 'verbal learning', and 'verbal fluency'. The 'working memory and executive function' composite included the letter-number sequencing from the Wechsler's Adult Intelligence Scale 3rd edition (WAIS-III), Spatial Working Memory (SWM) 'between errors' and 'strategy' from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the TMT-B (Army Individual Test Battery, 1944). The 'attention and psychomotor speed' composite was made up by the digit span forward and coding subtests from Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), the Trail Making Test-A (TMT-A) (Army Individual Test Battery, 1944), and the Rapid Visual Information Processing (RVP) subtest (A' and mean latency) from the CANTAB. The 'verbal learning' composite comprised trial I-V correct, trial VI correct, delayed recall and recognition from the Rey Auditory Verbal Learning Test (RALVT) (Rey, 1958). Finally, the 'verbal fluency' composite comprised verbal fluency with letters S and D.

2.3.3. Clinical measures, functioning, and IQ

Subsyndromal depression and mania symptoms were rated using the HDRS and YMRS, respectively. All participants scored $\leq$14 on HDRS and YMRS, to ascertain full or partial remission in BD patients. To assess overall functioning we used the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) a 24-item semi-structured interview. FAST is comprised of six subdomains of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Functional impairment is established by a total score of >11 (Bonnín et al., 2018). To assess predicted full-scale IQ, we used the Danish Adult Reading Task (DART) (Nelson and O'Connell, 1978).

2.4. Statistical analysis

Baseline values missing at random were imputed using multiple imputation method with 1000 imputations and cognitive scores as predictors. For the Social Scenarios Task, measures of 'emotion down-regulation' were calculated by subtracting the 'negative dampen'/ 'positive dampen' conditions from the 'negative view'/ 'positive view' conditions. For the Facial Expression Recognition task, reaction times were log-transformed, and a measure of discrimination accuracy of facial expressions (d′) was calculated for each facial expression using the formula [(number of hits + 0.5)/(number of targets + 1)] − [(number of false alarms + 0.5)/(number of distractors + 1)] (Corwin, 1994). We collapsed facial expressions of positive (happy, surprise) and negative (anger, disgust, fear, sadness) valence. For the Faces Dot-Probe Task, we calculated vigilance scores by subtracting median RT in congruent trials from incongruent trials. Positive values reflect vigilance (i.e., attention towards the emotional face), and negative values reflect avoidance (i.e., attention away from the emotional face). Emotional and non-emotional cognition raw test scores were standardized to z-scores based on HCs' baseline means (M) and standard deviations (SD) using the formula: (test score - HC test M)/HC test SD (i.e., $M = 0$, SD=1). Outlying z-scores of ±4 were truncated to $z = -4.0$ or 4.0, respectively. The z-scores for speed during recognition of positive and negative faces, TMT-A, TMT-B, SWM 'between errors' and 'strategy', and RVP 'mean latency' were inverted so that lower scores represented poorer performance. Z-scores of the neurocognitive tests were averaged to four neurocognitive domains (e.g.: 'working memory and executive function', 'attention and psychomotor speed', 'verbal learning', and 'verbal fluency') and the four domains were averaged to calculate a measure of global non-emotional cognition.

2.4.1. Hierarchical cluster analysis

All analyses conducted were performed with the IBM Statistical Package for Social Sciences version 25. To investigate homogeneous subgroups of patients based on emotional cognition performance, we conducted a hierarchical cluster analysis (HCA) with squared Euclidian distance and Ward's linkage with the emotional cognition variables comprising: (i) emotional reactivity and down-regulation of emotions in negative and positive social scenarios; (ii) accuracy (d') and speed during facial expression recognition of positive and negative faces; and (iii) attentional vigilance to masked and unmasked fearful and happy faces. The dendrogram and agglomeration schedule were visually inspected to establish the appropriate number of subgroups to be retained (Yim and Ramdeen, 2015). Additionally, we conducted a discriminant function analysis (DFA) with leave-one-out classification to test the validity of the cluster solutions.

2.4.2. Comparisons between subgroups and healthy controls

For baseline comparisons between groups, the resulting subgroups of patients and HC were compared in emotional cognition to ascertain their emotional-cognitive profile, as well as in non-emotional cognition, demographic, clinical and functional variables, respectively, using analysis of variance (ANOVA) and pair-wise comparisons with Sidak correction and chi-square, as appropriate.

To investigate differential change over time in the subgroups of patients with BD and HC, we employed linear mixed models analyses with time and group (emotional cognition subgroups of patients with BD and HC) as fixed effect and adjusting for age, sex, and time between assessments. For any significant effects of group, secondary analyses adjusted additionally for (i) subsyndromal depression and mania symptoms (HDRS and YMRS total scores) and (ii) lithium medication use. Multiple comparisons were corrected for using Sidak in all analyses. Analyses were two-tailed, and significance-levels set to α=0.05.

2.4.3. Associations between baseline emotional cognition deficits and symptoms, functioning, non-emotional cognition and clinical characteristics

For the respective subgroups, post hoc Pearson correlation analyses were conducted to investigate whether baseline aberrant emotional cognition *within the respective subgroup* was associated with (i) lower functioning, more subsyndromal symptoms, impairments in non-emotional cognition (both subgroups); (ii) clinical characteristics specific to the subgroup (i.e., duration of depressive episodes for patients in subgroup 1 and hospitalizations, frequency, and duration of mixed episodes for patients in subgroup 2 during the follow-up time).

3. Results

3.1. Emotional cognition clustering

Patients at baseline were optimally clustered into two distinct subgroups based on their emotional cognition performance: one subgroup of 179 patients (65%) characterized by heightened emotional reactivity and a subgroup of 97 patients (35%) with broad emotional cognition deficits (see Figure S1 for dendrogram). Specifically, the DFA revealed that the two-cluster solution had the best predictive power and best results for classification sensitivity (90.2%), (see supplement for more information on selection of cluster solutions). Results from the DFA revealed a discriminant function (Wilks' λ=0.44, χ^2 (13) =222.42, p<.001) with 'speed during recognition of negative faces' contributing most to

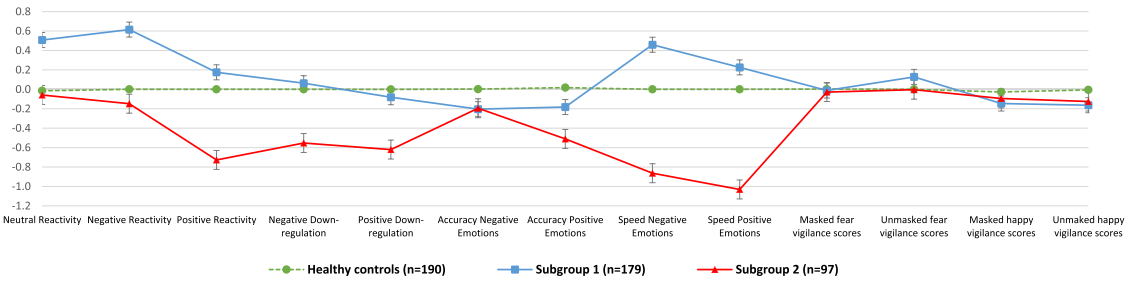

Fig. 1 Baseline emotional cognition across the two subgroups of patients with bipolar disorder classified according to emotional cognition clustering and healthy controls.

clustering by comprising the highest loading task for the discriminant function ($r = 0.54$). The classification results revealed high sensitivity with 90.2% of original cases correctly classified (Figure 1).

3.2. Emotional cognition profiles: comparisons between patient subgroups and healthy controls at baseline

There was a statistically significant difference between the two emotional cognition subgroups of patients with BD and HC at baseline in all emotional cognition measures (all ps<0.001), except for discrimination accuracy of negative emotions and all measures from the Faces Dot Probe Task (ps≥.12) (Table 1; Figure 1). These significant differences were driven by patients in subgroup 2 presenting with emotional cognition difficulties with moderate to large effect sizes (z-scores: −.55 to −1.03), reflected by (I) lower emotional reactivity in positive scenarios (ps<0.001); (II) less successful downregulation of emotional responses in positive and negative social scenarios (ps<0.001); (III) poorer recognition accuracy of positive facial expressions (ps≤.03); and (IV) slower recognition of both positive and negative faces (ps<0.001) than HC and patients in subgroup 1. Patients in subgroup 1 exhibited mild to moderate aberrancies in emotional cognition (z-scores: 0.23 to 0.62), reflected by (I) higher negative emotional reactivity in neutral and negative social scenarios (ps<0.001); and (II) faster recognition of both positive (ps≤.049) and negative facial expressions (ps<0.001) than patients in subgroup 2 and HC (i.e., a *supranormal* fast recognition of facial expressions).

3.3. Baseline characteristics

The subgroups of patients and HC were comparable in IQ (p=.32) (Table 2). There was a significant difference between the three groups in sex (F(2463)=8.58, p<.001), age (F(2454)=3.11, p=.046) and years of education (F(2462)=9.34, p<.001). These interactions were driven by more females in subgroup 1 (74%) when compared to subgroup 2 (50%) and HC (62%) (ps<0.001), with no significant difference between subgroup 2 and HC (p=.05). Subgroup 1 were younger compared to subgroup 2 (p=.04), with no significant differences for both subgroups when compared to HC (ps≥.34). Patients in subgroup 1 had completed fewer years of education compared to patients in subgroup 2 (p=.03) and HC (p<.001). Moreover, there were significant differences between the groups in subsyndromal depressive (F(2462)=105.10, p<.001) and manic (F(2462)=35.32, p<.001) symptoms, which were driven by more symptoms in both patient subgroups compared to HC (ps<0.001), with no differences between the subgroups (ps≥.33). There was a significant difference between subgroups and HC in functioning (FAST total score; F(2458)=170.00, p<.001), as the patients were more functional impaired relative to HC (ps<0.001), however there was no difference between the subgroups (p=.054). With regards to clinical characteristics, patients in subgroup 2 had been more frequently hospitalized than patients in subgroup 1 (F(1273)=4.30, $p = 0.04$). However, there were no differences between the subgroups in BD type (BD-I versus BD-II), illness duration, untreated illness, number of previous suicide attempts, comorbid anxiety disorders or current medication (lithium, anticonvulsants, antidepressants, antipsychotics) (ps≥.11) at baseline.

3.4. Change in emotional cognition over time

3.4.1. Emotion reactivity and down-regulation in social scenarios

The results revealed statistically significant trajectory differences between the two patient's subgroups and HC (i.e., time-by-group interactions) in negative emotional reactivity in neutral scenarios (F(2368.50)=11.04, p<.001). While patients in subgroup 1 displayed *decreased* emotional reactivity over time (p=.001) compared to HC who remained stable (p=.24), patients in subgroup 2 displayed *increased* reactivity over time (p=.01) (Figure 2A). There was also a significant time-by-group interaction for emotional reactivity in positive social scenarios (F(2328.50)=4.17, $p = 0.02$): whereas patients in subgroup 1 and HC showed the same slope of normative decrease in reactivity over time (ps≤.04), patients in subgroup 2 did not change (p=.51) (Figure 2B). Similarly, a significant time-by-group interaction for emotional reactivity in negative scenarios (F(2327.29)=3.92, $p = 0.02$) was driven by normative decrease in emotional reactivity over time in patients in subgroup 1 (p=.009), whereas patients in subgroup 2 did not change over time (p=.20) (Figure 2C). All significant interaction effects prevailed after adjusting for subsyndromal depression and mania symptoms (ps≤0.03) and lithium use (ps≤.003).

With regards to emotion down-regulation in negative scenarios, there was a significant time-by-group interaction (F(2349.33)=3.07, $p = 0.048$); whereas patients in subgroup

Table 1 Emotional cognition across subgroups of patients with bipolar disorder and healthy controls (HC) at baseline, follow-up, and group-by-time interactions.

	Baseline							**Follow Up**							Main effect of group, p-value	Group-by-time interaction. p-value
	Subgroup 1 ($n = 179$)	Subgroup 2 ($n = 96$)	HC ($n = 190$)	p	Pairwise comparison SG1 vs. SG2	SG1 vs. HC	SG2 vs. HC	Subgroup 1 ($n = 118$)	Subgroup 2 ($n = 57$)	HC ($N = 146$)	p	Pairwise comparison SG1 vs. SG2	SG1 vs. HC	SG2 vs. HC		
Social Scenarios Task																
Neutral emotion reactivity	0.51 (1.28)	−0.06 (0.64)	−0.01 (0.92)	**<0.001**	**<0.001**	**<0.001**	0.98	0.16 (1.09)	0.41 (1.28)	0.16 (1.19)	0.29				**0.04**	**<0.001**
Positive emotion reactivity	0.18 (0.95)	−0.72 (1.38)	0.00 (1.00)	**<0.001**	**<0.001**	0.32	**<0.001**	0.18 (0.95)	−0.73 (1.39)	0.00 (1.00)	**0.02**	0.06	0.98	**0.02**	**<0.001**	**0.02**
Negative emotion reactivity	0.62 (0.83)	−0.15 (1.11)	0.00 (1.00)	**<0.001**	**<0.001**	**<0.001**	0.52	0.33 (1.07)	0.50 (1.13)	−0.09 (1.11)	**0.01**	0.32	**0.008**	0.78	**<0.001**	**0.02**
Positive downregulation	0.08 (1.03)	−0.62 (0.82)	0.00 (1.00)	**<0.001**	**<0.001**	0.81	**<0.001**	0.01 (1.03)	−0.36 (1.10)	−0.00 (0.99)	**<0.001**	0.12	0.26	**0.002**	**<0.001**	0.64
Negative downregulation	0.06 (0.93)	−0.56 (0.91)	0.00 (1.00)	**<0.001**	**<0.001**	0.89	**<0.001**	0.00 (0.93)	−0.25 (1.17)	−0.03 (1.05)	0.29				**0.005**	**0.048**
Facial Recognition Task																
Discrimination Accuracy (d'):																
Positive emotions	−0.12 (0.93)	−0.51 (1.32)	0.02 (0.90)	**<0.001**	**0.03**	0.17	**<0.001**	−0.18 (0.93)	−0.51 (1.32)	0.02 (0.90)	0.42				**0.01**	**0.008**
Negative emotions	−0.20 (1.00)	−0.19 (1.17)	0.00 (1.00)	0.12				−0.19 (1.12)	−0.19 (1.17)	0.00 (0.99)	0.91				0.61	**0.01**
Speed:																
Positive emotions	0.22 (0.79)	−1.03 (0.90)	0.00 (1.00)	**<0.001**	**<0.001**	**0.049**	**<0.001**	−0.40 (1.03)	−0.74 (0.99)	−0.54 (1.09)	0.23				**<0.001**	**<0.001**
Negative emotions	0.46 (0.84)	−0.87 (0.97)	0.00 (1.00)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	−0.54 (1.09)	−0.44 (1.02)	−0.33 (1.24)	0.71				**<0.001**	**<0.001**
Dot Probe Task																
Masked fear	−0.01 (1.00)	−0.03 (1.11)	0.00 (1.00)	0.97				−0.13 (1.05)	0.26 (1.03)	0.09 (0.80)	**0.04**	0.80	0.18	0.06	0.17	0.24
Masked happy	−0.14 (0.94)	−0.09 (0.96)	−0.03 (0.84)	0.45				0.71 (0.71)	0.09 (0.61)	−0.04 (0.78)	0.45				0.84	0.13
Unmasked fear	0.13 (0.84)	−0.00 (0.92)	0.00 (1.00)	0.34				0.21 (0.95)	0.43 (1.14)	0.01 (1.01)	**0.03**	0.46	0.34	**0.03**	**0.049**	0.06
Unmasked happy	−0.16 (0.66)	−0.12 (1.05)	−0.01 (0.84)	0.17				0.12 (0.81)	0.00 (1.01)	−0.02 (0.83)	0.41				0.79	0.10

Abbreviations: SG1= subgroup 1 patients with bipolar disorder, SG2 = subgroup 2 patients with bipolar disorder. Values reflect means (standard deviations) unless otherwise noted. Bold text in the table indicates significant values.

Table 2 Demographic and clinical variables at baseline, follow-up, and group-by-time interaction in the two emotional subgroups of patients with bipolar disorder and healthy controls (HC).

	Baseline							**Follow Up**								
	Subgroup 1 ($n = 179$)	Subgroup 2 ($n = 96$)	HC ($n = 190$)	*p*	Pairwise comparison			Subgroup 1 ($n = 118$)	Subgroup 2 ($n = 57$)	HC ($N = 146$)	*p*	Pairwise comparison			Main effect of group, p-value	Group-by-time interaction, p-value
					SG1 vs SG2	SG1 vs HC	SG2 vs HC					SG1 vs SG2	SG1 vs HC	SG2 vs HC		
Sex. n (% female)	132 (74%)	48 (50%)	117 (62%)	**<0.001**	**<0.001**	**0.01**	0.05									
Age. years (SD)	30.16 (8.15)	33.36 (10.17)	31.43 (11.16)	**0.046**	**0.04**	0.53	0.34									
Education	14.63 (3.15)	15.70 (3.85)	16.08 (3.05)	**<0.001**	**0.03**	**<0.001**	0.73	15.41 (3.77)	16.24 (3.12)	16.23 (1.97)	0.06	0.24	0.08	1.0	**<0.001**	0.41
HDRS	5.56 (4.28)	5.39 (3.77)	0.99 (1.48)	**<0.001**	0.96	**<0.001**	**<0.001**	4.80 (3.92)	4.37 (3.61)	0.97 (1.46)	**<0.001**	0.76	**<0.001**	**<0.001**	**<0.001**	**0.04**
YMRS	2.83 (3.18)	2.34 (2.85)	0.69 (1.40)	**<0.001**	0.33	**<0.001**	**<0.001**	2.34 (3.28)	3.51 (3.90)	0.65 (1.56)	**<0.001**	**0.03**	**<0.001**	**<0.001**	**<0.001**	**0.002**
IQ	111.74 (5.71)	112.28 (5.32)	112.64 (5.60)	0.32												
FAST Score																
FAST Total	19.01 (12.84)	16.12 (11.45)	1.33 (2.16)	**<0.001**	0.054	**<0.001**	**<0.001**	12.09 (10.33)	15.56 (11.30)	1.69 (3.33)	**<0.001**	**0.02**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FAST autonomy	1.99 (2.32)	1.53 (1.97)	0.13 (0.47)	**<0.001**	0.09	**<0.001**	**<0.001**	1.13 (1.68)	1.82 (2.28)	0.11 (0.41)	**<0.001**	**0.01**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FAST occupation	6.45 (6.96)	5.79 (6.37)	0.16 (0.53)	**<0.001**	0.68	**<0.001**	**<0.001**	3.65 (5.33)	5.98 (6.53)	0.57 (2.50)	**<0.001**	**0.006**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FAST cognition	4.39 (3.49)	4.17 (3.27)	0.40 (0.76)	**<0.001**	0.88	**<0.001**	**<0.001**	3.64 (2.66)	3.55 (2.77)	0.45 (0.89)	**<0.001**	0.88	**<0.001**	**<0.001**	**<0.001**	**0.001**
FAST financial	1.22 (1.69)	1.13 (1.63)	0.10 (0.39)	**<0.001**	0.92	**<0.001**	**<0.001**	1.22 (1.69)	1.13 (1.63)	0.10 (0.39)	**<0.001**	0.92	**<0.001**	**<0.001**	**<0.001**	**0.006**
FAST relationships	3.44 (3.38)	2.79 (2.60)	0.35 (0.88)	**<0.001**	0.11	**<0.001**	**<0.001**	2.29 (2.60)	2.44 (2.74)	0.33 (0.75)	**<0.001**	0.96	**<0.001**	**<0.001**	**<0.001**	**0.001**
FAST leisure.	1.51 (1.67)	0.72 (1.12)	0.19 (0.48)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.78 (1.18)	0.96 (1.25)	0.17 (0.54)	**<0.001**	0.55	**<0.001**	**<0.001**	**<0.001**	**<0.001**
BD Type II. N (%)	122 (68%)	68 (71%)		0.65												
Comorbid anxiety disorder (F40-F42), n (%)	20 (11%)	11 (12%)		0.90												
Illness duration[a]	7.85 (7.46)	8.87 (7.84)		0.29				9.00 (7.12)	8.87 (7.84)		0.32					
Untreated illness[b]	6.69 (7.49)	7.18 (7.49)		0.60												
Hospitalizations	0.73 (1.41)	1.13 (1.65)		**0.04**				0.73 (1.08)	1.25 (1.60)		**0.01**				0.06	0.79
Suicide attempts	0.52 (1.55)	0.54 (2.62)		0.96												
ECT	0.61 (3.29)	0.44 (2.24)		0.99				0.73 (3.80)	0.49 (2.61)		0.63					0.99
Lithium, n (%)	85 (48%)	40 (42%)		0.36				42 (36%)	29 (51%)		0.054				0.31	**0.04**
Anticonvulsants, n (%)	70 (39%)	44 (46%)		0.28				76 (64%)	36 (63%)		0.87				0.65	0.42
Antidepressants, n (%)	39 (22%)	13 (14%)		0.10				13 (11%)	7 (12%)		0.81				0.44	0.16
Antipsychotic, n (%)	60 (34%)	34 (35%)		0.75				48 (41%)	16 (28%)		0.11				0.32	0.10
Polypharmacy	1.42 (0.86)	1.36 (0.95)		0.56				1.52 (0.76)	1.54 (0.96)		0.94					0.57
Episodes between baseline and follow-up																
No of depressive episodes								1.29 (1.42)	0.95 (1.27)		0.10					
Duration of depressive episodes, days								93.32 (130.83)	47.25 (73.95)		**0.03**					
No of (hypo)manic episodes								1.09 (2.65)	0.63 (0.93)		0.85					
Duration of (hypo)manic episodes, days								25.41 (85.89)	10.87 (24.02)		0.49					
No of mixed episodes								0.03 (0.18)	0.14 (0.40)		**0.03**					
Duration of mixed episodes, days								1.47 (9.14)	7.61 (31.34)		**0.03**					

Abbreviations: HDRS= Hamilton Depression Rate; YMRS=Young Mania Rating Scale; IQ=intelligence quotient; FAST=Functioning Assessment Short Test; SG1= subgroup 1 patients with bipolar disorder; SG2 = subgroup 2 patients with bipolar disorder; ECT=Electroconvulsive Therapy. Values reflect means (standard deviations) unless otherwise noted. Bold text in the table indicates significant values. *a* = calculated from first (hypo)manic/mixed episode to cognitive test; *b* = calculated from first (hypo)manic/mixed episode to time of diagnosis.

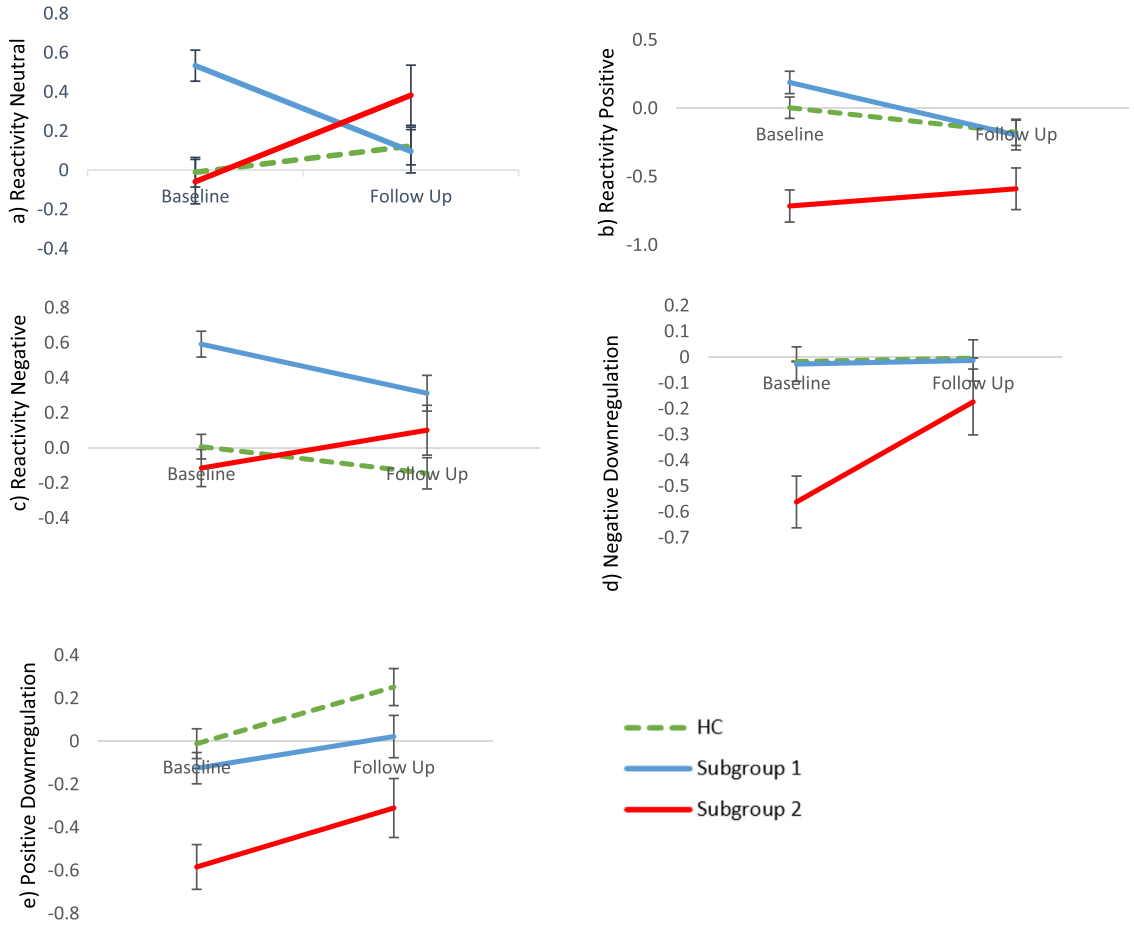

Fig. 2 Trajectory differences between the two emotional subgroups of patients with bipolar disorder and healthy controls (HC) for the social scenarios task: in emotional reactivity in (a) neural; (b) positive; and (c) negative social scenarios, as well as success during down-regulation of emotion in (d) negative; and (e) positive social scenarios. Error bars represent standard error of the mean.

1 and HC remained stable over time (ps = 0.93), patients in subgroup 2 improved in their ability to down-regulate emotion in *negative* scenarios over time (p=.03) (Figure 2D). However, this interaction effect was reduced to a trend after adjusting for subsyndromal symptoms (p=.08). We found no time-by-group interaction for emotion down-regulating in positive social scenarios. However, there was a significant main effect of group (F(2410.61)=11.69, p<.001), driven by patients in subgroup 2 generally being less successful at down-regulating their positive emotions compared to patients in subgroup 1 (p=.004) and HC (p<.010), with no significant differences between patients in subgroup 1 and HC (p=.19) (Figure 2E). The effect of group remained significant after adjusting for subsyndromal symptoms (p<.001) and lithium use (ps≤.03).

3.4.2. Accuracy and speed during facial expression recognition

A significant time-by-group interaction was found for discrimination accuracy of positive faces (F(2278.63)=4.94, p=.008); whereas patients in subgroup 1 and HC displayed the same lack of change over time,patients in subgroup 2 significantly improved over time (p=.002) compared to both patients in subgroup 1 (F(1140.43)=8.56, p=.004) and HC (F(1, 193.23)=8.37, p = 0.004) (Fig. 3A). We found no significant interaction effect or main effect of group for discrimination accuracy during recognition of negative faces (ps≥.10; Fig. 3B).

We additionally found a significant time-by-group interaction for speed during recognition of positive faces (F(2276.13)=10.20, p<.001); while patients in subgroup 1 and HC showed normative slower responses over time (ps≤.002) with no difference in trajectory between the two groups (p=.54), the reduced speed in patients within subgroup 2 remain stable over time (p=.13) (Fig. 3C). There was also a significant time-by-group interaction for speed during recognition of negative faces (F(2263.60)=14.90, p<.001); whereas patients in subgroup 1 became significantly slower in their responses compared to HC, patients in subgroup 2 displayed increased speed over time (p=.01) (Fig. 3D). Significant interactions prevailed after adjusting for subsyndromal symptoms (ps≤.009) and lithium use (ps≤.005).

3.4.3. Attentional vigilance toward emotional faces

For the Dot Probe task, we found a significant main effect of group for attentional vigilance towards supraliminal, effortful fearful faces (F(2, 389.50)=3.04, p=.049); however, none of the pairwise comparisons between groups were sig-

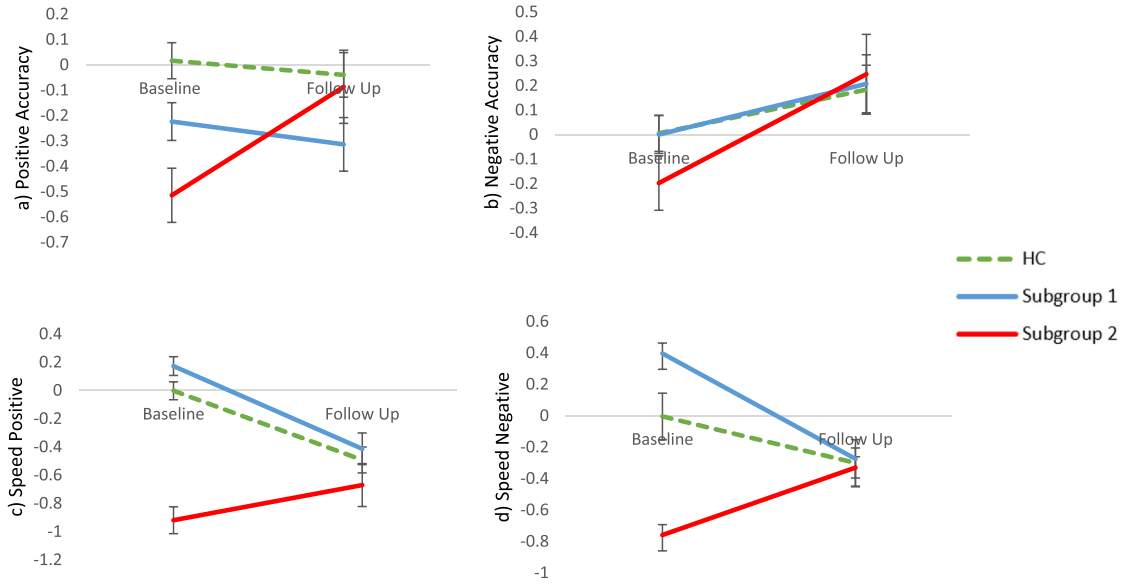

Fig. 3 Trajectory differences between the two emotional subgroups of patients with bipolar disorder and healthy controls (HC) for the facial expression recognition task showing speed during recognition of (a) negative and (b) positive faces; as well as facial expression recognition accuracy during recognition of (c) negative; and (d) positive faces. Error bars represent standard error of the mean.

nificant (ps≥.11). There were no other significant effects of group (p≥.10).

3.5. Change in subsyndromal symptoms, functioning, and clinical characteristics over time

A group-by-time interaction was observed for subsyndromal depressive symptoms (i.e., total HDRS score) (F(2364.40)=3.22, p=.04); however, follow-up analyses investigating trajectory of depressive symptoms within groups were non-significant (ps≥.29). We additionally observed a significant main effect of group for subsyndromal depression symptoms (F(2416.55)=124.64, p<.001), which was driven by the two patient subgroups generally having more symptoms of depression than HC (ps<0.001), with no significant difference between the two patient subgroups (p=.45). A significant group-by-time interaction was observed for subsyndromal mania symptoms (F(2384.90)=6.57, p=.002): whereas mania symptoms for patients in subgroup 1 and HC decreased (ps≤.005), patients in subgroup 2 showed no change over time (p=.95) (Fig. 4). Additionally, results revealed a significant group-by-time interaction for overall functioning (F(2372.01)=19.95, p<.001): while patients in subgroup 2 and HC remained stable over time (ps≥.49), functional impairments decreased in patients in subgroup 1 (p<.001) (Fig. 4).

With regards to clinical characteristics, we found a trend towards a significant main effect of group for number of hospitalizations (F(1222.29)=3.55, p=.06), driven by patients in subgroup 2 generally being hospitalized more compared to patients in subgroup 1. With regards to frequency and duration of mood episodes during the follow-up time, patients in subgroup 1 experienced longer episodes of depression than subgroup 2 (p=.03), whereas patients in subgroup 2 experienced more and longer mixed episodes than subgroup 1 (ps = 0.03) (Table 2).

3.6. Change in non-emotional cognition over time

Results revealed no significant trajectory differences between the two subgroups of patients and HC over time in non-emotional cognition (ps≥.07). Nevertheless, there was a significant main effect of group for 'global cognition' (F(2412.30)=21.75, p<.001) and 'working memory and executive function' (F(2420.46)=32.23, p<.001); which were driven by poorer performance in both patient subgroups compared to HC (ps<0.001), with no difference between the subgroups (ps≥.75) (Figure S2). These effects of group prevailed after adjusting for subsyndromal symptoms (p<.001) but disappeared when adjusting for lithium use (ps≥.52). There was also a main effect of group for 'attention and psychomotor speed' (F(2, 443.26)=24.15, p<.001), driven by patients in subgroup 2 underperforming patients in subgroup 1 (p=.048) and HC (p<.001), and patients in subgroup 1 performing poorer than HC (p<.001). This significant main effect of group prevailed after adjusting for subsyndromal symptoms (ps<0.001) and lithium use (p=.03) (Table 3). See supplement material for non-emotional cognition at baseline.

3.7. Associations between baseline emotional cognition deficits and symptoms, functioning, non-emotional cognition and clinical characteristics

Regarding subgroup 1, higher reactivity in negative scenarios was mildly associated with more subsyndromal depres-

Table 3 Z-scores of non-emotional cognition across the two emotional cognitive subgroups of patients with bipolar disorder and healthy controls (HC).

	Baseline							**Follow Up**							Main effect of group, p-value	Group-by-time interaction, p-value
	Subgroup 1 ($n = 179$)	Subgroup 2 ($n = 96$)	HC ($n = 190$)	*p*	Pairwise Comparison SG1 vs. SG2	SG1 vs. HC	SG2 vs. HC	Subgroup 1 ($n = 118$)	Subgroup 2 ($n = 57$)	HC ($N = 146$)	*p*	Pairwise Comparison SG1 vs. SG2	SG1 vs. HC	SG2 vs. HC		
Global cognition	−0.24 (0.57)	−0.33 (0.62)	0.00 (0.54)	**<0.001**	0.53	**<0.001**	**<0.001**	−0.03 (0.50)	−1.50 (0.46)	0.18 (0.42)	**<0.001**	0.29	**<0.001**	**<0.001**	**<0.001**	0.76
Executive function and working memory	−0.37 (0.75)	−0.47 (0.82)	0.00 (0.69)	**<0.001**	0.67	**<0.001**	**<0.001**	−0.24 (0.66)	−0.29 (0.67)	0.21 (0.53)	**<0.001**	0.10	0.74	0.09	**<0.001**	0.18
Attention and psychomotor speed	−0.34 (0.63)	−0.51 (0.72)	0.00 (0.67)	**<0.001**	0.13	**<0.001**	**<0.001**	−0.03 (0.59)	−0.31 (0.65)	0.17 (0.60)	**<0.001**	**0.014**	**0.02**	**<0.001**	**<0.001**	0.07
Verbal learning	−0.08 (0.86)	−0.26 (0.96)	0.00 (0.84)	**0.049**	0.27	0.71	**0.04**	0.02 (0.95)	0.01 (0.86)	0.13 (0.82)	**0.04**	0.10	0.71	0.71	0.12	0.96
Verbal fluency	−0.17 (0.99)	−0.08 (1.02)	0.00 (0.87)	0.21				0.13 (0.00)	0.00 (0.94)	0.20 (0.93)	0.36				0.15	0.55

Abbreviations: HDRS= Hamilton Depression Rate; YMRS=Young Mania Rating Scale; IQ=intelligence quotient; FAST=Functioning Assessment Short Test; BD=bipolar disorder, SG1= subgroup 1 patients with BD, SG2 = subgroup 2 patients with BD. Values reflect means (standard deviations) unless otherwise noted. Bold text in the table indicates significant values.

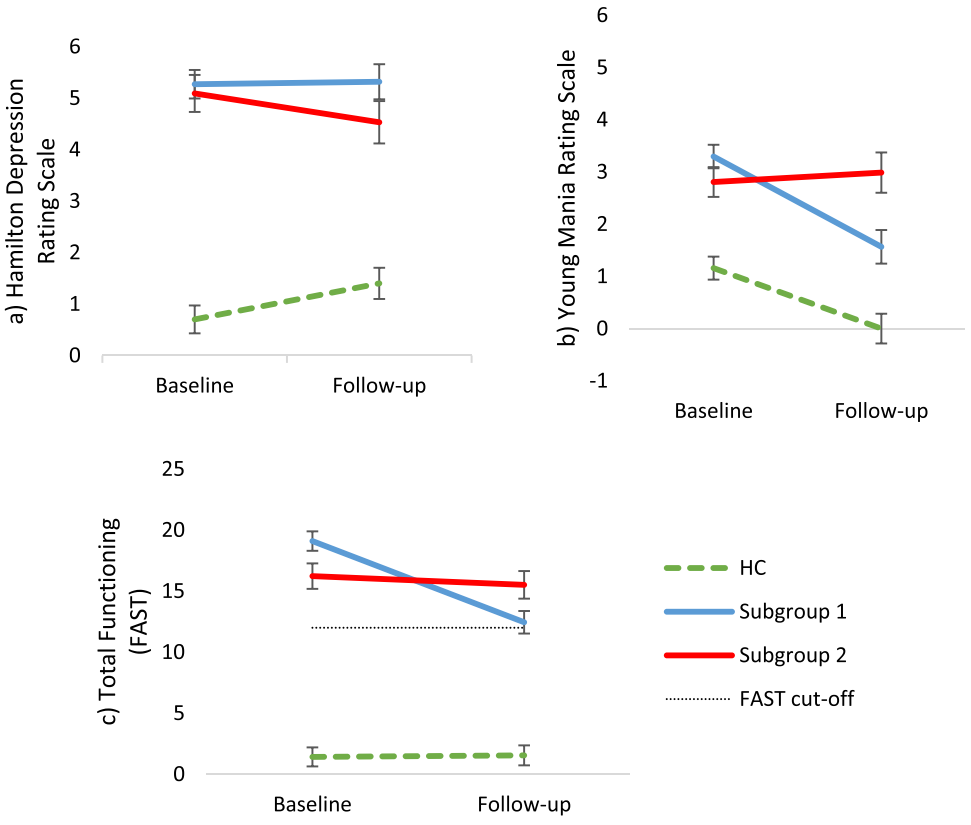

Fig. 4 Change over time in subsyndromal (a) depression and (b) mania symptoms and (c) total functioning measured with the functioning assessment short test (FAST) across the two emotional cognition subgroups of patients with bipolar disorder and healthy controls (HC). FAST cutoff is represented by 12 points in the FAST scale, indicating mild impairments. Error bars represent standard error of the mean.

sive symptoms ($r = 0.21$, p=.005). Faster recognition of facial expressions correlated with greater performance in the 'attention and psychomotor speed' domain (positive faces: $r = 0.23$, p=.002; negative faces: $r = 0.19$, p=.009). Aberrant emotional cognition did not significantly correlate with subsyndromal mania symptoms, functioning, or the subsequent duration of depressive episodes (ps≥.09).

We additionally investigated whether aberrant baseline emotional cognition in subgroup 2 was associated with subsyndromal symptoms, functioning, baseline hospitalizations, and impairments in non-emotional cognition as well as the greater frequency and duration of mixed episodes identified in this subgroup. There was a significant correlation between more hospitalizations and less successful down-regulation of emotions in negative social scenarios (r=−.23, p=.03) and, at a trend level, in positive social scenarios (r=−.18, p=.09). Lower reactivity in positive social scenarios, lower accuracy in the recognition of positive faces, and slower recognition of negative faces correlated with poorer global cognition (r=−.34, p=.001; $r = 0.35$, p<.001; and $r = 0.33$, p=.001, respectively) and poorer attention and psychomotor speed (r=−.40, p<.001; $r = 0.20$, p=.045; $r = 0.39$, p<.001, respectively). Lower recognition of positive faces and slower recognition of negative faces were also associated with poorer performance in 'working memory and executive function' ($r = 0.24$, p=.02 and $r = 0.35$, p=.001). However, aberrant emotional cognition did not correlate with subsyndromal symptoms, functioning or with the number or duration of mixed episodes for patients in subgroup 2 (ps≥.15).

4. Discussion

This is the first study using a data driven approach to investigate the trajectory of emotional cognition subgroups within a 16-month follow-up period in a large sample of recently diagnosed, clinically remitted patients with BD and HC. Two emotional cognition subgroups of patients were identified. In the larger subgroup 1 (65%), patients reacted more negatively in negative and neutral social situations, were quicker at recognizing faces, but with preserved emotion regulation abilities. In the smaller subgroup 2 (35%), patients exhibited more blunted reactivity in positive social scenarios and were less successful at down-regulating emotional responses in both negative and positive social scenarios, less able to identify positive faces, and slower at recognizing all facial expressions. Over the 16-month follow-up time, patients in subgroup 1 displayed (i) a normalization of the heightened emotional reactivity in neutral and negative scenarios and quicker facial expression recognition; and (ii) remained intact in emotion regulation and accu-

racy during facial expression recognition. Patients in subgroup 2 exhibited (i) amelioration of their impaired emotion regulation abilities in negative scenarios and normalized speed during recognition of negative faces, but also (ii) persistent blunted reactivity in positive scenarios, difficulties down-regulating emotions in positive social scenarios and slower identification of positive faces were stable impairments that prevailed over time; (iii) whereas they had no impairments in emotional reactivity in neutral scenarios at baseline, they reacted more negatively to these at the follow-up assessment. Importantly, patients in subgroup 1 experienced improvements in subsyndromal manic symptoms and overall functioning over the follow-up time, whereas patients in subgroup 2 showed stable impairments in non-emotional cognition and functioning and experienced more and longer mixed episodes and a trend for more hospitalizations in the follow-up time.

Our results are consistent with previous cross-sectional studies indicating heterogeneity within emotional cognition in BD (Szmulewicz et al., 2020; Varo et al., 2021, 2020), although previous studies found a subgroup with intact emotional cognition and in our sample of subgroup 1 patients showed mild to moderate deficits. No study has assessed emotional cognition subgroups longitudinally. Notably, recent longitudinal examinations of *non-emotional* cognition subgroups in BD suggest that the most impaired subgroups improve the most over time (Ehrlich et al., 2022; Kjærstad et al., 2022b). In contrast, our first study of the trajectory of emotion cognition subgroups showed greatest improvement in the less impaired subgroup 1 and only limited improvements in the most impaired and lower functioning subgroup 2. It is possible that the persistent emotional cognition impairment in this subgroup of patients is associated with illness progression, given that patients in subgroup 2 experience more and longer mixed episodes and more hospitalizations. However, while poorer emotion regulation was associated with more hospitalizations, aberrant emotional cognition did not correlate with subsyndromal symptoms, functioning or with the number or duration of mixed episodes for patients in subgroup 2. Unremitting problems with processing of positive affect found in subgroup 2 have been previously reported in literature. For instance, reduced positive affect is associated with concurrent and prospective social anxiety and depression in BD (Cohen et al., 2017), and reduced tendency to update beliefs in response to positive information predicts earlier time to relapse (Ossola et al., 2020). Moreover, we recently found that blunted amygdala activity during emotion regulation was associated with greater frequency of mixed episodes in a subgroup of patients with BD (Kjærstad et al., 2022a), although this was a partially overlapping smaller sample. Indeed, persistent difficulties processing positively valenced emotional information in subgroup 2 may generate greater mood instability, which in turn can lead to more severe prodromal symptoms and maintenance of these symptoms over time and consequently increase vulnerability to more relapses (Kjærstad et al., 2022a; Ossola et al., 2020). Nevertheless, due to our short follow-up time, we cannot determine whether poorer emotional cognition influence greater illness severity or whether poorer emotional cognition is a byproduct of greater illness severity, hence future studies investigating emotional cognition onset may aid in this question. Regarding non-emotional cognition, our results revealed that attention and psychomotor speed deficits were more impaired in patients in subgroup 2, when compared to subgroup 1 and HC. Attention and psychomotor speed are cognitive processes essential for the perception of accurate information. Hence, such impairments in non-emotional cognition may mutually influence emotional cognition (Baune and Malhi, 2015; Keramatian et al., 2021; Miskowiak and Varo, 2021). Although we did see a significant increase in lithium use in subgroup 2, evidence suggests that treatment with lithium has a minor negative impact on cognitive functioning regarding verbal learning, memory creativity and a moderate negative effect on psychomotor performance (Wingo et al., 2009). This is in line with our results showing a modulating effect of lithium on non-emotional - but not emotional- cognitive impairments in BD.

Interestingly, our findings showing that the quicker facial expression recognition and negative bias in subgroup 1 normalized over time suggest that these impairments may be more prevalent during the early stages of BD illness for this subgroup of patients. We hypothesize that this normalization over time may be partially due to the specialized treatment that this sample received for their newly diagnosed BD, consisting of pharmacological intervention and psychoeducation. This is in line with previous studies that have found that negative bias can be ameliorated with selective serotonin reuptake inhibitors in patients with major depression (Harmer et al., 2009; Tranter et al., 2009). Also, psychoeducation interventions are first line adjunctive treatment and previous studies have reported positive outcomes such as decreased mood fluctuations, increased functioning (Colom and Lam, 2005) and emotion regulation (Stafford and Colom, 2013; Van Dijk et al., 2013).

Our results show that subgroup 2 appears to be more compromised, especially regarding persistent problems with processing of positive affect. Also, the lack of significant impairments found in the dot probe task reveal that these emotional cognition impairments reflect more conscious and effortful processing of emotional information, hence psychological interventions may be the best way to target such deficits. Difficulties in emotion regulation in BD could be related to a relative absence of emotion awareness, regarding knowledge of what strategies to use and when to use them. For instance, interventions with focus on rehabilitating social cognition impairments, such as Social Cognition Interaction Training (Lahera et al., 2013; Zhang et al., 2019), The Learning Affective Understanding for a Rich Emotional Life (LAUREL) intervention (Painter et al., 2019) and Meta Cognitive Training (Haffner et al., 2018), may be useful in ameliorating difficulties that relate to social and emotional awareness seen in subgroup 2. Additionally, the use of reappraisal strategies in psychological interventions, for instance, show reductions in emotion reactivity across subjective, behavioural and physiological response domains and may be an effective regulation strategy BD (Gruber et al., 2014). Dampened reaction to facial recognition, such as happy faces, can also be targeted with specific interventions. In particular, a recent study reported that erythropoietin (EPO) treatment not only improved aspects of non-emotional cognition but also enhanced the recognition of happy facial expressions in patients with BD in remission, which was accompanied by and correlated with increase in

dorsal prefrontal activity (Miskowiak et al., 2018). Hence, the modulation of higher-order prefrontal neurocircuitry activity may be a target for treatments for some aspects of emotional cognitive impairments in BD.

Strengths of the study is the longitudinal design, large sample size and the extensive cognitive battery comprising both emotional and non-emotional cognition. Nevertheless, it was a limitation that we did not investigate other relevant multi-dimensional social cognitive subdomains, such as theory of mind, attributional bias, and emotional intelligence, that have been implicated with deficits in individuals with BD (de Siqueira Rotenberg et al., 2022; Miskowiak et al., 2019b). Although FERT task is common task used to access facial emotion expression, due to its paradigm of static images, low ecological validity can be argued (Hogenelst et al., 2015). Future studies should include a more dynamic emotional expression task, since using different variants of facial emotion stimuli aids in a more robust ecological validity and can be achieved by using virtual reality software to capture real-world nuances (Bekele et al., 2016; Cha et al., 2020). Moreover, we had a lower number of participants with follow-up data (30% drop out rate), a common limitation observed in longitudinal research and fewer group 2 patients (59.4%) were seen a follow-up than group 1 patients (65.9%). However, the proportion between patients with BD and HC remained similar at both time points (baseline: 59% and 41%; follow up: 55% and 45% for BD and HC, respectively) and participants with only baseline assessment did not significantly differ from those with both assessments in demographic or clinical characteristics (Tables S1 and S2). Another limitation is that some practice effects were observed in HC, due to mild to moderate normative change between the two time points since familiarity with certain tasks may lead to this bias. Future studies should strive to find a more consistent protocol and consensus-based battery for emotional cognition, which may solve the current issue of conflicting findings between studies. Moreover, we cannot exclude prior mood episodes may have influenced emotional cognitive impairments due to neuroprogressive deterioration in association with illness progression, and thus we suggest future longitudinal studies examine emotional cognition in individuals who are at high risk of BD, since this may provide a better understanding of the development and progression of the illness (Keramatian et al., 2021; Passos et al., 2016). Finally, Pearson's correlation analyses were exploratory and thus not corrected for multiple comparisons.

In conclusion, this study shows two distinct emotional cognition subgroups in patients with recently diagnosed BD and changes over a period of 16 month follow- up. In subgroup 1, corresponding to approximately two thirds, patients with BD displayed heightened negative emotional reactivity and faster recognition of emotional faces. This subgroup of patients showed normalization of their aberrant emotional cognitive responses over time, which may be a consequence of specialized treatment they received. In contrast, the last third of patients, subgroup 2, were characterized by more severe emotional cognition impairments, including persistent blunted reactivity in positive social scenarios, difficulties down-regulating emotions in these scenarios and slower facial expression recognition, which did not improve over time. They also experienced more lack of improvement in subsyndromal mania symptoms and functioning over time, as well as trend for more hospitalizations more and longer mixed episodes and presented more significant impairments in attention and psychomotor speed, which may indicate a need for more targeted clinical treatment regarding this specific subgroup. These findings suggest that screening for emotional cognitive impairments could aid treatment stratification to improve the clinical course for the approximately one-third of patients with persistent emotion cognition impairment and poorer prognosis.

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Contributors

LVK, MV and KWM were principal investigators of the BIO study. LVK and KWM were responsible for the Conceptualization of the study. HLK was responsible for data curation and Project administration, under the supervision of KWM. LSR and HLK were responsible for the Investigation, Methodology, formal analyses, writing - original draft, as well as writing - review & editing. CV, MV, BL, LK reviewed the manuscript. All authors contributed to interpretation of the data. All authors have approved the final manuscript. LVK, MV and KWM were principal investigators of the BIO study. LVK and KWM were responsible for the original study design and draft of protocol. HLK was responsible for participant recruitment, conducting diagnostic interviews, rating of mood symptoms, neuropsychological testing, MR-scanning, and data collection, under the supervision of KWM. LSR and HLK wrote the initial manuscript draft. HLK and LSR conducted the analyses. MV, BL, LK reviewed the manuscript. All authors contributed to interpretation of the data. All authors have approved the final manuscript.

Declaration of Competing Interest

MV has received consultancy fees from Angelini, Janssen, aviators, and Lundbeck 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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.03.005.

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