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IMAGING STUDIES

Multivariate brain morphological patterns across mood disorders: key roles of frontotemporal and cerebellar areas

Sevdalina Kandilarova ,[1] Eleonora Maggioni ,[2,3] Letizia Squarcina,[4] Diyana Najar,[5] Maysam Homadi,[5] Emma Tassi,[2,3] Drozdstoy Stoyanov ,[1] Paolo Brambilla[3,4]

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[1]Department of Psychiatry and Medical Psychology, Research Institute and SRIPD-MUP, Medical University of Plovdiv, Plovdiv, Bulgaria
[2]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Lombardy, Italy
[3]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Lombardy, Italy
[4]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
[5]Medical University of Plovdiv, Plovdiv, Bulgaria

Correspondence to
Dr Sevdalina Kandilarova, Department of Psychiatry and Medical Psychology, Research Institute and SRIPD-MUP, Medical University of Plovdiv, Plovdiv 4000, Bulgaria; sevdalina.kandilarova@mu-plovdiv.bg

SK and EM are joint first authors.

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ABSTRACT

Background Differentiating major depressive disorder (MDD) from bipolar disorder (BD) remains a significant clinical challenge, as both disorders exhibit overlapping symptoms but require distinct treatment approaches. Advances in voxel-based morphometry and surface-based morphometry have facilitated the identification of structural brain abnormalities that may serve as diagnostic biomarkers.

Objective This study aimed to explore the relationships between brain morphological features, such as grey matter volume (GMV) and cortical thickness (CT), and demographic and clinical variables in patients with MDD and BD and healthy controls (HC) using multivariate analysis methods.

Methods A total of 263 participants, including 120 HC, 95 patients with MDD and 48 patients with BD, underwent T1-weighted MRI. GMV and CT were computed for standardised brain regions, followed by multivariate partial least squares (PLS) regression to assess associations with demographic and diagnostic variables.

Findings Reductions in frontotemporal CT were observed in MDD and BD compared with HC, but distinct trends between BD and MDD were also detected for the CT of selective temporal, frontal and parietal regions. Differential patterns in cerebellar GMV were also identified, with lobule CI larger in MDD and lobule CII larger in BD. Additionally, BD showed the same trend as ageing concerning reductions in CT and posterior cerebellar and striatal GMV. Depression severity showed a transdiagnostic link with reduced frontotemporal CT.

Conclusions This study highlights shared and distinct structural brain alterations in MDD and BD, emphasising the potential of neuroimaging biomarkers to enhance diagnostic accuracy. Accelerated cortical thinning and differential cerebellar changes in BD may serve as targets for future research and clinical interventions.

Clinical implications Our findings underscore the value of objective neuroimaging markers in increasing the precision of mood disorder diagnoses, improving treatment outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) often share overlapping clinical presentations, making accurate diagnosis challenging. Structural neuroimaging has been increasingly used to identify brain abnormalities associated with these disorders. However, the specific patterns of cortical thickness and grey matter volume changes differentiating MDD and BD remain unclear.

WHAT THIS STUDY ADDS

⇒ This study introduces a multivariate approach to identify disorder-specific brain changes. Key findings include transdiagnostic frontotemporal thinning, which was also linked with depressive symptom severity, diagnosis-specific cerebellar changes, and an inverse association of BD, age, and total intracranial volume with posterior cerebellar and striatal volumes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings demonstrate the value of multivariate neuroimaging in identifying shared and distinct structural brain features, contributing to developing objective biomarkers which may reduce misdiagnosis and improve treatment specificity. These findings emphasise the need for incorporating neuroimaging measures into clinical assessments, potentially influencing both research methodologies and psychiatric diagnostic protocols.

BACKGROUND

Neuroscientific research aims to integrate objective measures to enhance psychiatric assessments, which rely heavily on subjective clinical interviews. Distinguishing major depressive disorder (MDD) from bipolar disorder (BD) remains challenging, with BD often misdiagnosed as MDD, leading to ineffective treatment and resource misuse.[1] Structural MRI offers promise in identifying brain abnormalities that aid in differential diagnosis.[2] Volume-based and surface-based analyses enable a comprehensive understanding of morphological brain features such as grey matter volume (GMV) and cortical thickness (CT), resulting in valuable tools for searching

for imaging-based diagnostic markers.[3] Recent studies have proposed structural and functional brain markers distinguishing MDD from BD, suggesting key roles of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and cuneus.[4 5]

Earlier research found that BD exhibits larger surface areas in brain regions such as the left superior temporal gyrus, precentral gyrus, superior and inferior parietal gyri, precuneus and right middle temporal gyrus.[6] MDD involves structural deficits in prefrontal and orbitofrontal regions, impairing executive function and emotional regulation. A staging model based on progressive cortical thinning in recurrent depressive episodes was recently proposed.[7] BD is associated with structural and functional changes including temporal CT reductions, impacting cognitive performance.[8]

GMV reductions seem to differ between disorders, with MDD-related reductions in the ACC, DLPFC, dorsomedial PFC, left insula, bilateral parahippocampal gyrus and hippocampus, while BD shows reductions in the left precentral gyrus, left precuneus and bilateral ACC.[9] Comparative studies reveal MDD-related GMV loss in frontal and temporal lobes, insular cortex and occipital regions, while BD shows reductions in the medial orbitofrontal cortex, inferior temporal and fusiform regions, insular cortex, hippocampus and cerebellum. Nevertheless, quantitative brain markers for differential diagnosis are missing.

Multivariate techniques, such as partial least squares (PLS) analysis, have gained significant attention for identifying complex neuroimaging patterns in psychiatric disorders.[10] Unlike traditional univariate approaches, which examine one variable at a time, PLS allows for the joint analysis of multiple variables, including neuroimaging, clinical, environmental and demographic variables, clarifying their relationships.[10]

PLS identifies latent components that explain covariance among these variables, revealing patterns that traditional between-group statistical methods may overlook. By extracting latent components that summarise shared variance, PLS minimises collinearity-induced biases and enhances reliability. A key strength of PLS lies in its ability to model complex relationships between imaging features, clinical diagnostic variables and confounders simultaneously. By doing this, it accounts for the interactions among brain predictors and factors like age and sex, rather than removing their effects beforehand, as often done in conventional approaches. This capacity allows PLS to preserve meaningful variance shared between diagnostic categories and confounders, improving the interpretability of findings and enhancing their translation into clinical practice. Moreover, PLS is robust to violations of normality assumptions, making it particularly suitable for neuroimaging studies involving small sample sizes and non-Gaussian data distributions.

As such, PLS enhances not only sensitivity and specificity in detecting brain structural correlates of mood disorders, but also discriminant power in distinguishing between specific diagnostic categories, while considering complex biological interactions. Thus, PLS offers a robust and clinically informative framework for identifying brain markers relevant for both shared and differential diagnosis of MDD and BD.

OBJECTIVE

In this study, an integrated surface-based and volume-based approach is applied to MRI data of patients with MDD or BD and healthy controls (HC) to unravel the complex relationships between demographic, diagnostic and neuroimaging features using multivariate PLS analysis framework.

METHODS

Subjects

We recruited 263 participants, of which 120 HC (mean age 40.2 years, 46 men), 95 MDD (mean age 42.9 years, 30 men) and 48 BD (mean age 43.3 years, 13 men). Structured Mini International Neuropsychiatric Interview, Young Mania Rating Scale (YMRS) and Montgomery–Åsberg Depression Rating Scale (MADRS) were used for screening, diagnosis and symptom severity assessment. Patients were enrolled during a moderate/severe episode (MADRS>20). Further details are given in online supplemental materials.

Neuroimaging data acquisition and processing

Structural MRI was performed on a 3T GE Discovery 750w system with a 3D T1-weighted sequence: 1 mm slice thickness, 512×512×368 matrix, 7.2 ms relaxation time, 2.3 ms echo time, 12° flip angle and sagittal prescription. Image processing was performed on Matlab 2021 (The Mathworks, Natick) using CAT12 (https://neuro-jena.github.io/cat/) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Preprocessing modules for voxel-based morphometry (VBM) and surface-based morphometry (SBM) were used, followed by computation of GMV and CT measures using CoBra and Desikan-Killiany-Tourville (DK) atlas, respectively. These atlases are developed for VBM and SBM and provide complementary views of brain structure, covering subcortical and cortical regions. Details of the processing are given in the online supplemental materials.

Multivariate data analysis

The relationships between brain morphological characteristics and demographic and clinical ones were investigated by means of the PLS regression method. Given two sets of variables (or data blocks) X and Y, PLS aims to establish a prediction model between them by finding a suitable subspace projection that maximises their covariance, yielding a least-squares solution. Thus, the X and Y blocks are decomposed into a set of orthogonal latent variables (LVs) representing the weighted linear combinations of the original variables that maximally covary. The LVs for X and Y are extracted through consecutive iterations. After estimating the loadings and LVs at each iteration, the data matrices are deflated by the variance explained by the just computed LVs and given as input to the following iteration. LVs resulting from consecutive iterations are sorted in descending order based on the variance explained in the X and Y data blocks. The maximum number of iterations, equal to the number of LVs, is equal to the minimum number of variables among the two blocks. PLS results in components consisting of pairs of LVs for X and Y extracted across consecutive iterations. PLS does not require a strict normality assumption and is robust to non-Gaussian distributions of the data; it is also specifically designed to handle multicollinearity, making it suitable for high-dimensional datasets.

In our study, two sets of PLS analyses were performed to extract the associations between brain features (Y block), considering GMV and CT separately, and demographic and clinical features (X block). The main PLS analyses focused on diagnosis. In the GMV analysis, Y was composed of CoBra regional measures (n=42), whereas X included age, sex, diagnosis (HC, MDD and BD) and TIV as a confounder (n=7, equal to the number of PLS components). In the CT analysis, Y was composed of DK regional CT measures (n=68), whereas X encompassed age, sex and diagnosis (HC, MDD and BD) (n=6, equal to the number of PLS components). This multivariate configuration, which

integrates demographics, diagnosis and confounders into a single response block, follows established PLS strategies and reflects the method's strength in modelling shared variance across heterogeneous sources. Supplementary PLS analyses were performed considering clinical severity scores: (1) a multigroup (HC, MDD and BD) analysis where MADRS scores were added to X and (2) a disease group (MDD and BD) analysis where age of onset, episode duration, MADRS and YMRS scores were added to X.

Statistical analysis

The participants' demographic and clinical characteristics were subjected to statistical analysis using IBM SPSS Statistics for Windows, V.27. Student's t-tests or Analysis of Variance (ANOVA) and χ^2 tests were used for continuous and categorical variables, respectively. The level of significance was set to $p<0.05$.

In all PLS analyses, the components' significance was assessed based on covariance, by calculating the significance of the Pearson correlation between the relative LVs ($p<0.05$). Because PLS evaluates the relationships between multiple variables in a multivariate framework, it inherently controls for multiple comparisons. The PLS components' significance was further assessed with permutation tests (n=1000). The components with $p<0.001$ (i.e., with no permutation occurrences having the PLS covariance greater than the empirical one) were considered significant.

Of note, PLS leads to the identification of direct or inverse associations between the variables within X and Y blocks, such that the covariance between blocks is maximised. The PLS analysis enables the statistical test of the covariance between LVs but does not enable the testing of the correlation between variables in the original blocks. For each PLS component, considering two variables in the same block, the concordant/opposite sign of the PLS loadings should be interpreted as a direct/inverse correlation between them in relation to the LV from the other block; likewise, considering two variables in different blocks, the concordant/opposite sign of the PLS loadings reflects their direct/inverse correlation in the data explained by the component.

RESULTS

Demographic and clinical characteristics

There were no significant differences between the patients and the HC in age and sex. There were significant differences in the level of education and total YMRS and MADRS scores. The ANOVA post-hoc results demonstrated that HCs had higher years of education (about 1 year more) compared with MDD ($p=0.003$) and BD ($p=0.017$), while there were no education differences between MDD and BD. Similarly, mean MADRS and YMRS scores differed between HC and patients but not between MDD and BD. Episode duration and age at onset were not significantly different between BD and MDD, but there was a difference in mean duration of illness, which was longer in BD of about 40 months (see table 1).

Associations of demographics and diagnosis with CT

The CT-based PLS analysis yielded six components, equal to the number of variables in X. Components n.1, 2, 5 and 6 showed highly significant covariance ($p<0.001$), whereas the first four components (n.1–4) survived the permutation test ($p\_perm<0.001$). The components (in descending order based on explained variance) are illustrated in figure 1 and described below. All PLS loadings are reported in online supplemental table S1.

Component n.1

An inverse association is shown between age, with the greatest loading in X, and CT of multiple brain regions, especially bilateral transverse temporal gyrus, left pars triangularis and pars orbitalis, bilateral caudal middle frontal gyrus and right precentral gyrus. The component's covariance is significant ($p<0.001$) and survives permutation test ($p\_perm<0.001$).

Component n.2

The component highlights differences in parietal, frontal and temporal CT between men and women but also captures smaller differences among HC and patients, especially BD. Specifically, men have greater CT in parietal and temporal brain regions than women, especially in right supramarginal gyrus, left insula, right superior and middle temporal gyri, and right entorhinal cortex. Conversely, women show greater CT than men in left frontal pole, right cingulate cortex and right temporal regions. HC have the same trends as men, and BD as women, although with smaller weights. The component's covariance is significant ($p<0.001$) also following permutation test ($p\_perm<0.001$).

Component n.3

This component reflects differences between HC and patients, especially BD, and smaller differences between sexes in relation to CT. HC have greater frontotemporal CT — especially in left

Table 1 Demographic and clinical characteristics of the subjects

	BD (n=48)	MDD (n=95)	HC (n=120)	P value
Age (mean±SD)	43.3±11.0	42.9±13.4	40.2±11.9	0.055†
Sex (M/F)	13/35	30/65	46/74	0.276‡
Education (years, SD)	13.5±2.9	13.7±2.6	15.4±2.9	0.000*† MDDvsBD 1.0
MADRS Score (mean±SD)	28.5±7.2	29.7±6.0	2.6±5.2	0.000*† MDDvsBD 0.812
YMRS Score (mean±SD)	1.2±0.9	1.5±0.9	0.7±0.9	0.005*† MDDvsBD 0.566
Age of onset (years)	29.0±10.8	32.1±11.5		0.132§
Duration of illness (months)	175.2±115.3	121.9±117.2		0.014*§
Duration of current episode (weeks)	14.6±15.7	26.7±52.		0.133§

*p<0.05.
†One-way Analysis of Variance
‡χ^2 test.
§Independent samples t-test.
BD, bipolar disorder; HC, healthy controls; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; YMRS, Young Mania Rating Scale.

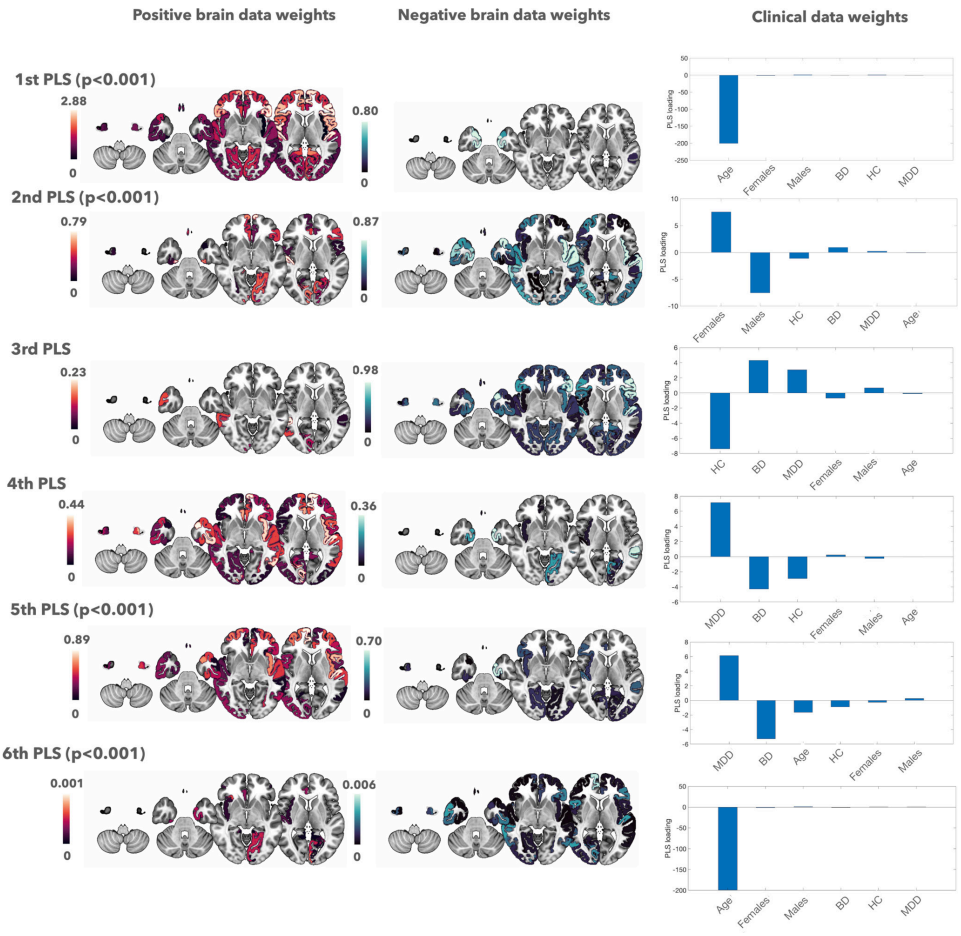

Figure 1 Representation of PLS weights of components sorted based on descending explained variance. These include the PLS weights for regional cortical thickness measures and those related to demographic and diagnostic variables. BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; PLS, partial least squares.

transverse temporal gyrus and temporal pole, left ACC and left pars orbitalis and opercularis — compared with BD and MDD. Here, male sex has the same trends as patients. The component's covariance is non-significant ($p>0.05$), but the component is significant based on permutations ($p\_perm<0.001$).

Component n.4

The component captures a difference of MDD compared with BD and HC, with MDD characterised by greater CT in left pars orbitalis, right pericalcarine, left transverse temporal cortex, and other frontal and temporal regions in the left hemisphere, and by lower CT in left entorhinal cortex. The component's covariance is non-significant ($p>0.05$), but the component survived the permutation test ($p\_perm<0.001$).

Component n.5

A differential association between MDD and BD is found with CT in left temporal and bilateral frontal and parietal cortices, being greater in MDD than in BD, and in left entorhinal and caudal ACC, being greater in BD than in MDD. Among the regions with greater CT in MDD, the greatest loadings were observed for left transverse temporal gyrus and right superior frontal and parietal gyri. Age-related changes, having the third top-ranked loading, are in the same direction of BD group differences compared with MDD. The component's covariance is highly significant ($p<0.001$) but does not survive permutation test ($p\_perm>0.05$).

Component n.6

An inverse association is shown between age, having the greatest loading in X, and CT in frontal, parietal and temporal regions, mainly in the right hemisphere. The component's covariance is highly significant ($p<0.001$), but the component is non-significant based on permutations ($p\_perm>0.05$).

Associations of demographics and diagnosis with GMV

The GMV-based PLS analysis yielded seven PLS components, equal to the number of variables in X. Of these, the first and sixth showed significant covariance ($p<0.001$), but none survived the permutation test ($p\_perm<0.001$). A tendency was observed for the fifth component ($p\_perm=0.001$). The main components (in descending order based on explained variance) are illustrated in figure 2. Only significant or nearly significant components are described below. All PLS loadings and non-significant components are described in online supplemental table S2.

Component n.1

A direct association is shown between TIV, which has the greatest loading in X, and GMV of multiple brain regions, especially bilateral superior posterior cerebellum and striatum. Age, although with a much lower loading, is inversely related to TIV and the above GMV. The component's covariance is strongly significant ($p<0.001$), but does not survive permutation test ($p\_perm>0.05$).

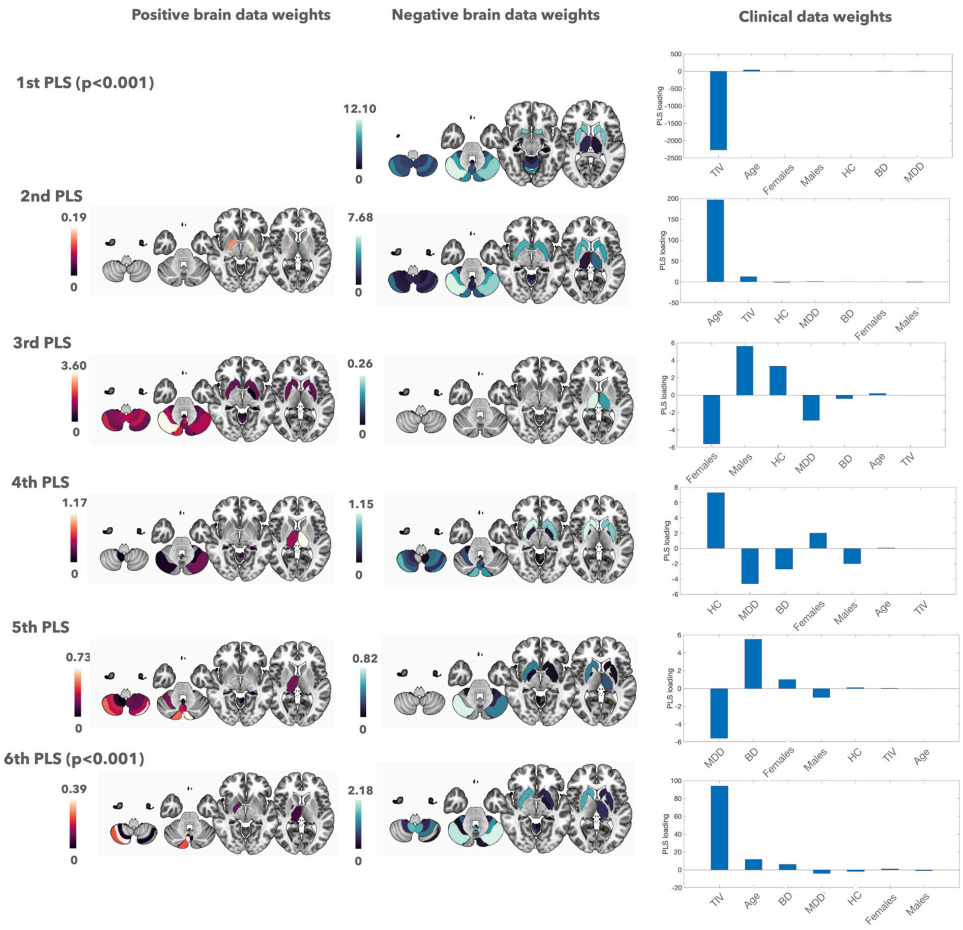

Figure 2 Representation of PLS weights of components sorted based on descending explained variance. These include the PLS weights for regional GM volume measures and the PLS weights related to demographic and diagnostic variables. BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; PLS, partial least squares; TIV, total intracranial volume.

Component n.5

A difference between MDD and BD, having the two greatest loadings in X, is shown for the GMV of superior posterior cerebellum, lobule CI, being greater in MDD than in BD, and lobule CII, being greater in BD than in MDD. Sex contributes to a lower loading, with women having opposite loading compared with MDD. The component's covariance demonstrates a trend to significance ($p=0.07$); in the permutation test, the component is near to significance ($p\_perm=0.001$).

Component n.6

The component highlights inverse associations of TIV (with the greatest loading), age and BD with GMV in posterior cerebellum (superior portion of lobule CI and inferior portion of lobule IX) and right striatum. The component's covariance is highly significant ($p<0.001$) but does not survive the permutation test ($p\_perm>0.05$).

Associations of demographics and clinical scores with CT and GMV

In the entire sample, MADRS scores captured a high portion of transdiagnostic covariance with CT features. In the first PLS component, greater MADRS scores and ageing are found to be inversely correlated with CT in bilateral temporal and left frontal cortices. When considering only MDD and BD, the top PLS component highlight a positive correlation between episode duration and frontal CT that is shared between the two disease groups. All the significant components emerging from the clinical–CT analyses are described in the online supplemental materials. No significant results emerged from the clinical–GMV analyses.

DISCUSSION

In this study, we applied a PLS multivariate analysis to examine the complex associations between demographic factors, MDD and BD diagnosis, and brain morphological characteristics. This approach allowed us to explore the relationship between diagnosis and brain features while accounting for demographic factors, which are often regarded as confounders. One of our key results was the CT reduction in frontotemporal regions shared between MDD and BD compared with controls. In the two disease groups, a similar contribution of episode duration on CT was also found, whereas across all groups, including HC, similar CT decreases were observed with ageing and with greater depressive symptoms based on MADRS. Findings from various studies, including reports from consortia (Enhancing NeuroImaging Genetics through Meta Analysis, ENIGMA) and meta-analytic data, suggest that frontotemporal thinning may be a shared vulnerability of both MDD and BD.[11] Age-related alterations have been associated with BD, suggesting a possible neurodegenerative process.[12] Thus, our findings of ageing-like frontotemporal thinning add to the growing body of evidence suggesting a shared vulnerability to neurodegeneration in MDD

and BD across brain regions implicated in language, attention and motor control.

We further identified differential associations of MDD and BD with CT, with patients with BD exhibiting greater CT in the left transverse temporal, right superior frontal and right superior parietal gyri, while patients with MDD demonstrated more pronounced thinning in the left entorhinal and left caudal ACC. These findings suggest that BD may accelerate cortical thinning in frontotemporal regions linked to auditory and executive control networks (ECNs). Consistent with this, meta-analytic data indicate that patients with BD experience greater brain ageing than patients with MDD compared with healthy individuals.[12] The preserved ACC volume in patients with BD may be linked to lithium treatment, as suggested by some studies.[13]

Conversely, our MDD group demonstrated significant thinning in left entorhinal and caudal ACC, both of which are implicated in memory, emotion and attention. ACC reductions have been widely reported in depression, though affected subregions and sides vary.[14] Entorhinal cortex thinning has been less often reported in MDD but is associated with more severe memory loss, a common clinical complaint.[15]

The role of ACC in depression is supported by structural, functional and connectivity studies. GMV reductions have been associated with demographic and clinical characteristics such as age and treatment response, while task-related hyperfunction and metabolic activity were linked to treatment resistance.[16] Moreover, convergent disruptions of structural and functional connectivity have been linked to the effects of both pharmacological and non-pharmacological management strategies.[17]

Another interesting result, though trend-level significant, highlights GMV differences in cerebellar subregions between MDD and BD. Specifically, lobule CI shows increased GMV in MDD compared with BD, while lobule CII shows the opposite. Historically overlooked in psychiatric research, the cerebellum is increasingly recognised for its role in higher-order functions. Schmahmann and Sherman's 'cerebellar cognitive affective syndrome' concept highlights behavioural abnormalities in patients with cerebellar lesions, supporting its potential involvement in affective disorders.[18]

This aligns with previous findings suggesting cerebellar involvement in depression. A meta-analysis by Serra-Blasco *et al* found significant bilateral GMV reductions in the cerebellum in MDD compared with HCs, with both CI and CII demonstrating decreases.[19] An intriguing pilot study links damage to the left posterior cerebellar hemisphere (CI and CII) with depressive symptom severity in cerebellar stroke patients.[20] CI and CII have been linked to large-scale brain networks associated with psychiatric disorders — the default mode network (DMN), salience network (SN) and Executive control network (ECN). The DMN is thought to be linked to Crus I, with studies reporting reduced connectivity in depression.[21] In contrast, a recent study involving treatment-naive patients with MDD found increased connectivity between Crus I and the DMN.[22] Moreover, the posterior cerebellum also contributes to both SN and ECN, which play a role in affective disorders. Our findings of structural changes in the ACC (a key region of the SN) and in Crus I and II (posterior cerebellum) further support the involvement of the posterior cerebellum and cerebello–cortical interactions in affective disorders.[23]

Generally, our findings align with recent evidence of significant cerebellar involvement in mood disorders. The concept of 'cerebellar cognitive affective syndrome' underscores its role in higher-order functions and potential impact on these disorders.[24] Cerebellar soft signs in BD, correlated with disorder severity, and suggested their potential as staging biomarkers. Consistent GM reductions in the cerebellum, particularly in the right hemisphere, are linked to BD symptomatology and treatment effects. However, conflicting data on cerebellar volume as a BD marker — for example, differences between type 1 and early-onset BD — highlight the need for larger studies.[25]

In addition, we detected an inverse association of TIV, ageing and BD with the posterior cerebellar and striatal volumes. We propose that BD may be inducing structural changes in these regions, resembling those seen in ageing. GMV alterations in the striatum are frequently reported, with reductions in later-stage BD and increases in first-episode patients or those treated with lithium or antipsychotics. Distinct striatal subregions may exhibit different GMV, activity and connectivity changes, but increased reward-related activity and reduced prefrontal regulation in decision-making and impulsivity are commonly observed.[26] Moreover, striatal functional connectivity patterns also correlate with distinct mood symptoms.[27]

Thus, the transdiagnostic frontotemporal thinning suggests shared vulnerability, while distinct cortical thinning and cerebellar involvement may serve as differentiating markers between MDD and BD. Our study underscores the importance of integrating surface-based and volume-based neuroimaging measures to better understand mood disorder pathophysiology. Combining CT, which reflects fine-scale cortical organisation, with GMV, a global structural measure, provides a more comprehensive perspective on brain morphological bases of mood disorders.

Regarding PLS design and the association of variable types to predictors–response blocks, it is important to note that the blocks can include different variables based on study objectives. The selection of these variables is guided by the specific relationships the study seeks to explore. PLS has been applied with demographic features as part of the predictor blocks to examine their relationship with neuroimaging, measures and behavioural responses, integrating diverse variables within a single framework.[28] A recent review by Zhuang *et al* highlighted the flexibility of multivariate techniques like canonical correlation analysis and PLS in exploring associations between neuroimaging, physiological data and clinical–demographic variables.[29]

Limitations and future perspectives

First, although the overall size of our sample is limited, it should be sufficient to discriminate among groups with an adequate statistical power.[30] A possible source of bias is that the HC subgroup was over-represented, with a sample size approximately two times that of the MDD subgroup, which in turn was two times that of the BD subgroup. The second main limitation regards the non-consideration of social and clinical variables, including education, illness duration and treatment in the PLS analyses. This choice was imposed by the availability of this information only for a subset of participants. Although years of education differed significantly between groups, the actual mean difference was approximately 1 year. Prior studies suggest that larger educational differences are typically required to observe substantial effects on brain structure.

Moreover, medications were heterogeneous (including antidepressants, tranquillisers, and mood stabilisers in different dosages), and their effects on brain measures could not be ruled out. Another possible confounder could be the illness duration, which was significantly longer in BD with about 40 months. Research on MDD and BD has shown varying results, with some studies indicating prefrontal cortical thinning correlating with illness duration, while others do not. These discrepancies may

stem from methodological differences, sample characteristics, medication status and comorbidities across studies. Pharmacological treatments for MDD and BD can lead to significant structural brain changes. While medications like lithium may exert neuroprotective effects, others, particularly certain antipsychotics, might contribute to cortical thinning. The heterogeneity of medication use reduces the likelihood that a single class of medication drives the observed effects in our study.

From a methodological perspective, our findings are limited by the lack of replication on independent samples, which are needed to confirm these findings and translate them into clinical practice. Furthermore, PLS components were extracted using an unbalanced multigroup sample, including HC, MDD and BD. To measure their ability for differential diagnosis, future work should use the PLS components as input features for classification between patient groups in an independent MDD versus BD dataset.

Future studies should comprehensively explore the integration of CT and GMV, which may reveal additional insights into the complex relationship between subcortical and cortical brain alterations in mood disorders. Specifically, approaches that integrate these measures within a unique framework, such as multiblock PLS, would help uncover insights into the mutual relationships between deep GMV and CT alterations, enhancing our understanding of mood disorders.

CONCLUSION

Our study suggests that brain structural abnormalities of mood disorders are partly specific and partly shared between MDD and BD. We observed transdiagnostic reductions in frontotemporal CT, which were also linked with depressive symptom severity, as well as group-specific CT reductions in left transverse temporal, right superior frontal and parietal cortices in BD, and left entorhinal cortex and ACC in MDD. A tendency of inverse association between TIV, ageing and BD with posterior cerebellar and striatal volumes was found. These findings align with existing literature and provide insights for a nuanced understanding of structural brain markers of mood disorders.

CLINICAL IMPLICATIONS

Our study advances the search for objective diagnostic markers for mood disorders. Identifying specific structural alterations that could differentiate MDD and BD is a crucial step in the long path to finding biomarkers in contemporary psychiatry. From this perspective, our findings could be seen as an advancement in bridging the gap between research and clinical practice, aiming to enhance the precision of diagnostic assessments and improve treatment outcomes. Moreover, with the advancement of automated analysis techniques and the increasing use of MRI in clinical settings, our approach contributes to the future development of reliable methods of differential diagnosis in mood disorders, reducing the burden of misdiagnosis and inadequate treatment.

Contributors SK and EM are the guarantors. SK and EM had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SK, EM, DS and PB. Acquisition and analysis of data: SK, EM, DN and MH. Data interpretation: SK, EM, ET, DS, PB and LS. Drafting of the manuscript: SK, EM, DN, MH, ET, DS, PB and LS. Critical revision of the manuscript: DS, PB and LS. All authors significantly reviewed, edited and contributed to the final version of the manuscript. Supervision: DS and PB.

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Competing interest None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee at the Medical University of Plovdiv, P-8632/13/11/2020. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data are available on reasonable request. The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research, supporting data are not publicly available.

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ORCID iDs
Sevdalina Kandilarova http://orcid.org/0000-0002-5594-4370
Eleonora Maggioni http://orcid.org/0000-0003-4331-4029
Drozdstoy Stoyanov http://orcid.org/0000-0002-9975-3680

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