Original Investigation | META-ANALYSIS

Identification of a Common Neurobiological Substrate for Mental Illness

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IMPORTANCE Psychiatric diagnoses are currently distinguished based on sets of specific symptoms. However, genetic and clinical analyses find similarities across a wide variety of diagnoses, suggesting that a common neurobiological substrate may exist across mental illness.

OBJECTIVE To conduct a meta-analysis of structural neuroimaging studies across multiple psychiatric diagnoses, followed by parallel analyses of 3 large-scale healthy participant data sets to help interpret structural findings in the meta-analysis.

DATA SOURCES PubMed was searched to identify voxel-based morphometry studies through July 2012 comparing psychiatric patients to healthy control individuals for the meta-analysis. The 3 parallel healthy participant data sets included resting-state functional magnetic resonance imaging, a database of activation foci across thousands of neuroimaging experiments, and a data set with structural imaging and cognitive task performance data.

DATA EXTRACTION AND SYNTHESIS Studies were included in the meta-analysis if they reported voxel-based morphometry differences between patients with an Axis I diagnosis and control individuals in stereotactic coordinates across the whole brain, did not present predominantly in childhood, and had at least 10 studies contributing to that diagnosis (or across closely related diagnoses). The meta-analysis was conducted on peak voxel coordinates using an activation likelihood estimation approach.

MAIN OUTCOMES AND MEASURES We tested for areas of common gray matter volume increase or decrease across Axis I diagnoses, as well as areas differing between diagnoses. Follow-up analyses on other healthy participant data sets tested connectivity related to regions arising from the meta-analysis and the relationship of gray matter volume to cognition.

RESULTS Based on the voxel-based morphometry meta-analysis of 193 studies comprising 15 892 individuals across 6 diverse diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety), we found that gray matter loss converged across diagnoses in 3 regions: the dorsal anterior cingulate, right insula, and left insula. By contrast, there were few diagnosis-specific effects, distinguishing only schizophrenia and depression from other diagnoses. In the parallel follow-up analyses of the 3 independent healthy participant data sets, we found that the common gray matter loss regions formed a tightly interconnected network during tasks and at resting and that lower gray matter in this network was associated with poor executive functioning.

CONCLUSIONS AND REVELANCE We identified a concordance across psychiatric diagnoses in terms of integrity of an anterior insula/dorsal anterior cingulate–based network, which may relate to executive function deficits observed across diagnoses. This concordance provides an organizing model that emphasizes the importance of shared neural substrates across psychopathology, despite likely diverse etiologies, which is currently not an explicit component of psychiatric nosology.

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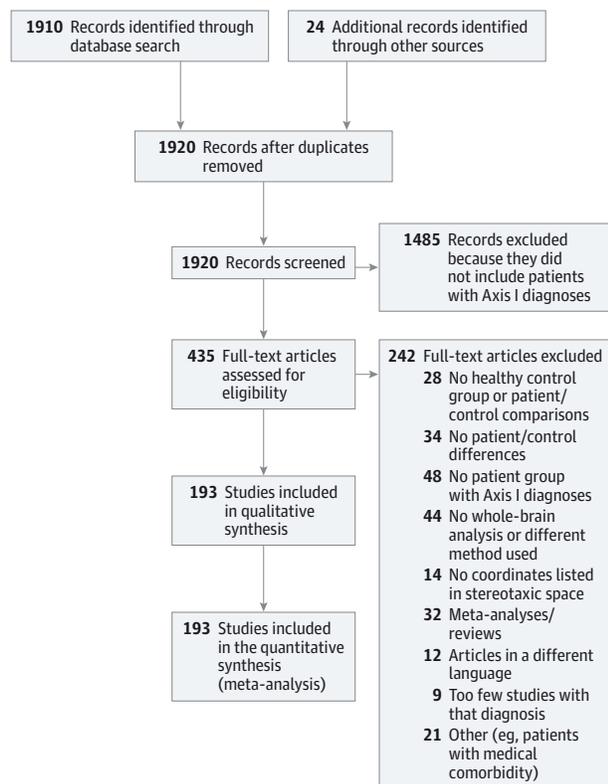
During the past several decades, psychiatry has focused on establishing diagnostic categories based on clinical symptoms.[1,2] Accordingly, most neuroimaging studies have compared brain structure or function in patients with a single, specific diagnosis with healthy participants. In turn, even closely related diagnostic categories are rarely compared with each other. Nonetheless, neuroimaging research is suggestive of common neurobiological abnormalities across phenotypically related diagnoses (eg, schizophrenia [SCZ] and bipolar disorder [BPD] or anxiety and depression).[3-6] These data have also converged on the idea that psychiatric illnesses affect the operation of commonly observed distributed neural circuits.[7,8] Additionally, genetic analyses have identified common polymorphisms associated with a large range of psychiatric diagnoses,[9] and comorbidity between diagnoses is considerably higher than expected by chance.[10] Thus, there is a disconnection between current psychiatric nosology and rapidly emerging biological findings, which emphasizes the need to look for neurobiological substrates shared across diagnoses.

To search for a potential transdiagnostic neural signature, we first conducted a meta-analysis of psychiatric neuroimaging studies that used voxel-based morphometry (VBM) to assess patient/control differences in regional brain volume from structural neuroimaging data. Voxel-based morphometry analysis of brain structure holds several advantages: (1) VBM analyses use standardized methods, which allow for pooling across studies; (2) they assess the entire brain, thus alleviating the need for a priori assumptions on which neural circuits are thought to be affected; (3) the major psychiatric diagnoses have been examined across numerous independent VBM studies; and (4) structural markers are relatively stable across time and may provide trait measures of brain abnormalities.[11] While there have been many advances in structural brain imaging methods beyond VBM, our goal here was to quantitatively summarize the very large body of existing (VBM) findings so that this knowledge can be used to guide new studies with improved methods. The use of meta-analytic methods furthermore allows for the summation of large amounts of structural imaging data in a spatially unbiased manner, thereby reflecting conclusions based on much of the structural imaging work in psychiatric disorders during the past 15 years. Doing so further allows for direct comparisons of diagnoses that were never compared with each other in the original data sets.[4,12] To more fully contextualize potential transdiagnostic brain abnormalities in patients, we also contrasted specific diagnoses or diagnosis groupings, as supported by prior studies of symptom or genetic covariation across large and diverse patient cohorts.[13-17] We used these groupings to guide our meta-analytic contrasts because they are data-driven parcellations that best reflect the current understanding of relationships between diagnoses and thus do not require an assumption that individual diagnoses represent independent entities.

Despite the advantages of VBM, measures of brain structure are ambiguous with respect to the connectivity between the identified brain regions, as well as with respect to their behavioral relevance. Thus, we also conducted parallel analyses of 3 data sets of healthy participants to test whether patterns of perturbed brain structure reflects a disruption in a functionally interrelated neural circuit and whether there are behavioral correlates of altered structural integrity even within a healthy range of functioning. Although these data are derived from healthy participants, they can nonetheless aid in the interpretation of patient/control differences in brain structure and help constrain hypotheses for more targeted studies of potential transdiagnostic neural markers.

Methods

VBM Meta-analysis: Study Selection

We searched PubMed for all studies through July 2012 using VBM (**Figure 1**). Of these, we selected those studies that investigated Axis I psychiatric diagnoses. Studies including patients with SCZ, schizophreniform, or schizoaffective disorder were included in a psychotic diagnoses category. This included both chronic and first-onset psychosis. There were no studies of transient psychotic disorders. Also, although individuals with depression or bipolar disorder may present with psychotic features, studies of these patients were included in separate categories; in these cases, the mood disorder was the primary diagnosis and, in general, these patients did not have psychosis. One study of patients with affective psychosis was excluded because it was unclear how

Figure 1. Flow Diagram of Study Selection


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1910  Records identified through        24  Additional records identified
      database search                        through other sources

                          1920  Records after duplicates
                                removed

         1920  Records screened  ──►  1485  Records excluded
                                            because they did
                                            not include patients
                                            with Axis I diagnoses

          435  Full-text articles  ──►  242  Full-text articles excluded
                assessed for                  28  No healthy control
                eligibility                       group or patient/
                                                  control comparisons
                                              34  No patient/control
                                                  differences
                                              48  No patient group
                                                  with Axis I diagnoses
          193  Studies included               44  No whole-brain
                in qualitative                    analysis or different
                synthesis                         method used
                                              14  No coordinates listed
                                                  in stereotaxic space
                                              32  Meta-analyses/
                                                  reviews
          193  Studies included               12  Articles in a different
                in the quantitative               language
                synthesis                      9  Too few studies with
                (meta-analysis)                   that diagnosis
                                              21  Other (eg, patients
                                                  with medical
                                                  comorbidity)
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to categorize it. We excluded neurological disorders, diagnoses presenting predominantly in childhood (eg, attention-deficit/hyperactivity disorder), personality disorders, and any diagnosis that had fewer than 10 studies and could not be readily grouped with another diagnosis (eg, affective psychosis).[4] Additionally, while autism spectrum disorders present symptoms throughout the lifespan, they typically first present very early in life and are associated with altered developmental trajectories of brain structure,[18-20] which may furthermore interact with key features of the diagnosis (eg, as indicated by IQ).[18,19] In light of this, and the fact that the 10 VBM studies we identified of adults with autism spectrum disorders largely did not address this heterogeneity, we opted to exclude autism to maximize interpretability of our results. Studies in which some patients were younger than age 18 years were included so that for the diagnoses selected all available studies were included.

Studies were selected if they (1) used VBM to analyze gray matter in patients with a psychiatric diagnosis, (2) included a comparison between these patients and matched healthy control participants, (3) performed a whole-brain analysis, and (4) reported coordinates in a defined stereotaxic space (eg, Talairach space or Montreal Neurological Institute space). This meant that any studies that only reported results after small-volume correction within a region of interest were excluded. Some studies included multiple patient groups and we included as separate contrasts each patient/healthy control participant comparison. While it is not possible to determine whether some participants in a prior publication were included in subsequent publications, this confound was minimized because we included a large number of studies that represented a diversity of authors, scanners, and institutions. It is also unlikely that this type of error would explain the existence of a common gray matter change pattern across diagnoses. Coordinates reported in Talairach space were converted into Montreal Neurological Institute space for the meta-analysis.[21]

Activation Likelihood Estimation Meta-analysis

We used the revised activation likelihood estimation (ALE) algorithm to identify consistent patterns of gray matter change across studies.[22,23] This algorithm aims to identify areas showing a convergence of reported coordinates across experiments, which is higher than expected under a random spatial association. The key idea behind ALE is to treat the reported foci not as single points, but rather as centers for 3-dimensional gaussian probability distributions capturing the spatial uncertainty associated with each focus. Then, for each voxel, the probabilities of all foci of a given experiment were aggregated, yielding a modeled activation map.[24] The union of all modeled activation maps then resulted in voxelwise ALE scores, which reflect the convergence of results at each particular location of the brain. Significant convergence was assessed by comparison of ALE scores with an empirical null distribution that reflects a random spatial association between experiments with a fixed within-experiment distribution of foci.[22] Hereby, random-effects inference was applied, which does not cluster foci within a particular study but rather as-

sesses above-chance convergence between experiments. The observed ALE scores were tested against the expectation on the ALE scores under the null distribution of random spatial association across experiments. The resulting nonparametric *P* values were then thresholded at a cluster-level familywise error–corrected threshold of $P < .05$ (cluster-forming threshold at voxel-level $P < .005$) and transformed into *z* scores for display. To identify the regions showing common gray matter changes in psychotic and nonpsychotic diagnosis groups, we conducted a conjunction analysis. That is, by using the minimum statistics under the conjunction null hypothesis[25,26] and computing the intersection of the thresholded meta-analytic maps derived from both approaches, we aimed to delineate consistent patterns of gray matter change across patient groups. The conjunction null hypothesis tests whether all effects are different from null rather than whether the combined effect is null (ie, the global null hypothesis).

Differences in activation likelihood between were tested by performing ALE separately on the experiments associated with either group and computing the voxelwise difference between the ensuing ALE maps. All experiments contributing to either analysis were then pooled and randomly divided into 2 groups of the same size as the 2 original sets of experiments (eg, findings in psychotic and nonpsychotic diagnosis groups).[27] Activation likelihood estimation scores for these 2 randomly assembled groups, reflecting the null hypothesis of label exchangeability, were calculated and the difference between these ALE scores was recorded for each voxel in the brain. Repeating this process 10 000 times then yielded a voxelwise null distribution on the differences in ALE scores between the 2 (sub) analyses. The true differences in ALE scores were then tested against this null distribution, yielding a *P* value for the difference at each voxel based on the proportion of equal or higher differences under label exchangeability. The resulting *P* values were thresholded at $P > .95$ (95% chance of true difference), transformed into *z* scores, and inclusively masked by the respective main effects (ie, the significant effects in the ALE for a particular group).

Functional Significance of the Identified Gray Matter Regions

To test whether the identified regions of common gray matter loss identified in the patient VBM meta-analysis formed an interconnected network and to understand its functional significance, we analyzed 3 large complimentary healthy participant data sets.

1. Task-Based Connectivity: Meta-analytic Connectivity Modeling

In the first healthy participant data set, we assessed the normal pattern of task-based coactivation throughout the brain for each of the VBM common gray matter loss regions. Meta-analytic connectivity modeling (MACM) assesses connectivity by determining brain areas that coactivate with a seed region across many neuroimaging experiments at a level above chance.[28] This analysis was conducted using the BrainMap database.[29-31] We constrained our analysis to functional magnetic resonance imaging (MRI) and positron emission tomographic experiments from normal mapping neuroimaging studies (no interventions and no group comparisons) in healthy

participants, which report results as coordinates in stereotaxic space. These inclusion criteria yielded approximately 7500 eligible experiments at the time of analysis.

The first step in an MACM analysis is to identify all experiments in a database that activate the seed region (ie, that reported at least 1 focus within the seed volume). Subsequently, quantitative meta-analysis is used to test for convergence across the foci reported in these experiments.[28,32] Significant convergence outside the seed, as computed using the ALE methods previously described and tested by a cluster-level familywise error–corrected threshold of $P < .05$ (cluster-forming threshold of $P < .005$), indicates consistent coactivation. Identification of overlapping regions of meta-analytic coactivation with each of the common gray matter loss region seeds was performed using the minimum statistics just described. Significance in this conjunction indicated that a region was coactivated separately with each of the seed regions (and combination) and is not sensitive to the fact that there may be an overlap between coactivated regions in one map and a seed in another map because it evaluates the conjunction null hypothesis.[25,26]

2. Task-Independent Connectivity: Resting-State Functional MRI Connectivity

In the second healthy participant data set, our goal was to determine patterns of task-independent functional connectivity patterns across the whole brain for each of the VBM meta-analysis common gray matter loss regions as seeds in a task-free resting state (RS). In total, the processed sample consisted of 99 healthy individuals between 21 and 60 years (mean [SD] age, 36.3 [11.1] years; 63 men and 36 women) with 260 echoplanar images per individual. We limited our sample to nongeriatric adults to diminish the influence of development or aging on our results. See the eAppendix in the Supplement for a description of scan parameters and processing methods for functional connectivity analyses.

The main effect of connectivity for individual clusters and conjunctions across those were tested using the standard SPM8 implementations with the appropriate nonsphericity correction. The results of these random-effects analyses were cluster-level thresholded at $P < .05$ (cluster-forming threshold at voxel level: $P < .005$), analogous to the MACM analysis. Similarly, conjunction maps were created using the minimum statistics just described to identify overlapping patterns of functional MRI connectivity across each of the common gray matter loss region seeds. Finally, a minimum statistics conjunction analysis between MACM and RS results was performed to detect areas showing both task-dependent and task-independent functional connectivity across all of the common gray matter loss seed regions. Thus, regions significant across these conjunctions were connected separately with each of the seed regions during both tasks and rest.

3. Behavioral Task Performance and VBM Gray Matter Volumes

In the third healthy participant data set, our goal was to determine whether gray matter decreases in the common gray matter loss regions predicted performance on behavioral tests of a range of cognitive functions. In total, 163 healthy individuals between 21 and 60 years (mean [SD] age, 38.2 [12.7] years; 72 men and 91 women) were drawn from the BRAINnet Foundation Database.[33,34] Exclusion criteria were any known neurological disorder, previous head injury, mental retardation, *DSM-IV* Axis I diagnosis, and history of drug dependence. See the eAppendix in the Supplement for MRI acquisition parameters and processing methods for VBM and behavioral data.

The standardized computerized behavioral performance battery included 10 tasks, probing a range of cognitive domains[35]: digit span task (working memory), span of visual memory task (working memory), trail-making task (task switching), color-word Stroop task (interference resolution), maze task (visuospatial navigation), verbal fluency task, continuous performance task (sustained attention), go/no go task (response inhibition), choice reaction time task (information processing speed), and a finger tapping task (motor speed). Performance metrics are listed in eTable 1 in the Supplement for each task.

The relationship between regional gray matter volume and behavioral performance was examined by regressing the average of z score–normalized volumes of each of the common gray matter loss regions of interest against each of the behavioral performance principal components, while controlling for age, education, sex, and their interactions because these demographics predicted either behavior or gray matter volume.

Results

### VBM Meta-analysis Across Psychiatric Disorders

Included in the meta-analysis were peak voxel coordinates from published studies that compared a psychiatric group with healthy participants, which thus represented indicators of regional gray matter volume change associated with that diagnosis (see the Methods section for study selection criteria). Our final sample included 212 comparisons between patients and control individuals from 193 peer-reviewed articles, representing a total of 7381 patients and 8511 matched healthy control individuals (eTable 2 in the Supplement). Included diagnostic groups were SCZ (including schizoaffective and schizophreniform diagnoses), BPD, major depressive disorder (MDD), substance use disorder, obsessive-compulsive disorder (OCD), and a group of several anxiety disorders combined for adequate sample size (ANX). Thus, the meta-analysis included a highly diverse sample of diagnoses from across the major categories of adult Axis I psychopathology.

Meta-analyses were conducted using the revised ALE method,[22] with a familywise error correction for multiple comparisons. Across all studies, the clear majority (85%) of peak voxels represented decreased gray matter in patients compared with control individuals. Consistent gray matter decreases in patients were found in the bilateral anterior insula, dorsal anterior cingulate (dACC), dorsomedial prefrontal cortex, ventromedial prefrontal cortex, thalamus, amygdala, hippocampus, superior temporal gyrus, and parietal operculum (**Figure 2**A and eTable 3 in the Supplement). By contrast, gray matter increases in patients were found exclusively in the striatum (eFigure 1A and eTable 3 in the Supplement).

Because one of the most fundamental diagnostic divisions in psychopathology is between primarily psychotic diagnoses (ie, SCZ) and primarily nonpsychotic diagnoses,[15,16] we next assessed for common gray matter changes across these fundamental categories. In doing so, we also ensured that our

findings were not driven by studies of SCZ, which represented nearly half of the included studies. A conservative minimum statistic conjunction across the psychotic and nonpsychotic diagnosis groups revealed significant gray matter loss in the bilateral anterior insula and dACC of both groups (Figure 2B and C; eTables 4-6 in the Supplement). Furthermore, the presence of gray matter loss in one region predicted a higher than chance probability of gray matter loss in the other regions ($\chi_1^2 > 4.3$; $P < .05$ for all),[36,37] suggesting that these gray matter losses may occur in a coordinated fashion across a structural network including these regions. By contrast, the gray matter increases in the striatum of patients were evident only in the psychotic diagnosis group (eFigure 1B and eTable 4 in the Supplement).

For follow-up analyses, we extracted per-voxel probabilities of decreased gray matter in the VBM meta-analysis for each of the 3 common regions and conducted nonparametric Kruskal-Wallis tests to examine the effects of diagnosis, age, medication, and comorbidity. The values represent the probability of identifying a gray matter abnormality for an average voxel within the region of interest derived from the modeled activation maps. We found similar magnitude effects for gray matter loss across all nonpsychotic diagnoses, as shown in **Figure 3** (Kruskal-Wallis H test: $H[4] < 3.3$; $P > .51$ for all). These effects were significantly larger in the psychotic than the nonpsychotic diagnosis group ($H[1] > 4.9$; $P < .03$ for all; see voxelwise comparison in eFigure 2A and eTable 7 in the Supplement). Gray matter differences were not related to either age at onset (reported in 106 studies) or duration of illness (reported in 148 studies) using either nonparametric correlations (Spearman rho < 0.13; $P > .18$ for all) or Kruskal-Wallis tests based on a median split ($H[1] < 0.52$; $P > .47$ for all).
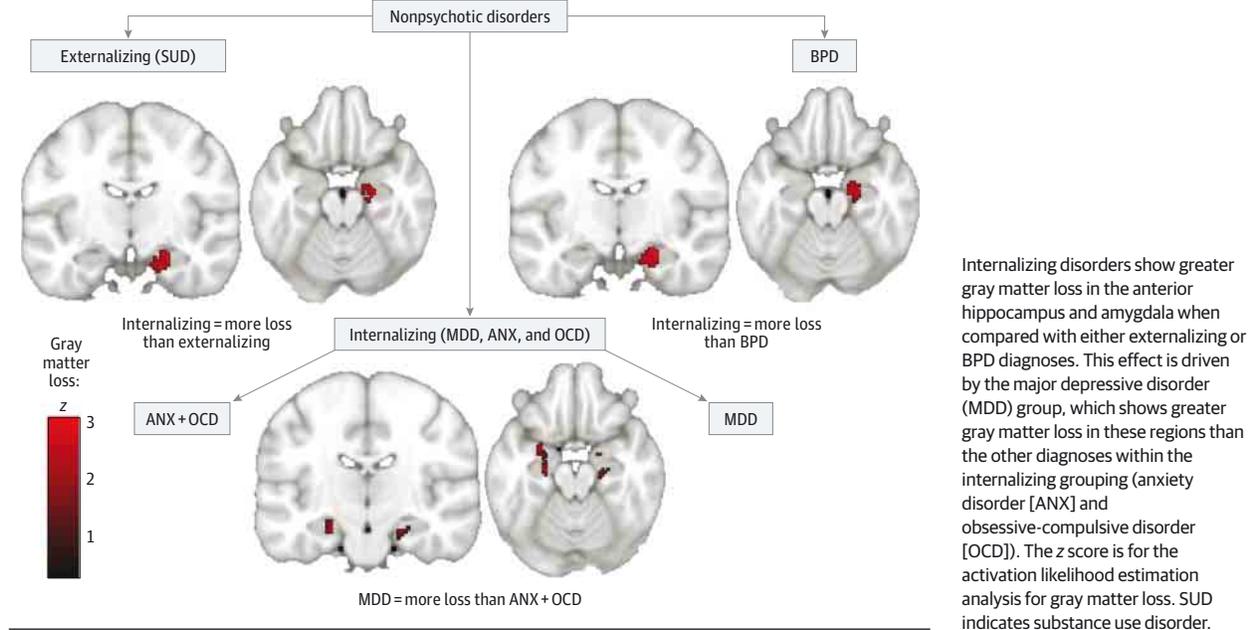
Next, we examined the potential role of medications. Within the nonpsychotic diagnosis group, 64% of studies included medicated patients; however, this did not explain insula and dACC gray matter loss ($H[1] < 0.9$; $P > .35$ for all). Within the psychotic diagnosis group, 90% of studies included medicated patients, and here too medication did not

Figure 2. Shared Patterns of Decreased Gray Matter From the Voxel-Based Morphometry Meta-analysis
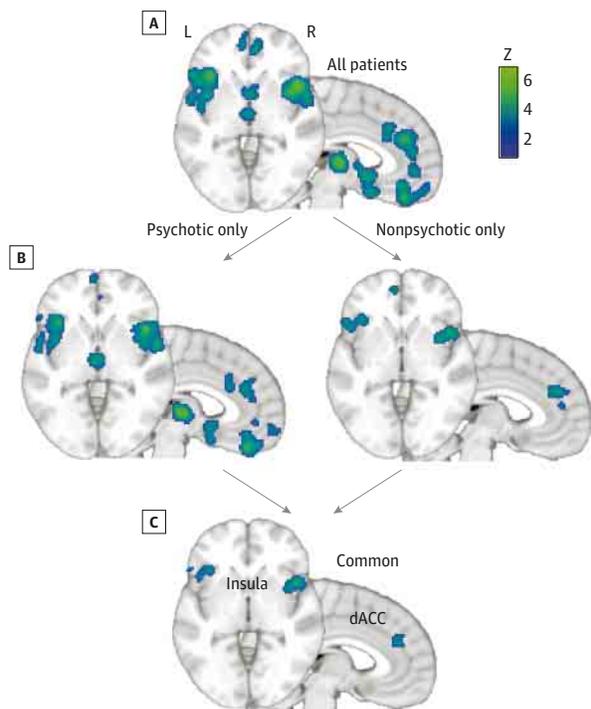
Results are from patient vs healthy participant comparisons for studies pooled across all diagnoses (A), separately by psychotic or nonpsychotic diagnosis studies (B), and from a conjunction across the psychotic and nondiagnosis diagnosis group maps in panel B (C). Results show common gray matter loss across diagnoses in the anterior insula and dorsal anterior cingulate (dACC). The z score is for the activation likelihood estimation analysis for gray matter loss. L indicates left; and r, right.

Figure 3. Extracted per-Voxel Probabilities of Decreased Gray Matter in the Voxel-Based Morphometry Meta-analysis, Separated by Individual Diagnosis and Common Gray Matter Loss Region (Left and Right Anterior Insula)
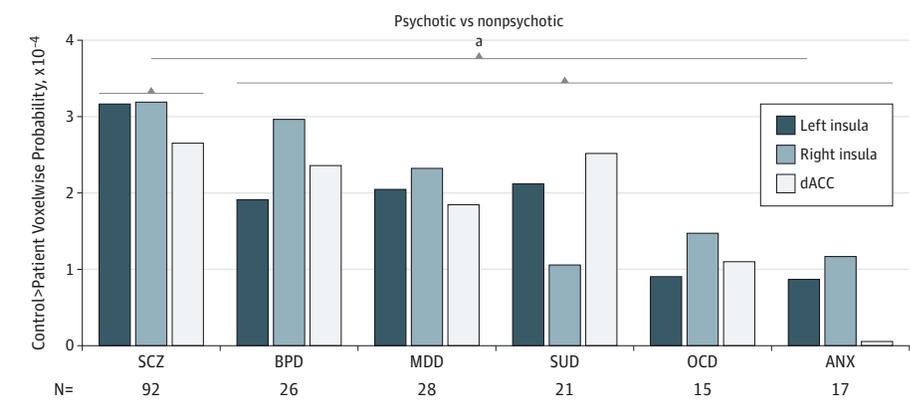
Values represent the probability of identifying a gray matter abnormality for an average voxel within the region of interest, derived from the modeled activation maps. ANX indicates anxiety disorders; BPD, bipolar disorder; dACC, dorsal anterior cingulate; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; and SUD, substance use disorder.
[a] $P < .05$ for comparison of the psychotic with the nonpsychotic disorders.

Figure 4. Voxel-Based Morphometry Meta-analysis Contrasts Between Subdivisions of the Nonpsychotic Disorder Studies Group, Broken Down by Internalizing, Externalizing, and Bipolar Disorder (BPD) Groupings

Internalizing disorders show greater gray matter loss in the anterior hippocampus and amygdala when compared with either externalizing or BPD diagnoses. This effect is driven by the major depressive disorder (MDD) group, which shows greater gray matter loss in these regions than the other diagnoses within the internalizing grouping (anxiety disorder [ANX] and obsessive-compulsive disorder [OCD]). The z score is for the activation likelihood estimation analysis for gray matter loss. SUD indicates substance use disorder.

predict gray matter loss ($H[1] < 0.7$; $P > .40$ for all). Antipsychotic medication has been associated with increases in striatal gray matter, consistent with our finding of increased striatal gray matter only in the psychotic group (eFigure 1 in the Supplement).[38-40] We have not identified reports of decreased insular volume with antipsychotic medications in either humans or animals. Reports of decreased frontal volumes (determined using a very broad region of interest)[41] in humans appear to reflect volume decreases in the lateral prefrontal cortex.[40,42] In turn, if anything, volume in midline regions located within a few centimeters of our dACC cluster were reported to be increased with antipsychotic medication.[40,43] Opposite effects of typical and atypical antipsychotics on brain volume have also been reported,[44] while other effects have not survived a correction for multiple comparisons.[45,46] Critically, the medications typically used in psychotic patients differ highly from those used with nonpsychotic patients, making it unlikely that medication could explain a common decrease in the insula and dACC across both psychotic and nonpsychotic patients.

Finally, we considered whether the common gray matter loss findings were owing to the presence of a common comorbid diagnosis among those studies reporting on comorbidity (reported in 90% of all studies). Overall, rates of comorbidity varied across diagnosis: substance use disorder, 9%; SCZ, 10%; BPD, 18%; MDD, 24%; OCD, 50%; and ANX, 58%. However, the presence of comorbidity did not account for differences in gray matter in either the insula or dACC ($H[1] < 1.7$; $P > .20$ for all). We also observed a similar pattern of common gray matter loss in the anterior insula and dACC, as just described, after excluding studies with Axis I comorbidity (eFigure 2 in the Supplement). In summary, these results suggest that anterior insula and dACC gray matter loss represent a transdiagnostic neural

abnormality evident across a wide variety of mental illnesses, most pronounced in psychosis.

In a contrast of psychotic and nonpsychotic diagnosis groups, we found that the psychotic group had both greater gray matter loss in the medial prefrontal cortex, insula, thalamus, and amygdala (eFigure 3A and eTable 7 in the Supplement), as well as greater increases in striatal gray matter (eFigure 3B and eTable 8 in the Supplement). We then further subdivided the nonpsychotic diagnosis group into 3 groupings: internalizing (depression [MDD], OCD, and anxiety disorders [ANX]), externalizing (substance use disorders), and BPD. These groupings were based on prior symptom and genetic covariation studies of the structural organization of psychiatric disorders.[13-15,17] Contrasts between these groups identified clusters in the anterior hippocampus, extending into the amygdala. Specifically, internalizing disorders had greater hippocampal/amygdala gray matter loss than both the externalizing (eFigure 3A and eTable 1 in the Supplement) or BPD (Figure 4; eTable 8 in the Supplement) diagnostic groups. This effect was driven by the MDD group, wherein we found greater hippocampal/amygdala gray matter loss than in the other internalizing (OCD and ANX; Figure 4; eTable 1 in the Supplement), externalizing, or BPD groups (eFigure 4 and eTable 1 in the Supplement).

Task-Dependent and Task-Independent Connectivity

To determine whether these common gray matter loss regions are normally part of a coherent brain circuit, we examined their patterns of task-dependent coactivation and task-independent RS functional connectivity (FC). We constructed MACMs[47] using the BrainMap database that identify above-chance task-based coactivations across thousands of neuroimaging studies in healthy individuals, given activation in one

Figure 5. Common Gray Matter Loss Regions From the Voxel-Based Morphometry Meta-analysis Are Part of an Interconnected Brain Network
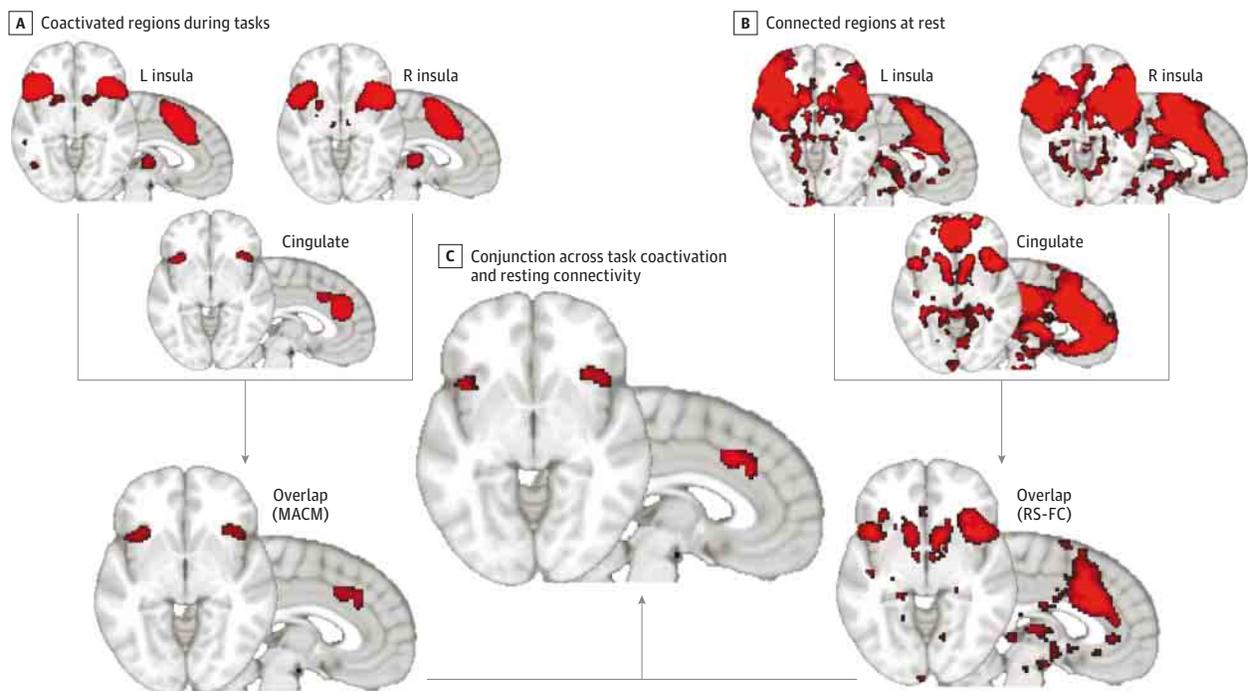
A, Meta-analytic coactivation maps (MACMs) showing regions coactivated with each of the common gray matter loss regions in healthy participant task-based activation studies in the BrainMap database, as well as a conjunction across all 3 MACM maps. B, Resting-state (RS) functional connectivity (FC) in healthy individuals seeded by each of the common gray matter loss regions, as well as a conjunction across all RS-FC maps. C, Conjunction across all of the MACMs and RS-FC map demonstrates that each of the common gray matter loss regions shows both task-dependent and task-independent FC with the bilateral anterior insula and dorsal anterior cingulate (the regions showing consistent gray matter changes) as well as the thalamus. L indicates left; and R, right.

of the identified regions of convergent gray matter loss (**Figure 5**A). A minimum statistic conjunction across the 3 MACMs (left/right anterior insula or dACC seeded) revealed overlapping coactivation in all 3 of these regions. Using RS functional MRI data from 99 healthy participants (21-60 years old), we similarly seeded each of the common gray matter loss regions in task-independent FC analyses (Figure 5B). A conjunction across the 3 RS-FC maps revealed a similar overlapping pattern of connectivity as in the MACM analysis. This overlap was further verified in a conjunction across the MACMs and RS-FC maps (Figure 5C; eTable 9 in the Supplement), which demonstrated coactivation and RS-FC with the anterior insulae and dACC for each of the common gray matter loss regions. Thus, we showed in 2 independent healthy participant data sets that the regions in which gray matter loss was observed in a transdiagnostic fashion in the VBM meta-analysis form a closely interacting functional network across a broad range of tasks and in the task-independent RS.[48]

Behavioral Correlates of Decreased Anterior Insula and dACC Structural Integrity

Among other functions, activity in the dACC and anterior insula is thought to signal events that deviate from expectations, which is then used to drive adaptive behavioral control.[48-51] Executive dysfunction is an important transdiagnostic domain of disrupted adaptive control in mental illness.[52]

Altered structural integrity of the common gray matter loss regions may predict performance on cognitive tests of executive function. To test this hypothesis, we used a separate data set of 163 healthy participants (21-60 years old) who had completed a computerized neurocognitive assessment battery that covered a broad range of basic cognitive and higher-level executive functions. Because these tasks assessed overlapping cognitive domains and because performance data are partially correlated across tasks, we conducted a data-reduction step using a principal components analysis. This resulted in the identification of 3 principal components (eTable 10 in the Supplement), which reflected general executive functioning (task switching, interference, and working memory), the specific domain of sustained attention, and combined general cognitive and performance speed (simple reaction time and finger tapping), consistent with identification of an overriding executive function factor in latent variable analyses of cognitive performance data.[53,54] We then correlated individual behavioral performance on each of these components with participant-specific gray matter volumes, measured using whole-brain volume-corrected VBM, while controlling for age, education, sex, and their interactions. After adjusting for these covariates, lower gray matter across the 3 common gray matter loss regions still predicted worse performance in terms of general executive function (standardized β = 0.24; P = .007; r^2 change over covariate-only model, 0.025; **Figure 6**A), with a

Figure 6. Relationship Between Gray Matter Volume in the Common Gray Matter Loss Regions and Performance on a Computerized Battery of Behavioral Cognitive Tests
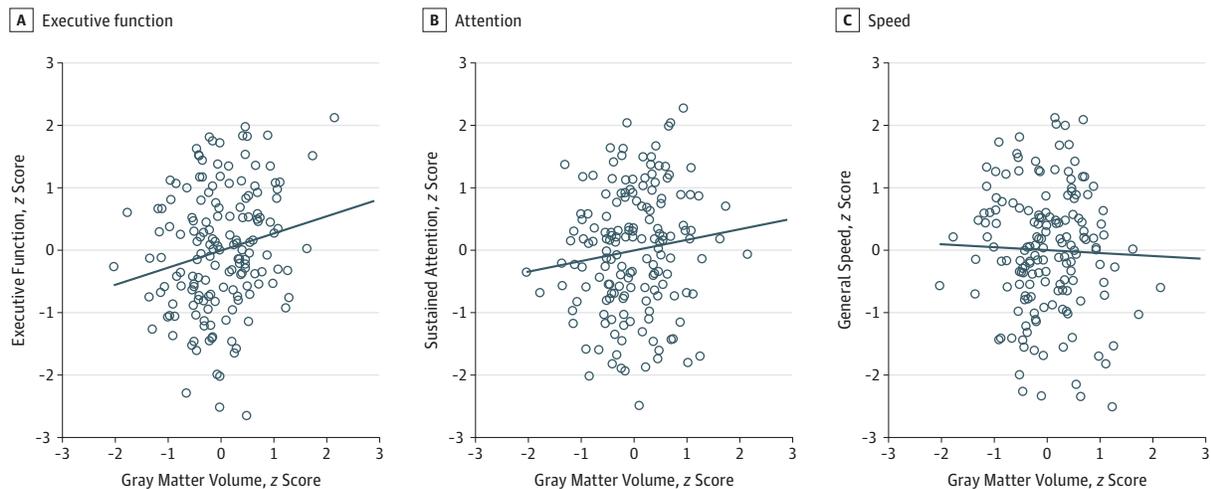
Based on a principal components analysis, cognitive test performance was reduced to 3 components: general executive function, the specific domain of sustained attention, and general cognitive performance and performance speed. Lower voxel-based morphometry–measured gray matter volume in these regions is associated with worse executive functioning (A) and a trend for worse sustained attention (B) but not general performance and speed (C).

similar-direction trend for sustained attention (β = 0.19; P = .10; Figure 6B), but no effect on general cognitive and performance speed (β = −0.06; P = .63; Figure 6C). Gray matter volume in the primary visual cortex, a control region, was not related to any of the performance measures (β < 0.07; P > .43 for all). These results suggest that lower gray matter in the common gray matter loss regions (ie, more patient-like regional volume) is associated with poorer executive functioning but not general aspects of task performance.

Discussion

In this study, we identified a transdiagnostic pattern of gray matter loss in the anterior insula and dACC across psychiatric patients, reflecting volumetric change within an interconnected network. Follow-up analyses in healthy participants suggest that decreased gray matter in these regions is associated with worse executive functioning. In contrast to this shared neural substrate, diagnosis-specific effects were found only for SCZ and depression. Secondary analyses also suggest that these findings are likely not due to medication effects or the presence of a common comorbid diagnosis across our groups.

Cognitive symptoms are part of the diagnostic criteria for many (but not all) psychiatric diagnoses. Our connection of executive functioning to integrity of a well-established brain network that is perturbed across a broad range of psychiatric diagnoses helps ground a transdiagnostic understanding of mental illness in a context suggestive of common neural mechanisms for disease etiology and/or expression. Executive dysfunction also predicts socio-occupational impairment, a central problem in the lives of many patients with psychiatric illness.[55,56] In light of these associations, it may be that

the common gray matter loss in the anterior insula and dACC accounts for this aspect of dysfunction in psychiatric disorders and perhaps less so diagnosis-specific symptoms.

While our data did not include tests of emotional processing, there may also be a relationship between the volumes of these regions and emotional perturbations, given the role of the anterior insula and dACC in emotional processing and their abnormal activation during affective tasks in at least some of the assessed disorders.[4,5,57-59] Additional emotion-related abnormalities in individuals with decreased anterior insula and dACC gray matter would only further compound their functional impairment. Moreover, graph theoretical work with RS data suggests that there may even be 2 adjacent but functionally distinct insula-dACC networks,[60] one potentially more involved in task control while the other in salience processing.

Convergent data also come from work on neurodegenerative disorders. Specific dementia syndromes have been related to regionally specific gray matter loss in well-described brain networks.[36] Of these, the anterior insula and dACC have been implicated in behavioral variant frontotemporal dementia, the most psychiatric like of dementia syndromes,[61] which can be mistaken for a psychiatric disorder early in its course.

Available evidence in SCZ and posttraumatic stress disorder suggests that insula and dACC gray matter loss may reflect the illness itself rather than a risk state. In SCZ, volume in these regions decreases with psychosis onset relative to individuals in a high-risk state.[62,63] Decreased insula or dACC volume is seen in individuals with recent-onset posttraumatic stress disorder,[64,65] but not the twin of patients with posttraumatic stress disorder, who would carry their genetic risk but not have been exposed to trauma.[66] However, there may be certain risk states in which insula/dACC volumes are reduced, such as childhood maltreatment,[67,68] which is a risk factor for most psychiatric diagnoses.

Structural neuroimaging meta-analyses have been previously reported for a number of psychiatric disorders.[3,69-83] However, these have either focused on either single diagnoses or on only 2 phenotypically closely related groups.[71,77] As a consequence, interpretation of findings has often reflected diagnosis-specific neural circuit models. Likewise, other meta-analyses have not provided spatially unbiased information across the brain (eg, in manual volumetric tracing studies).[84] In meta-analytically summarizing a more complete spectrum of psychopathology across the entire brain, our findings emphasized the biological commonalities that may have been underappreciated in prior work. Indeed, our only diagnosis-specific findings are in the association of decreased gray matter volumes with MDD[84] and association of SCZ with a combination of decreased medial prefrontal, medial temporal, and thalamic gray matter and increased striatal gray matter. The lack of an effect of comorbid disorder (which may otherwise reflect common neurobiology) may be partly owing to the fact that many investigators may have recruited more clinically pure populations. In light of the common neurobiological changes observed here, which are greatest in the disorder that is most disruptive to functioning (ie, SCZ), future work can focus on determining which aspect of the course of mental illnesses insula and dACC gray matter loss best represent. For example, the severity of an illness may be indexed by its chronicity, diagnostic comorbidity, and current symptom levels, any or all of which may be reflected in greater gray matter loss.

A few additional factors are also important to consider in interpreting our findings. First, we found no effects of current medication use on gray matter volume, and prior work examining these effects have not implicated reductions in anterior insula and dACC gray matter as a result of psychotropic medication.[38-44] Nonetheless, we cannot rule out a more subtle effect of prior medication use. Similarly, nonabuse levels of smoking, alcohol, or other drug use cannot be excluded as explanatory factors.[85] Second, comparisons between individual diagnoses may fail to yield evidence of distinct deficits by virtue of insufficient power due to limited sample size for smaller magnitude effects.

Conclusions

Our findings suggest that a general mapping exists between a broad range of symptoms and the integrity of an anterior insula/dACC-based network across a wide variety of neuropsychiatric illnesses. These results do not imply that phenotypic differences between diagnoses are negligible. Rather, they provide an organizing model that emphasizes the import of shared endophenotypes across psychopathology, which is not currently an explicit component of psychiatric nosology. This transdiagnostic perspective is consistent, however, with newer dimensional models such as the National Institute of Mental Health's Research Domain Criteria Project.[86] Although this shared neural substrate suggests common brain structural changes at some level, it is likely that these changes reflect a diverse set of etiologies. Nonetheless, the fact that common structural changes are seen despite potentially differing etiologies raises the possibility that some interventions that target the anterior insula and dACC may prove of broad use across psychopathology.

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