



King's Research Portal

DOI:

[10.1016/j.biopsych.2024.10.020](https://doi.org/10.1016/j.biopsych.2024.10.020)

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Forteza, L., Ortuño, M., De Prisco, M., Oliva, V., Albajes-Eizagirre, A., Forteza, A., Madero, S., Solanes, A., Vilajosana, E., Yao, Y., Del Fabro, L., Galindo, E. S., Verdolini, N., Farré-Colomé, A., Serra-Blasco, M., Picó-Pérez, M., Lukito, S., Wise, T., Carlisi, C., ... Radua, J. (2024). Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders. *Biological psychiatry*. Advance online publication. <https://doi.org/10.1016/j.biopsych.2024.10.020>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders

Lydia Fortea^{1 2*}, MSc., Maria Ortuño^{1 2}, MSc., Michele De Prisco^{1 2 3 4}, MSc., Vincenzo Oliva^{1 2 4 5}, MSc., Anton Albajes-Eizaguirre¹, Ph.D., Adriana Fortea^{1 2 3 6}, Ph.D., Santiago Madero^{1 7}, M.D., Aleix Solanes¹, Ph.D., Enric Vilajosana¹, BSc., Yuanwei Yao^{8 9}, MSc., Lorenzo Del Fabro¹⁰, MSc., Eduardo Soler¹, BSc., Norma Verdolini^{1 2 3 4 11}, Ph.D., Alvar Farré-Colomé¹², MSc., Maria Serra-Blasco^{3 13 14}, Ph.D., Maria Picó-Pérez^{15 16 17}, Ph.D., Steve Lukito¹⁸, Ph.D., Toby Wise^{19 20 21}, Ph.D., Christina Carlisi^{18 22}, Ph.D., Danilo Arnone^{23 24 25}, Matthew Kempton M.J.^{26 27}, Ph.D., Alexander Omar Hauson^{28 29}, Ph.D., Scott Wollman²⁸, Ph.D., Carles Soriano-Mas^{3 30 31}, Ph.D., Katya Rubia¹⁸, Prof., Luke Norman^{18 32 33}, Ph.D., Paolo Fusar-Poli^{27 34 35 36}, Prof., David Mataix-Cols^{27 37 38}, Prof., Marc Valenti^{1 2 3 4}, Ph.D., Esther Via³⁹, Ph.D., Narcis Cardoner^{3 40}, Ph.D., Marco Solmi^{24 41 42 43}, Ph.D., Jintao Zhang⁴⁴, Ph.D., Pinglei Pan⁴⁵, Ph.D., Jae Il Shin^{46 47}, Ph.D., Miquel Àngel Fullana^{1 3 6}, Ph.D., Eduard Vieta^{1 2 3 4 6}, Prof., Joaquim Radua^{1 2 3*} Ph.D.

¹ Institut d'Investigacions Biomèdiques August Pi I Sunyer, Barcelona, Spain.

² Department of Medicine, University of Barcelona, Institute of Neuroscience, Barcelona, Spain.

³ Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain.

⁴ Bipolar and Depressive Disorders Unit, Hospital Clinic, Barcelona, Spain.

⁵ Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy.

⁶ Psychiatric and Psychology Service, Hospital Clinic, Barcelona, Spain.

⁷ Schizophrenia Unit, Hospital Clinic, Barcelona, Spain

⁸ Department of Psychology, The University of Hong Kong, Hong Kong SAR, China.

⁹ Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

¹⁰ Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

¹¹ Local Health Unit Umbria 1, Department of Mental Health, Mental Health Center of Perugia, Perugia, Italy.

¹² Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, Medical Faculty of Mannheim, Heidelberg University, Mannheim, Germany.

¹³ eHealth IConnecta't Program and Psycho-Oncology Service, Institut Català d'Oncologia, 08908 L'Hospitalet de Llobregat, Spain.

¹⁴ Psycho-oncology and Digital Health Group, Health Services Research in Cancer, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), 08908 L'Hospitalet del Llobregat, Spain

¹⁵ Live and Health Sciences Research Institute (ICVS), University of Minho, Braga, Portugal

¹⁶ ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal.

¹⁷ Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castelló de la Plana, Spain.

¹⁸ Department of Child and Adolescent Psychiatry Institute of Psychology, Psychiatry, and Neuroscience, King's College London, London, UK.

¹⁹ Max Planck UCL Centre for Computational Psychiatry and Ageing Research, University College London, London, UK.

²⁰ Division of the Humanities and Social Sciences, California Institute of Technology, California, CA, USA.

²¹ Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK.

²² Division of Psychology and Language Sciences, University College London, London, UK.

²³ Centre for Affective Disorders, Psychological Medicine, King's College London, London, UK.

²⁴ Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada.

²⁵ Department of Mental Health, The Ottawa Hospital, Ottawa, ON, Canada.

²⁶ Department of Neuroimaging, Institute of Psychiatry, Psychology & Neurosciences, King's College London, UK.

²⁷ Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

²⁸ California School of Professional Psychology, San Diego, CA, USA.

²⁹ Department of Psychiatry, University of California, San Diego, CA, USA.

³⁰ Department of Psychiatry, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain.

³¹ Department of Social Psychology and Quantitative Psychology, Universitat de Barcelona, Barcelona, Spain.

³² Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA.

³³ The Social and Behavioral Research Branch, National Human Genome Research Institute, National Institute of Health, Bethesda, Maryland, USA.

³⁴ Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology, London, UK.

³⁵ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy.

³⁶ Outreach and Support in South London (OASIS) Service, South London and Maudsley NHS Foundation Trust, London, UK.

³⁷ Department of Clinical Neuroscience, Center for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden.

³⁸ Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden.

³⁹ Department of Child and Adolescent Mental Health, Hospital Sant Joan de Déu, Barcelona, Spain.

⁴⁰ Sant Pau Mental Health Group, Institut d'Investigació Biomèdica Sant Pau (IBB-Sant Pau), Hospital de la Sant Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain.

⁴¹ Regional Centre for the Treatment of Eating Disorders and On Track: The Champlain First Episode Psychosis Program, Department of Mental Health, The Ottawa Hospital, Ottawa, ON, Canada.

⁴² Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program University of Ottawa, Ottawa, ON, Canada.

⁴³ Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

⁴⁴ State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China.

⁴⁵ Department of Neurology, Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Affiliated Yancheng Hospital of Southeast University, Yancheng, China.

⁴⁶ Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea.

⁴⁷ Severance Underwood Meta-research Center, Institute of Convergence Science, Yonsei University, Seoul 03722, South Korea.

*** Correspondence:**

Joaquim Radua and Lydia Fortea

Department of Experimental Neurociences, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

Rosselló 149, 08036 Barcelona, Spain

radua@recerca.clinic.cat and lfortea@recerca.clinic.cat

Short Title:

Atlas of GMV differences across mental disorders

Keywords:

meta-analysis; gray matter volume; psychiatric conditions; comorbidity; major depressive disorder; anxiety disorders.

ABSTRACT

Background:

Regional gray matter volume (GMV) differences between individuals with mental disorders and comparison subjects may be confounded by co-occurring disorders. To disentangle the disorder-specific GMV correlates, we conducted a large-scale multi-disorder meta-analysis using a novel approach that explicitly models co-occurring disorders.

Methods:

We systematically reviewed voxel-based morphometry studies indexed in PubMed and Scopus up to January 2023 comparing adults with major mental disorders (anorexia nervosa, schizophrenia-spectrum, anxiety, bipolar, major depressive, obsessive-compulsive, and post-traumatic stress disorders, plus attention-deficit/hyperactivity, autism spectrum, and borderline personality disorders) to comparison subjects. Two authors independently extracted data and assessed quality using the Newcastle-Ottawa Scale. We derived GMV correlates for each disorder using: a) a multi-disorder meta-analysis accounting for all co-occurring mental disorders simultaneously; b) separate standard meta-analyses for each disorder ignoring co-occurring disorders. We assessed the alterations' extent, intensity (effect size), and specificity (inter-disorder correlations and transdiagnostic alterations) for both approaches.

Results:

We included 433 studies (499 datasets) involving 19,718 patients and 16,441 comparison subjects (51% females, aged 20-67 years). We provide GMV correlate maps for each disorder using both approaches. The novel approach, which accounted for co-occurring disorders, produced GMV correlates that were more focal and disorder-specific (less correlated across disorders and fewer transdiagnostic abnormalities).

Conclusions:

This work offers the most comprehensive atlas of GMV correlates across major mental disorders. Modeling co-occurring disorders yielded more specific correlates, supporting this approach's validity. The atlas NIfTI maps are available online.

INTRODUCTION

Hundreds of studies have reported a plethora of brain features statistically associated with mental disorders (1–4). And even if neuroimaging has long refrained from uncovering pathognomonic anatomical markers, improved knowledge of the features statistically associated with the disorders would help advance brain-targeted research and interventions (5). However, this knowledge is still inconsistent, partly because of the demographic and clinical variation between studies (1,6,7) and partly because of the common but usually overlooked presence of co-occurring disorders.

Arguably, the frequent co-occurrence of mental disorders is one of the most significant contributors to the limited knowledge about the neural underpinnings of mental disorders (5). Indeed, approximately half of the individuals with a mental disorder meet the diagnostic criteria for at least one other disorder simultaneously (8). For example, in a meta-analysis of obsessive-compulsive disorder (OCD), 75% of the studies included patients with co-occurring mental disorders, such as major depressive disorder (MDD, up to 40%) or anxiety disorders (up to 80%) (9). Numerous studies have investigated common and distinct gray matter volume (GMV) features associated with mental disorders, employing various methods to address the issue of co-occurring disorders. Some meta-analyses decided to exclude these patients, including possible non-representative patient groups, and consequently limiting the generalizability of findings at the brain level (10). Other studies decided to include these patients, which provides more representative patient groups but may lead to non-disorder-specific findings influenced by the co-occurring disorders. Although they often tried to assess the impact of the co-occurring disorder in the main results by secondary analysis, there are no current robust methods to account for it adequately.

The present study aimed to establish a new methodology to account for the presence of co-occurring mental disorders. Furthermore, it sought to provide an updated structural magnetic resonance imaging (MRI)-based atlas to map the common and distinct GMV alterations associated with each major mental disorder. For that, we systematically searched all voxel-based morphometry (VBM) studies comparing major psychiatric disorders and comparison subjects and conducted a novel meta-analysis of all mental disorders simultaneously, considering the percentage of individuals with each disorder. This methodology (11) differs from prior multi-disorder meta-analyses, which often carried out a separate meta-analysis for each disorder. Nevertheless, Goodking et al. (2018) (2) made a significant contribution by identifying a common neurobiological substrate of GMV alterations across several mental disorders, which remained significant after excluding studies with patients having co-occurring disorders. Finally, we conducted additional analyses to capture the magnitude and uniqueness of the GMV alterations associated with each mental disorder. We hypothesized that different disorders would show shared and specific alterations.

METHODS AND MATERIALS

We conducted this meta-analysis as per PRISMA guidelines (12,13) (see Supplement) and pre-registered and published the protocol (PROSPERO: CRD42021245098 and (11)). The present study focuses on non-

substance-related psychiatric disorders in adults. Two researchers independently conducted the systematic search, data extraction, and quality assessment (LF, MO, MDP, VO, AF, SM, YWY, and LDF) and resolved discrepancies with a third researcher (JR).

Systematic literature search and data extraction

Our systematic search strategy had two stages: identifying meta-analyses of case-control whole-brain VBM studies for each psychiatric disorder listed in the ICD-11 (14) and enriching our samples with additional eligible studies. We conducted both searches in PubMed and Scopus up to 31st December 2021 (see keywords and full search queries in the Supplement). We screened all results by title/abstract, followed by full-text review. We excluded substance use disorders because they add complexity to the model, as different substances have some common and distinct effects on the brain (15). Further studies should use this methodology to model and focus on the common and distinct effects of substances. Note that for schizophrenia, we also included other psychotic-related disorders (e.g., schizoaffective disorder). Further information about both stages of the search process, inclusion and exclusion criteria, and data extraction is presented in the Supplement.

Novel meta-analysis considering co-occurring disorders

To investigate the regional differences in GMV between each mental disorder and comparison subjects, we employed SDM-PSI version 6.23 (www.sdmproject.com) (16,17), recently adapted to enable investigation into all co-occurring mental disorders simultaneously (11). Briefly, the meta-analysis employed a linear model without an intercept, where the dependent variable was the brain anatomical difference between patients and comparison subjects in a voxel, and the independent variables were the percentages of patients diagnosed with each included disorder (whether as a primary or co-occurring disorder). For example, consider a study involving patients with MDD, of whom 30% also had an anxiety disorder and 10% had OCD. In this case, the meta-analysis would explain the brain anatomical differences between patients and comparison subjects by the effects of MDD, plus 30% of the effects of anxiety disorders, plus 10% of the effects of OCD. This modeling differs from previous works where all brain anatomical differences between patients and comparison subjects would exclusively be attributed to MDD. To perform the novel meta-analytical analyses, we excluded those studies that lacked complete information about co-occurring mental disorders. Details of the methods employed by SMD-PSI and the used SDM code are presented in the Supplement.

This linear model allowed us to derive the GMV correlates of each disorder and conduct an ANOVA (followed by post hoc t-tests) to detect differences across pairs of disorders. To prevent significant results with very small effect sizes (standardized mean difference, Hedges' $g < |0.2|$), we set a z threshold based on the mean of z-values corresponding to a $g = 0.2$, ensuring that $z \geq 3.09$ ($p < 0.001$). We used Gaussian Random Fields to correct for multiple testing; we report findings at $\text{FWER} < 0.05$. In the Supplement, we list findings at more lenient threshold (uncorrected $p < 0.005$). Finally, we independently evaluated potential publication bias for each significant meta-analytic peak and calculated the percentage of variability that reflected the residual heterogeneity across studies (the I^2 statistic).

We also explored a linear model that accounts for interactions between disorders (Supplement).

Separate standard meta-analyses ignoring co-occurring disorders

To compare the novel approach with the commonly used method, we conducted separate meta-analyses for each primary mental disorder using the standard SDM-PSI methodology without considering co-occurring mental disorders.

Extent, intensity, and specificity of the GMV differences

We assessed the observed GMV alterations' extent, intensity (effect size), and specificity (inter-disorder correlations and transdiagnostic alterations) for both the novel meta-analysis that considers co-occurring disorders vs. the standard one that ignores them. From this analysis, we excluded ADHD and ASD due to their classification as neurodevelopmental disorders and BPD because it is a personality disorder. Detailed information is presented in the Supplement.

Data availability

We provide the meta-analytic images at <https://neurovault.org/collections/17834/> under the CC-BY license to allow other groups to use our anatomical atlas. We also provided the meta-analytical maps obtained with the separate standard meta-analyses for each mental disorder without accounting for co-occurring disorders. SDM software can be downloaded at <https://www.sdmproject.com/>, and the new function to correlate brain images is freely available as the “nifti.pbcor” R package.

RESULTS

The literature search yielded a total of 499 datasets investigating 19,718 individuals with mental disorders and 16,441 comparison subjects (See Table 1 for demographics and Table S2-6 for co-occurring disorders). The included mental disorders were anorexia nervosa, anxiety, bipolar disorder (BD), MDD, OCD, post-traumatic stress disorder (PTSD), and schizophrenic disorders, plus attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), borderline personality disorder (BPD), internet gaming disorder. After excluding studies that lacked complete information about co-occurring disorders, we had 290 datasets (11,395 patients and 8,826 comparison subjects). For internet gaming disorder, only nine studies reported full information about co-occurring disorders, so we discarded it from the main analysis. We describe the systematic search results in the Supplement.

Results from the novel and standard meta-analyses

For anorexia, both meta-analyses found smaller GMV in the temporal lobe, precuneus, supplementary motor area, and middle cingulate, while the standard analysis also in the anterior cingulate (ACC) and cerebellum. For anxiety disorders, both identified smaller GMV in the temporal and occipital lobes; the novel analysis found smaller GMV in the thalamus and right striatum and larger GMV in the right cerebellum, while the standard analysis found smaller GMV in the middle cingulate and insula. For BD, both revealed smaller GMV

in the prefrontal cortex (PFC), orbitofrontal cortex, temporal lobes, insulas, cerebellum, and striatum. For MDD, both identified smaller GMV in the PFC, ACC, middle cingulate, bilateral insula, and cerebellum, and the novel analysis also in the thalamus, hippocampus and left striatum. For OCD, both found smaller GMV in the parietal lobe and larger GMV in the right cerebellum; the novel analysis found smaller GMV in the orbitofrontal cortex, and the standard analysis in the ACC and superior temporal gyrus. For PTSD, both identified smaller GMV in the left lingual gyrus, and the standard approach also in the superior frontal gyrus. For schizophrenia, both identified widespread smaller GMV across cortical and subcortical regions. Detailed information can be found in the Supplement (Table 2 and Fig. 2-3), including uncorrected results (Table S7) and standard meta-analyses (Table S8, Fig. S1).

In the ANOVA to detect GMV differences across disorders, we identified 14 cortical clusters (Table S9). Significant results from the post-hoc pairwise t-tests are presented in Table S10. Briefly, anorexia showed distinctly smaller GMV in the precuneus compared to other mental disorders. PTSD exhibited larger GMV compared to most other disorders in regions where, in the primary analyses, they showed reduced GMV relative to controls, while PTSD did not. Finally, OCD showed smaller GMV in the right inferior parietal gyrus compared to anxiety disorders and PTSD.

Results from the novel meta-analysis accounting for interactions are presented in the Supplement (Tables S12-13).

Extent, intensity, and specificity of the GMV differences

As shown in Fig. 4, schizophrenic disorders exhibited the highest percentage of voxels (20%), showing GMV differences with comparison subjects with a Hedges' $g > 0.2$, followed by BD (12%), anorexia (8%), anxiety disorders (5%), and PTSD (4%). Anorexia exhibited the highest intensity of GMV differences ($g = 0.94$), followed by PTSD ($g = 0.83$). MDD and OCD showed differences in 3% of voxels with milder intensity ($g < 0.34$). In the standard meta-analysis, we observed a higher percentage of voxels showing GMV differences in all the disorders except BD, while a similar intensity (or occasionally smaller, e.g., anorexia: $g = 0.69$ vs. 0.94 ; BD: $g = 0.35$ vs. 0.46).

The correlation analysis (Fig. 4) showed similarities in GMV differences between schizophrenic disorders and those from BD, MDD, OCD, and anxiety disorders ($r = [0.39-0.56]$), moderate similarities between BD and those from MDD, anxiety disorders, and OCD ($r = [0.27-0.40]$), and weakly similarities between MDD and anorexia ($r = 0.25$). The standard meta-analysis revealed more significant correlations between all mental disorders.

In the transdiagnostic analysis, several clusters showed smaller GMV ($g \geq 0.2$) in at least three disorders, including the PFC, orbitofrontal cortex, ACC, middle cingulate, and temporal gyrus, including the insulas (Table 3, Fig. S2). This transdiagnostic map significantly correlated with alterations associated with schizophrenic disorders ($r = 0.99$), BD ($r = 0.95$), anxiety ($r = 0.65$), MDD ($r = 0.52$), anorexia ($r = 0.43$), OCD

($r=0.38$) and PTSD ($r=0.65$). The standard analysis showed more transdiagnostic regions, including the precuneus, fusiform gyrus, and parietal lobe (Table S11, Fig. S3).

Findings from the standard meta-analysis were similar when we repeated the analysis using only studies with complete information on co-occurring disorders (Table S12).

DISCUSSION

This work provides a comprehensive GMV neuroanatomical atlas of major mental disorders, accounting for co-occurring disorders. Here, we report the main GMV alterations associated with anorexia, anxiety disorders, BD, MDD, OCD, PTSD, and schizophrenic disorders (Table 2-S8, Fig. 2-S1), with further details provided in the Supplement. Alterations associated with ADHD, ASD, and BPD are reported in the Supplement. We discuss the results for each disorder below, including the extent and intensity of the alterations. We also discuss separately their specificity, based on the correlations between disorders and the extent of transdiagnostic alterations. Finally, we comment on the strengths and limitations of this work.

Importantly, GMV alterations derived from this novel meta-analysis were more focal (fewer voxels included) and disorder-specific (less correlated and shared among disorders) than when we conducted separate standard meta-analyses per each disorder (i.e., ignoring co-occurring disorders), even when we included the same studies. The presence of more focal and disorder-specific alterations supports the increased validity of the novel approach. Or, seen from the opposite side, the maps from the standard meta-analyses would mix alterations from different co-occurring disorders, resulting in more extensive alterations over-correlated across disorders with inflated transdiagnostic alterations.

Results from the novel and standard meta-analyses

Anorexia nervosa

Findings from both meta-analyses aligned with previous work (18–20), except for smaller GMV in ACC and cerebellum that was found in previous work and our standard meta-analyses, but not in our novel approach, likely to our adjustment for co-occurring disorders. Indeed, these regions have been associated with MDD, which is commonly co-occurring in anorexia (Table 2). Interestingly, smaller GMV in the precuneus was unique to anorexia. However, this finding should be interpreted cautiously due to significant study heterogeneity, which may be linked to individual variability in anorexia, particularly in weight recovery, warranting further investigation.

Anxiety disorders

Findings from both meta-analyses partially matched previous studies (1,21,22). A main difference is that previous research often reported larger GMV in the parietal and occipital lobes (21,22), primarily associated with SAD (23), whereas our analysis included all anxiety disorders. Another discrepancy was smaller GMV in the middle cingulate and insula, reported by the standard approach (1). In the interaction meta-analysis, we found smaller GMV in these regions for individuals with anxiety but without MDD or OCD, suggesting that

the neural correlates of anxiety disorders may vary based on the presence of co-occurring mental disorders. Notably, individuals with anxiety and MDD/OCD showed an effect size of $g=0.3$ in these regions, though not statistically significant, likely due to the small sample size.

Bipolar disorders

Findings from both meta-analyses are consistent with previous studies (6,23,24), supporting smaller GMV in the dorsal/ventral PFC and ACC as a common substrate of mood disorders (24).

Major depressive disorder

Findings from both meta-analyses aligned with previous studies (1,26), further supporting evidence for biomarkers in mood disorders (24). The novel meta-analysis also identified differences in several subcortical regions, contrasting with the standard approach and prior research, which often reported subcortical alterations only in the hippocampus (1,24,25). This discrepancy may arise from including patients with co-occurring disorders, usually excluded, as MDD has been found to cluster in distinct biotypes with different neural correlates (26). As a result, previous studies may have overlooked biotypes less likely to co-occur with other psychiatric disorders. Interestingly, controlling for the interaction with co-occurring anxiety disorders, these subcortical regions were no longer significant, suggesting that the neural correlates of MDD may vary depending on the presence of co-occurring mental disorders. Finally, the effect sizes of the GMV alterations were generally small ($g<0.25$), which may be attributed to the fact that MDD is primarily driven by brain functional irregularities rather than structural ones (3,27).

Obsessive-compulsive disorder

Findings from both meta-analyses partially aligned with previous studies (31–33), although the novel approach did not identify smaller GMV in the temporal gyrus, as reported in previous research and the standard analysis. This discrepancy may be due to the presence of co-occurring disorders (23% had MDD, and 17% anxiety disorders). Indeed, abnormalities in the temporal lobes have often been associated with these mental disorders (1,24) and are supported by our present findings. Interestingly, smaller GMV in the parietal gyrus was statistically different between OCD and other anxiety-related disorders (anxiety and PTSD).

Post-traumatic stress disorder

The main finding of the novel meta-analysis, supported by the standard approach, was consistent with previous studies (1,30). However, previous meta-analyses also reported alterations in regions from the frontolimbic circuit, such as the PFC and hippocampus (31,32), essential for threat processing and emotion regulation (33). We observed smaller GMV in the dorsal PFC in both meta-analyses (uncorrected $p<0.005$) but no significant differences in the hippocampus, possibly due to previous studies specifically targeting that region.

Schizophrenic disorders

Findings from both meta-analyses align with previous research and established models for schizophrenic disorders, as discussed in previous meta-analyses and ENIGMA findings (34,35). Interestingly, the findings also included the GMV decreases found to estimate relapse risk after a first episode of psychosis (right middle temporal, right inferior frontal/precentral, right middle frontal, bilateral rectus, and right Angular) (36).

Specificity of the GMV differences – correlations across disorders

Schizophrenic disorders showed the highest percentage of voxels with GMV alterations, affecting multiple brain networks. Additionally, the spatial pattern of GMV alterations of schizophrenic disorders was correlated with those of BD, MDD, OCD, and anxiety. These findings are consistent with those reported by the ENIGMA (4), which identified strong correlations among mood disorders, schizophrenic disorders, and OCD, involving regions like the insula, hippocampus, and fusiform gyrus, explaining 42% and 89% of the variance. Supporting these ENIGMA findings, the abnormality pattern of BD also correlated with MDD, OCD, and anxiety. The GMV abnormality pattern of MDD also correlated with anorexia, possibly due to the common depressive symptoms in these patients, without reaching the threshold of MDD. Surprisingly, the GMV abnormality pattern of PTSD did not correlate with any other mental disorder, showing significant differences with other mental disorders.

These findings contrast with those from the standard meta-analyses, where almost all mental disorders significantly correlated with each other. This discrepancy may rely on the high prevalence of co-occurring disorders not accounted for in the standard meta-analysis. For instance, in the standard analysis, the GMV abnormality pattern of MDD significantly correlated with those from anxiety ($r=0.60$) and OCD ($r=0.47$). Therefore, the observed similarities are likely due to the common co-occurrence of these disorders, where 28% of the individuals with anxiety and 23% of the individuals with OCD presented co-occurring MDD. This finding supports the need to adjust for co-occurring mental disorders when investigating specific brain alterations associated with each mental disorder. It also suggests that our method successfully mitigated this potential confounding effect.

Specificity of the GMV differences – extent of transdiagnostic alterations

Our study identified smaller GMV in the dorsal PFC, orbitofrontal cortex, dorsal ACC, middle cingulate, and insula across psychotic, mood, and anxiety disorders. This finding supports previous hypotheses of common neurobiological substrates across mental disorders (2–4), specifically the dorsal ACC and insula, highlighting that they are not due to the presence of co-occurring disorders. Previous studies have also reported smaller GMV in the PFC associated with mood disorders (24) and in the middle cingulate linked to mood, anxiety, and trauma-related disorders (1).

These regions are crucial for emotion regulation, social behavior, and cognitive and executive functions (39,40), commonly impaired across mental disorders. Therefore, these GMV alterations could be associated with cognitive impairments rather than diagnosis-specific symptoms (2,39). Although evidence

suggests that those common substrates are associated with the disorders rather than a risk state, we cannot rule out that our findings could stem from early life trauma. Notably, evidence showed that early life trauma is associated with an increased risk of developing specific disorders in adulthood, such as mood or psychotic disorders (40). Additionally, childhood maltreatment is associated with smaller GMV in several brain regions, including the ACC, even though they did not develop any mental disorder (41). Another potential explanation could be the shared genetic pattern across disorders. For instance, a study investigating the genetic architecture of 11 mental disorders (42) identified four factors explaining the genetic structure for (i) compulsive behaviors (anorexia, OCD), (ii) psychotic features (schizophrenic disorders, BD), (iii) neurodevelopmental disorders (ADHD, ASD), and (iv) internalizing disorders (anxiety, MDD). This genetic clustering partially differs from our neuroanatomical patterns (e.g., there are no overlapping structures between anorexia and OCD). Additionally, there is converging evidence of a shared genetic pattern across mood and psychotic disorders (MDD, BD, and schizophrenic disorders) (43). Our findings suggest that genetics and neuroanatomy can provide different and complementary information about the neurobiological underpinnings of mental disorders.

Strengths of this work

Despite multiple efforts to investigate disorder-specific and transdiagnostic structural alterations in mental disorders (1–4), prior studies often exclude patients with co-occurring disorders or investigate their potential effect via meta-regressions. Our work presents the first large-scale meta-analysis considering all mental disorders simultaneously in a single linear model, effectively accounting for co-occurring disorders and providing a more accurate disorder-specific spatial pattern of GMV alterations. We also investigated the similarities of GMV alterations across disorders, supporting findings by Opel (4). Finally, we presented new and complementary evidence regarding ACC and insula being a transdiagnostic biomarker, as suggested by Godking (2).

There are several applications of the current work. Firstly, we provide a new meta-analytical methodology, overcoming the previous limitation of not fully accounting for co-occurring mental disorders when investigating disorder-specific brain alterations. This methodology can be extended to other MRI modalities, including functional MRI and diffusion tensor imaging, contributing to a deeper comprehension of the psycho-pathological processes underlying mental disorders. Additionally, the provided atlas of GMV alterations offers an improved localization of alterations in mental disorders, which may also enhance the efficacy of therapies targeting specific brain regions to improve symptom severity, such as deep brain stimulation or non-invasive brain stimulations (44).

Finally, the atlas could benefit future machine learning research, particularly in improving the diagnoses of mental disorders. We fully acknowledge the low accuracy of MRI-based machine learning tools (45,46), which is expected considering that the diagnostic labels are a pragmatic but conventional classification. For this reason, we should not think about diagnostic prediction but risk estimation,

acknowledging the uncertainty of the estimates. Similarly, we must remind here some rules for properly using machine learning in mental health research, such as pre-registering the analysis, starting with simpler algorithms, avoiding data leakage, considering implementation issues, or mitigating racial and gender biases (47). Taking all these considerations into account, we believe that this atlas may help create models that estimate the risk of different mental disorders, offering the clinician additional information that might help enhance diagnostic accuracy and, thus, a more focused treatment earlier.

Limitations

The current study has several limitations. Firstly, the included studies' cross-sectional nature impedes the causality inference; thus, findings must be interpreted as statistical associations. Additionally, there is a limitation concerning the debatable nosology of current mental disorders based on clinical consensus rather than known biological underpinnings (48). Further, the proportion of co-occurring disorders in our study did not reflect those in the general population (Table S6). However, our focus was not on the comorbidity patterns in the general population but on disentangling the specific neuroanatomy of co-occurring mental disorders. We also must consider limitations inherent to meta-analysis, such as results being based on summarized data (e.g., peak and effect sizes) rather than raw data (49). Similarly, we did not examine the effects of potential clinical and methodological moderators such as symptom severity, body mass index, or software used. We decided not to analyze the effects of these covariates to avoid adding complexity to the current paper and invite future studies to investigate them. Another limitation is that we only included those mental disorders for which a meta-analysis has already been published and examined by at least ten studies. Finally, we must highlight that even when, for simplicity, we talk about GMV differences, we should more appropriately refer to differences in T1-MRI signal, given that the acquired MRI data are not a direct measure of brain structure (50).

Conclusion

In summary, we present the first large-scale atlas of specific and transdiagnostic GMV alterations statistically associated with major psychiatric conditions, considering the confounding effect of co-occurring disorders. This innovative meta-analysis, which involved 19,718 patients and 16,441 comparison subjects, represents a significant contribution to our understanding of the shared and distinct neural substrates underlying mental disorders. This work adds to admirable initiatives, such as the Health's Brain Research Through Advanced Innovative Neurotechnology (BRAIN) (51), ENIGMA consortium (4) or Psychiatric Genetics Consortium (42), that enhance our knowledge of the physiopathology of mental disorders, paving the way for future diagnostic aid tools and precision-based interventions directed to specific brain targets. To allow other groups to use our anatomical atlas, we have uploaded the images at <https://neurovault.org/collections/17834/> under the CC-BY license.

ACKNOWLEDGMENTS

This work was supported by the Spanish Ministry of Science and Innovation (PI19/00394), integrated into the Plan Nacional de I+D+I, and co-financed by ERDF Funds from the European Commission ("A Way of Making Europe"). LF thanks the support from an educational grant from the Instituto de Salud Carlos III (FI20/00047). JR receives support from Instituto de Salud Carlos III and the European Regional Development Fund (FEDER) (CPII19/00009) and the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2021 SGR 1128). MPP is supported by a grant RYC2021-031228-I funded by the Spanish Ministerio de Ciencia e Innovación (MCIN/AEI/10.13039/501100011033) and by the European Union NextGenerationEU/PRTR. JZ receives support from the National Natural Science Foundation of China (No.32171083, No.31871122). CS-M receives support from "La Marató de TV3" (202201-31) and the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2021 SGR 01017). KR was supported by the Efficacy and Mechanism Evaluation (EME) programme, an MRC and NIHR partnership (NIHR130077; NIHR203684), and by the National Institute for Health Research (NIHR) and the UK Department of Health via the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and the Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London. The views expressed are those of the authors and not necessarily the funders. EVia thanks the CERCA Programme /Generalitat de Catalunya.

FINANCIAL DISCLOSURES

MV has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, and Lundbeck. KR received a grant from TAKEDA Pharmaceuticals for another study and consultation fees from SUPERNUS and Lundbeck. EV has received grants and served as a consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Abbvie, Aimentia, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Casen-Recordati, Celon, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Idorsia, Janssen, Lundbeck, Novartis, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatrix. Evia has participated as a co-investigator in a Janssen-Cilag, S.A., clinical trial and as a speaker for Novo Nordisk. JR has received CME honoraria from Inspira Networks for a machine learning course promoted by Adamed, outside the submitted work. All other authors report no biomedical financial interest or potential conflicts of interest.

REFERENCES

1. Serra-Blasco M, Radua J, Soriano-Mas C, Gómez-Benlloch A, Porta-Casteràs D, Carulla-Roig M, et al. (2021): Structural brain correlates in major depression, anxiety disorders, and post-traumatic stress disorder: A voxel-based morphometry meta-analysis. *Neurosci Biobehav Rev* 129: 269–281.
2. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, et al. 2015): Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* 72(4): 305.
3. Brandl F, Weise B, Mulej Bratec S, Jassim N, Hoffmann Ayala D, Bertram T, et al. (2022): Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: A transdiagnostic multimodal meta-analysis of structural and functional MRI studies. *Neuropsychopharmacology* 47(5): 1071–1080.
4. Opel N, Goltermann J, Hermesdorf M, Berger K, Baune BT, Dannlowski U. (2020): Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: A secondary analysis of mega- and meta-analytical findings from the ENIGMA consortium. *Biol Psychiatry* 88(9): 678–686.
5. Fusar-Poli P, Solmi M, Brondino N, Davies C, Chae C, Politi P. (2019): Transdiagnostic psychiatry: a systematic review. *World Psychiatry*. 18:192–207.
6. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. (2018): Cortical abnormalities in bipolar disorder: An MRI analysis of 6,503 individuals from the ENIGMA Bipolar Disorder Working Group. *Mol Psychiatry* 23(4): 932–942.
7. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N. (2017): Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. *Mol Psychiatry* 22: 900–909.
8. Caspi A, Houts RM, Ambler A, Danese A, Elliott ML, Hariri A. (2020): Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin Birth Cohort Study. *JAMA Netw Open* 3(4): e203221.
9. Carlisi CO, Norman LJ, Lukito SS, Radua J, Mataix-Cols D, Rubia K. (2017): Comparative multimodal meta-analysis of structural and functional brain abnormalities in autism spectrum disorder and obsessive-compulsive disorder. *Biol Psychiatry* 82(2): 83–102.
10. Wise T, Arnone D, Marwood L, Zahn R, Lythe K, Young A. (2016): Recruiting for research studies using online public advertisements: Examples from research in affective disorders. *Neuropsychiatr Treat* 12(2): 229–235.
11. Fortea L, Albajes-Eizagirre A, Yao YW, Soler E, Verdolini N, Hauson AO, et al. (2022): Focusing on comorbidity—A novel meta-analytic approach and protocol to disentangle the specific neuroanatomy of co-occurring mental disorders. *Front Psychiatry* 12: 807839.

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. (2021): The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 372: n71.
13. Radua J. (2021): PRISMA 2020 – An updated checklist for systematic reviews and meta-analyses. *Neurosci Biobehav Rev* 124: 324–325.
14. World Health Organization. (2022): ICD-11: International classification of diseases (11th revision). Available from: <https://icd.who.int/>
15. Hall MG, Alhassoon OM, Stern MJ, Wollman SC, Kimmel CL, Perez-Figueroa A, et al. (2015): Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: A neuroimaging meta-analysis. *Am J Drug Alcohol Abuse* 41(4): 290–299.
16. Albajes-Eizagirre A, Solanes A, Vieta E, Radua J. (2019): Voxel-based meta-analysis via permutation of subject images (PSI): Theory and implementation for SDM. *NeuroImage* 186: 174–184.
17. Albajes-Eizagirre A, Solanes A, Fullana MA, Ioannidis JPA, Fusar-Poli P, Torrent C. (2019): Meta-analysis of voxel-based neuroimaging studies using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI). *J Vis Exp* 153: e59841.
18. Zhang S, Wang W, Su X, Kemp GJ, Yang X, Su J, et al. (2018): Psychoradiological investigations of gray matter alterations in patients with anorexia nervosa. *Transl Psychiatry* 8(1): 242.
19. Walton E, Bernardoni F, Batury VL, Bahnsen K, Larivière S, Abbate-Daga G, et al. (2022): Brain structure in acutely underweight and partially weight-restored individuals with anorexia nervosa: A coordinated analysis by the ENIGMA Eating Disorders Working Group. *Biol Psychiatry* 92(9): 730–738.
20. Su T, Gong J, Tang G, Qiu S, Chen P, Chen G, et al. (2021): Structural and functional brain alterations in anorexia nervosa: A multimodal meta-analysis of neuroimaging studies. *Hum Brain Mapp* 42(15): 5154–5169.
21. Shang J, Fu Y, Ren Z, Zhang T, Du M, Gong Q, et al. (2014): The common traits of the ACC and PFC in anxiety disorders in the DSM-5: Meta-analysis of voxel-based morphometry studies. *PLoS ONE* 9(3): e93432.
22. Liu H, Hao Z, Qiu S, Wang Q, Zhan L, Huang L, et al. (2024): Grey matter structural alterations in anxiety disorders: A voxel-based meta-analysis. *Brain Imaging Behav* 18(2): 456–474.
23. Gong J, Wang J, Chen P, Qi Z, Luo Z, Wang J, et al. (2021): Large-scale network abnormality in bipolar disorder: A multimodal meta-analysis of resting-state functional and structural magnetic resonance imaging studies. *J Affect Disord* 292: 9–20.
24. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, et al. (2017): Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: Evidence from voxel-based meta-analysis. *Mol Psychiatry* 22(10): 1455–1463.

25. Schmaal L, Pozzi E, C. Ho T, van Velzen LS, Veer IM, Opel N, et al. (2020): ENIGMA MDD: Seven years of global neuroimaging studies of major depression through worldwide data sharing. *Transl Psychiatry* 10(1): 1–19.
26. Tozzi L, Zhang X, Pines A, Olmsted AM, Zhai ES, Anene ET, et al. (2024): Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. *Nat Med* 30(7): 2076–2087.
27. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry* 72(4): 311–320.
28. Picó-Pérez M, Moreira PS, Melo Ferreira V, Radua J, Mataix-Cols D, Sousa N. (2020): Modality-specific overlaps in brain structure and function in obsessive-compulsive disorder: Multimodal meta-analysis of case-control MRI studies. *Neurosci Biobehav Rev* 112: 15–25.
29. Stevens BW, Morris JK, Diazgranados N, Ramchandani VA. (2022): Common gray matter reductions in alcohol use and obsessive-compulsive disorders: A meta-analysis. *Biol Psychiatry Glob Open Sci* 2(4): 421–431.
30. Wang X, Xie H, Chen T, Cotton AS, Salminen LE, Logue MW, et al. (2021): Cortical volume abnormalities in posttraumatic stress disorder: An ENIGMA-Psychiatric Genomics Consortium PTSD workgroup mega-analysis. *Mol Psychiatry* 26(8): 4331–4343.
31. Bromis K, Calem M, Reinders AATS, Williams SCR, Kempton MJ. (2018): Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *Am J Psychiatry* 175(10): 989–998.
32. Colvonen PJ, Glassman LH, Crocker LD, Buttner MM, Orff H, Schiehser DM, et al. (2017): Pretreatment biomarkers predicting PTSD psychotherapy outcomes: A systematic review. *Neurosci Biobehav Rev* 75: 140–156.
33. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. (2007): Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* 62(5): 446–454.
34. Picó-Pérez M, Vieira R, Fernández-Rodríguez M, Barros MAP, Radua J, Morgado P. (2022): Multimodal meta-analysis of structural gray matter, neurocognitive and social cognitive fMRI findings in schizophrenia patients. *Psychol Med* 52(11): 2042–2054.
35. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, et al. (2018): Cortical brain abnormalities in 4,474 individuals with schizophrenia and 5,098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Consortium. *Biol Psychiatry* 84(9): 644–654.
36. Solanes A, Mezquida G, Janssen J, Amoretti S, Lobo A, González-Pinto A, et al. (2022): Combining MRI and clinical data to detect high relapse risk after the first episode of psychosis. *Schizophrenia* 8(1): 1–9.

37. Miller EK, Cohen JD. (2001): An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24: 167–202.
38. Etkin A, Büchel C, Gross JJ. (2015): The neural bases of emotion regulation. *Nat Rev Neurosci* 16(11): 693–700.
39. Smail MA, Wu X, Henkel ND, Eby HM, Herman JP, McCullumsmith RE. (2021): Similarities and dissimilarities between psychiatric cluster disorders. *Mol Psychiatry* 26(10): 5550–5564.
40. Carr CP, Martins CMS, Stingel AM, Lemgruber VB, Juruena MF. (2013): The role of early life stress in adult psychiatric disorders: A systematic review according to childhood trauma subtypes. *J Nerv Ment Dis* 201(11): 1007–1020.
41. Teicher MH, Gordon JB, Nemeroff CB. (2022): Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Mol Psychiatry* 27(3): 1331–1338.
42. Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, et al. (2022): Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis. *Nat Genet* 54(5): 548–559.
43. Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 45(9): 984–994.
44. Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, Diego-Adeliño J, Gironell A, et al. (2012): Deep brain stimulation of the subcallosal cingulate gyrus: Further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol* 15(1): 121–133.
45. Winter NR, Blanke J, Leenings R, Ernsting J, Fisch L, Sarink K, et al. (2024): A systematic evaluation of machine learning–based biomarkers for major depressive disorder. *JAMA Psychiatry* 81(4): 386–395.
46. Chekroud AM, Hawrilenko M, Loho H, Bondar J, Gueorguieva R, Hasan A, et al. (2024): Illusory generalizability of clinical prediction models. *Science* 383(6679): 164–167.
47. Radua J, Koutsouleris N. (2023): Ten Simple Rules for Using Machine Learning in Mental Health Research. *Biol Psychiatry*. Published online.
48. Sathyanarayanan A, Mueller TT, Ali Moni M, Schueler K, Baune BT, Lio P, et al. (2023): Multi-omics data integration methods and their applications in psychiatric disorders. *Eur Neuropsychopharmacol* 69: 26–46.
49. Radua J, Vieta E, Shinohara R, Kochunov P, Quidé Y, Green MJ, et al. (2020): Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *NeuroImage* 218: 116956.
50. Weinberger DR, Radulescu E. (2021): Structural magnetic resonance imaging all over again. *JAMA Psychiatry* 78(1): 11–12.

51. Insel TR, Landis SC. (2013): The NIH BRAIN initiative. *Science* 340(6133): 687–688.

Figure 1. Flowchart of the systematic literature searches for all mental disorders included.

Footnote: VBM: voxel-based morphometry

Figure 2. Atlas of gray matter volume alterations in mental disorders – maps of the main findings at family-wise error rate (FWER) <0.05 and $k \geq 100$ for anxiety disorder, anorexia nervosa, attention-deficit hyperactivity disorder, autism spectrum disorders, and bipolar disorder.

Region names indicated the location of the maximum peak of the significant clusters. Regions with larger GMV are displayed in yellow/red. Regions with smaller GMV are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to $z = -25, -15, 0, 15, 30, 45$. ADHD: attention-deficit hyperactivity disorder, ASD: autism spectrum disorders, B: bilateral, BD: bipolar disorder, IFG: inferior frontal gyrus, L: left, MFG: middle frontal gyrus, MOG: middle occipital gyrus, MTG: middle temporal gyrus, PHG: parahippocampal gyrus, R: right, SFG: superior frontal gyrus, SMA: supplementary motor area, SMA: supramarginal gyrus, SOG: superior occipital gyrus, STG: superior temporal gyrus, STR: striatum, THAL: thalamus.

Figure 3. Atlas of gray matter volume alterations in mental disorders – maps of the main findings at family-wise error rate (FWER) <0.05 and $k \geq 100$ for borderline personality disorder, major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and schizophrenia-spectrum disorders.

Region names indicated the location of the maximum peak of the significant clusters. Regions with larger GMV are displayed in yellow/red. Regions with smaller GMV are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to $z = -25, -15, 0, 15, 30, 45$. B: bilateral, BPD: borderline personality disorder, IPG: inferior parietal gyrus, ITG: inferior temporal gyrus, L: left, MDD: major depressive disorder, MTG: middle temporal gyrus, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, R: right, SCH Dis.: schizophrenic disorders, STG: superior temporal gyrus.

Figure 4. Extent of gray matter volume differences between disorders and similarity of the differences across disorders

Footnote: GMV: gray matter volume, g : Hedges' g , ADHD: attention-deficit/hyperactive disorder, ASD: autism spectrum disorder, BD: bipolar disorder; BPD: borderline personality disorder, GMV: gray matter volume, IGD: internet gaming disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, SCH Dis: schizophrenic disorders.

Table 1. Demographic and clinical characteristics of the included participants.

Mental Disorder	N	Females (%)	Age Mean	Age SD	Duration of illness mean (years)	Duration of illness SD (years)	Co-occurring disorders (%)	Medication (%)
Anorexia nervosa	484	91.9%	28.05	8.3	7.80	8	14% anxiety 10% MDD 8% OCD 2% PTSD	Total: 25.5% 21% AntiD 5% AP
Anxiety disorders	1844	59.3%	32.87	11.1	8.40	9	1% ADHD 20% MDD	Total: 24% 21.5% AntiD 10% AA
ADHD	788	42.5%	32.04	12.4	-	-	2% anorexia 12% anxiety 1% BD 2% BPD 14% MDD	Total: 29% 29% STM
ASD	493	11.8%	29.69	8.7	-	-	3% anxiety 3% ADHD 7% MDD 1% SSD	Total: 15% 11% AntiD 6% AA 5% AP
BD	3350	56.1%	36.82	12.9	12.07	10	4% anxiety 1% ADHD	Total: 86% 19% AntiD 12% AA 45% AP 65% MS
BPD	414	83.5%	30.89	8.9	-	-	7% anorexia 20% anxiety 38% MDD 3% OCD 21% PTSD	Total: 35% 21% AntiD 8% AA 17% AP 15% MS
Internet gaming disorder	312	5.8%	22.61	2.6	-	-	0%	0%
MDD	6897	61.7%	35.82	13.1	7.58	10	6% anxiety	Total: 49% 42% AntiD 5% AA 6% AP
OCD	1204	49%	32.26	9.8	10.11	9	13% anxiety 15% MDD	Total: 61% 56%AntiD 5% AP
PTSD	464	53.7%	34.51	11.7	7.3	8	3% anxiety 22% MDD	Total: 21% 20% AntiD
Schizophrenic disorders	5465	36.2%	33.12	11.2	9.37	10	0%	Total: 80% 80% AP

AA: anxiolytics, AntiD: antidepressants, ADHD: attention-deficit hyperactivity disorder, AP: antipsychotic, ASD: autism spectrum disorder, BD: bipolar disorder; BPD: borderline personality disorder, MDD: major depressive disorder, MS: mood stabilizer, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, SD: standard deviation, STM: stimulants.

Table 2. Atlas of gray matter volume alterations in mental disorders – location and statistics of the main differences with healthy controls. Significance was set at family wise error rate (FWER)<0.05.

	Peak				Clusters	
	MNI	Hedges'g (95% CI)	Z-value	I2 p-bias	N voxels (P-value)	Breakdown
Anorexia Nervosa (Z > 3.09)						
Anorexia < Comparison subjects						
L supplementary motor area	-2,-10,60	-0.94 (-1.17, -0.71)	7.96	42% p=0.17	2639 (<0.001)	B supplementary motor area (1303) B middle cingulate cortex (685) B paracentral lobule (225)
R precuneus	6,-70,40	-0.94 (-1.16, -0.70)	7.95	52% p=0.99	990 (<0.001)	B precuneus (680) B cuneus cortex (103)
L middle temporal gyrus	-46,-2,-24	-0.67 (-0.89, -0.46)	6.09	13% p=0.97	872 (<0.001)	R middle temporal gyrus (281)
R middle temporal gyrus	58,-18,-16	-0.67 (-0.88, -0.45)	6.10	15% p=0.96	387 (0.012)	R middle/inferior temporal gyrus (270)
Anxiety Disorders (Z > 3.09)						
Anxiety < Comparison subjects						
R superior temporal gyrus	54,-22,12	-0.36 (-0.49, -0.24)	5.56	10% p=0.78	1924 (<0.001)	R superior temporal gyrus (818) R rolandic operculum (535) R heschl gyrus (148)
L supramarginal gyrus	-54,-42,24	-0.39 (-0.51, -0.27)	6.47	4% p=0.43	1312 (<0.001)	L superior temporal gyrus (462) L supramarginal gyrus (415)
R striatum	22,14,-4	-0.38 (-0.51, -0.25)	5.83	24% p=0.09	420 (0.004)	R putamen (99) R striatum (88)
R thalamus	18,-26,12	-0.45 (-0.57, -0.33)	7.47	8% p=0.55	282 (0.021)	R thalamus (154)
L middle occipital gyrus	-22,-90,20	-0.37 (-0.51, -0.24)	5.40	0% p=0.17	271 (0.026)	L superior/middle occipital gyrus (136)
Anxiety > CS						
R cerebellum	10,-74,-16	0.31 (0.18, 0.44)	4.57	2% p=0.83	262 (0.029)	R cerebellum (218)
Attention deficit/hyperactive disorder (Z > 3.09)						
ADHD < Comparison subjects						
R supramarginal gyrus	54,-42,28	-0.33 (-0.48, -0.18)	4.40	12% p=0.40	333 (<0.001)	R supramarginal gyrus (221)

Autism spectrum disorder (Z > |3.09|)

ASD < Comparison subjects

R cerebellum	18,-66,-16	-0.47 (-0.65, -0.28)	4.98	60% p=0.15	389 (0.014)	R cerebellum (335)
B calcarine fissure*	6,-74,12	-0.49 (-0.68, -0.30)	5.05	39% p=0.74	396 (0.015)	B calcarine fissure (221)

Bipolar Disorder (Z > |3.97|)

BD < Comparison subjects

L superior frontal gyrus, medial	2,34,36	-0.33 (-0.43, -0.23)	9.70	6% p=0.64	15652	B superior frontal gyrus, dorsal (5193) R middle temporal gyrus (2727) B middle frontal gyrus (1349) R inferior frontal gyrus (1336) B anterior cingulate cortex (919) R insula (838) R inferior temporal gyrus (536) B middle cingulate cortex (526) B supplementary motor area (227) R amygdala (101)
L middle temporal gyrus	-46,-70,8	-0.27 (-0.36, -0.18)	7.41	1% p=0.86	3920	L postcentral gyrus (1012) L inferior parietal gyrus (779) B supramarginal gyrus (483) L middle temporal gyrus (385) L angular gyrus (329) L precentral gyrus (283) L superior temporal gyrus (253) L middle occipital gyrus (171)
R parahippocampal gyrus	18,-34,-12	-0.41 (-0.50, -0.33)	7.27	2% p=0.82	1603	R cerebellum (675) R fusiform gyrus (231) R parahippocampal gyrus (180)
L superior temporal gyrus	-34,6,-24	-0.31 (-0.40, -0.23)	6.89	2% p=0.96	1457	L superior temporal gyrus (359) L inferior temporal gyrus (271) L insula (151) L middle temporal gyrus (147)
L fusiform gyrus	-26,-54,-16	-0.32 (-0.41, -0.23)	7.12	1% p=0.57	1474	L cerebellum (700) L fusiform gyrus (299)

						L lingual gyrus (176)
L gyrus rectus	-10,34,-28	-0.32 (-0.41, -0.23)	7.23	4% p=0.55	1219	B gyrus rectus (499) B superior frontal gyrus, orbital (306)
R caudate	2,10,8	-0.32 (-0.41, -0.24)	8.70	4% p=0.26	701	R caudate (124)
R cerebellum	6,-62,-28	-0.32 (-0.41, -0.23)	6.27	33% p=0.96	523	R cerebellum (379)
R middle occipital gyrus	38,-86,8	-0.38 (-0.47, -0.30)	7.30	35% p=0.06	445	R middle occipital gyrus (397)
R angular gyrus	42,-66,48	-0.29 (-0.38, -0.20)	6.48	3% p=0.20	475	R angular gyrus (286) R inferior parietal gyrus (173)
L calcarine fissure	-10,-74,12	-0.32 (-0.40, -0.23)	5.91	1% p=0.44	291	B calcarine fissure (123)
BD > Comparison subjects						
L precuneus	-10,-46,64	0.30 (0.20, .39)	6.26	15% p=0.69	864	B paracentral lobe (356) L precuneus (307)
R superior frontal gyrus	22,26,48	0.30 (0.22, .39)	7.17	2% p=0.63	561	R middle frontal gyrus (362) R superior frontal gyrus (146)
L superior occipital gyrus	-10,-94,8	0.28 (0.18, .37)	5.95	0% p=0.56	336	L superior occipital gyrus (117)

Borderline Personality Disorder (Z > |3.09|)

BPD vs. Comparison subjects

No significant results

Major depressive disorder (Z > |4.65|)

MDD < Comparison subjects

R cerebellum	6,-38,-12	-0.25 (-0.32, -0.19)	7.49	17% p=0.65	23891	B cerebellum (2800) B middle cingulate cortex (1816) R inferior frontal gyrus (1815) B middle frontal gyrus (1811) B middle temporal gyrus (1419) B supplementary motor area (13549) B superior frontal gyrus, dorsal (1282) B anterior cingulate cortex (1231) B precuneus (1204) R precentral gyrus (1158) B fusiform gyrus (910) B inferior temporal gyrus (758)
--------------	-----------	-------------------------	------	---------------	-------	--

						R postcentral gyrus (653) R superior temporal gyrus (628) B lingual gyrus (540) R insula (503) B cuneus cortex (280) L calcarine fissure (213) R hippocampus (146)
L inferior temporal gyrus	-46,-14,-36	-0.22 (-0.28, -0.16)	7.11	2% p=0.34	7160	L insula (928) L superior temporal gyrus (824) L inferior frontal gyrus (489) B striatum (445) L inferior temporal gyrs (360) L middle frontal gyrus (248) L fusiform gyrus (245) L putamen (237) L rolandic operculum (181) L middle temporal gyrus (175) L parahippocampal gyrus (169) L caudate (120)
L angular	-46,-66,36	-0.23 (-0.29, -0.16)	6.96	0% p=0.51	1222	L angular (638) L inferior parietal gyrus (249) L superior parietal gyrus (147)
B gyrus rectus	2,58,-20	-0.23 (-0.30, -0.17)	6.99	3% p=0.72	795	B gyrus rectus (352) L superior frontal gyrus, orbital (214)
L inferior parietal gyrus	-42,-26,44	-0.18 (-0.25, -0.11)	5.15	1% p=0.95	566	L postcentral gyrus (390) L inferior parietal gyrus (61)

Obsessive-compulsive disorder ($Z > |3.09|$)

OCD < Comparison subjects

R angular gyrus	54,-50,36	-0.33 (-0.45, -0.22)	5.70	2% p=0.84	723 (<0.001)	R angular gyrus (347) R inferior parietal gyrus (206) R supramarginal gyrus (141)
B gyrus rectus	2,30,-28	-0.31 (-0.43, -0.20)	5.26	19% p=0.89	299 (0.024)	B gyrus rectus (153)

OCD > Comparison subjects

R cerebellum	10,-34,-16	0.34 (0.22, 0.45)	5.69	25% p=0.78	1186 (<0.001)	R cerebellum (403) R fusiform gyrus (167)
--------------	------------	----------------------	------	---------------	----------------------	--

Posttraumatic stress disorder (Z > |3.09|)**PTSD < Comparison subjects**

L lingual gyrus	-10,-66,-4	-0.83 (-1.08, -0.57)	6.41	7% p=0.66	859 (<0.001)	L lingual gyrus (334) L fusiform gyrus (185) L cerebellum (144)
-----------------	------------	-------------------------	------	--------------	-----------------	---

Schizophrenic disorders (Z > |6.12|)**Schizophrenic disorders < CS**

L superior temporal gyrus	-58,-10,0	-0.48 (-0.57, -0.40)	10.80	4% p=0.88	30642 (<0.001)	B superior frontal gyrus (4623) B middle cingulate cortex (2513) Left superior temporal gyrus (1926) B anterior cingulate cortex (1782) L inferior frontal gyrus (1745) L insula (1496) B middle frontal gyrus (1187) L middle temporal gyrus (1051) B gyrus rectus (764) L rolandic operculum (653) B supplementary motor area (498) L putamen (260) L parahippocampal gyrus (239) L precentral gyrus (228) L postcentral gyrus (218) L heschl gyrus (184) L precuneus (149) L fusiform gyrus (145) L amygdala (131) L striatum (117)
R postcentral gyrus	62,-10,16	-0.46 (-0.55, -0.36)	9.47	22% p=0.72	10958 (<0.001)	R superior temporal gyrus (2160) R inferior frontal gyrus (1336) R insula (1016) R rolandic operculum (981) R middle temporal gyrus (833) R precentral gyrus (743) R postcentral gyrus (713) R supramarginal gyrus (618) R heschl gyrus (185)

L middle temporal gyrus	-42,-66,20	-0.29 (-0.38, -0.20)	6.52	3% p=0.55	1864 (<0.001)	L middle temporal gyrus (497) L inferior parietal gyrus (398) L angular gyrus (358) L inferior temporal gyrus (325)
R middle occipital gyrus	46,-74,16	-0.23 (-0.32, -0.14)	4.99	5% p=0.74	1040 (0.006)	R middle temporal gyrus (597) R middle occipital gyrus (220) R angular gyrus (131)
R hippocampus	26,-18,-16	-0.25 (-0.34, -0.16)	5.30	0% p=0.78	816 (0.015)	R cerebellum (375) R fusiform gyrus (133) R hippocampus (111)
L lingual gyrus	-26,-46,-8	-0.23 (-0.32, -0.14)	5.09	0% p=0.93	601 (0.037)	L cerebellum (116) L lingual gyrus (110) L fusiform gyrus (105)

ADHD: attention-deficit hyperactivity disorder, ASD: autism spectrum disorders, BD: bipolar disorder, BPD: borderline personality disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, .

Table 3. Transdiagnostic abnormalities: regions showing a smaller gray matter volume in at least three disorders compared to healthy controls.

	Peak		N voxel	Cluster	
	MNI	Hedges'g		Breakdown	Mental disorders
R heschl gyrus	54,-6,4	-0.43	2118	R superior temporal gyrus (772) R rolandic operculum (424) R middle temporal gyrus (316) R heschl gyrus (95) R insula (83)	Anxiety disorder, BD, MDD, schizophrenic disorders
L supplementary motor area	2,18,52	-0.35	1362	B superior frontal gyrus medial (468) B anterior cingulate cortex (630) B middle cingulate cortex (123) B supplementary motor area (94)	BD, MDD, OCD, PTSD, schizophrenic disorders
L insula	-34,-2,-24	-0.38	456	L superior temporal gyrus (184) L insula (68)	Anorexia nervosa, BD, MDD, schizophrenic disorders
L gyrus rectus	2,34,-24	-0.33	467	B gyrus rectus (262) B superior frontal gyrus, orbital (148)	BD, OCD, schizophrenic disorders
R inferior frontal gyrus	50,18,4	-0.41	316	R inferior frontal gyrus (225) R insula (90)	BD, MDD, schizophrenic disorders

BD: bipolar disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder.