

Atlas of Gray Matter Volume Differences Across Psychiatric Conditions: A Systematic Review With a Novel Meta-Analysis That Considers Co-Occurring Disorders

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ABSTRACT

BACKGROUND: Regional gray matter volume (GMV) differences between individuals with mental disorders and comparison participants may be confounded by co-occurring disorders. To disentangle disorder-specific GMV correlates, we conducted a large-scale multidisorder 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 that compared adults with major mental disorders (anorexia nervosa, schizophrenia spectrum, anxiety, bipolar, major depressive, obsessive-compulsive, and posttraumatic stress disorders plus attention-deficit/hyperactivity, autism spectrum, and borderline personality disorders) with comparison participants. Two authors independently extracted data and assessed quality using the Newcastle-Ottawa Scale. We derived GMV correlates for each disorder using: 1) a multidisorder meta-analysis that accounted for all co-occurring mental disorders simultaneously and 2) separate standard meta-analyses for each disorder in which co-occurring disorders were ignored. We assessed the alterations' extent, intensity (effect size), and specificity (interdisorder correlations and transdiagnostic alterations) for both approaches.

RESULTS: We included 433 studies (499 datasets) involving 19,718 patients and 16,441 comparison participants (51% female, ages 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.

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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 nonrepresentative 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.

In the current study, we aimed to establish a new methodology to account for the presence of co-occurring mental disorders. Furthermore, we 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 studies comparing major psychiatric disorders and comparison participants 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, Goodkind *et al.* (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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12,13) (see the Supplement) and preregistered and published the protocol [PROSPERO: CRD42021245098 and (11)]. The current 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, YY, and LDF) and resolved discrepancies with a third researcher (JR).

Systematic Literature Search and Data Extraction

Our systematic search strategy had 2 stages: identifying meta-analyses of case-control whole-brain voxel-based morphometry studies for each psychiatric disorder listed in the ICD-11 (14) and enriching our samples with additional eligible studies (Figure 1). We conducted both searches in PubMed and

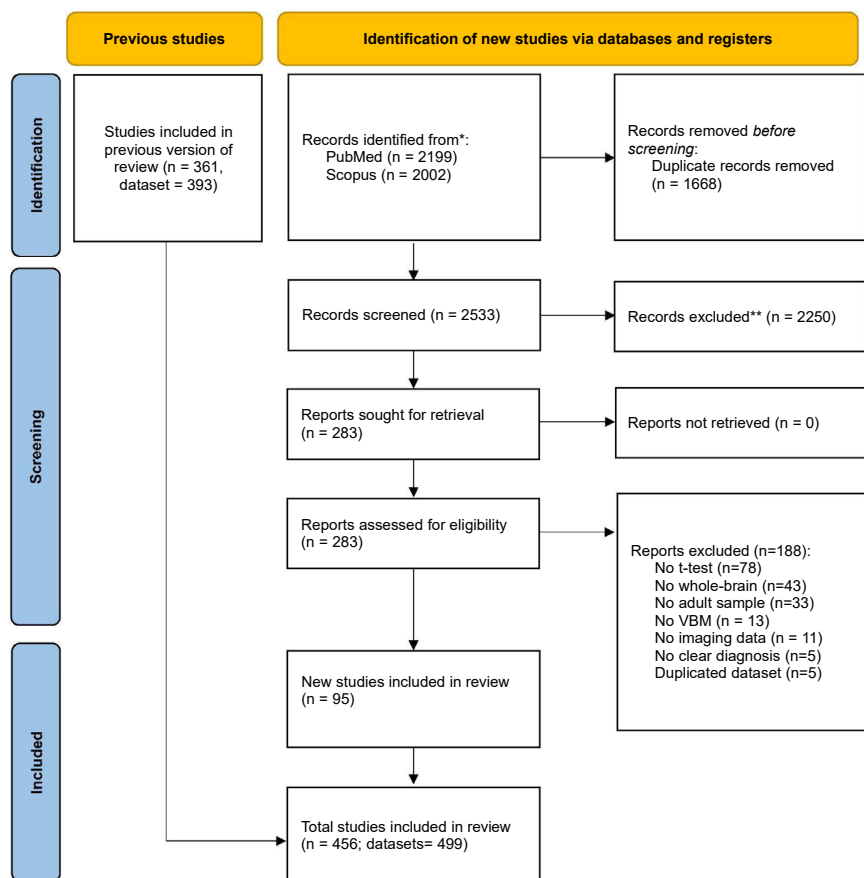


Figure 1. Flowchart of the systematic literature searches for all mental disorders included. VBM, voxel-based morphometry.

Scopus up to January 15, 2023 (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). More 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). Additional 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 participants, we employed SDM-PSI version 6.23 (<http://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 participants 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 participants 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 participants would exclusively be attributed to MDD. To perform the novel meta-analytic analyses, we excluded those studies that lacked complete information about co-occurring mental disorders. Details of the methods employed by SDM-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 analysis of variance (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 $z \geq 3.09$ ($p < .001$). We used Gaussian random fields to correct for multiple testing; we report findings at a familywise error rate of $< .05$. In the [Supplement](#), we list findings at a more lenient threshold (uncorrected $p < .005$). 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 (interdisorder correlations and transdiagnostic alterations) for both the novel meta-analysis that considers co-occurring disorders versus the standard one that ignores them. From this analysis, we excluded attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) due to their classification as neurodevelopmental disorders and borderline personality disorder 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-analytic 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 participants (see [Table 1](#) for demographics and [Tables S2–S6](#) for co-occurring disorders). The included mental disorders were anorexia nervosa, anxiety, bipolar disorder (BD), MDD, OCD, posttraumatic stress disorder (PTSD), and schizophrenic disorders plus ADHD, ASD, borderline personality disorder, and internet gaming disorder. After excluding studies that lacked complete information about co-occurring disorders, we had 290 datasets (11,395 patients and 8826 comparison participants). For internet gaming disorder, only 9 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 found smaller GMV also in the anterior cingulate cortex (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 identified it 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 found it in the ACC and superior temporal gyrus. For PTSD, both identified smaller GMV

Table 1. Demographic and Clinical Characteristics of the Included Participants

Mental Disorder	<i>n</i>	Gender, Female	Age, Years, Mean (SD)	Duration of Illness, Years, Mean (SD)	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, anxiolytic; ADHD, attention-deficit/hyperactivity disorder; AntiD, antidepressant; 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, posttraumatic stress disorder; SSD, schizophrenic spectrum disorder; STM, stimulant.

in the left lingual gyrus, and the standard approach also identified it in the superior frontal gyrus. For schizophrenia, both identified widespread smaller GMV across cortical and subcortical regions. Comprehensive details are presented in [Table 2](#) and [Figures 2](#) and [3](#), with additional information available in the [Supplement](#), including uncorrected results ([Table S7](#)) and standard meta-analyses ([Table S8](#) and [Figure S1](#)).

In the analysis of variance 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 than other mental disorders. PTSD exhibited larger GMV than most other disorders in regions where, in the primary analyses, they showed reduced GMV relative to control participants, while participants with PTSD did not. Finally, OCD showed smaller GMV in the right inferior parietal gyrus compared with anxiety disorders and PTSD.

Results from the novel meta-analysis accounting for interactions are presented in the [Supplement \(Tables S12 and S13\)](#).

Extent, Intensity, and Specificity of the GMV Differences

As shown in [Figure 4](#), schizophrenic disorders exhibited the highest percentage of voxels (20%), showing GMV differences with comparison participants 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 that showed 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).

Table 2. Atlas of Gray Matter Volume Alterations in Mental Disorders: Location and Statistics of the Main Differences With Healthy Control Participants

	Peak				Clusters	
	MNI	Hedges' <i>g</i> (95% CI)	<i>z</i> Value	<i>I</i> ² , <i>p</i> Bias	<i>n</i> Voxels (<i>p</i> Value)	Region (<i>n</i> Voxels)
Anorexia Nervosa, <i>z</i> > 3.09						
Anorexia < Comparison Participants						
L SMA	−2, −10, 60	−0.94 (−1.17 to −0.71)	7.96	42%, <i>p</i> = .17	2639 (<.001)	B SMA (1303) B MCC (685) B paracentral lobule (225)
R precuneus	6, −70, 40	−0.94 (−1.16 to −0.70)	7.95	52%, <i>p</i> = .99	990 (<.001)	B precuneus (680) B cuneus cortex (103)
L MTG	−46, −2, −24	−0.67 (−0.89 to −0.46)	6.09	13%, <i>p</i> = .97	872 (<.001)	R MTG (281)
R MTG	58, −18, −16	−0.67 (−0.88 to −0.45)	6.10	15%, <i>p</i> = .96	387 (.012)	R middle/ITG (270)
Anxiety Disorders, <i>z</i> > 3.09						
Anxiety < Comparison Participants						
R STG	54, −22, 12	−0.36 (−0.49 to −0.24)	5.56	10%, <i>p</i> = .78	1924 (<.001)	R STG (818) R RO (535) R Heschl's gyrus (148)
L SMG	−54, −42, 24	−0.39 (−0.51 to −0.27)	6.47	4%, <i>p</i> = .43	1312 (<.001)	L STG (462) L SMG (415)
R striatum	22, 14, −4	−0.38 (−0.51 to −0.25)	5.83	24%, <i>p</i> = .09	420 (.004)	R putamen (99) R striatum (88)
R thalamus	18, −26, 12	−0.45 (−0.57 to −0.33)	7.47	8%, <i>p</i> = .55	282 (.021)	R thalamus (154)
L MOG	−22, −90, 20	−0.37 (−0.51 to −0.24)	5.40	0%, <i>p</i> = .17	271 (.026)	L superior/MOG (136)
Anxiety > Comparison Participants						
R cerebellum	10, −74, −16	0.31 (0.18 to 0.44)	4.57	2%, <i>p</i> = .83	262 (.029)	R cerebellum (218)
ADHD, <i>z</i> > 3.09						
ADHD < Comparison Participants						
R SMG	54, −42, 28	−0.33 (−0.48 to −0.18)	4.40	12%, <i>p</i> = .40	333 (<.001)	R SMG (221)
ASD, <i>z</i> > 3.09						
ASD < Comparison Participants						
R cerebellum	18, −66, −16	−0.47 (−0.65 to −0.28)	4.98	60%, <i>p</i> = .15	389 (.014)	R cerebellum (335)
B calcarine fissure	6, −74, 12	−0.49 (−0.68 to −0.30)	5.05	39%, <i>p</i> = .74	396 (.015)	B calcarine fissure (221)
BD, <i>z</i> > 3.97						
BD < Comparison Participants						
L SFG, medial	2, 34, 36	−0.33 (−0.43 to −0.23)	9.70	6%, <i>p</i> = .64	15,652	B SFG, dorsal (5193) R MTG (2727) B MFG (1349) R IFG (1336) B ACC (919) R insula (838) R ITG (536) B MCC (526) B SMA (227) R amygdala (101)
L MTG	−46, −70, 8	−0.27 (−0.36 to −0.18)	7.41	1%, <i>p</i> = .86	3920	L postcentral gyrus (1012) L IPG (779) B SMG (483) L MTG (385) L angular gyrus (329) L precentral gyrus (283) L STG (253) L MOG (171)
R PHG	18, −34, −12	−0.41 (−0.50 to −0.33)	7.27	2%, <i>p</i> = .82	1603	R cerebellum (675) R fusiform gyrus (231) R PHG (180)
L STG	−34, 6, −24	−0.31 (−0.40 to −0.23)	6.89	2%, <i>p</i> = .96	1457	L STG (359) L ITG (271) L insula (151) L MTG (147)

Table 2. Continued

	Peak				Clusters	
	MNI	Hedges' <i>g</i> (95% CI)	<i>z</i> Value	I^2 , <i>p</i> Bias	<i>n</i> Voxels (<i>p</i> Value)	Region (<i>n</i> Voxels)
L fusiform gyrus	−26, −54, −16	−0.32 (−0.41 to −0.23)	7.12	1%, <i>p</i> = .57	1474	L cerebellum (700) L fusiform gyrus (299) L lingual gyrus (176)
L gyrus rectus	−10, 34, −28	−0.32 (−0.41 to −0.23)	7.23	4%, <i>p</i> = .55	1219	B gyrus rectus (499) B SFG, orbital (306)
R caudate	2, 10, 8	−0.32 (−0.41 to −0.24)	8.70	4%, <i>p</i> = .26	701	R caudate (124)
R cerebellum	6, −62, −28	−0.32 (−0.41 to −0.23)	6.27	33%, <i>p</i> = .96	523	R cerebellum (379)
R MOG	38, −86, 8	−0.38 (−0.47 to −0.30)	7.30	35%, <i>p</i> = .06	445	R MOG (397)
R angular gyrus	42, −66, 48	−0.29 (−0.38 to −0.20)	6.48	3%, <i>p</i> = .20	475	R angular gyrus (286) R IPG (173)
L calcarine fissure	−10, −74, 12	−0.32 (−0.40 to −0.23)	5.91	1%, <i>p</i> = .44	291	B calcarine fissure (123)
BD > Comparison Participants						
L precuneus	−10, −46, 64	0.30 (0.20 to 0.39)	6.26	15%, <i>p</i> = .69	864	B paracentral lobe (356) L precuneus (307)
R SFG	22, 26, 48	0.30 (0.22 to 0.39)	7.17	2%, <i>p</i> = .63	561	R MFG (362) R SFG (146)
L superior occipital gyrus	−10, −94, 8	0.28 (0.18 to 0.37)	5.95	0%, <i>p</i> = .56	336	L superior occipital gyrus (117)
MDD, <i>z</i> > 4.65						
MDD < Comparison Participants						
R cerebellum	6, −38, −12	−0.25 (−0.32 to −0.19)	7.49	17%, <i>p</i> = .65	23,891	B cerebellum (2800) B MCC (1816) R IFG (1815) B MFG (1811) B MTG (1419) B SMA (13,549) B SFG, dorsal (1282) B ACC (1231) B precuneus (1204) R precentral gyrus (1158) B fusiform gyrus (910) B ITG (758) R postcentral gyrus (653) R STG (628) B lingual gyrus (540) R insula (503) B cuneus cortex (280) L calcarine fissure (213) R hippocampus (146)
L ITG	−46, −14, −36	−0.22 (−0.28 to −0.16)	7.11	2%, <i>p</i> = .34	7160	L insula (928) L STG (824) L IFG (489) B striatum (445) L ITG (360) L MFG (248) L fusiform gyrus (245) L putamen (237) L RO (181) L MTG (175) L PHG (169) L caudate (120)
L angular	−46, −66, 36	−0.23 (−0.29 to −0.16)	6.96	0%, <i>p</i> = .51	1222	L angular (638) L IPG (249) L superior parietal gyrus (147)
B gyrus rectus	2, 58, −20	−0.23 (−0.30 to −0.17)	6.99	3%, <i>p</i> = .72	795	B gyrus rectus (352) L SFG, orbital (214)
L IPG	−42, −26, 44	−0.18 (−0.25 to −0.11)	5.15	1%, <i>p</i> = .95	566	L postcentral gyrus (390) L IPG (61)

Table 2. Continued

	Peak				Clusters	
	MNI	Hedges' <i>g</i> (95% CI)	<i>z</i> Value	I^2 , <i>p</i> Bias	<i>n</i> Voxels (<i>p</i> Value)	Region (<i>n</i> Voxels)
OCD, $z > 3.09 $						
OCD < Comparison Participants						
R angular gyrus	54, -50, 36	-0.33 (-0.45 to -0.22)	5.70	2%, $p = .84$	723 (<.001)	R angular gyrus (347) R IPG (206) R SMG (141)
B gyrus rectus	2, 30, -28	-0.31 (-0.43 to -0.20)	5.26	19%, $p = .89$	299 (.024)	B gyrus rectus (153)
OCD > Comparison Participants						
R cerebellum	10, -34, -16	0.34 (0.22 to 0.45)	5.69	25%, $p = .78$	1186 (<.001)	R cerebellum (403) R fusiform gyrus (167)
PTSD, $z > 3.09 $						
PTSD < Comparison Participants						
L lingual gyrus	-10, -66, -4	-0.83 (-1.08 to -0.57)	6.41	7%, $p = .66$	859 (<.001)	L lingual gyrus (334) L fusiform gyrus (185) L cerebellum (144)
Schizophrenic Disorders, $z > 6.12 $						
Schizophrenic Disorders < Comparison Participants						
L STG	-58, -10, 0	-0.48 (-0.57 to -0.40)	10.80	4%, $p = .88$	30,642 (<.001)	B SFG (4623) B MCC (2513) L STG (1926) B ACC (1782) L IFG (1745) L insula (1496) B MFG (1187) L MTG (1051) B gyrus rectus (764) L RO (653) B SMA (498) L putamen (260) L PHG (239) L precentral gyrus (228) L postcentral gyrus (218) L Heschl's 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 to -0.36)	9.47	22%, $p = .72$	10,958 (<.001)	R STG (2160) R IFG (1336) R insula (1016) R RO (981) R MTG (833) R precentral gyrus (743) R postcentral gyrus (713) R SMG (618) R Heschl's gyrus (185)
L MTG	-42, -66, 20	-0.29 (-0.38 to -0.20)	6.52	3%, $p = .55$	1864 (<.001)	L MTG (497) L IPG (398) L angular gyrus (358) L ITG (325)
R MOG	46, -74, 16	-0.23 (-0.32 to -0.14)	4.99	5%, $p = .74$	1040 (.006)	R MTG (597) R MOG (220) R angular gyrus (131)
R hippocampus	26, -18, -16	-0.25 (-0.34 to -0.16)	5.30	0%, $p = .78$	816 (.015)	R cerebellum (375) R fusiform gyrus (133) R hippocampus (111)

Table 2. Continued

	Peak				Clusters	
	MNI	Hedges' <i>g</i> (95% CI)	<i>z</i> Value	I^2 , <i>p</i> Bias	<i>n</i> Voxels (<i>p</i> Value)	Region (<i>n</i> Voxels)
L lingual gyrus	-26, -46, -8	-0.23 (0–0.32 to -0.14)	5.09	0%, <i>p</i> = .93	601 (.037)	L cerebellum (116) L lingual gyrus (110) L fusiform gyrus (105)

Significance was set at familywise error rate < .05. No significant results were obtained for borderline personality disorder vs. comparison participants ($z > |3.09|$).

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; B, bilateral; BD, bipolar disorder; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus; ITG, inferior temporal gyrus; L, left; MCC, middle cingulate cortex; MDD, major depressive disorder; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OCD, obsessive-compulsive disorder; PHG, parahippocampal gyrus; PTSD, posttraumatic stress disorder; R, right; RO, rolandic operculum; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; STG, superior temporal gyrus.

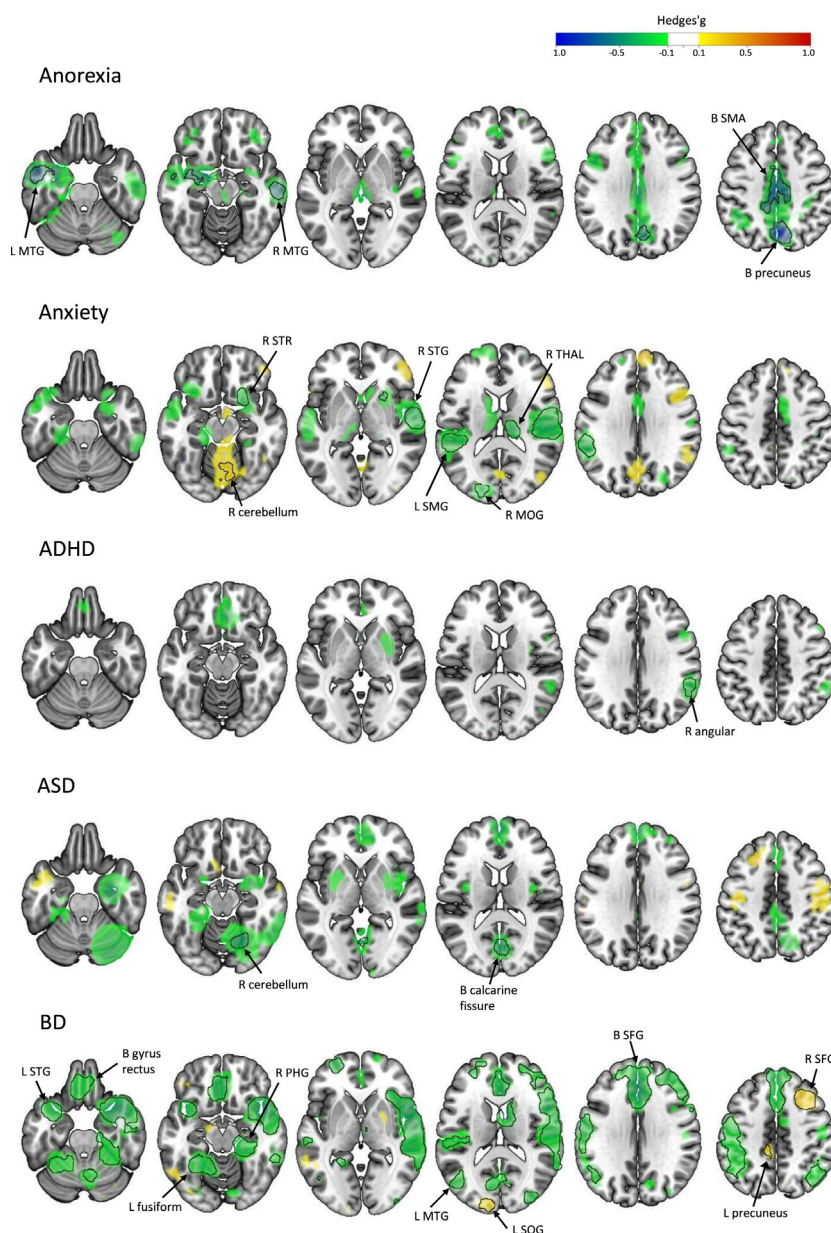


Figure 2. Atlas of gray matter volume alterations in mental disorders: maps of the main findings at a familywise error rate < .05 and $k \geq 100$ for anxiety disorder, anorexia nervosa, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and bipolar disorder (BD). Region names indicate the location of the maximum peak of the significant clusters. Regions with larger gray matter volume are displayed in yellow/red. Regions with smaller gray matter volume are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to $z = -25, -15, 0, 15, 30$, and 45 . B, bilateral; 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; SMG, supramarginal gyrus; SOG, superior occipital gyrus; STG, superior temporal gyrus; STR, striatum; THAL, thalamus.

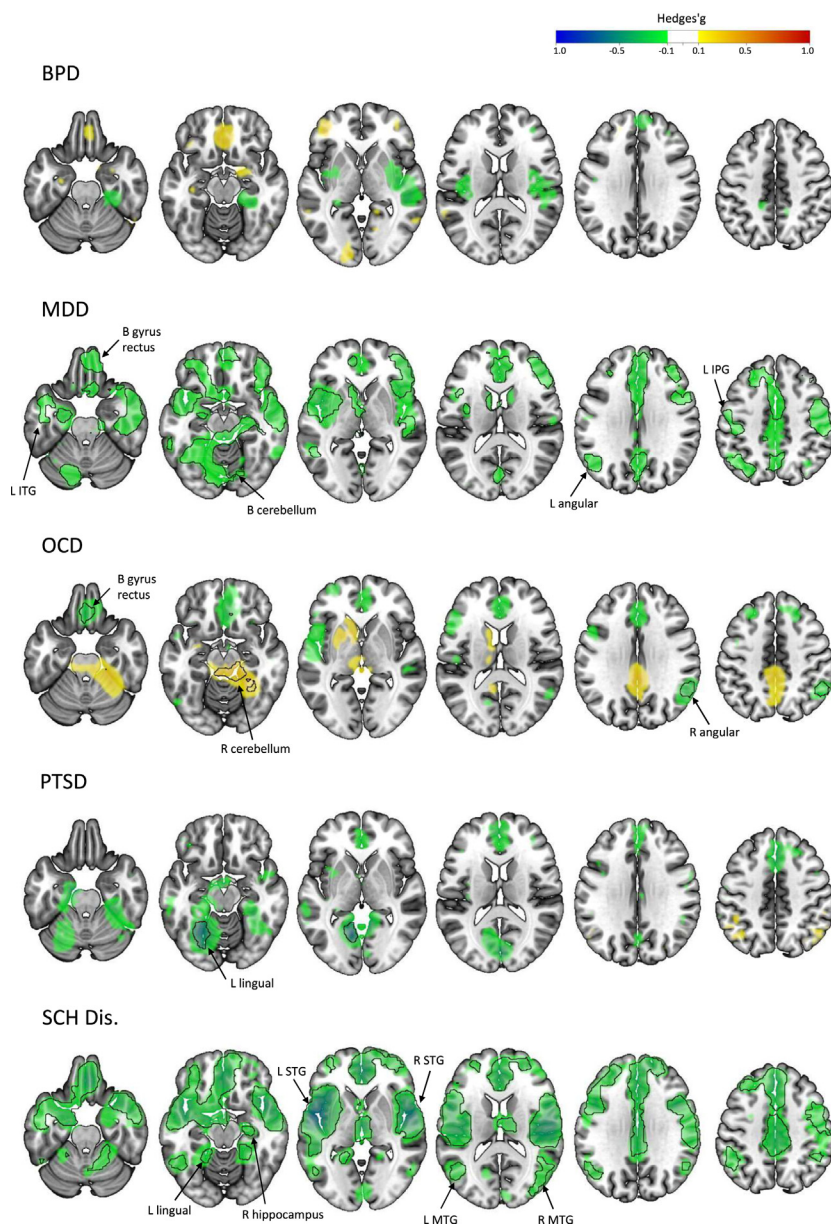


Figure 3. Atlas of gray matter volume alterations in mental disorders: maps of the main findings at a familywise error rate $< .05$ and $k \geq 100$ for borderline personality disorder (BPD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and schizophrenia spectrum disorders (SCH Dis.). Region names indicate the location of the maximum peak of the significant clusters. Regions with larger gray matter volume are displayed in yellow/red. Regions with smaller gray matter volume 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; IPG, inferior parietal gyrus; ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; R, right; STG, superior temporal gyrus.

The correlation analysis (Figure 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 weak similarities between MDD and anxiety ($r = 0.25$). 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 3 disorders, including the PFC, orbitofrontal cortex, ACC, middle cingulate, and temporal gyrus, including the insulas (Table 3 and Figure 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 and Figure 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

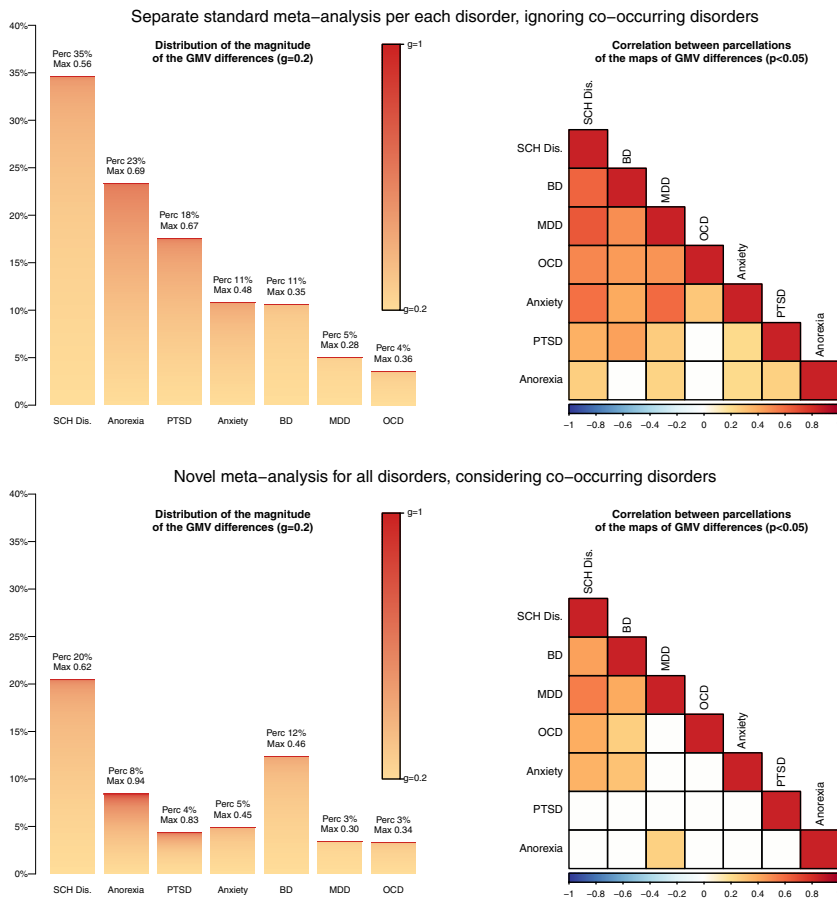


Figure 4. Extent of gray matter volume (GMV) differences between disorders and similarity of the differences across disorders. BD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SCH Dis., schizophrenic disorders.

schizophrenic disorders (Tables S2–S8 and Figures S1 and S2), with additional details provided in the Supplement. Alterations associated with ADHD, ASD, and borderline personality disorder

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

Table 3. Transdiagnostic Abnormalities: Regions Showing a Smaller Gray Matter Volume in at Least 3 Disorders Compared With Healthy Control Participants

	Peak		<i>n</i> Voxels	Cluster	
	MNI	Hedges' <i>g</i>		Region (<i>n</i> , Voxels)	Mental Disorders
R Heschl's Gyrus	54, −6, 4	−0.43	2118	R superior temporal gyrus (772) R rolandic operculum (424) R middle temporal gyrus (316) R Heschl's 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

B, bilateral; BD, bipolar disorder; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; R, right.

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 were consistent with previous work (18–20), except for smaller GMV in the ACC and cerebellum, which was found in previous work and our standard meta-analyses, but not in our novel approach, likely due to our adjustment for co-occurring disorders. These regions have been associated with MDD, which commonly co-occurs with 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, and therefore warrants additional 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 social anxiety disorder, 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, although 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 were consistent with previous studies (1,25), 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 previous 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 were partially consistent with previous studies (28,29), 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% had anxiety disorders). Abnormalities in the temporal lobes have often been associated with these mental disorders (1,24) and are supported by our current findings. Interestingly, smaller GMV in the parietal gyrus was statistically different between OCD and other anxiety-related disorders (anxiety and PTSD).

Posttraumatic 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), which are essential for threat processing and emotion regulation (33). We observed smaller GMV in the dorsal PFC in both meta-analyses (uncorrected $p < .005$) but no significant differences in the hippocampus, possibly due to previous studies specifically targeting that region.

Schizophrenic Disorders. Findings from both meta-analyses are consistent with previous research and established models for schizophrenic disorders, as discussed in previous meta-analyses and ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) findings (34,35). Interestingly, the findings also included the GMV decreases found to estimate relapse risk after the 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 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, respectively. 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 symptom threshold for MDD. Surprisingly, the GMV abnormality pattern of PTSD did not correlate with any other mental disorder, showing significant differences from 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 example, 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 with 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, orbito-frontal 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 (37,38), which are 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 the possibility that our findings could stem from early-life trauma. Notably, evidence has shown 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 the study participants did not develop any mental disorder (41). Another potential explanation could be the shared genetic pattern across disorders. For example, a study investigating the genetic architecture of 11 mental disorders (42) identified 4 factors that explained the genetic structure for 1) compulsive behaviors (anorexia, OCD), 2) psychotic features (schizophrenic disorders, BD), 3) neurodevelopmental disorders (ADHD, ASD), and 4) 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), previous studies often excluded patients with co-occurring disorders or investigated 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 and supported findings by Opel *et al.* (4). Finally, we presented new and complementary evidence regarding the ACC and insula being a transdiagnostic biomarker, as suggested by Goodkind *et al.* (2).

There are several applications of the current work. Firstly, we provide a new meta-analytic 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, thus contributing to a deeper comprehension of the psychopathological processes that underlie 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 noninvasive 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, it is important to remember some rules for properly using machine learning in mental health research, such as preregistering 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, thereby offering clinicians with additional information that may help enhance diagnostic accuracy and thus help identify a more focused treatment earlier.

Limitations

The current study has several limitations. Firstly, the included studies' cross-sectional nature means that we cannot make any inferences about causal relationships between variables; 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). Furthermore, 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 rather 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 mental disorders for which a meta-analysis had already been published and examined by at least 10 studies. Finally, we must highlight that even when, for simplicity, we talk about GMV differences, we should more appropriately refer to differences in T1-weighted MRI signal, given that the acquired MRI data are not a direct measure of brain structure (50).

Conclusions

We have presented the first large-scale atlas of specific and transdiagnostic GMV alterations statistically associated with major psychiatric conditions, while also considering the possible confounding effects of co-occurring disorders. This innovative meta-analysis, which involved 19,718 patients and 16,441 comparison participants, represents a significant contribution to our understanding of the shared and distinct neural substrates that underlie mental disorders. This work adds to admirable initiatives, such as the National Institute of Health's BRAIN (Brain Research Through Advancing Innovative Neurotechnologies) (51), ENIGMA consortium (4), or Psychiatric Genomics Consortium (42), that enhance our knowledge of the physiopathology of mental disorders and pave the way for future diagnostic aid tools and precision-based interventions directed to specific brain targets.

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