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Research paper

Cognitive hierarchy in mood disorders and relations to daily functioning

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ABSTRACT

Cognitive impairment affects approximately 50 % of patients with mood disorders during remission, which correlates with poorer daily-life functioning. The hierarchical organisation of cognitive processes may mean that some cognitive deficits, e.g., memory impairments, are secondary to impairments in suggested core processes, including executive functions, working memory, attention, and psychomotor speed. The exact structure of a cognitive hierarchy in mood disorders is unclear. In this study, we aimed to examine relationships between cognitive domains using network graphs. Further, we aimed to explore whether impairments in the proposed 'core cognitive domains' mediated patients' verbal memory impairment and functional disability using mediation and hierarchical regression analyses. We pooled data from patients with mood disorders and healthy controls (HC) from 10 original studies. In total, 1505 participants were included in the analyses (n = 900 patients; n = 605 HC). We found that cognitive domains were more intercorrelated in patients than in HC. Executive functions, working memory, and attention and psychomotor speed almost fully accounted for illness-associated verbal learning and memory impairments, indicating partial mediation. Of the core domains, working memory explained the largest amount of variance in memory impairments and functional disability. Our findings highlight the importance of targeting core cognitive domains in pro-cognitive interventions.

1. Introduction

Cognitive impairment is a central feature in mood disorders (bipolar disorder [BD] and major depressive disorder [MDD]) that affects approximately 50 % of all patients during remission (Kjærstad et al., 2021; Pu et al., 2018) can have persistent implications for patients' functional abilities, including socio-occupational outcomes (Tse et al., 2014). Patients present with objectively verifiable impairment as well as subjective complaints across several cognitive domains including attention, memory, and executive functions, with memory difficulties

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being particularly prevalent (Bora et al., 2013; Bourne et al., 2013; Burdick et al., 2005; Miebach et al., 2019). In healthy individuals, these cognitive domains are often conceptualised as discrete functions that operate relatively independently as demonstrated by factor structure studies on cognition (Agelink van Rentergem et al., 2020; Reuter-Lorenz and Park, 2014). Conversely, one study comparing cognitive factor structure between HC and patients with mood disorders found less specificity and more overlap between functions, indicating greater intercorrelations between cognitive domains in mood disorders (Gallagher et al., 2014). Cognitive difficulties in this patient group therefore likely involve a complex interplay between cognitive processes across domains of which impairments in some domains give rise to impairments in others (Gallagher, 2021; Gallagher et al., 2014). Hence, when patients experience poor memory, this can in some cases be partially caused by deficits in other domains, e.g., attention (failing to sustain attention during memory encoding) or executive functions (failing to strategically encode and retrieve information) (Duff et al., 2005; Kieseppä et al., 2005).

Indeed, emerging evidence points to a hierarchy among cognitive impairments in patients with mood disorders, with some impairments compared to HC being primary or "core" to others (Gallagher, 2021). One study of *euthymic* patients with BD found that memory impairments were mediated by a primary deficit in executive functions (Thompson et al., 2009). Importantly, reduced psychomotor speed did not account for executive dysfunction, suggesting that deficits in both domains represent "core cognitive impairments" in BD (Thompson et al., 2009). Similarly, studies in *symptomatic* MDD found that memory impairment was secondary to deficits in working memory and attention (Nebes et al., 2000), or deficits in executive functions and processing speed (Liu et al., 2019), respectively. Another study showed that reduced processing speed mediated impaired memory performance in the depressive state of MDD, whereas no cognitive impairments were found during remission (Zaremba et al., 2019). Taken together, these studies provide emerging evidence to indicate that deficits in executive functions, working memory, attention, and psychomotor speed can be primary drivers of impaired memory performance in mood disorders, although the exact structure of such a cognitive hierarchy may depend on mood state and ultimately remains to be uncovered (Liu et al., 2019; Nebes et al., 2000; Thompson et al., 2009; Zaremba et al., 2019).

Despite the high prevalence of cognitive impairment across domains in mood disorders, there is a paucity of evidence-based pro-cognitive interventions (Miskowiak et al., 2022). Elucidating whether impairments in cognitive domains are ordered in a hierarchy is crucial because core cognitive deficits could prove the most relevant targets for pro-cognitive interventions, triggering upstream benefits on secondary domains (Little et al., 2024). Notably, the emerging evidence for a cognitive hierarchy in mood disorders has been limited by smaller sample sizes, ranging from $N = 39$–225 patients and $N = 19$–142 HC, and the inclusion of patients in mixed mood states, which highlights the need for large-scale studies that include patients in full or partial remission (Liu et al., 2019; Nebes et al., 2000; Thompson et al., 2009; Zaremba et al., 2019). In addition, while it is well-established that cognitive impairment correlates with daily-life functioning disabilities (e.g., McIntyre et al., 2013; Mora et al., 2013; Tse et al., 2014) no studies to date investigated whether specific core cognitive domains are particularly related to functional disability in mood disorders.

1.1. Aims and hypotheses

The present study is a cross-sectional investigation of cognition and daily functioning based on data from a large cohort of patients with mood disorders (BD or MDD) and HC pooled from several studies conducted at the Neurocognition and Emotion in Affective Disorders (NEAD) Centre in 2008–2024. This will enable the largest to-date investigation of: (1) how cognitive domains are intercorrelated in patients with mood disorders and HC, respectively, (2) whether deficits in executive functions, working memory, and/or attention and psychomotor speed (i.e., proposed core cognitive domains) mediate patients' impairments in verbal learning and memory and (3) how cognitive impairment across domains relates to functional disability. The first aim will be investigated with network graphs, and we hypothesise that cognitive domains are more strongly intercorrelated in patients than in HC. For the second aim, we perform mediation analyses and hierarchical regression analyses to investigate if impairments in the core cognitive domains mediate verbal memory deficits in patients and explore which domain explains the greatest amount of variance in memory performance. The third aim will be examined with hierarchical regression analyses within the patient group to investigate which of the cognitive domains explains the greatest amount of variance in functional capacity.

2. Materials and methods

2.1. Participants and procedure

2.1.1. Participants

Baseline demographics, clinical, and neurocognitive data from patients with mood disorders and HC was based on data from the NEAD cohort database collected from 10 original studies (see Supplementary Table 1 and Supplementary Materials for details). Patients had an ICD-10 diagnosis of BD or MDD, which was either verified by a clinician or a trained clinical researcher using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990). Healthy participants had no history of treatment-requiring psychiatric disorders. For the present analyses, we included all participants in full or partial remission from current depressive and (hypo)manic symptoms. Further details on recruitment procedures and exclusion criteria for participants in the individual studies are available from ClinicalTrials.gov (see Supplementary Table 1).

All studies have been approved by the relevant authorities (see Supplementary Table 1 for approval numbers). Pooling data for the present study was approved by The Danish Data Protection Agency Capital Region of Denmark (P-2022-797). Pooling data from these prior studies was appropriate given the overlapping inclusion criteria, as well as the administration of equal neurocognitive tests, questionnaires, and ratings of functioning and mood symptoms. Written informed consent was obtained from all participants before study participation.

2.1.2. Cognitive tests and domains

All participants underwent neurocognitive testing of the following cognitive domains, although study protocols varied and therefore only partially overlapped (see Supplementary Table 2 for the specific tests for each study): executive functions, working memory, attention and psychomotor speed, and verbal learning and memory. These four cognitive domains consisted of the following test: "Executive Functions": Trail Making Test (TMT) Part B (Army Individual Test Battery, 1944), Verbal Fluency letters S & D (Borkowski et al., 1967), One Touch Stockings of Cambridge (OTS) from CANTAB (Cambridge Cognition Ltd.), and the Screening for Cognitive Impairment in Psychiatry (SCIP) Verbal Fluency Test (Purdon, 2005); "Working Memory": Wechsler Adult Intelligence Scale (WAIS)-III Letter-Number Sequencing (Wechsler, 1997), Spatial Working Memory (SWM) from CANTAB, and the SCIP Working Memory Test); "Attention and psychomotor speed": TMT Part A, The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Span & Coding (Randolph et al., 1998), Rapid Visual Processing (RVP) from CANTAB, and the SCIP Psychomotor Speed Test, and "Verbal Learning and Memory"; Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1995), the SCIP Verbal Learning Test. Participants' premorbid verbal intelligence quotient (IQ) was estimated using the Danish Adult Reading Task (DART) (Nelson and O'Connell, 1978).

2.1.3. Measures of daily functioning

Daily functioning was assessed with the following measures,

although study protocols varied and only partially overlapped (see Supplementary Table 2 for the specific functioning measures assessed in each study): Functioning Assessment Short test (FAST) (Rosa et al., 2007) or Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002). The FAST evaluates six domains of everyday functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time (Rosa et al., 2007). A higher FAST score reflects poorer daily functioning with scores above 11 indicating functional impairment (12–20 = mild impairment; 21–40 = moderate impairment; >40 = severe impairment) (Bonnín et al., 2018). The WSAS is a self-report scale of functional impairment with higher scores corresponding to greater functional disability (Mundt et al., 2002).

2.1.4. Mood ratings

Mood symptoms were assessed with the Hamilton Depression Rating Scale – 17 items (HDRS) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively. Partial remission was defined as a score between >7 and ≤ 14 on the HDRS and YMRS, respectively, whereas full remission was defined as a score of ≤7 on both the HDRS and YMRS.

2.2. Statistical procedure

All statistical analyses were conducted in RStudio (v2023.09.0) with $\alpha = 0.05$.

2.2.1. Composite score calculation and group comparisons

For cognition, we calculated *z*-scores for each cognitive test score based on the HC mean and SD data. We then calculated cognitive domain scores for each participant by taking the mean of the available *z*-scores from the relevant tests for each domain (for global cognition, domain scores were averaged). We controlled for the effect of age on cognition by regressing this variable out of each cognitive domain using robust regression and included the residuals from these regressions as domain scores in the primary analyses. For daily functioning, we calculated *z*-scores for each measure of functioning using the mean and SD based on the patient sample only and calculated functioning domain scores by averaging the available measures from each patient. See Supplementary Materials for details on composite score calculations and data cleaning.

Patients and HC were compared on demographic variables, mood symptoms, cognitive composite scores (not corrected for age), and functional assessments using independent samples *t*-tests or Mann Whitney *U* tests for continuous data and Pearson's Chi-square ($\chi 2$) tests for categorical data.

2.2.2. Network graphs

We used network graphs to visually explore relationships between cognitive domain performances (i.e., executive functions, working memory, attention and psychomotor speed, and verbal learning and memory) in the whole sample as well as within the patient and HC groups separately. We used the *qgraph* and *bootnet* packages in R to produce the graphs (Epskamp et al., 2018, 2012). We constructed regularised partial correlation networks (i.e., networks where sparse models are preferred over complex models) using the methods described by Epskamp and Fried (2018) (see Supplementary Materials for details).

2.2.3. Mediation and hierarchical regression analyses on verbal learning and memory

For mediation and hierarchical regression analyses on verbal learning and memory, we applied the methods described by Nebes et al. (2000). Here, we tested whether impairments in each proposed core cognitive domain (executive functions, working memory, and attention and psychomotor speed) separately or conjointly mediated verbal learning and memory impairment in patients. In the first level of the regression model (Model 0) we examined how much variance (adjusted R^2) in verbal learning and memory was explained by group (patients vs. HC). In the next level (Model 1), we first added one core cognitive domain (i.e., executive functions, working memory, or attention and psychomotor speed) and then the group variable. We examined the change in percent in group-related explained variance compared to Model 0 (i.e., ((Adjusted R^2 for group in Model 1 - Adjusted R^2 for group in Model 0) / Adjusted R^2 for group in Model 0) * 100). In Model 2 and Model 3, we added two or three core cognitive domains, respectively, before adding the group variable and examined changes in group-related explained variance compared to Model 0. These models were constructed with all possible combinations of 1, 2, and 3 core cognitive domains, respectively, as predictors. At each step, we examined the *F*-change statistic to test whether adding each variable to the regression model explained a significant amount of extra variance in verbal learning and memory compared to the previous step in the model. Full mediation was present if the effect of group (patients vs. HC) was rendered non-significant when the proposed core domains were accounted for (Baron and Kenny, 1986).

2.2.4. Hierarchical regression analyses on daily functioning

Within patients only, we conducted hierarchical regression models to examine the effects of the different cognitive domain performances on daily functioning. Again, each cognitive domain score was entered into the model in rotating orders to test the separate and combined effects, but here, we also included verbal learning and memory as a predictor. At each step, we examined the *F*-change statistic to test whether adding each cognitive variable to the model explained a significant amount of extra variance in daily functioning compared to the previous step. In post-hoc models, we constructed models with all possible combinations of 1, 2, 3, and 4 cognitive domains as predictors, respectively, to examine if order of entry would change the results.

2.2.5. Model fit validation

To evaluate model fit, we conducted leave-one-out cross-validation models (LOOCV) using the *caret* package in R (Kuhn, 2008). Here, we calculated the root mean squared error (RMSE) between predicted and observed values as a measure of how well the regression models predict unseen data (see Supplementary Materials for details).

2.2.6. Post-hoc analyses in full remissions

After conducting the main analyses, we repeated the regression analyses in participants in full remission (i.e., HDRS and YMRS scores ≤7) to assess potential effect of mood symptom severity on cognitive performance patterns and daily functioning. Further, we drew separate network graphs for patients in full or partial remission, respectively, to illustrate any potential differences in cognitive composition between these groups.

3. Results

3.1. Sample characteristics

Across the pooled studies, we included $N = 1505$ participants in the analyses ($n = 900$ patients with mood disorders ($n = 763$ BD; $n = 137$ MDD); $n = 605$ HC). Sample characteristics are presented in Table 1. Patients and HC were well-matched on age, verbal IQ, and sex ($ps \geq 0.23$), but patients had fewer years of education ($p < .001$). Compared to HC, patients showed lower cognitive performance scores in global cognition and across all domains, i.e., verbal learning and memory, executive functions, working memory, and attention and psychomotor speed ($ps < 0.001$; Fig. 1). On the individual measures of daily functioning (FAST and WSAS), patients presented with higher scores, indicating more functional disability in comparison with HC ($ps < 0.001$). Regarding clinical variables, patients presented with more subsyndromal mood symptoms (HDRS and YMRS total scores, respectively)

Table 1
Demographic and clinical characteristics in patients with mood disorders vs. healthy controls (HC) ($N = 1505$).

	Patients ($N = 900$)	HC ($N = 605$)	p-value
Demographics			
Sex (F/M%)	61/39	58/42	0.226
Age in years, median (IQR)	33 (16)	31 (19)	0.401
Educational years, mean (SD)	14.8 (3)	15.3 (3)	**<0.001**
Verbal IQ, mean (SD)	112 (6)	113 (6)	0.559
Cognition and functioning			
Global cognition composite z-score, mean (SD)	−0.4 (0.7)	0.0 (0.6)	**<0.001**
Verbal learning and memory composite z-score, mean (SD)	−0.4 (1)	0.0 (0.8)	**<0.001**
Executive functions composite z-score, mean (SD)	−0.3 (0.9)	0.0 (0.8)	**<0.001**
Working memory composite z-score, mean (SD)	−0.5 (0.9)	0.0 (0.9)	**<0.001**
Attention and psychomotor speed composite z-score, mean (SD)	−0.4 (0.8)	−0.1 (0.8)	**<0.001**
FAST total score, median (IQR)	18 (20)	1 (2)	**<0.001**
WSAS total score, median (IQR)	17 (13)	0 (0)	**<0.001**
Illness characteristics			
HDRS, median (IQR)	5 (6)	0 (2)	**<0.001**
YMRS, median (IQR)	1 (3)	0 (1)	**<0.001**
Diagnosis, BD/MDD %	85/15		
BD type I/II %	41/59		
Illness duration, median (IQR)	8 (12)		
Depressive episodes, median (IQR)	4 (7)		
(Hypo)manic episodes, median (IQR)	3 (8)		
Mixed state episodes, median (IQR)	0 (0)		
Total episodes, median (IQR)	8 (14)		
Psychotropic medications			
Any medication, no. (%)	714 (83)		
Antidepressants, no. (%)	201 (23)		
Antipsychotics, no. (%)	310 (35)		
Anticonvulsants, no. (%)	370 (42)		
Lithium, no. (%)	369 (42)		

Notes: HC = Healthy controls. Sex = Sex assigned at birth. SD = standard deviation. IQ = intelligence quotient. HDRS = Hamilton Depression Rating Scale 17-item version. YMRS = Young Mania Rating Scale. FAST = Functioning Assessment Short Test. WSAS = Work and Social Adjustment Scale. BD = Bipolar disorder. MDD = Major depressive disorder. Chi-square for categorical variables, Mann-Whitney for non-parametric data (median (IQR)), and independent t-tests for normally distributed data (mean (SD)). **Bold** = $p<.05$
Data was missing/not collected for $N = 173$ for verbal IQ (165 patients, 8 HC), $N = 12$ for years of education (9 patients, 3 HC), $N = 8$ for HDRS (7 patients, 1 HC), 51 for YMRS (50 patients, 1 HC), $N = 55$ for FAST total (51 patients, 4 HC), $N = 633$ for WSAS (278 patients, 355 HC), $N = 6$ for verbal learning and memory (all patients), $N = 4$ for executive functions (all patients). For patients, data was missing for $n = 72$ for bipolar type, $n = 231$ for illness duration, $n = 141$ for depressive episodes, $n = 185$ for (hypo)manic episodes, $n = 357$ for mixed episodes, $n = 368$ for total episodes, n = 36 for antidepressants, $n = 23$ for antipsychotics, $n = 25$ for anticonvulsants, n = 23 for lithium, and $n = 38$ for any medication.

than HC ($ps < 0.001$), most were diagnosed with BD (85 %), used psychotropic medication (83 %), and their median illness duration was 8 years (for further details, see Table 1).

3.2. Network graphs on cognition

Fig. 2 displays the network graphs that illustrate relationships between cognitive domains in the whole sample (A) and separately in patients (B) and HC (C). Across the entire sample, verbal learning and memory showed a moderate positive relationship with working memory ($r = 0.22$) and weak relationships with executive functions ($r = 0.16$) and attention and psychomotor speed ($r = 0.15$). The proposed core cognitive functions (i.e., executive functions, working memory, and attention and psychomotor speed) were generally more strongly interrelated to each other than to verbal learning and memory, with the strongest relationship of the entire graph being between attention and psychomotor speed and executive functions ($r = 0.33$). We observed the same pattern in the network graph for the patient sample alone. Here, the relationship between attention and psychomotor speed and executive functions was even stronger ($r = 0.38$), and only weak to moderate correlations were present between verbal learning and memory and the three core functions ($rs = 0.15$–0.21). In HC, we observed very weak relationships between verbal learning and memory and the three core functions ($rs = 0.06$–0.16). The core functions were still moderately, positively correlated with each other, as in the network graph for the entire sample, but for HC, the strongest correlation was between working memory and executive functions ($r = 0.29$).

3.3. Mediation and hierarchical regression analyses in verbal learning and memory

Results from the regression models on verbal learning and memory are presented in Table 2. All regression models were significant ($ps < 0.001$). Model 0, where group (patients vs. HC) was entered as the sole predictor of memory performance, explained 4.7 % of variance in verbal learning and memory. In Model 1, we added one proposed core cognitive domain (executive functions, working memory, or attention and psychomotor speed, respectively) prior to adding group to the regression model. Here, adding group explained 1.4 %–2.7 % extra variance ($ps < 0.001$), representing a reduction in the effect of group of 42 %–69 % compared to Model 0. In Model 2, two cognitive domains were included before adding group. At this step, group added 0.8 %–1.6 % variance explained ($ps < 0.001$), i.e., a reduction of 66 %–83 % in comparison with Model 0. At the final step, in Model 3, where all proposed core cognitive domains were added before group, group added 0.8 % of extra variance explained ($ps < 0.001$), representing a total reduction in the group effect of 83 % compared to Model 0. The full model, including the group effect and the effect of executive functions, working memory, and attention and psychomotor speed explained 20 % of the variance in verbal learning and memory.

Every time a new core domain was added to the model, a significant amount of additional variance in verbal learning and memory was accounted for, irrespective of the variable and order of entry ($ps < 0.001$). However, changes in adjusted R^2 and the F-change statistic showed that adding working memory consistently led to the largest amount of additional variance explained, regardless of the order in which this domain was entered into each model. The LOOCV RMSE ranged from 0.80 to 0.87 across regression models.

3.4. Hierarchical regression analyses in daily functioning

Results from the hierarchical regressions on daily functioning are presented in Table 3. Data on daily functioning was missing for 6 patients, yielding a sample size of $n = 894$. All regression models were significant ($ps < 0.001$), although the full model, including all cognitive domains, only explained 6.5 % of the variance in daily functioning. In these models, adding working memory and attention and psychomotor speed, respectively, resulted in significant amounts of additional variance explained in daily functioning, irrespective of entry order ($ps \leq 0.001$). This contrasted with adding executive functions and verbal learning and memory to the regression models, which generally did not significantly explain additional amounts of variance (except for adding verbal learning and memory to the model of attention and psychomotor speed ($p = .01$)). In accordance with the cognitive hierarchy, adding working memory to the model consistently produced the largest F-change statistic and increments in adjusted R^2 compared to the other cognitive domains. The LOOCV RMSE ranged from 0.89 to 0.92 across these regression models. Cognitive variable order of entry did not affect the results (Supplementary Table 3).

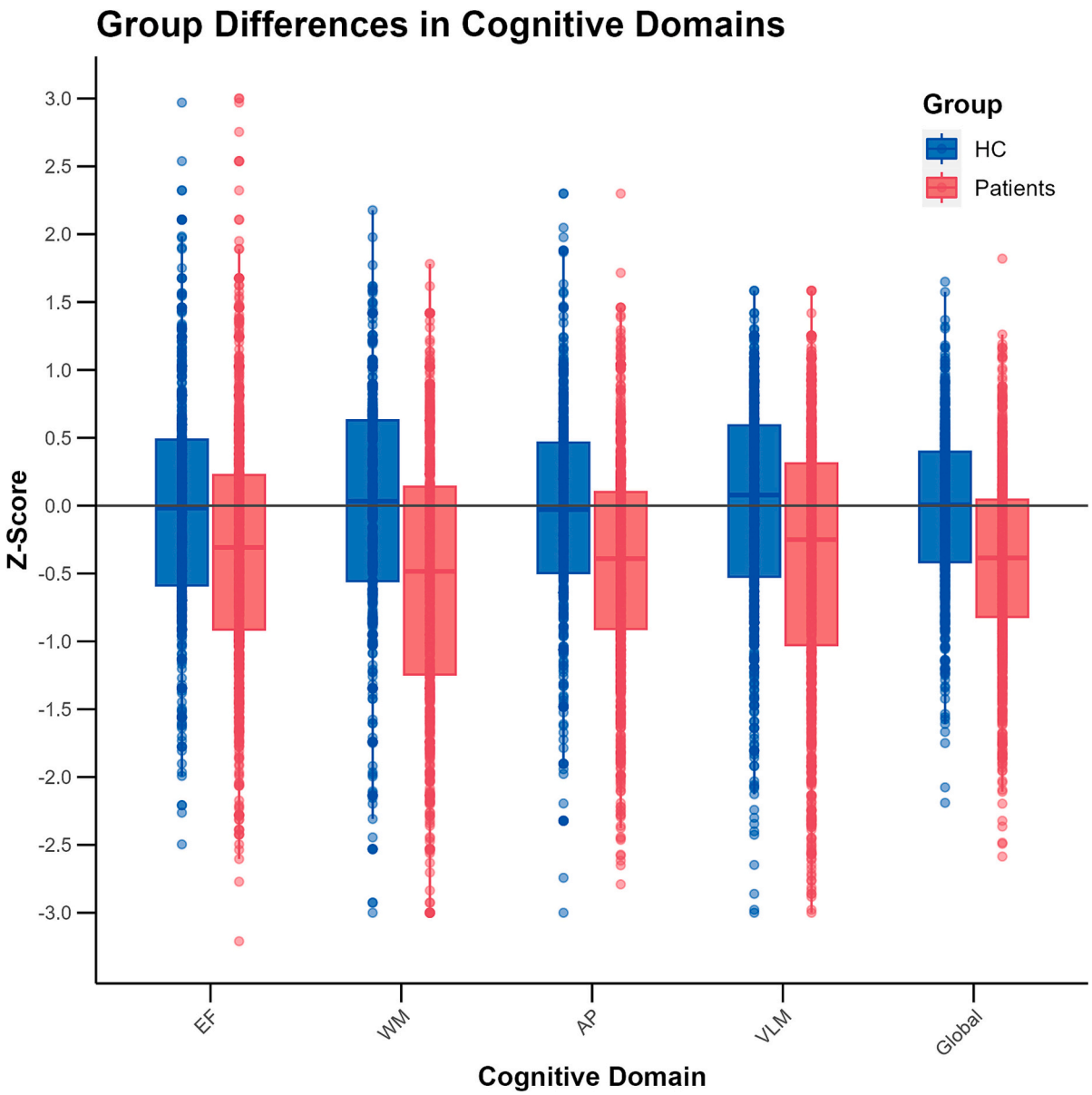

Fig. 1. Boxplots of cognitive domain scores for patients and healthy controls.
Legend: Fig. 1 shows uncorrected cognitive domain z-scores for patients and HC. Abbreviations: HC = Healthy controls. EF = Executive functions. WM = Working memory. AP = Attention and psychomotor speed. VLM = Verbal learning and memory. Global = Global cognition.

3.5. *Post-hoc analyses in fully-remitted patients*

As $n = 289$ patients presented with HDRS or YMRS scores >7, we repeated all the regression analyses including only fully remitted patients ($n = 591$) to examine if the observed associations were confounded by mood symptoms. The results were highly consistent with the analyses that included the entire patient sample, indicating that the results were robust to the presence of subthreshold depressive and (hypo)manic symptomatology. Specifically, the magnitude of the effect of group (patients vs HC) on verbal learning and memory impairment was reduced from 4.9 % to 1 % when the deficits in the proposed core cognitive domains were accounted for, representing a reduction of 79 % (Supplementary Table 4). Working memory consistently explained the largest amount of variance in verbal learning and memory in the regression models, in accordance with the models in the full sample (adjusted R^2 changes ranging from 4 %–6 %, $ps < 0.001$) (Supplementary Table 4). For daily functioning, working memory and attention and psychomotor speed led to equal adjusted R^2 changes, (ranging from 1 %–3 % in working memory and 2 % in attention and psychomotor speed, $ps < 0.003$), which slightly contrasts the findings in the full sample where working memory alone consistently emerged as the most influential factor (Supplementary Table 5).

We also drew exploratory network graphs in patients in full and partial remission, respectively, to investigate if cognitive network structures were different between the groups (Fig. 3). When comparing the two network graphs, patients in only partial remission (Fig. 3E) showed a stronger relationship between the verbal learning and memory domain and the core domains attention and psychomotor speed ($r = 0.19$) and working memory ($r = 0.23$), respectively, as opposed patients in full remission ($rs = 0.16$–0.21). Thus, the relationships between verbal learning and memory and the core cognitive functions in patients in full remission were generally weaker, which mirrors the pattern observed in the HC sample, where we also saw only minor correlations between memory and the core domains (Fig. 1C). Further, fully remitted patients showed a general interrelatedness of the core cognitive functions which was also largely present in the HC sample (Fig. 1C).

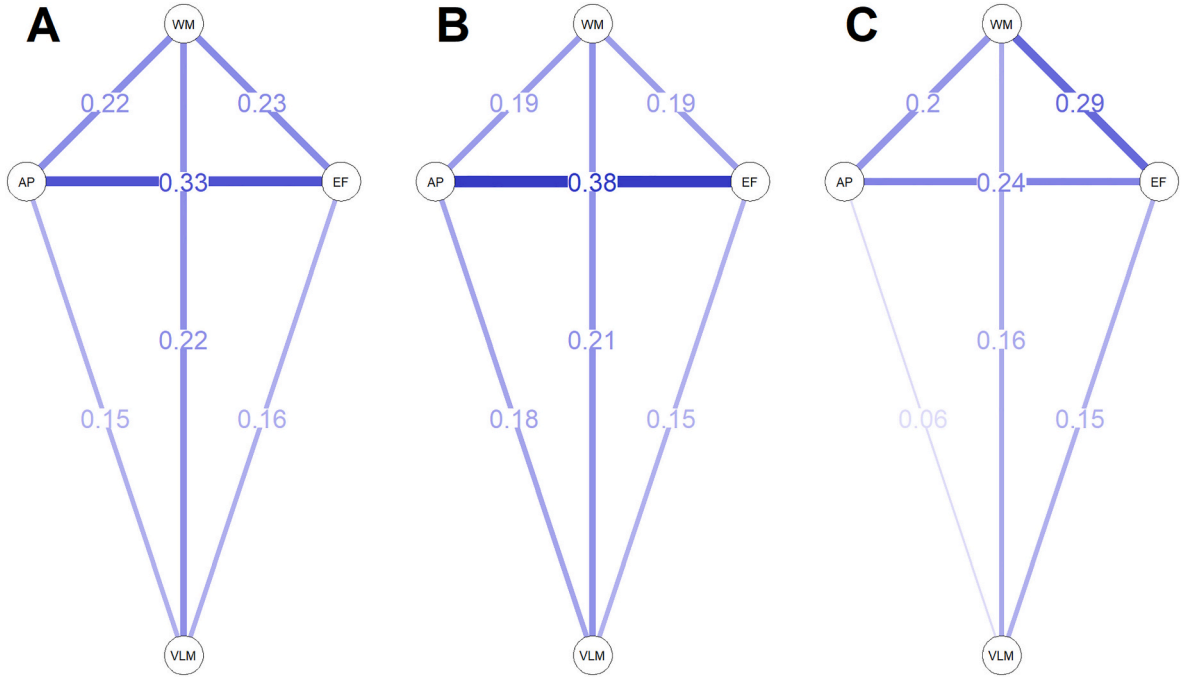

Fig. 2. Network graphs for cognitive domains for the entire sample, patients, and healthy controls.
Legend: Fig. 2 shows the network graphs for the different cognitive functions for (A) the entire sample ($N = 1505$), (B) patients ($n = 900$), and (C) healthy controls ($n = 605$). Each network displays relationships between cognitive domains estimated with regularised partial correlations using LASSO penalty and EBIC model selection with hyperparameter gamma = 0. The partial correlation coefficient for each relationship between the cognitive domains is displayed on the edge between the two corresponding nodes. Nodes were placed manually in a set layout. All cognitive scores were corrected for age. Abbreviations: AP = attention and psychomotor speed; VLM = verbal learning and memory; WM = working memory; EF = executive functions.

Specifically, patients in full remission had a stronger relationship between attention and psychomotor speed and executive functions ($r = 0.41$) as well as working memory ($r = 0.22$) compared to patients in only partial remission ($r = 0.15$–0.3). Together, the graphs point to slightly different cognitive network structures in full and partial remission, respectively, with the network in full remission being more like the HC network.

4. Discussion

This largest to-date study of cognitive hierarchy in 900 fully or partially remitted patients with mood disorders (BD and MDD) and 605 HC provides several novel insights into the hierarchy of cognitive impairments in mood disorders and its relation to functional disability. First, the study showed that cognitive domains were generally more interrelated in mood disorders compared to HC. Second, deficits in attention and psychomotor speed, working memory, and executive functions represented "core cognitive impairments" that accounted for most of the verbal learning and memory difficulties in patients, reducing the effect of group (patients vs. HC) by 83 % in line with a partial mediation effect. Third, working memory deficits emerged as the core impairment that consistently explained the largest amount of variance in verbal memory difficulties in mood disorders. In keeping with this, working memory and attention and psychomotor speed, as opposed to executive functions and verbal learning and memory, accounted for significant variance in daily functioning in the patient sample, indicating that impairments in these domains could be primary cognitive drivers of functional disability in mood disorders.

The observed larger correlations in the network graphs between cognitive domains in the patient sample compared to HC are in line with existing research on "cognitive scaffolding" in aging, which could manifest in mood disorders as well (Reuter-Lorenz and Park, 2014; Rizzo et al., 2014). Cognitive scaffolding refers to the engagement of supplementary neuronal circuitry to sustain cognitive functioning in the aging brain (Reuter-Lorenz and Park, 2014). As an example of cognitive scaffolding in mood disorders, one study showed that patients hyperactivated prefrontal regions (which are involved in executive functions) during memory retrieval to obtain performance equivalent to that in HC (van Eijndhoven et al., 2012). Cognitive scaffolding thus entails that domains become less dissociable during cognitive decline in mood disorders (Gallagher et al., 2014; Reuter-Lorenz and Park, 2014). Accordingly, when all the proposed core cognitive domains were significantly correlated and predictive of verbal learning and memory impairment in the present sample, this could suggest a loss of specificity and recruitment of additional domains to sustain cognitive performance. However, in this study, the network graphs showed that cognitive domains were also intercorrelated in HC, where we would not expect a need for cognitive scaffolding. This may reflect the test-impurity problem, i.e., different cognitive tests may load on different domains than what they are traditionally grouped as. For instance, research shows that TMT—B, a traditional test of executive functions, may load more onto psychomotor speed (Salthouse, 2011). Thus, the larger correlations between the core domains observed in this study, i.e., executive functions and attention and psychomotor speed, could reflect that TMT-B is a test of both domains. This limits any analyses of cognitive hierarchy because each cognitive function may not be properly assessed in a more isolated fashion, which further reflects a general limitation of the research field. Further validation of the network approach is required to test these interpretations.

In line with previous research, our results indicate that impairments in executive functions, working memory, and attention and psychomotor speed account for most of the verbal learning and memory difficulties observed in patients with mood disorders (Liu et al., 2019; Nebes et al., 2000; Thompson et al., 2009; Zaremba et al., 2019). Our study included patients in full or partial remission contrary to previous studies which have focused on symptomatic MDD, highlighting that a hierarchical organization of cognitive impairment could be trait-related in mood disorders. Nevertheless, the effect of group (patients vs. HC) on

Table 2
Results from mediation and hierarchical regression analyses on the effects of core cognitive domains and group (patients ($n = 900$) vs. healthy controls ($n = 605$)) on verbal learning and memory.

			Model statistics		Change statistics			
Model		Predictors	Adj. R^2	LOOCV RMSE	Adj. R^2 change	*F*-change	*p*	Change in group-related explained variance (%)
0		Group	0.047	0.87				
1	a	EF	0.114	0.84				
		+ Group	0.141	0.83	0.027	48.2	**<0.001**	−42.4
	b	WM	0.132	0.83				
		+ Group	0.146	0.83	0.014	26.0	**<0.001**	−69.4
	c	AP	0.112	0.84				
		+ Group	0.131	0.83	0.019	33.6	**<0.001**	−59.7
2	a	EF	0.114	0.84				
		+ WM	0.175	0.81	0.060	111.0	**<0.001**	
		+ Group	0.187	0.81	0.012	22.8	**<0.001**	−74.5
	b	EF	0.114	0.84				
		+ AP	0.154	0.82	0.040	71.4	**<0.001**	
		+ Group	0.170	0.82	0.016	30.2	**<0.001**	−65.5
	c	WM	0.132	0.83				
		+ AP	0.174	0.81	0.042	77.0	**<0.001**	
		+ Group	0.182	0.81	0.008	15.4	**<0.001**	−83.1
	d	WM	0.132	0.83				
		+ EF	0.175	0.81	0.043	78.8	**<0.001**	
		+ Group	0.187	0.81	0.012	22.8	**<0.001**	−74.5
	e	AP	0.112	0.84				
		+ EF	0.154	0.82	0.042	74.9	**<0.001**	
		+ Group	0.170	0.82	0.016	30.2	**<0.001**	−65.5
	f	AP	0.112	0.84				
		+ WM	0.174	0.81	0.061	112.7	**<0.001**	
		+ Group	0.182	0.81	0.008	15.4	**<0.001**	−83.1
3	a	EF	0.114	0.84				
		+ WM	0.175	0.81	0.060	111.0	**<0.001**	
		+ AP	0.194	0.80	0.019	36.4	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1
	b	EF	0.114	0.84				
		+ AP	0.154	0.82	0.040	71.4	**<0.001**	
		+ WM	0.194	0.80	0.040	75.1	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1
	c	WM	0.132	0.83				
		+ AP	0.174	0.81	0.042	77.0	**<0.001**	
		+ EF	0.194	0.80	0.020	38.1	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1
	d	WM	0.132	0.83				
		+ EF	0.175	0.81	0.043	78.8	**<0.001**	
		+ AP	0.194	0.80	0.019	36.4	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1
	e	AP	0.112	0.84				
		+ EF	0.154	0.82	0.042	74.9	**<0.001**	
		+ WM	0.194	0.80	0.040	75.1	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1
	f	AP	0.112	0.84				
		+ WM	0.174	0.81	0.061	112.7	**<0.001**	
		+ EF	0.194	0.80	0.020	38.1	**<0.001**	
		+ Group	0.202	0.80	0.008	16.0	**<0.001**	−83.1

Notes: Table shows results from hierachical regression models that examine if adding executive functions, working memory, attention and psychomotor, or the effect of group to regression models on verbal learning and memory explains a significant amount of additional variance. *P* = *P*-value of the F-change statistic. Group = Patients with mood disorders vs. healthy controls. [a] = Change statistic compared to model 0. Abbreviations: EF = Executive functions. WM = Working memory. AP = Attention and psychomotor speed. Adj. = Adjusted. LOOCV RMSE = Leave one out cross-validation root mean squared error. **Bold** = $p<.05$

memory performance was still significant when all core cognitive domains were accounted for, i.e., verbal memory impairments in mood disorders were not entirely explained by deficits in the proposed core domains. However, the amount of variance that group explained along each step of the hierarchical regression models was greatly reduced with the addition of each core cognitive domain. Ultimately, only a trivial 0.8 % of the variance in verbal learning and memory was *not* explained by impairments across the core domains, indicating partial mediation.

We found that deficits in working memory, specifically, explained the most amount of variance in verbal learning and memory impairments compared to impairments in other core domains. The working memory domain employed in our analyses includes two tests that involve letter/number manipulation, i.e., letter-number sequencing and the SCIP working memory test. These tests involve active manipulation and retention of several stimuli. Thus, working memory resources may be required to uphold performance in word list tests (i.e., maintaining and strategically encoding words), which was used to assess verbal learning and memory. Similarly, these working memory tests may mirror challenging situations in real-life (e.g., shopping in a supermarket or working in a shared office space), where patients need to navigate multiple inputs and disturbances when completing a task (Mahmood et al., 2018). Indeed, the present study highlights that working memory is a particularly strong predictor of daily functioning compared to the other included cognitive domains. However, the cognitive domains only explained a total of 6.5 % of the variance in daily functioning, highlighting that other factors may contribute to the functional disability observed in our patient sample. Indeed, previous research highlights that illness characteristics, including comorbidities, polypharmacy, and

Table 3
Results from hierarchical regression analyses on the effects of cognitive domains on daily functioning in patients with mood disorders (n = 894).

Model	Predictors	Model statistics		Change statistics		
		Adj. R^2	LOOCV RMSE	Adj. R^2 change	*F*-change	*p*
1	EF	0.012	0.92			
	EF + WM	0.047	0.90	0.035	34.4	**<0.001**
	EF + WM + AP	0.063	0.90	0.016	16.0	**<0.001**
	EF + WM + AP + VLM	0.065	0.90	0.002	2.44	0.119
2	WM	0.047	0.90			
	WM + AP	0.064	0.89	0.016	16.5	**<0.001**
	WM + AP + VLM	0.065	0.89	0.001	2.02	0.156
	WM + AP + VLM + EF	0.065	0.90	0.000	0.97	0.325
3	AP	0.041	0.91			
	AP + VLM	0.047	0.90	0.006	6.50	**0.011**
	AP + VLM + EF	0.046	0.90	−0.001	0.04	0.841
	AP + VLM + EF + WM	0.065	0.90	0.019	18.7	**<0.001**
4	VLM	0.022	0.91			
	VLM + EF	0.025	0.91	0.003	3.71	0.054
	VLM + EF + WM	0.052	0.90	0.027	26.0	**<0.001**
	VLM + EF + WM + AP	0.065	0.90	0.013	13.4	**<0.001**

Notes: The table shows results from hierarchical regression models that examine if adding cognitive domains in sequential orders (verbal learning and memory, executive functions, working memory, or attention and psychomotor) explains a significant amount of additional variance in daily functioning in patients with mood disorders. Daily functioning data was missing for 6 patients. *P*=*P*-value of the F-change statistic. EF = Executive functions. WM = Working memory. AP = Attention and psychomotor speed. VLM = Verbal learning and memory. Adj. = Adjusted. LOOCV RMSE = Leave one out cross-validation root mean squared error. **Bold** = p<.05

greater number of previous episodes and hospitalisations are also strong predictors of functional disability in conjunction with cognitive impairment (Burdick et al., 2022; Tse et al., 2014).

Our findings suggest that memory impairments are partially mediated by deficits in executive functions, working memory, and attention and psychomotor speed, and that these core functions are intercorrelated. This suggests that it is relevant to target impairments in all these aspects of cognition in patients with mood disorders in pro-cognitive interventions, with working memory and attention and psychomotor speed being particularly relevant for daily functioning. Importantly, targeted interventions must only include patients in full or partial remission, as per the International Society of Bipolar Disorders' recommendations, since cognitive hierarchy may be mood state-dependent (Miskowiak et al., 2017; Zaremba et al., 2019). Notably, mood disorders are characterised by great cognitive heterogeneity that also may differ between MDD and BD and between BD type I and BD type II (Ehrlich et al., 2022; Kjærstad et al., 2021; Pu et al., 2018). Thus, there may be unique hierarchies or scaffolding methods from person to person. This is supported by the findings in several neuropsychiatric and neurological disorders that similar cognitive and affective symptoms may arise from atrophy or disrupted activity in variable frontal and subcortical structures implicated in cognition and mood-regulation (Bonelli and Cummings, 2007; Tekin and Cummings, 2002). Based on this, there could be great potential in uniquely tailored cognitive interventions, where a cognitive screening could be implemented to identify potential cognitive strengths that may be used to explicitly scaffold impaired domains, regardless of the individual's underlying brain pathology. Critically, alleviating impairments in core cognitive domains could also have clinical benefits, as better cognitive performance at baseline may predict treatment response to psychotherapy and antidepressants (Deckersbach et al., 2018; Groves et al., 2018).

The present study is the largest study on cognitive hierarchy and functional ability to date. Notably, patients were in partial or full remission, which enabled the investigation of state-independent cognitive hierarchy. However, a key limitation was the variability in test protocols across the pooled studies, with some including only a short cognitive screening (SCIP) instead of a full neuropsychological evaluation. Consequently, we could not conduct principal component analyses on cognition data, and instead, tests were grouped into predefined cognitive composite measures. Thus, interpretability is limited by the task-impurity problem inherent to cognitive testing, as tests thought to measure one cognitive domain may capture other cognitive processes. Future research should test interactions between cognitive functions with a consistent test protocol and leverage statistical approaches to disentangle cognitive processes and address the task-impurity problem (Little, 2023). The correlational nature of the study precludes any causal inference, necessitating longitudinal studies to test whether impairments in core processes predict wider cognitive and general functioning over time, which further may differ between cognitive subgroups in mood disorders (Ehrlich et al., 2022; Kjærstad et al., 2022). Despite comparable IQ, our patient sample had fewer years of education than the included HC, which potentially contributed to the difference in cognitive scores between the groups. However, it has been recommended that mood disorder samples should be matched to HC on IQ rather than education years, as educational attainment is often disrupted by affective illness episodes and therefore shorter than in HC despite comparable intelligence (Glahn et al., 2006). We were not able to adjust for the impact of IQ on cognition in the analyses. This is because not every included study had collected an IQ measure, which should be considered a limitation. Our patient sample was heterogenous and included varying medication statuses andillness durations, between the included diagnoses (BD and MDD), which could have affected the results, although the BD and MDD groups had largely similar cognitive and functioning impairment profiles (see Supplementary Table 6 for sample characteristics of each diagnostic group). Specifically, remitted BD and MDD could be characterised by distinct cognitive hierarchies, and the inclusion of both groups in the analyses can be considered a limitation (Thompson et al., 2009; Zaremba et al., 2019). However, the network analyses applied in the present study require large sample sizes to produce robust results, which discouraged us from creating separate networks for MDD and BD (Epskamp et al., 2018). Further, cognitive impairment has been highlighted as a transdiagnostic trait in psychiatric disorders, thus warranting the investigation of a shared cognitive hierarchy within mood disorders (Millan et al., 2012).

In conclusion, we found that verbal learning and memory impairment was partially mediated by deficits in the proposed core cognitive domains, and that working memory was a particularly strong predictor of memory performance and everyday functioning in patients with mood disorders. Our findings highlight the importance of targeting cognition broadly in pro-cognitive interventions and future studies should investigate if encouragement of explicit and individually tailored scaffolding methods can improve cognitive impairment in patients with mood disorders.

CRediT authorship contribution statement

Johanna Mariegaard Schandorff: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Viktoria Damgaard:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Bethany Little:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Hanne Lie Kjærstad:** Writing – review & editing, Writing – original draft, Data curation. **Jeff Zarp:** Writing – review & editing, Writing – original draft, Data

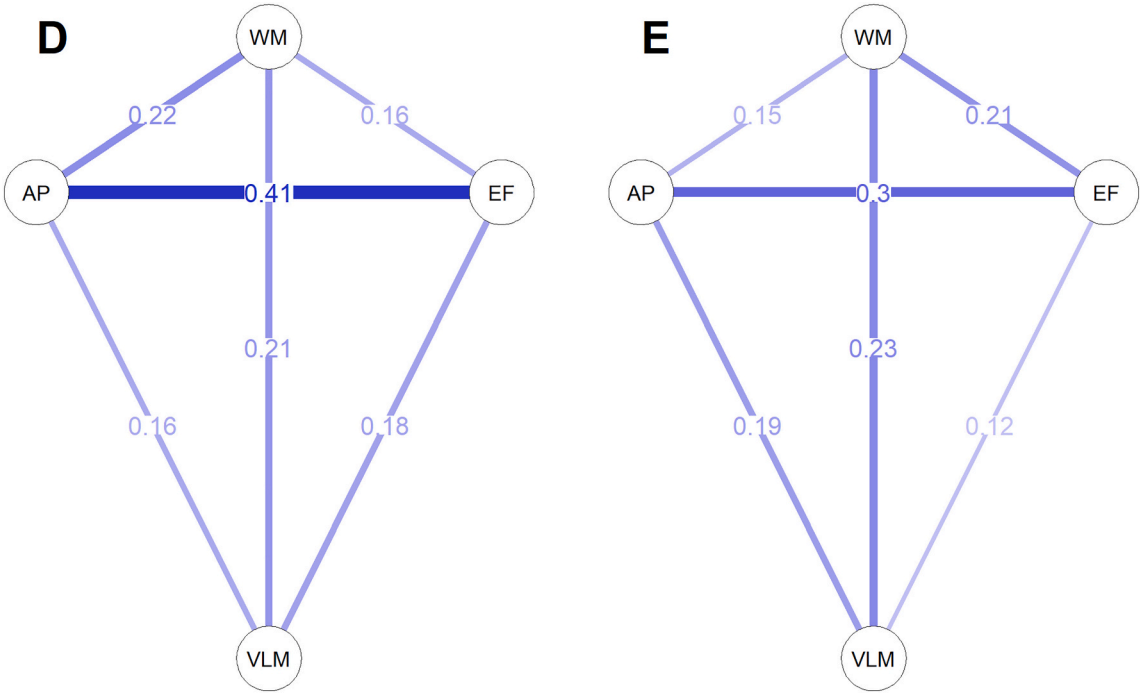

Fig. 3. Network graphs for cognitive domains for patients in full and partial remission.
Legend: Fig. 3 shows the network graphs for the different cognitive functions for (D) patients in full remission (n = 591) and (E) patients in partial remission (n = 293). Each network displays relationships between cognitive domains estimated with regularised partial correlations using LASSO penalty and EBIC model selection with hyperparameter gamma = 0. The partial correlation coefficient for each relationship between the cognitive domains is displayed on the edge between the two corresponding nodes. Nodes were placed manually in a set layout. All cognitive scores were corrected for age. Abbreviations: AP = attention and psychomotor speed; VLM = verbal learning and memory; WM = working memory; EF = executive functions.

curation. **Anne Juul Bjertrup:** Writing – review & editing, Data curation. **Lars Vedel Kessing:** Writing – review & editing, Data curation. **Ulla Knorr:** Writing – review & editing, Data curation. **Maj Vinberg:** Writing – review & editing, Data curation. **Peter Gallagher:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Kamilla Woznica Miskowiak:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

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Declaration of competing interest

JMS, VD, BL, AJB, UK, and PG report no conflict of interest. HLK has received consultancy fee from Lundbeck. JZ has within the last three years received honoraria from Lundbeck Pharma A/S. LVK has within the last three years received honoraria from Lundbeck Pharma and Teva. MV has received consultancy fee from Lundbeck and Janssen-Cilag. KWM has received honoraria from Lundbeck, Angelini, Janssen-Cilag and Gedeon Richter in the past three years.

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Appendix A. Supplementary data

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