Emotional cognition subgroups in mood disorders: Associations with familial risk

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Abstract
Patients with mood disorders show heterogeneity in non-emotional cognition. However, it is unclear whether emotional cognition (EC) is characterised by similar heterogeneity. We aimed to investigate the heterogeneity in EC among remitted patients with mood disorders and explore its association with familial risk. Data from 269 partially or fully remitted patients with mood disorders, 87 of their unaffected relatives (UR) and 203 healthy controls (HC) were pooled from two cohort studies. Hierarchical cluster analysis was conducted using the EC data from patients. UR were categorised into groups consistent with their affected relatives' cluster assignment. Clusters were compared to HC on EC, non-emotional cognition, clinical characteristics and functioning. We identified three clusters: an 'emotionally preserved' (57%), an 'emotionally blunted' (26%) and an 'emotionally volatile' cluster (17%). 'Emotionally blunted' and 'emotionally volatile' patients also presented more deficits in non-emotional cognition (global cognition read $z=-0.3$ and -0.5 respectively). Relatives of 'emotionally preserved' patients were more successful at dampening negative emotions ($p=.01$, $d=0.39$, 95% CI [-0.76,-0.09]), whereas UR

of 'emotionally impaired' patients underperformed in verbal fluency (p=.03, d=0.46, 95% CI [.03, 0.68]) compared to HC. The existence of impaired EC groups in remitted mood disorder highlights a need to screen for and treat EC in mood disorders. Improved ability to dampen emotions in UR of 'emotionally preserved' patients may reflect a resilience marker while impaired verbal fluency in UR of 'emotionally impaired' patients may reflect distinct genetic risk profiles in these EC subgroups.

1. Introduction

Considerable research on mood disorders indicates that patients with bipolar disorder (BD) and unipolar disorder (UD) exhibit broad, trait-related neurocognitive difficulties during acute mood episodes that commonly persist in remission (Panchal et al., 2019; Porter et al., 2015; Rock et al., 2014; Van Rheenen et al., 2019). These difficulties are not limited to non-emotional neurocognitive domains but are also evident across aspects of emotional cognition (EC). Specifically, mood disorders are associated with abnormalities in emotion processing and difficulties with emotion regulation that persist during periods of remission (Leppänen, 2006; Mercer and Becerra, 2013; Miskowiak and Carvalho, 2015; Miskowiak et al., 2019). The abnormalities are to some degree present in early stages of the disorder and also displayed in individuals at familiar risk of mood disorders (Kjærstad et al., 2019a; 2019b). Together, the findings suggest that aberrant EC is a putative endophenotype for mood disorders (Elliott et al., 2011; Miskowiak and Carvalho, 2015; Miskowiak et al., 2017).

Heterogeneity within non-emotional cognition amongst fully or partially remitted patients with mood disorders has been established in previous studies. Several recent data-driven cluster analysis studies have identified distinct cognitive profiles within non-emotional aspects cognition among patients with mood disorders with differing patterns and levels of impairments (Cotrena et al., 2017). Cognition cluster analyses studies in BD showed that 30-50% of patients are relatively cognitively preserved in comparison with norms, 30-40% display selective deficits and 10-40% of patients present global cognitive performance decline across all domains (Burdick et al., 2014; Jensen et al., 2016; Kjærstad et al., 2019a; Lima et al., 2019; Solé et al., 2016). Only one study to date has examined cognitive heterogeneity in UD. In this study, three discrete neurocognitive clusters were found: globally impaired (34%), selectively impaired (13%), and a cognitively intact cluster (53%) (Pu et al., 2018). Emerging findings point to the distinct neurocognitive subgroups as being associated with differential EC (Burdick et al., 2014; Kjærstad et al., 2019a; Lima et al., 2019). Compared to BD patients who were cognitively intact, those with neurocognitive deficits exhibited difficulties with facial expression recognition, emotion regulation (Kjærstad et al., 2019a) and social cognition (Lima et al., 2019). In contrast, remitted patients who were cognitively intact displayed superior social cognition compared to healthy controls (HC) (Burdick et al., 2014). Only one recent study examined cognitive heterogeneity in patients with BD and their unaffected relatives, as well as how this relates to EC (Kjærstad et al., 2019a). This revealed that the globally impaired neurocognitive subgroup was characterised by distinct, albeit milder, impairments in EC, including facial expression recognition and emotion regulation in social scenarios.

Only two published studies examined the potential variability of social and EC in BD using hierarchical cluster analysis methods (Szmulewicz et al., 2020; Varo et al., 2020). Preliminary findings from these studies indicated the presence of two distinct socio-emotional cognition subgroups, with nearly two thirds of patients showing intact performance and one third presenting with socio-emotional cognition deficits, including theory of mind, attributional bias (Varo et al., 2020) and emotional processing (Szmulewicz et al., 2020; Varo et al., 2020). However, no cluster analysis study has investigated the heterogeneity within EC domains *across* remitted patients with BD or UD or its relation to familial risk. Evidence for EC subgroups across these mood disorders -and an association with familial risk- would point to new transdiagnostic biomarkers for subtypes of patients with distinct genetic risk profiles in line with the Research Domain Criteria (RDoC) framework (Cuthbert, 2014) and aid targeting of treatments for EC deficits in mood disorders.

This study aimed to investigate (i) whether EC in mood disorders is characterised by heterogeneity in an unprecedented large sample of patients with mood disorders in full or partial remission using a data-driven hierarchical cluster analysis approach; (ii) whether any distinct EC profiles would be associated with differences in non-emotional cognition functions, functional capacity and differences in demographic and clinical characteristics; and (iii) whether unaffected first-degree relatives (UR) of patients within the respective EC clusters would show similar impairments within emotional and non-emotional cognition. We hypothesised that: (i) patients would exhibit heterogeneous EC profiles as reflected by distinct EC subgroups; (ii) impaired EC subgroups would be characterised by poorer non-emotional cognition, lower functioning and greater illness chronicity than patients with preserved EC and HC; and (iii) UR of patients in the impaired EC subgroups would show EC differences compared with HC.

2. Methods

2.1. Participants

Data was pooled from two studies from our research group conducted between Dec 2014 and Oct 2019; the Bipolar Illness Onset (BIO) study (Kessing et al., 2017) and the Neurocognition and Emotion in Affective Disorders (NEAD) study (Meluken et al., 2019). The sample included 559

individuals: 269 remitted patients with mood disorders, 87 UR and 203 HC.

Patients from the BIO study were recruited from the Copenhagen Affective Disorder Clinic, Psychiatric center Copenhagen (Kessing et al., 2017). Affected monozygotic twins in the NEAD study were recruited from the Danish Twin Registry, the Danish Psychiatric Central Research Register and the Danish Civil Registration System (Meluken et al., 2019). Patients met criteria for an ICD-10 (World Health Organization, 1993) diagnosis of UD or BD confirmed with the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990), were in full or partial remission (Hamilton Depression Rating Scale 17-item [HDRS-17] (Hamilton, 1960) and Young Mania Rating Scale [YMRS] (Young et al., 1978) ≤14, respectively). Unaffected relatives were siblings or children (BIO study) or monozygotic twins discordant for UD or BD (NEAD study) and had no personal history of mood or schizophrenia spectrum disorders. Age and sex matched HC with no personal or first-degree family history of psychiatric disorder were recruited from the blood bank at Copenhagen University Hospital (BIO study) or through the Danish twin register (NEAD study). All participants were aged 15–70 years. General exclusion criteria were current mood episodes (HDRS-17 or YMRS>14), organic mental disorder, pregnancy, history of brain injury, current substance misuse disorder or severe somatic illness. Participants were asked to refrain from smoking prior to neurocognitive assessments. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Regional Ethics Committee (protocol numbers: H-7-2014-007 and H-3-2014-003) and data protection agency in Capital Region of Copenhagen (RHP-2015-023 and 2014-331-0751). Written informed consent was obtained from all participants.

2.2. Assessments

2.2.1. Emotional cognition measures
The Social Scenarios Task was used to assess emotion reactivity and regulation to social scenarios (Kjærstad et al., 2016). Each scenario consisted of 11 sentences describing the situation, 10 self-beliefs and 10 emotion ratings. An emotion rating requiring participants to evaluate their discomfort or pleasure. Participants were instructed to either naturally react to or dampen their emotional response to the social scenarios. Participants were not given any instructions as to which emotion regulation strategy to use since the aim was to investigate their habitual use of emotion regulation strategies.

The Facial Expression Recognition Task (Harmer et al., 2004) assessed facial expression identification. Pictures of faces were shown one of six basic emotions: anger, disgust, fear, happiness, sadness and surprise, morphed between a neutral face and full emotion. Participants were shown 250 randomly presented faces (500 ms) and were asked to indicate the emotion shown. Four examples of every emotion and intensity level were shown, including a neutral face for every emotion. Accuracy and reaction times were registered.

The Faces Dot-Probe Task assessed attentional vigilance towards emotional face (Murphy et al., 2008). Pairs of happy-neutral, fearful-neutral or neutral-neutral faces were displayed horizontally masked (17 ms) or unmasked (100 ms). One of the two faces was promptly replaced by two dots displayed either vertically (:) or horizontally (••). Participants were instructed to indicate the orientation of the dots. The paradigm consisted of sixteen blocks (eight masked and eight unmasked) in total, and each block included 12 alternately presented trials.

2.2.2. Non-emotional cognition measures
Both studies included Danish Adult Reading Task (DART), which was used to estimate premorbid verbal intelligence (Nelson and O'Connell, 1978) and the Trail Making Test parts A and B (TMT A/B) (Reitan, 1958). In the NEAD study, non-emotional cognition was assessed using the Screen of Cognitive Impairment in Psychiatry (SCIP-D) (Purdon, 2005). In the In the BIO study, non-emotional cognition was assessed using a larger neuropsychological test battery exploring different cognitive domains: processing speed, working memory, executive functions, verbal learning, verbal fluency and attention (for details, see Kjærstad et al. (Kjærstad et al., 2019a)).

2.2.3. Functioning
Participants completed the Functional Assessment Short Test (FAST), which includes 6 domains of functioning (autonomy, occupational, cognitive, financial issues, interpersonal relationships, and leisure time) and the FAST total score (Rosa et al., 2007).

2.3. Statistical analysis

All analyses were performed with the IBM Statistical Package for Social Sciences version 22. Emotional and non-emotional cognition tests raw scores were standardised to z-scores based on HCs' performance (for information on the calculation of EC and non-emotional cognition domains composite see Supplementary Materials). A hierarchical cluster analysis (HCA) was conducted to identify homogeneous subgroups of patients based on their EC performance regarding (i) emotional reactivity and down-regulation of emotions in negative and positive social scenarios (ii) recognition accuracy and reaction time (RT) during positive and negative facial expression recognition; and (iii) attentional vigilance to masked and unmasked fearful faces. Similarity between cases was computed with squared Euclidian distance and Ward's linkage as an agglomeration procedure. The dendrogram was visually inspected to establish the appropriate number of clusters to be retained. A discriminant function analysis (DFA) was conducted in order to test the validity of the clusters. Emotional cognition clusters and HC were compared on EC tasks, demographic, clinical and functional variables using a series of series of ANOVAs with Least Significant Difference (LSD) correction and chi-square, as appropriate. Post-hoc exploratory non-emotional cognition comparisons between EC clusters and HC were conducted (ANOVAs with LSD). The UR were assigned a group based on the EC cluster membership of their affected proband. Comparisons between the UR clusters and HC were also con-

ducted using the same method as above. Effect sizes are reported in partial eta-squared (η_p^2) and Cohen's d (*d*). Statistical significance was set at $p<.05$. Bonferroni corrections were not used due to the exploratory nature of the study.

3. Results

3.1. Emotional cognition clustering

Patients with mood disorders were optimally clustered based on their EC performance, into three different clusters: 57% (*n* = 153) were *'emotionally preserved'*; 26% (*n* = 69) *'emotionally blunted'* and 17% (*n* = 47) *'emotionally volatile'* (Table 1; see Figure S1 for discriminant functions plot in supplemental material). Results from the DFA revealed two discriminant functions explaining 64.4% and 35.6% of the variance, respectively (Wilks' $\lambda=0.225$, $\chi^2(20)=388.415$, $p<.001$ and Wilks' $\lambda=0.554$, $\chi^2(9)=154.038$, $p<.001$). Emotional reactivity to pleasant social scenarios (highest loading task for Function 1: $r = 0.63$) and speed during positive facial expression recognition (highest loading task for Function 2: $r = 0.59$) contributed most to clustering. The classification results revealed high sensitivity with 87% of original grouped cases being correctly classified.

3.2. Emotional cognition profiles: comparisons between patient clusters and HC

There was a statistically significant difference between the three EC clusters of patients and HC on all EC measures with mild to moderate/large effect sizes (z-scores: 0.3-1.1), except for attention vigilance towards unmasked (consciously processed) fearful faces (Table 1). Follow-up LSD analyses of what was driving these significant differences showed that **(A)** patients in the *'emotionally preserved'* cluster exhibited *higher* emotional reactivity (aversive: $p<.001$, $d = 0.73$, 95%CI[$-0.86,-0.47$]; pleasant: $p=.001$, $d = 0.37$, 95%CI[$-0.54,-0.13$]) but also *more successful* downregulation of emotions in both aversive and pleasant social scenarios than HC ($p<.001$, $d = 0.65$, 95%CI[$-0.86,-0.43$]; and $p=.049$, $d = 0.21$, 95%CI[$-0.42,-0.00$], respectively). These patients were also *faster* at recognizing both negative ($p<.001$, $d = 0.60$, 95%CI[.35,.76]) and positive ($p<.001$, $d = 0.50$, 95%CI[.24,.62]) facial expressions. **(B)** Patients in the 'emotionally blunted' cluster displayed *lower* emotional reactivity (aversive: $p<.001$, $d = 0.47$, 95%CI[.22,.73]; pleasant: $p<.001$, $d = 1.28$, 95%CI[1.16,1.69]), *less successful downregulation* of emotions in pleasant social scenarios ($p<.001$, $d = 0.78$, 95%CI[.48,1.01]), *poorer* recognition accuracy for positive facial expressions ($p=.003$, $d = 0.44$, 95%CI[.13,.67]) and *longer* latencies during recognition of emotions (positive: $p<.001$, $d = 0.74$, 95%CI[$-0.92,-0.43$]; negative: $p<.001$, $d = 0.52$, 95%CI[$-0.72,-0.21$]) than HC and patients in the 'emotionally preserved' cluster (ps<0.021). They also showed *poorer recognition* accuracy of negative facial expression than HC ($p=.006$, $d = 0.40$, 95%CI[.11,.65]). Finally, they also exhibited *less successful down-regulation* of emotions in aversive social scenarios than patients in

Table 1 Emotional cognition according to the three emotional clusters in patients with mood disorders and healthy controls (HC).

	Emotionally preserved (C1) (n = 153) M (SD)	Emotionally blunted (C2) (n = 69) M (SD)	Emotionally volatile (C3) (n = 47) M (SD)	Healthy controls (HC) (n = 203) M (SD)	F	p	C1 vs C2	C1vs C3	C2 vs C3	HC vs C1	HC vs C2	HC vs C3
Social Scenarios Task												
Negative reactivity	0.7 (0.8)	−0.5 (1.0)	0.6 (0.8)	0.0 (1.0)	31.45	<0.001	<0.001	.732	<0.001	<0.001	<0.001	<0.001
Positive reactivity	0.3 (0.8)	−1.4 (1.2)	0.6 (0.8)	0.0 (1.0)	63.11	<0.001	<0.001	.081	<0.001	.001	<0.001	<0.001
Negative dampen	0.6 (1.0)	−0.0 (1.0)	0.9 (1.2)	0.0 (1.0)	20.37	<0.001	<0.001	.111	<0.001	<0.001	.728	<0.001
Positive dampen	0.2 (1.0)	−0.7 (0.9)	0.7 (1.1)	0.0 (1.0)	25.92	<0.001	<0.001	<0.001	<0.001	.049	<0.001	<0.001
Facial Expression Recognition Accuracy												
Negative emotions	−0.1 (0.8)	−0.4 (0.9)	−0.4 (1.1)	0.0 (1.0)	3.45	.017	.041	.113	.864	.354	.006	.027
Positive emotions	−0.1 (0.8)	−0.4 (0.9)	−0.4 (1.3)	0.0 (1.0)	4.40	.005	.021	.037	.946	.415	.003	.009
Facial Expression Recognition Task, ms												
Negative emotions	−0.6 (0.8)	0.5 (0.8)	1.0 (0.9)	0.0 (1.0)	45.19	<0.001	<0.001	<0.001	.001	<0.001	<0.001	<0.001
Positive emotions	−0.4 (0.7)	0.7 (0.8)	1.1 (0.9)	0.0 (1.0)	50.59	<0.001	<0.001	<0.001	.019	<0.001	<0.001	<0.001
Facial Dot-Probe, Vigilance scores, median RT												
Masked fear	0.1 (0.8)	0.3 (0.9)	−0.9 (1.6)	0.0 (1.0)	15.30	<0.001	.337	<0.001	<0.001	.354	.006	<0.001
Unmasked fear	−0.1 (0.6)	−0.0 (0.6)	0.0 (0.8)	0.0 (0.7)	0.32	.810						

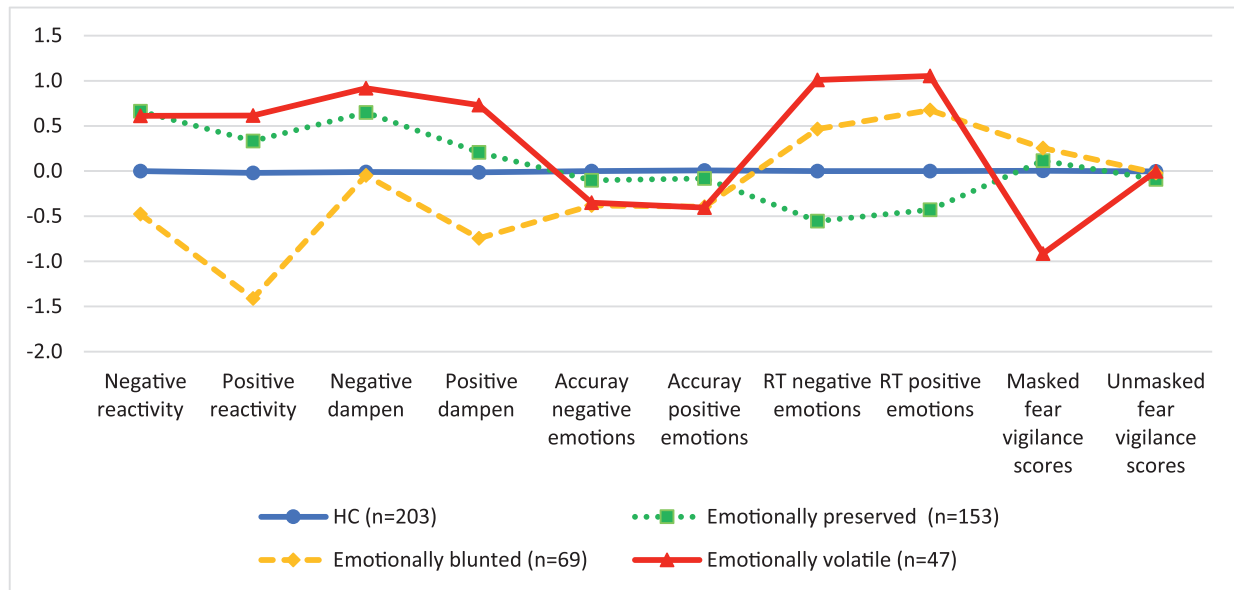Bold text in the table indicates significant values.

Fig. 1 Emotional cognition profiles according to the three emotional clusters in patients with mood disorders and healthy control persons (HC).

the 'emotionally preserved' cluster ($p<.001$, $d = 0.70$, 95%CI[.41,.99]). **(C)** Patients in *'emotionally volatile'* cluster displayed *higher* emotional reactivity across both aversive ($p<.001$, $d = 0.69$, 95%CI[−0.90,−0.32]) and pleasant ($p<.001$, $d = 0.69$, 95%CI[−0.92,−0.31]) social scenarios but were also more successful at dampening emotions across these scenarios when instructed to do so compared to HC (aversive: $p<.001$, $d = 0.85$, 95%CI[−1.24,−0.59]; pleasant: $p<.001$, $d = 0.84$, 95%CI[−1.13,−0.50]) and the 'emotionally blunted' cluster (ps<0.001). Compared to patients in the 'emotionally preserved' cluster, they were also more successful at dampening emotions in pleasant social scenarios ($p<.001$, $d = 0.63$, 95%CI[−0.93,−0.28]). In the facial expression recognition task, they showed *poorer* recognition of negative and positive facial expressions than HC ($p=.027$, $d = 0.33$, 95%CI[.04,.66] and $p=.009$, $d = 0.35$, 95%CI[.11,.72], respectively) and of positive expressions compared to the 'emotionally preserved' cluster ($p=.037$, $d = 0.30$, 95%CI[.02,.63]). They also showed the *longest latencies* during recognition of both positive ($p<.001$, $d = 1.12$, 95%CI[−1.33,−0.77]) and negative ($p<.001$, $d = 1.04$, 95%CI[−1.31,−0.71]) facial expressions compared with HC and all clusters (ps≤.019). In the dot-probe task, patients in the 'emotionally volatile' cluster also showed the greatest *attentional avoidance* of masked (non-consciously processed) fearful faces compared with HC ($p<.001$, $d = 0.69$, 95%CI[.60,1.24) and all other clusters (ps<0.001) (Figure 1; Table 1).

3.3. Demographic and clinical variables

The EC clusters were comparable to HC in age and IQ (see details in Table 2). There was a significant difference between EC clusters and HC in years of education ($p<.001$), gender ($p=.011$), subsyndromal depression and mania symptoms (ps<0.001) and HDRS-17 *anxiety symptoms* ($p<.001$). The 'emotionally preserved' and 'emotionally volatile' clus-

ters had undergone fewer years of education and all patient clusters showed more mood subsyndromal symptoms compared with HC. Patients in the 'emotionally preserved' cluster were mostly female ($p=.031$) and exhibited more *psychic and somatic anxiety* ($p<.001$) than HC. However, there were *no differences* between EC clusters in age at illness onset, illness duration, illness chronicity, current medication or current subsyndromal depression or mania symptoms (ps≥.059). A significant group difference was found for diagnostic distribution across the EC clusters ($\chi2=9.094$; $p=.011$) with the 'emotionally volatile' and 'emotionally blunted' clusters including more patients with BD than the 'emotionally preserved' cluster (65% vs. 83% and 81%, ps≤.022). We therefore conducted a post-hoc *sensitivity analysis* excluding all patients with UD. Comparison of EC between the clusters did not significantly change the reported differences, indicating that the higher percentage of BD in the 'emotionally volatile' and 'emotionally blunted' cluster *did not* drive these findings (for further details see Table 1). Among the three clusters, there was a significant difference in educational levels; patients in the 'emotionally preserved' and 'emotionally volatile' clusters had undergone fewer years of education than patients in the 'emotionally blunted' cluster (ps<0.014). The three clusters also differed in gender ($p=.011$), driven by the 'emotionally preserved' cluster including significantly more females compared to the 'emotionally blunted cluster'. Finally, HDRS-17 *anxiety symptoms* differed between the EC clusters; the 'emotionally preserved' cluster showed *more psychic and somatic anxiety* than the 'emotionally blunted' cluster ($p=.011$) (Table 2).

3.4. Non-emotional cognition

There was a significant difference between the EC clusters and HC in global cognition and on all non-emotional cognition domains (ps≤.038) (for detailed comparisons,

Table 2 Demographic and clinical variables according to the three emotional clusters in patients with mood disorders and healthy controls (HC).

	Emotionally preserved (C1) (n = 153) M (SD)	Emotionally blunted (C2) (n = 69) M (SD)	Emotionally volatile (C3) (n = 47) M (SD)	Healthy controls (HC) (n = 203) M (SD)	p	Group comparisons					
						C1 vs C2	C1 vs C3	C2 vs C3	HC vs C1	HC vs C2	HC vs C3
Age	33.0 (8.8)	34.5 (9.8)	~~364.5~~ 34.5 (11.1)	32.6 (10.9)	.426						
Years of education	14.5 (2.9)	15.7 (4.5)	14.1 (3.6)	16.1 (2.9)	<0.001	.014	.449	.011	<0.001	.384	<0.001
IQ	112.7 (6.6)	113.0 (5.8)	112.1 (6.2)	113.2 (5.8)	.709						
Sex, female n (%)	113 (74)	36 (52)	33 (70)	128 (63)	.011	**.001**	.623	.052	**.031**	.111	.356
Diagnosis, BD vs. UD					.011	**.017**	**.022**	.803			
UD n **(%) within each cluster / (%) within diagnosis**	53 (35) **(72)**	13 (19) **(18)**	8 (17) **(11)**								
BD n **(%) within each cluster / (%) within diagnosis**	100 (65) **(51)**	56 (81) **(29)**	39 (83) **(20)**								
BD-II **(%) within each cluster / (%) within diagnosis**	60(60) **(50)**	38 **(68) (32)**	21 **(54) (18)**		370						
BD-I n **(%) within each cluster / (%) within diagnosis**	40 **(40) (53)**	18 **(32) (24)**	18 **(46) (24)**								
Age at illness onset	22.9 (7.8)	24.1 (8.8)	22.9 (8.3)		.550						
Illness duration	10.2 (7.5)	10.4 (8.5)	11.6 (9.6)		.588						
No. of depressive episodes	8.9 (18.4)	8.7 (12.7)	6.0 (6.1)		.518						
No. of manic episodes	0.9 (3.4)	0.5 (1.9)	1.3 (4.8)		.505						
No. of hypomanic episodes	5.6 (12.0)	7.8 (13.8)	4.1 (6.2)		.251						
No. of mixed episodes	0.4 (2.5)	0.4 (2.2)	0.2 (0.6)		.893						
No. of psychotic episodes	0.4 (1.6)	0.4 (0.7)	0.2 (0.7)		.756						
Total no. of episodes	16.6 (29.7)	17.8 (26.0)	12.2 (12.6)		.544						
Antidepressants (yes) n (%)	10 (27.8)	39 (21.7)	22 (41.5)		.324						
Antipsychotics (yes) n (%)	11 (30.5)	40 (22.2)	17 (32)		.061						
Anticonvulsants (yes) n (%)	15 (41.7)	39 (21.7)	14 (26.4)		.059						
Lithium (yes) n (%)	15 (41.7)	58 (32.2)	21 (39.6)		.366						
HDRS-17	5.1 (4.1)	4.8 (3.6)	5.2 (3.9)	1.2 (1.7)	<0.001	.434	.960	.519	<0.001	<0.001	<0.001
YMRS	2.4 (3.0)	2.6 (3.2)	2.2 (2.8)	0.8 (1.4)	<0.001	.562	.360	.593	<0.001	<0.001	<0.001
Anxiety symptoms*	0.4 (1.0)	0.1 (0.6)	0.2 (0.6)	0.0 (0.2)	<0.001	**.011**	.161	.476	<0.001	.207	.056
FAST Total	15.8 (12.1)	14.7 (11.7)	17.7 (12.5)	1.6 (2.9)	<0.001	.403	.234	.091	<0.001	<0.001	<0.001

Abbreviations: M= mean; SD=standard deviation; IQ=intelligence quotient; UD= Unipolar disorder; BD= Bipolar disorder; BD-I= Bipolar disorder type I; BD-II= Bipolar disorder type II; HDRS-17=Hamilton Depression Rating Scale; YMRS=Young Mania Rating Scale; FAST=Functioning Assessment Short Test. * Anxiety symptoms were determined based on mean scores from items 10 and 11 using the HDRS-17. Bold text in the table indicates significant values.
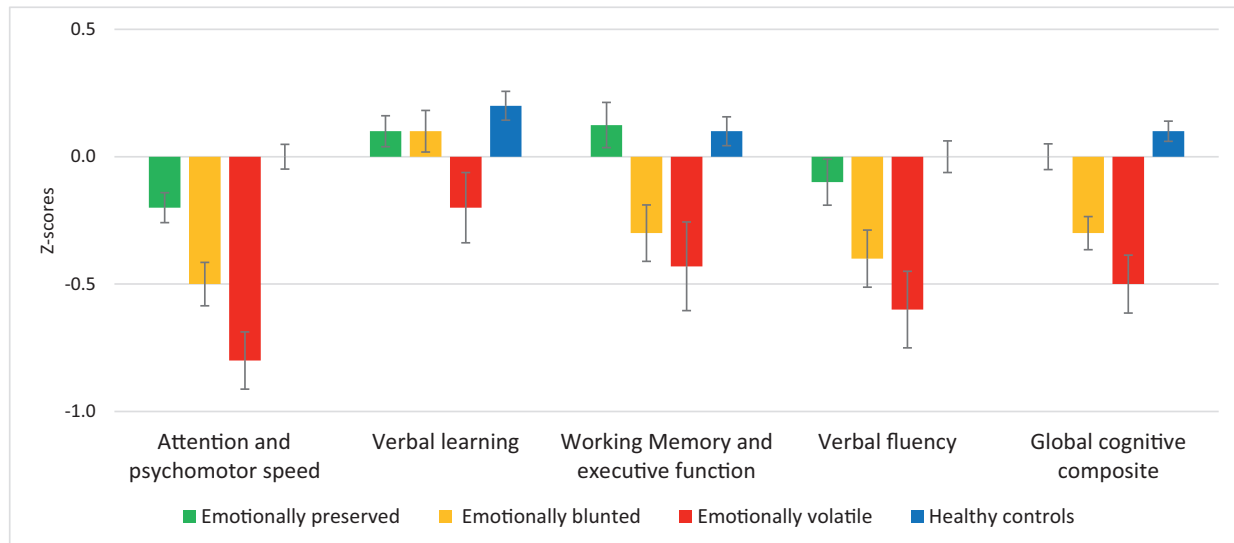
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Fig. 2 Non-emotion cognition according to the three emotional clusters in patients with unipolar and bipolar disorder and healthy control persons. The X-axis denotes the mean non-emotional cognition z-score for the three groups. Error bars represent standard error of the mean.

see Table 3 and Figure 2). Follow-up LSD analysis showed that the patients in the 'emotionally preserved' cluster performed comparatively to HC on all non-emotional cognitive domains except for attention and psychomotor speed where patients performed lower than HC ($p=.015$, $d = 0.26$, 95%CI[.04,.34]). Contrary, the 'emotionally blunted' and 'emotionally volatile' clusters performed significantly poorer than HC on global cognition with mild to moderate effect sizes (ps$\leq$.001; $z= -0.3$ and -0.5, respectively) as well as in the domains of attention and psychomotor speed, working memory and executive functions and verbal fluency (ps$\leq$.004). Patients in the 'emotionally volatile' cluster also performed worse than HC on verbal learning ($p=.004$, $d = 0.42$, 95%CI[.11,.62]). Accordingly, comparisons among the three clusters revealed that the 'emotionally volatile' patients displayed more impairments than 'emotionally preserved' patients on global cognition ($p<.001$, $d = 0.70$, 95%CI[$-0.69,-0.30$]) as well as all individual non-emotional cognitive domains (ps$\leq$.034). They also exhibited poorer attention and psychomotor speed than the 'emotionally blunted' cluster ($p=.011$, $d = 0.47$, 95%CI[$-0.61,-0.08$]). Finally, patients in 'emotionally blunted' cluster displayed worse global cognition ($p=.005$, $d = 0.43$, 95%CI[$-0.42,-0.08$]), attention and psychomotor speed ($p=.010$, $d = 0.37$, 95%CI[$-0.47,-0.06$]) and working memory and executive function ($p=.001$, $d = 0.44$, 95%CI[$-0.72,-0.17$]) than patients in the 'emotionally preserved' cluster (Figure 2; Table 3).

3.5. Functioning

There was a significant difference between clusters and HC on the FAST Total, with all patients presenting with functional impairments relative to controls (ps<0.001), but no differences between the three EC clusters (ps$\geq$.091) (see Table 2 for details).

3.6. Emotional cognition in unaffected relatives of patients

The majority of UR ($n = 50$; 57%) were relatives of patients in the 'emotionally preserved' cluster, while relatively few were relatives of the 'emotionally volatile' and 'emotionally blunted' clusters ($n = 18$ [20% of relatives] and $n = 19$ [22% of relatives], respectively). We therefore combined the relatives of the two clusters of patients with EC impairments into one group of 'impaired EC' clusters ($n = 37$). There were no differences between UR of 'preserved' and 'impaired' EC patient clusters in their EC, non-emotional cognition or functioning (ps$\geq$.063). There was, however, a significant difference between UR clusters and HC in ability to dampen emotions in aversive social scenarios (F(2, 282)=3.25, $p=.040$, $\eta_p^2=0.023$), which was driven by UR of 'emotionally preserved' patients being significantly *more successful* at dampening their emotions in aversive social scenarios than HC ($p=.012$, Cohen's $d = 0.39$, 95%CI[$-0.76,-0.09$]). For non-emotional cognition, a significant difference between groups was found for verbal fluency (F(2, 287)=3.22, $p=.041$, $\eta_p^2=0.022$), driven by UR of the 'impaired' EC clusters exhibiting lower verbal fluency than HC ($p=.033$, Cohen's $d = 0.46$, 95%CI[.03,.68]).

Regarding functioning, results revealed significant group differences in FAST total score (F(2, 279)=10.55, $p<.001$, $\eta_p^2=0.069$.), which was driven by decreased functioning in both UR clusters compared to HC (UR 'impaired' vs. HC: $p=.001$, Cohen's $d = 0.43$, 95%CI[$-4.1,-1.0$]; UR 'intact vs. HC: $p<.001$, Cohen's $d = 0.58$, 95%CI[$-3.9,-1.2$]).

4. Disussion

This is the first study investigating the heterogeneity within EC in a large sample of fully or partially remitted patients with mood disorders and their UR using a data-

Table 3 Non-emotional cognition across the three emotional cognitive clusters in patients with mood disorders and healthy controls (HC).

	Emotionally preserved (C1) (n = 153) M (SD)	Emotionally blunted (C2) (n = 69) M (SD)	Emotionally volatile (C3) (n = 47) M (SD)	Healthy controls (HC) (n = 203) M (SD)	F	p	Group comparisons					
							C1 vs C2	C1 vs C3	C2 vs C3	HC vs C1	HC vs C2	HC vs C3
Attention and psychomotor speed	−0.2 (0.7)	−0.5 (0.7)	−0.8 (0.8)	0.0 (0.7)	19.29	**<0.001**	**.010**	**<0.001**	**.011**	**.015**	**<0.001**	**<0.001**
Verbal learning	0.1 (0.8)	0.1 (0.7)	−0.2 (0.9)	0.2 (0.8)	2.83	**.038**	.992	**.034**	.060	.288	.420	**.004**
Working Memory and executive function	0.1 (1.1)	−0.3 (0.9)	−0.4 (1.2)	0.1 (0.8)	8.75	**<0.001**	**<0.001**	**<0.001**	.328	.975	**<0.001**	**<0.001**
Verbal fluency	−0.1 (1.1)	−0.4 (0.9)	−0.6 (1.0)	0.0 (0.9)	5.69	**.001**	.055	**.010**	.424	.232	**.004**	**<0.001**
Global cognitive composite	0.0 (0.6)	−0.3 (0.5)	−0.5 (0.7)	0.1 (0.6)	15.31	**<0.001**	**.005**	**<0.001**	**.032**	.129	**<0.001**	**<0.001**

Bold text in the table indicates significant values.

driven approach. Three district EC clusters were identified; an 'emotionally preserved' (57%) cluster, an 'emotionally blunted' (26%) cluster and an 'emotionally volatile' (17%) cluster. Patients in the 'emotionally preserved' cluster exhibited both higher emotional reactivity and more ability to dampen emotions and faster recognition of facial expressions. Patients in the 'emotionally blunted' and 'emotionally volatile' clusters presented poorer accuracy and slowed recognition of facial expressions in general. However, while patients in the 'emotionally blunted' cluster were characterized by lower emotional reactivity and less down-regulation of emotions, patients in the 'emotionally volatile' cluster showed a somewhat opposite profile characterized by heightened emotional reactivity but also increased down-regulation of emotions when required to do so. They also showed increased attentional avoidance of fearful faces. The distinct EC subgroups showed no differences in age, IQ, age at illness onset, illness duration, illness chronicity, current medication or current subsyndromal depression or mania symptoms or functioning. However, they differed in terms of gender, years of education, anxiety levels, diagnostic composition, and non-emotional cognition. Relatives of 'emotionally preserved' patients were more successful at dampening emotions in aversive social scenarios, whereas relatives of 'emotionally impaired' patients underperformed in verbal fluency compared to HC.

The detection of three EC subgroups of patients with mood disorders document an intriguing heterogeneity in patients' EC abilities that transcend traditional diagnostic categories (Cuthbert, 2014). These subgroups could explain the heterogenous findings in the field (Miskowiak et al., 2019) and mirrors the well-documented heterogeneity within non-emotional cognition (Burdick et al., 2014; Jensen et al., 2016; Kjærstad et al., 2019a; Pu et al., 2018; Solé et al., 2016). Our results were consistent with the previous demonstration of variability in social cognition, where EC was measured with the Mayer-Salovey-Caruso Emotional Intelligence Test and Reading the Mind in the Eyes Test (Varo et al., 2020) and the Emotional Recognition Task (Szmulewicz et al., 2020) in patients with BD. Specifically, two distinct socio-emotional cognition profiles among BD were detected with HCA: one with normal performance and another cluster showing mild to moderate impairments in social cognition domains such as theory of mind, attributional bias (Varo et al., 2020) and emotional processing (Szmulewicz et al., 2020; Varo et al., 2020). The detection of two as opposed to three EC subgroups, as seen in the current study, may partly reflect (i) the different EC tests used to obtain the clusters, which in the previous study tapped into more complex social cognitive abilities, including theory of mind and attributional bias (ii) the somewhat larger sample in the present study (n = 269 vs. n = 212 (Szmulewicz et al., 2020) and n = 71 (Varo et al., 2020)) and (iii) our inclusion of both UD and BD patients. Despite these differences, all the three studies showed consistently that two-thirds of patients were relatively emotionally intact.

Together, the present and previous studies (Szmulewicz et al., 2020; Varo et al., 2020) indicate that aberrant EC during remission is only characteristic of a minority of patients with mood disorders. Moreover, patients characterised by aberrant EC displayed intact

performance in some domains of EC, which was either on par with, or even better than, HC. Notably, aberrant EC within these patient clusters tended to be relatively subtle, as evidenced by z-scores ranging from $z = -0.9$ to -0.4 below HCs' (with the exception of greater emotional reactivity in social scenarios in emotionally blunted patients, $z = -1.4$). It thus seems that EC abnormalities are less common than impairments in non-emotional cognition that occur in 40-70% of patients during remission (Burdick et al., 2014; Jensen et al., 2016; Kjærstad et al., 2019a; Solé et al., 2016). Further, for those with EC impairments, the *magnitude* of the difficulties was smaller than impairments in non-emotional cognition (Lee et al., 2013), with an estimated 0.3-0.5 SD below the normative mean decline in EC for every 1 SD decline in non-emotional cognition (Miskowiak et al., 2019). However, even mild EC abnormalities may produce significant difficulties in functioning given the crucial importance of EC for social relations. In keeping with this, it has been suggested that even mild impairments deserve to be targeted in treatments (Fulford et al., 2014; Miskowiak and Varo, 2021). Although all patients were functionally impaired, we found no differences between the three EC clusters in observer-rated psychosocial functioning (ie., FAST scores). This result is in line with a recent study on social cognitive heterogeneity in BD that also found no differences between social cognitive clusters of patients with BD on functioning (Varo et al., 2020). This suggests that, beyond FAST scores, which are not always proportional to the level of emotional cognitive abilities, there are other factors that also influence the relationship between EC and functioning including: the difference between emotional regulation strategies used by the patients (Gruber et al., 2013), subjective quality of life and work situation (Hoertnagl et al., 2011), non-emotional cognition (Van Rheenen and Rossell, 2014) and a family history of affective disorders (Varo et al., 2019). In light of these findings, a measure of social functioning with increased sensitivity than the FAST may thus be better suited for the detection of social implications or distinct EC.

Further group comparisons provided information about the relationship between gender and non-emotional cognition among the clusters. The highest proportion of females was belonging to the 'emotional preserved cluster', which is in line with previous studies that found that females performed better than males on EC measures in both clinical sample (DeTore et al., 2018; Varo et al., 2020; Varo et al., 2019) and non-clinical populations (Donges et al., 2012; Hall, 1978). Regarding non-emotional cognition, we found that EC subgroups exhibited differential impairments in non-emotional cognitive domains. While the 'emotionally volatile' and 'the emotionally blunted' clusters exhibited impairment in non-emotional cognition, patients in the 'emotionally preserved' cluster retained normal non-emotional cognitive performance in most domains. Among the emotionally impaired clusters, the non-emotional cognition impairment was more severe and widespread in patients categorised as 'emotionally volatile'. A possible explanation is that these patients' heightened sensitivity and reactivity to emotional stimuli resulted in greater allocation of attention resources to down-regulation of emotions at the expense of the non-emotional cognitive tests. These

findings are in line with the results from other studies where suggests that high levels of emotion may interfere with non-emotional performance, in part because of the resources consumed by prioritizing attention to highly salient, emotion-relevant stimuli (Lima et al., 2018; Pessoa, 2009). The present results suggest that certain level of intact EC may be required for successful in non-emotional cognition. This interpretation would be consistent with evidence that emotional and non-emotional cognition impairments are indeed interrelated (Hoe et al., 2012; Kjærstad et al., 2019a; Lee et al., 2013). Cusi et al. (2012) found that social cognition in patients with mood disorders exhibited enhanced activation in limbic and emotion-related structures and attenuated activity within frontal regions associated with emotion regulation and higher cognitive functions (Cusi et al., 2012). Further, *behavioural* evidence suggests that patients with BD who are neurocognitively impaired experience difficulties with facial expression recognition (Kjærstad et al., 2019a; Van Rheenen and Rossell, 2016). Contrary, patients who are neurocognitively intact display no facial expression recognition difficulties (Kjærstad et al., 2019a; Van Rheenen and Rossell, 2016) but rather superior social cognition relative to HC (Burdick et al., 2014). This partial overlap among non-emotional cognition and EC raises the question of whether the group differences observed in EC tasks stem from neurocognition. However, due to the complexity of these processes and their mutual interplay, it is difficult to discern whether aberrant EC in this group was primary or secondary to deficits in non-emotional cognition. Studies of EC in UR of patients with mood disorders have provided conflicting results; while some indicate that EC abnormalities are risk markers or endophenotypes of mood disorders (Bora and Özerdem, 2017; Miskowiak and Carvalho, 2015; Miskowiak et al., 2017), other studies found no such evidence (McCormack et al., 2016; Meluken et al., 2019). Our study revealed no association between EC clusters among patients with mood disorders and aberrant EC in UR, since UR exhibited no EC impairments. Thus, aberrant EC does not seem to represent an endophenotype for mood disorders, since only patients, but not their UR, exhibited EC impairments but may rather result from scars of illness. In fact, UR of 'emotionally preserved' patients exhibited superior ability to dampen emotions compared to HC. This could reflect a resilience marker in these individuals who remained healthy despite their familial predisposition for mood disorder. Contrary, the impairment in verbal fluency in patients categorised as 'emotionally blunted' and 'emotionally volatile', as well as their UR, suggest that impairment in verbal fluency may reflect a cognitive biomarker of distinct genetic risk profiles (Deveci et al., 2013; Maziade et al., 2009).

The evidence of EC subgroups of patients with mood disorders has important clinical implications. The use of different patterns of the responses used by the groups across the EC tasks may be conceptualised in terms of compensatory mechanisms (Broch-Due et al., 2018). The greater than normal skill to dampen emotions in patients of the 'emotionally preserved' and 'emotionally volatile' clusters may indicate the presence of acquired EC strategies in these patients to control their heightened emotional reactivity. Specifically, these patients may have over time developed conscious strategies to dampen their emotions to maintain

mood stability. Conversely, the lower reactivity in social scenarios and in recognition of positive facial expressions displayed by patients in the 'emotionally blunted' cluster suggests that they at *an implicit level* regulate their emotions through avoidance and detachment. These emotionally blunted individuals presented less down-regulation of emotions, which is possibly a consequence of not needing to down-regulate blunted emotional response. It is important to note that the patients belonging to the blunted group had more years of education than the other two groups. Therefore, one could speculate whether their emotional coping strategies (i.e., lower emotional reactivity and avoidance of social relations) helped them stay focused on their studies and work. However, lack of conscious, adaptive emotional coping strategies in 'emotionally blunted' patients might also impact negatively on the course of the illness given the association between poor emotion regulation skills and mood instability (Carvalho et al., 2020). There are a number of psychotherapeutic approaches to treat emotional cognition but BD patients typically receive much fewer psychotherapeutic interventions than patients with UD. Our findings provide support for a transdiagnostic view of EC. This approach aid to target treatments for emotionally impaired clusters that share common EC deficits beyond clinical diagnosis. Thus, emotional cognitive strategies such as rumination, thought suppression, reappraisal, and problem-solving, which have already been widely demonstrated to be effective in UD (Aldao and Nolen-Hoeksema, 2010), might have effects transdiagnostically, proving to be effective in patients with BD.

Our results add to the compiling evidence for heterogeneity in mood disorders despite patients being relatively symptom-free. EC abnormalities were independent of subsyndromal mood symptoms and may thus represent trait-related abnormalities in subgroups of patients that are not addressed by current treatments. Our findings highlight the need to screen for EC difficulties in the clinical management of patients with mood disorders in partial or full remission and to develop treatments that target EC impairments in these patients.

Strengths of the study included the comprehensive assessment of EC. The three EC paradigms were selected as they cover the major areas of affective cognition; including emotional face processing, attentional interference of emotional stimuli, reactivity to and regulation of emotions (Miskowiak et al., 2019) and because they overlapped between the two pooled studies. However, the tasks did not cover other areas of higher-order, multi-dimensional social cognitive functions previously implicated in mood disorders, such as reward processing, theory of mind, mentalizing abilities (Bora et al., 2016; Bora and Berk, 2016; Weightman et al., 2014). It is indeed plausible that tasks assessing other areas of emotional cognition would be more advantageous in detecting emotional cognition differences between subgroups that would more characteristically define subgroups of patients with mood disorders. However, there is at present no consensus test battery for assessment of EC in mood disorders. Also, our study included a large well-defined sample of patients with mood disorders in remission and their first-degree relatives, which provided strong statistical power for the HCA and deep characterization of the EC clusters. A limitation was the cross-

sectional design as this provides no insight into the developmental trajectory of EC heterogeneity in mood disorders. Further, for comparison of non-emotional cognition, different neuropsychological tests were used in the two studies from which the data was pooled, which impeded direct comparison of performance on the specific non-emotional cognition tests. The only moderate samples of UR in the 'emotionally volatile' and 'emotionally blunted' clusters ($n = 18$ and $n = 19$, respectively) impeded analysis of group differences across these UR. Therefore, we cannot exclude that the findings for relatives represent a type II error. In keeping with previous studies assessing cognitive heterogeneity in mood disorders (Burdick et al., 2014; Jensen et al., 2016; Kjærstad et al., 2019a), we did not correct for multiple comparisons, which could have introduced type-I error. However, due to the exploratory nature of the study, apply the Bonferroni method would be highly conservative and might miss real differences, increasing the risk of running type II error. Alternatively, post hoc comparisons were made to investigate the characteristics of the clusters.

The differences between the groups in variables such as diagnosis composition and anxiety levels could have confounded our results. However, the larger proportion of BD than UD in the emotionally impaired clusters could not explain the EC abnormalities, as indicated by no change in the observed EC differences between the clusters in a sensitivity analysis excluding UD patients. Finally, although there were no differences between EC clusters in current medication, we could not rule out the potential effect of the type of medication on EC performance given we did not control for dosages. Future studies including a larger number of measures of EC will be important in establishing and refining these profiles.

In conclusion, this study provides the first evidence for distinct EC subgroups across unipolar and bipolar disorders. About half of patients with mood disorders in full or partial remission displayed preserved EC, and the remaining patients were characterised by distinct EC abnormalities (displaying a volatile or blunted response to emotional stimuli), which should be targeted in the clinical treatment. In contrast, no EC impairments were observed in patients' UR, suggesting that these do not represent an endophenotype. The improved ability to dampen emotions in UR of 'emotionally preserved' patients may reflect a resilience marker while impaired verbal fluency in UR of 'emotionally impaired' groups likely reflects a risk marker of distinct genetic risk profiles in these EC subgroups.

Conflicts of interest

KWM has received consultancy fees from Lundbeck and Janssen-Cilag in the past three years. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Galenica, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sage, Sanofi-Aventis, Servier, Shire, Sunovion, and Takeda, unrelated to the present work. LVK has within recent three years been a

Contributors

CV and HLK undertook the literature searches and statistical analyses and wrote the first draft of the manuscript under supervision of KWM. EP, IM and HLK managed participant recruitment and testing. EV, MV and LVK contributed with a revision of the draft. All authors contributed to and have approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.05.003.

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