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Cortical similarities in psychiatric and mood disorders identified in federated VBM analysis via COINSTAC

Highlights

- COINSTAC allows for federated analyses of neuroimaging data
- Alterations in insula show possible vulnerability for multiple psychiatric disorders

Authors

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In brief

In the current study, cortical and subcortical alterations in the brains of individuals across eight different psychiatric diagnoses were examined to illustrate the use of a new open-source analysis application, COINSTAC, for federated analyses of neuroimaging data. COINSTAC allows for multiple sites and institutions to run analyses together without the need for sharing data, allowing for compliance with patient privacy. The findings showed similarities within certain brain regions across different disorders, indicating possible shared etiology.

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Cortical similarities in psychiatric and mood disorders identified in federated VBM analysis via COINSTAC

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THE BIGGER PICTURE Federated analysis is a decentralized approach used in large-scale collaborative research, which can overcome the barriers associated with sharing sensitive biomedical datasets. One such example is structural brain imaging data. These data can reveal information about alterations associated with different mental disorders, but sharing and combining such data is extremely challenging. Applying federated analysis approaches to brain imaging data could allow researchers to develop a better understanding of the physiological patterns of mental disorders while rigorously protecting the privacy of data donors.

SUMMARY

Structural neuroimaging studies have identified a combination of shared and disorder-specific patterns of gray matter (GM) deficits across psychiatric disorders. Pooling large data allows for examination of a possible common neuroanatomical basis that may identify a certain vulnerability for mental illness. Large-scale collaborative research is already facilitated by data repositories, institutionally supported databases, and data archives. However, these data-sharing methodologies can suffer from significant barriers. Federated approaches augment these approaches by enabling access or more sophisticated, shareable and scaled-up analyses of large-scale data. We examined GM alterations using Collaborative Informatics and Neuroimaging Suite Toolkit for Anonymous Computation, an open-source, decentralized analysis application. Through federated analysis of eight sites, we identified significant overlap in the GM patterns (n = 4,102) of individuals with schizophrenia, major depressive disorder, and autism spectrum disorder. These results show cortical and subcortical regions that may indicate a shared vulnerability to psychiatric disorders.

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INTRODUCTION

Mental illness can be severe, can negatively impact cognitive and social functioning, and may relate to years of suffering at the helm of misdiagnosis, medication trials, and evolving clinical presentations. Understanding the etiology and the related cortical underpinnings of these disorders can direct advances in treatment. However, another challenge is that psychotic disorders and mood disorders can have similar presentations and can overlap across multiple domains including symptoms, genetic predispositions, and regional cortical alterations.[1] A recent review of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), found that the clinical symptoms that repeated the most across diagnoses were (in order of frequency) insomnia, difficulty concentrating, hypersomnia, psychomotor agitation, and depressed mood.[2] Schizophrenia (SZ), affective disorders, autism spectrum disorder (ASD), and post-traumatic stress disorder (PTSD) all vary in presentation but share the categorization of cognitive impairments, varying affective symptoms, and behavioral dysfunction.

Structural neuroimaging studies have separately identified unique cortical alterations associated with certain psychiatric disorders, largely noting patterns of cortical deficits. Individuals with SZ have consistent regions of gray matter (GM) deficits in the bilateral insula, the anterior temporal lobe, and the medial frontal lobe,[3] whereas individuals with bipolar disorder (BP) have shown GM deficits in the medial superior frontal gyrus and gyrus rectus but more GM in the cortico-striato-cerebellar and default mode networks.[4] Psychiatric neuroimaging has also identified regions of similarities between some psychiatric disorders, indicating a possible shared cortical underpinning. Even between SZ and BP, similar brain correlates were identified in the bilateral insula, cingulate gyrus, cerebellum, thalamus, vermis, and supplemental motor cortices.[5,6] A voxel-based morphometry (VBM) study found more GM concentration in the putamen of individuals with diagnoses of PTSD, unipolar depression, psychosis, and obsessive-compulsive disorder and that this finding was correlated with symptom severity.[7] Common patterns of GM deficits in the dorsal anterior cingulate and bilateral insula were identified in a meta-analysis of voxel-based studies comparing SZ, BP, unipolar depression, addiction disorders, obsessive-compulsive disorder, and anxiety disorders.[8] Given the overlap in symptom presentations and, specifically, the similarities in GM alterations, some of these disorders may have a common neuroanatomical basis that may branch into different diagnostic categories. In this study, we sought to examine the unique and similar cortical alterations across eight different psychiatric and developmental diagnoses (described below) using a federated analysis approach.

Psychiatric disorders and their related symptoms

SZ is characterized by cognitive, behavioral, and emotional dysfunction.[1,9] Symptom presentations include varying combinations of positive symptoms (hallucinations, delusions), negative

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symptoms (anhedonia, apathy, low mood), cognitive dysfunction (difficulties with abstract thinking, memory deficits, disorganized thinking), and abnormal motor behavior (agitation or catatonia). Structural neuroimaging studies found regional GM reductions throughout the cortex,[3,10–12] with the largest GM effects identified in the superior temporal gyrus[3] and the cerebellum[13] in individuals with SZ.

BP is a mood disorder marked by extreme polar mood states, from depression and hypomania to mania.[1] BP has different classifications defined mainly by severity of mood states; for example, type I indicates fluctuation from depressed to manic states, and type II indicates fluctuations from depressed to hypomanic states.[1] Both BP and major depressive disorder (MDD) can present with impaired cognitive abilities, appetite changes, and psychosis.[14] Structural neuroimaging shows similar volumetric reductions across the cortex in BP to those identified in SZ with smaller effect sizes.[6,15–17]

MDD is another prevalent mood disorder associated with negative symptoms of anhedonia, apathy, and low mood.[1] MDD is the leading cause of disease burden worldwide and has a lifetime prevalence of 5%–17%.[18] Structural studies show inconsistent findings in MDD in the hippocampus and amygdala, with a caveat of smaller volumes largely being attributed to age more than the disorder. However, advanced brain aging was observed across the cortex in MDD.[19–22]

PTSD is categorized under the stress-disorder group in the DSM-5 and can develop after a person has experienced one or more traumatic events.[1] PTSD symptoms typically present along four clusters: re-experiencing or trauma memory reliving, avoidance, persistent negative emotions or cognitive biases, and sleep disturbances largely related to hyperarousal.[1] The prevalence rate of PTSD in the US is 3.6%, with females presenting with higher rates (5.2%) than males (1.8%).[23] The trauma association with PTSD has resulted in numerous imaging studies focusing on regions of interest related to fear/threat circuitry, particularly the amygdala and hippocampus, where volumes are largely reduced when compared to healthy controls (HCs).[24–26] In addition to the fear circuit, significant effects of PTSD have also been identified in the insula, anterior cingulate cortex, superior frontal gyrus, and temporal gyri.[25]

ASD is a development disorder that lies along a spectrum of deficits in social communication, repetitive behaviors, and cognitive deficits.[1] The current prevalence of ASD in the US is estimated at one in every 59 individuals.[27] Structural MRI studies have identified increases in the cortical thickness of the frontal lobe and reduced cerebellar volume in individuals with ASD. However, there are also inconsistent findings reported across the cortex, including both increases and decreases in the hippocampus, amygdala, basal ganglia, and thalamus.[28]

Mild cognitive impairment (MCI) is defined as cognitive decline that is greater than expected (given age and education) but does not significantly impact or interfere with functioning.[1] Current estimates of prevalence range from 3% to 19% in adults older than 65 years.[29,30] MCI is considered a risk state for dementia because more than half of individuals diagnosed with MCI progress to some form of dementia within 5 years. There is limited research focused solely on MCI, but structural studies have identified nodes specific to MCI (as opposed to Alzheimer's disease) within the parietal lobe, cerebellum, and occipital lobe.[31]

Comorbidity across diagnoses

Although these disorders are classified as separate diagnoses, there are many symptoms and genetic and neuroanatomical features that are shared by multiple disorders. Previous studies have even examined the DSM to explore possible comorbidity among diagnoses.[32,33] The symptoms of sleep disturbance, difficulty concentrating, psychomotor agitation, and depressed mood overlap across several psychiatric disorders including, but not limited to, SZ, MDD, PTSD, and BP.[2] There is also symptomatic overlap between SZ and ASD; both disorders can present with deficits in social cognition and have a male sex bias.[34,35]

There are also common genetic and structural features that have been identified between SZ and BP.[6,36–39] Structural neuroimaging studies have identified similarities in the regions of GM deficits in individuals with SZ and BP.[5,40–43] These two disorders may be better described along a continuum of varying cognitive deficits and psychoses.[44,45] The genetic variations shared between SZ and BD is 15%, between BD and MDD is 10%, and between SZ and MDD is 9%.[37] In addition to similarities, there are often comorbid presentations across disorders. MDD is the most commonly seen in individuals with PTSD when compared to all other psychiatric disorders.[46] Although, it should be noted that there is some evidence that depressive and anxiety disorders may increase the risk for PTSD, and vice versa.[47] Therefore, the comorbidity may not be the presentation of independent disorders but more a shared etiology, shared set of risk factors, or even symptom overlap. Future research is needed to examine the shared and unique cortical alterations of these disorders.

Unaffected relatives

Unaffected relatives of individuals with psychosis have shown inconsistencies in cognitive tasks, with some relatives having similar impairments to those affected and some performing similarly to HCs.[48,49] Structural studies identified the left orbitofrontal cortex and right cerebellum as regions in both individuals with BP and relatives of individuals with BP that were significantly smaller than HCs.[50] In fMRI studies, striatal dysfunction was related to poorer performance in individuals with SZ; however, in the unaffected relatives, this same dysfunction was thought to relate to a compensatory pattern because it was not related to poor performance.[51] Given these presentations, unaffected relatives may offer insight into both a heritable risk load and correlates of resistant factors associated with psychiatric disorders.

Federated approaches

Single studies tend to have small effects, masking true results or even leading to false results. Open data and consortia like ENIGMA have helped move beyond these limitations, but there are many datasets (often highly relevant clinical datasets) that are unable to be openly shared (or shared at all) and high-dimensional (e.g., voxelwise analysis) or iterative approaches (e.g., classification/machine learning) that are challenging or impossible to perform using a manual consortia approach. Federated analysis as in the Collaborative Informatics and Neuroimaging Suite Toolkit for Anonymous Computation (COINSTAC) tool mitigates this issue by allowing analysis of

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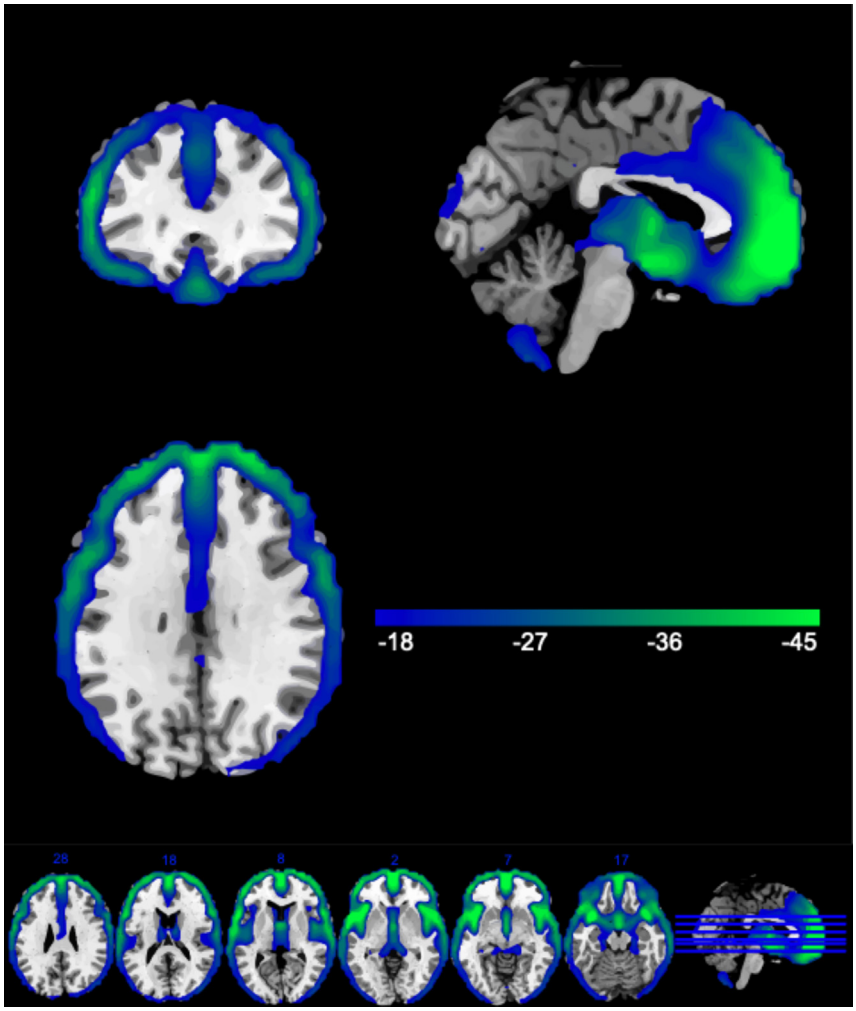

Figure 1. Gray matter alteration in schizophrenia

Alterations in the gray matter of individuals with schizophrenia when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

data that would be otherwise inaccessible, hence increasing the sample size, without moving data from their original location or exposing the individual subject data to the other consortia members.[52]

The aim of this project was to leverage federated analyses to examine transdiagnostic presentations in individuals with SZ, BP, MDD, PTSD, MCI, or ASD or unaffected relatives of individuals with psychosis with the aim of uncovering possible relatedness and distinct mechanisms underneath their respective diagnoses.

RESULTS

In general, comparing across the diagnoses, there was common tendency of GM concentration reductions in the disorder groups except for the unaffected relatives. The GM reductions were largely seen in the bilateral insula, medial prefrontal cortex, parahippocampal gyrus, and rectus. Below is a breakdown of the results for each diagnostic category. All results listed below are compared to HCs.

SZ results

Individuals with SZ (n = 572) had global reductions across the entire cortex when compared to HCs and had the largest effect size of any diagnosis. The results showed reduced GM concentration in the bilateral insula, cingulate, parahippocampal gyrus, and ventromedial prefrontal cortex compared to HCs. See Figure 1 for more details.

BP results

Individuals with BP (n = 121) showed GM concentration reductions centered around the bilateral insula and ventromedial prefrontal cortex; these reductions were similar to those identified in SZ but to a smaller effect. There was also a small cluster of GM reductions in the occipital lobe. There were no areas of increased GM concentration in these individuals compared to HCs. See Figure 2 for more details.

MDD results

Individuals with MDD (n = 44) had clusters of reduced GM concentration in the bilateral insula, bilateral cerebellum, cingulum, rectus, and medial prefrontal cortex (peak of cluster: x = 1, y = 55, z = −6). There were no clusters of increased GM concentration when compared to HCs. See Figure 3 for more details.

PTSD results

Individuals with PTSD (n = 32) had less GM concentration in the cingulate, precuneus, left insula, retrosplenial cortex, and bilateral superior occipital gyrus. There were clusters of increased GM identified in the bilateral superior parietal lobules (peak of R cluster: x = 25, y = −55, z = 62). See Figure 4 for more details.

ASD results

Individuals with ASD (n = 88) had small clusters of GM reductions in the bilateral insula, parahippocampal gyrus, and Heschl's gyrus. There were also reductions identified in the olfactory and fusiform gyri. Individuals with ASD showed a small cluster of GM increase in the right putamen and cerebellum IX. See Figure 5 for more details.

MCI results

Individuals with MCI (n = 259) also had global reductions in subcortical regions but with a smaller effect size than individuals with SZ. Results showed reduced GM in the bilateral hippocampus, cerebellum VI, Crus I, amygdala, cingulum, and bilateral insula. There

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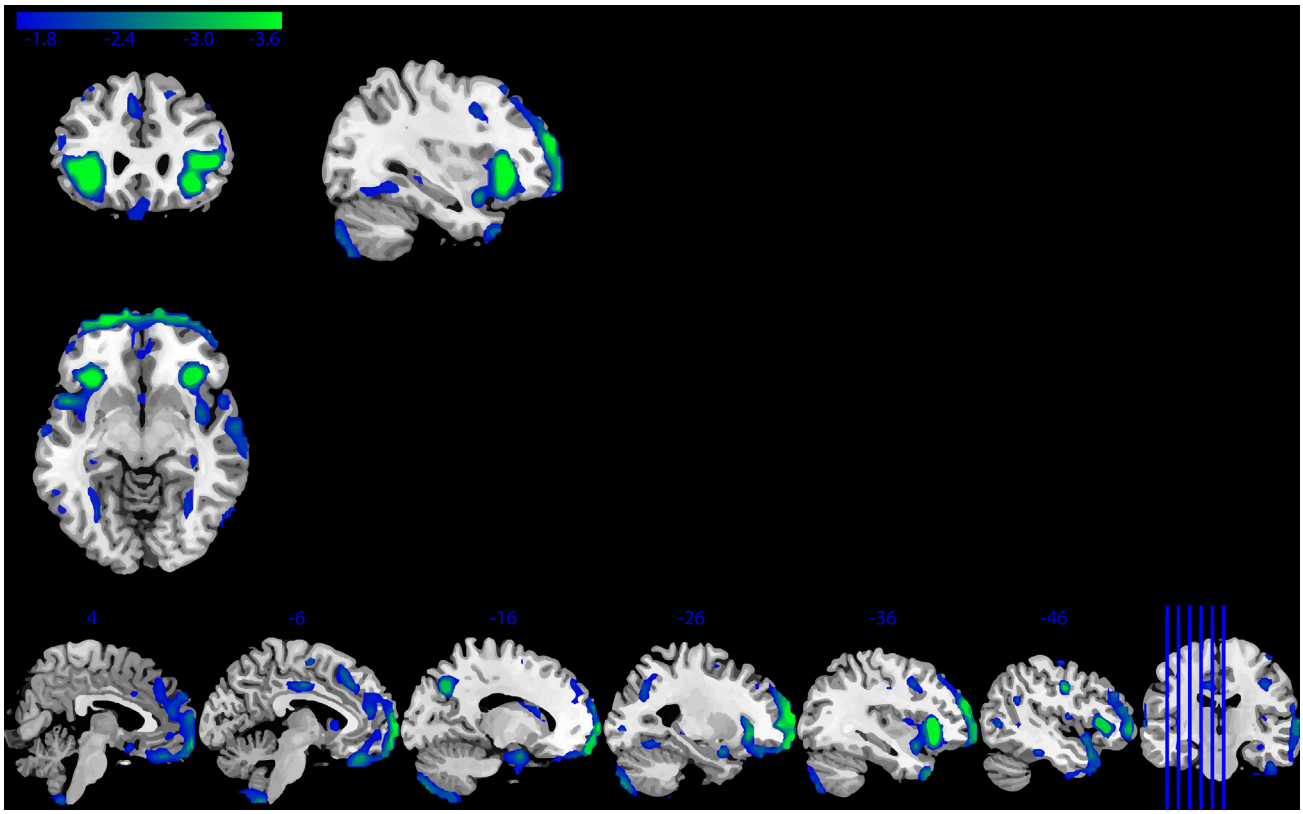

Figure 2. Gray matter alteration in bipolar disorder

Alterations in the gray matter of individuals with bipolar disorder when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

were no notable increases in GM concentration. See Figure 6 for more details.

Spectrum results

Individuals classified as spectrum ($n = 96$) showed GM increases in the bilateral pallidum and putamen and the left inferior occipital lobe. There were decreases in the GM of the bilateral insula, temporal poles, ventromedial prefrontal cortex, and cingulum. See Figure 7 for more details.

Unaffected relatives

Individuals with first-degree relatives with psychosis ($n = 147$) had one of the only patterns of global GM increase across the cortex. Results show GM increases in the temporal poles, supplemental motor regions, cerebellum VI, precuneus, and occipital lobes. There was also a small cluster of GM reductions in the right hippocampus. See Figure 8 for more details.

Spatial correlations

The spatial correlations are displayed in a heatmap distribution in Figure 9. There was an overall significant positive correlation between the groups at the whole-brain level: SZ and the spectrum group ($r = 0.79$), SZ and MDD ($r = 0.72$), and ASD and SZ ($r = 0.69$). As mentioned above, individuals with SZ had global reductions across the entire cortex. Individuals with MDD had GM reductions in the cingulum, bilateral insula, rectus, amygdala, and Heschl's gyrus. SZ and MDD overlapped in the bilateral insula (peak: x = 37, y = 11, z = −12) and the medial prefrontal cortex. SZ and spectrum overlapped in a similar pattern: both groups had reduced GM concentration in the bilateral insula, ventromedial prefrontal cortex, and cingulum. SZ and ASD overlapped in GM reductions in the olfactory bulb, parahippocampal gyrus, and, to a lesser extent, bilateral insula.

Unaffected relatives showed general increases in GM across the cortex and therefore were anticorrelated with ASD ($r = -0.13$), SZ ($r = -0.29$), and, to a lesser extent, MDD ($r = -0.09$). Individuals with PTSD were largely uncorrelated with all other disorders, even though there were decreases observed in the left insula and bilateral superior occipital gyrus. Individuals with PTSD were positively correlated with unaffected relatives ($r = 0.31$). Overlap between unaffected relatives and PTSD was largely seen in the superior parietal lobule, motor region, and posterior insula.

Post hoc analysis

We completed a subsequent post hoc analysis on the spatial correlations with individuals with MCI removed because of the potential for cognitive deficits to underlie psychiatric disorders (Figure 10). The directionality did not change for any correlation. In the post hoc analyses, unaffected relatives were more anticorrelated with spectrum ($r = -0.24$), SZ ($r = -0.37$), MDD ($r = -0.16$), and ASD ($r = -0.23$).

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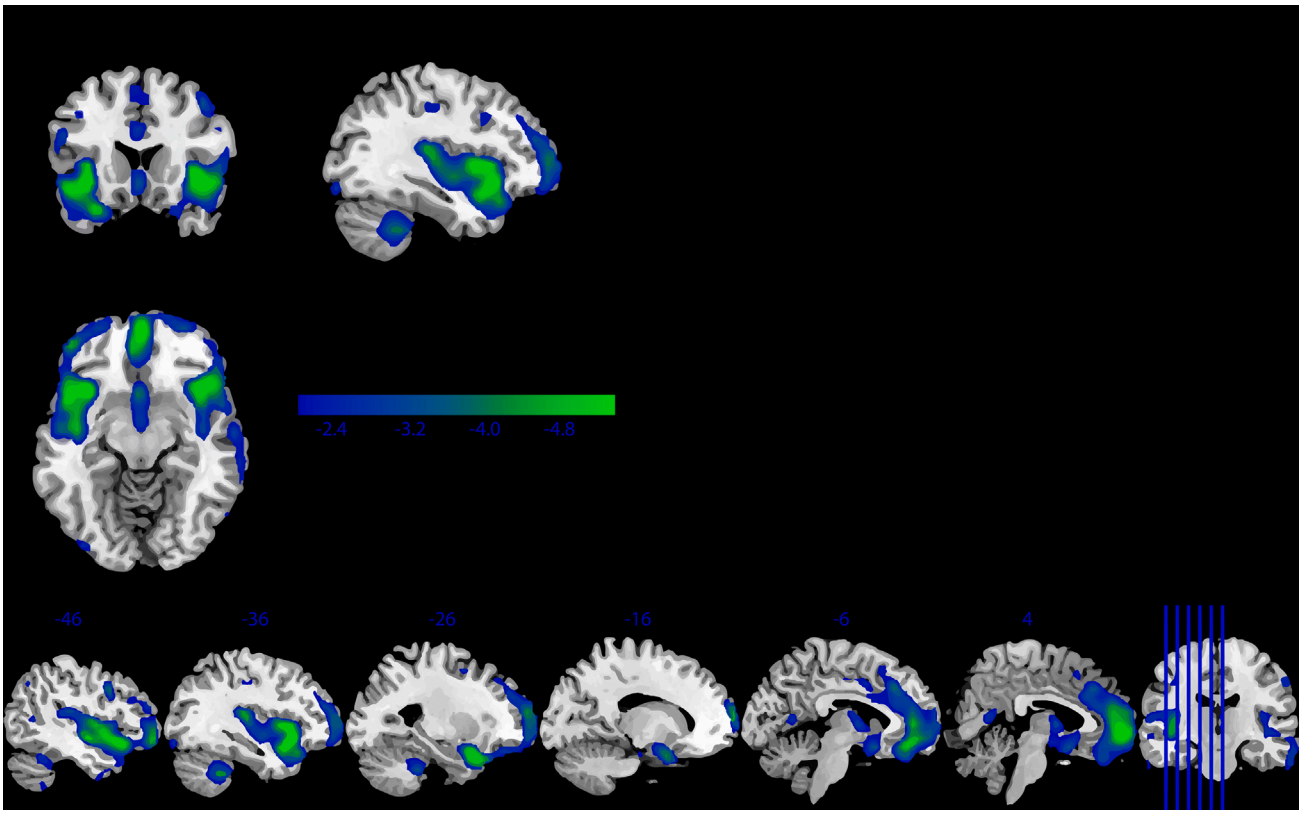

Figure 3. Gray matter alteration in major depressive disorder

Alterations in the gray matter of individuals with major depressive disorder when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

DISCUSSION

The goal of this paper was to examine the underlying neuroanatomic alterations across several diagnostic categories, as well as similarity to one another via a decentralized analysis of large datasets across multiple sites. Examination across multiple disorders allows for identification of possible interdiagnostic similarities as well as a possibly protective finding by comparing healthy volunteers to all diagnostic groups. In the current large-scale cross-disorder study, we identified both shared and disease-specific GM alterations in SZ, BP, MDD, ASD, MCI, and PTSD. In comparing healthy volunteers to each diagnostic category, we identified regions of significant GM reductions spanning the bilateral insula, hippocampus, and prefrontal cortex that showed significant differences when compared to healthy volunteers.

Individuals with SZ had the largest effect size of all diagnostic groups and overall global reductions throughout the cortex when compared to HCs. Our results largely support previous SZ findings of GM reductions in the bilateral insula, prefrontal cortex, and cerebellum and across the limbic system.[3,53,54] Individuals with MDD had a similar GM pattern to SZ, with strong correlation between these spatial *p* value maps. Previous studies have reported that initial, prodromal symptoms of SZ are low mood and anhedonia. Our findings support the notion that these disorders may have a similar neuroanatomical underpinning.

Individuals with PTSD did not have significant overlap in affected cortical regions with any other examined disorders. The alterations in PTSD appear unique and may indicate that PTSD is dissimilar to other psychiatric disorders in terms of biological basis. We found that the retrosplenial cortex was an area of reduced GM concentration in individuals with PTSD. The retrosplenial cortex has been identified as a region relating to multiple sensory functions including navigation.[55] The anatomical location also indicates that it is a bridge for regions involved in sensorimotor processing and spatial processing. A recent review categorized the main functions as perspective shifting across a multitude of spatial reference frames and prediction updating and generation from highly complex spatiotemporal contexts.[55] Given the unique nature of PTSD developing following a traumatic experience, the alterations we observed may be related to a stress response and not just a biological vulnerability to psychiatric disorder. In our study, there was an unexpected positive correlation between PTSD and unaffected relatives, with significant overlap identified in increased GM in the superior parietal lobule. The superior parietal lobule has been identified as a hub for visual and sensory input, which may relate to some of the symptoms of PTSD (e.g., hypervigilance).[25,56]

A recent study identified increases in the bilateral putamen of multiple psychiatric disorders when compared to HCs.[7] Interestingly, this volumetric increase was also identified within their unaffected relatives.[7] We also found a significant cluster in the left putamen in our group of unaffected relatives. The putamen is

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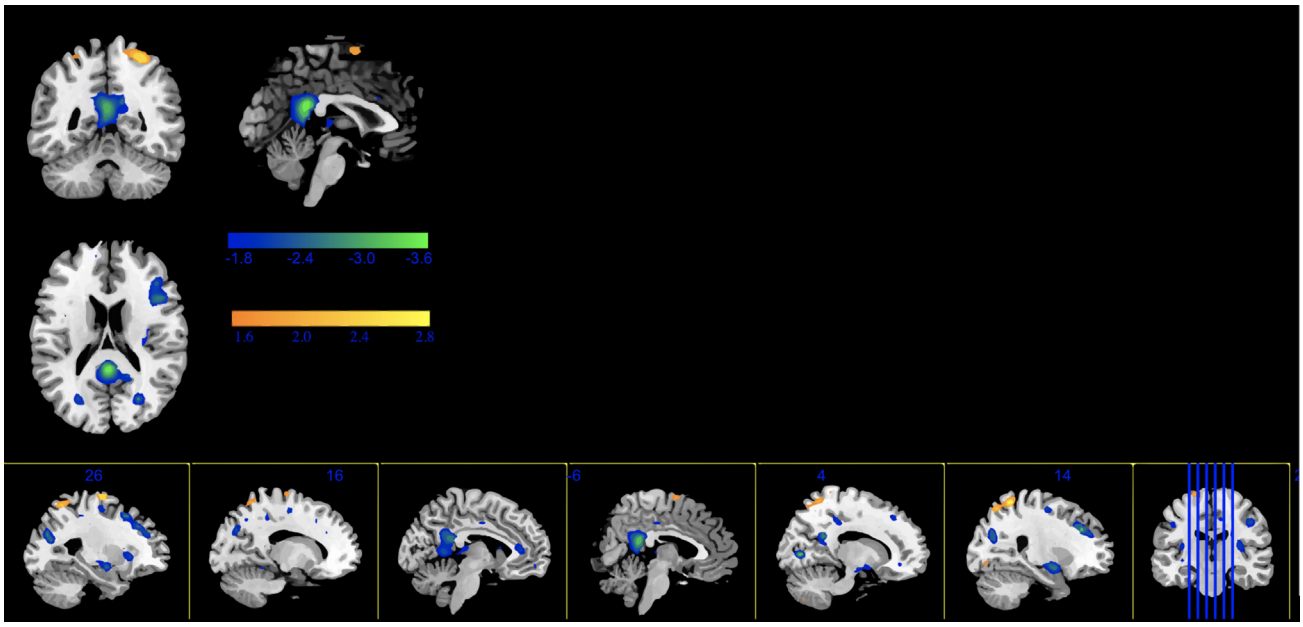

Figure 4. Gray matter alteration in post-traumatic stress disorder

Alterations in the gray matter of individuals with post-traumatic stress disorder when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

thought to serve as a center for the integration of high-level cognitive, motor, and limbic processes by receiving afferent inputs from other cortical regions and then transmitting them back to the neocortex through the thalamus.[57] Given these functions, dysregulation of this region is thought to underlie the emergence of some of the more severe cognitive and clinical symptoms in psychiatric disease.[58] Previous studies have reported larger GM volume in the putamen of individuals with SZ relative to HCs.[59,60] Our results showed a significant increase in GM concentration in the putamen of unaffected relatives and, to a much smaller extent, in individuals with SZ, ASD, and spectrum.

Significant findings in the insula

In our study, the insula was identified as an affected region in SZ, BP, MDD, ASD, PTSD, spectrum, and MCI. These findings are not surprising given the functionality of the subregions of the insula: the anterior and posterior insula.[61] The anterior lobe has largely been associated with executive control and sensory processing.[62–64] Dysfunction in this region may relate to altered orientation toward salient information, an often referenced explanation for psychosis as well as ASD. In functional studies, the anterior insula cortex was activated during errors in performance and error awareness.[65–67] Specifically, the insula-cortico-thalamic circuit, including the dorsal and ventral areas of the anterior insula, is responsible for both error awareness and the processing of salience.[65] In addition to motivated behaviors, the insula is also considered significant for attention and emotional regulation. The anterior insula has a significant role in empathy, and previous functional MRI studies have reported activation in this region in response to seeing other individuals in pain as well as to expressions of extreme emotions (e.g., fear and happiness) in others.[68] The dorsal mid-insula is also responsible for interoception, the detecting and regulating of the body's internal state.[69] Disruptions in interoceptive processing have previously been linked to multiple psychiatric disorders and a vulnerability to certain psychiatric symptoms.[64,70–73] In SZ, previous research found reduced connectivity in the insula and that differences in those connectivity profiles were related to different symptom profiles.[74] Taken together, our results and previous research indicate that the bilateral insula, with its numerous roles and connections to other vital subcortical regions, may have a pathological role in psychiatric disorders.[75–78] Future research should explore the association of the insula and its related networks in not only SZ but other psychiatric disorders.

Other regions identified within this study as potential regions of biological vulnerability support the long list of previous literature examining structural alterations in psychiatric disorders. Even in disorders with significant phenotypic heterogeneity (e.g., SZ), we were able to identify consistent alterations within the rectus, which has previously been associated with a genetic risk for SZ, BP, and psychosis,[79] and the cerebellum, with varying regions associated with cognitive losses (e.g., long-term and working memory) and psychosis.[13,80,81] Our findings within the hippocampus are also aligned with previous literature[82–85] that found reductions within MDD, BP, and SZ. Other cross-disorder studies found similar shared and disease-specific alterations in the hippocampus, amygdala, thalamus, and accumbens of individuals with SZ, BP, and MDD.[86] Future research is needed to examine these alterations in the whole-patient context to identify their relationships to cognitive and social functioning, course of illness, and medication.

Limitations of the study

There are a few limitations in this study. To start, the current study is cross-sectional in design; therefore, the potential changes in

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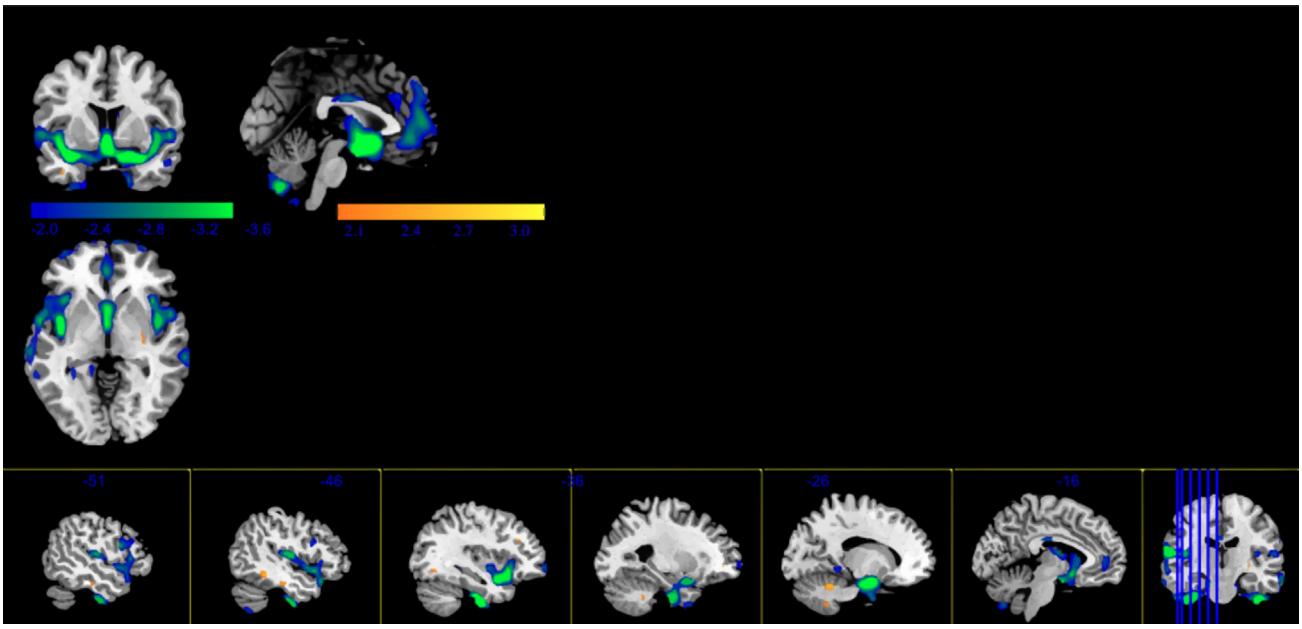

Figure 5. Gray matter alteration in autism spectrum disorder

Alterations in the gray matter of individuals with autism spectrum disorder when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

alterations over the course of disorder were not examined. Future studies should explore cross-disorder presentations using longitudinal approaches. Next, we did not examine additional social and environmental determinants such as duration of illness, medication, symptom profiles, race/ethnicity, or socio-economic status, as these factors were not a focus of the current study. We acknowledge that these factors may have significant impacts on diagnostic presentations and GM alterations. Future research should examine these differences further and could also benefit from directly comparing disorders to each another (as opposed to all disorders compared to HCs), a method we were not able to explore in the current study given insufficient power. In addition, given the federated analysis model, we only have the visual results for the site-specific effects and do not have the variance on those effects. Future research should examine the variance across the regression model averages. We also did not match the groups for age or sex and acknowledge that there were significant variations in those demographics across each diagnostic group. However, our results still showed significant differences across diagnostic groups, indicating valid representation of GM alterations among different disorders. The inclusion of age and sex on the regression models may have ameliorated the impact of these cohort differences to some extent, as our findings were still significant after accounting for these covariates.

Conclusions

Through federated analyses within COINSTAC, we were able to identify GM patterns that were disorder specific as well as those that overlapped across different psychiatric disorders. Overall, the findings followed a pattern of GM reductions in all examined disorders. The reductions were largely seen in the bilateral insula, medial prefrontal cortex, parahipppocampal gyrus, and rectus. There were some noted increases in GM concentration in the regions of the putamen and pallidum. We identified consistent overlap in alterations within the insula across all disorders. Given the functionality of the insula, we hypothesize that this region may play a critical role in the vulnerability to psychiatric disorders. We acknowledge that there is likely not a single point of vulnerability or deficit within the cortex that will solely explain the presence of a specific psychiatric disorder, let alone all mental illnesses. However, transdiagnostic comparisons allow for greater understanding of the physiological and neuroanatomical bases of psychopathology and our results, which show an overlapping pattern within the insula across SZ, ASD, MDD, BP, PTSD, and MCI, which may point to a transdiagnostic locus of disruption. COINSTAC allowed for this federated approach and may be a useful tool for classification models or additional transdiagnostic analyses in the future.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Kelly Rootes-Murdy, PhD is the lead contact and corresponding author (rootesmurdy@gmail.com).

Materials availability

Not applicable.

Data and code availability

COINSTAC and our source code are available at GitHub (https://github.com/trendscenter/coinstac) and have been archived at Zenodo.[87]

Methods

We performed a large-scale multisite meta-analysis of GM concentration alterations in seven psychiatric and developmental disorders and unaffected relatives compared to HCs using COINSTAC (http://coinstac.trendscenter.org).

Participants

This study included data from 4,102 individuals: 572 individuals with SZ, 259 individuals with MCI, 147 unaffected relatives of an individual diagnosed with psychosis, 121 individuals with BP, 96 individuals classified as spectrum (further

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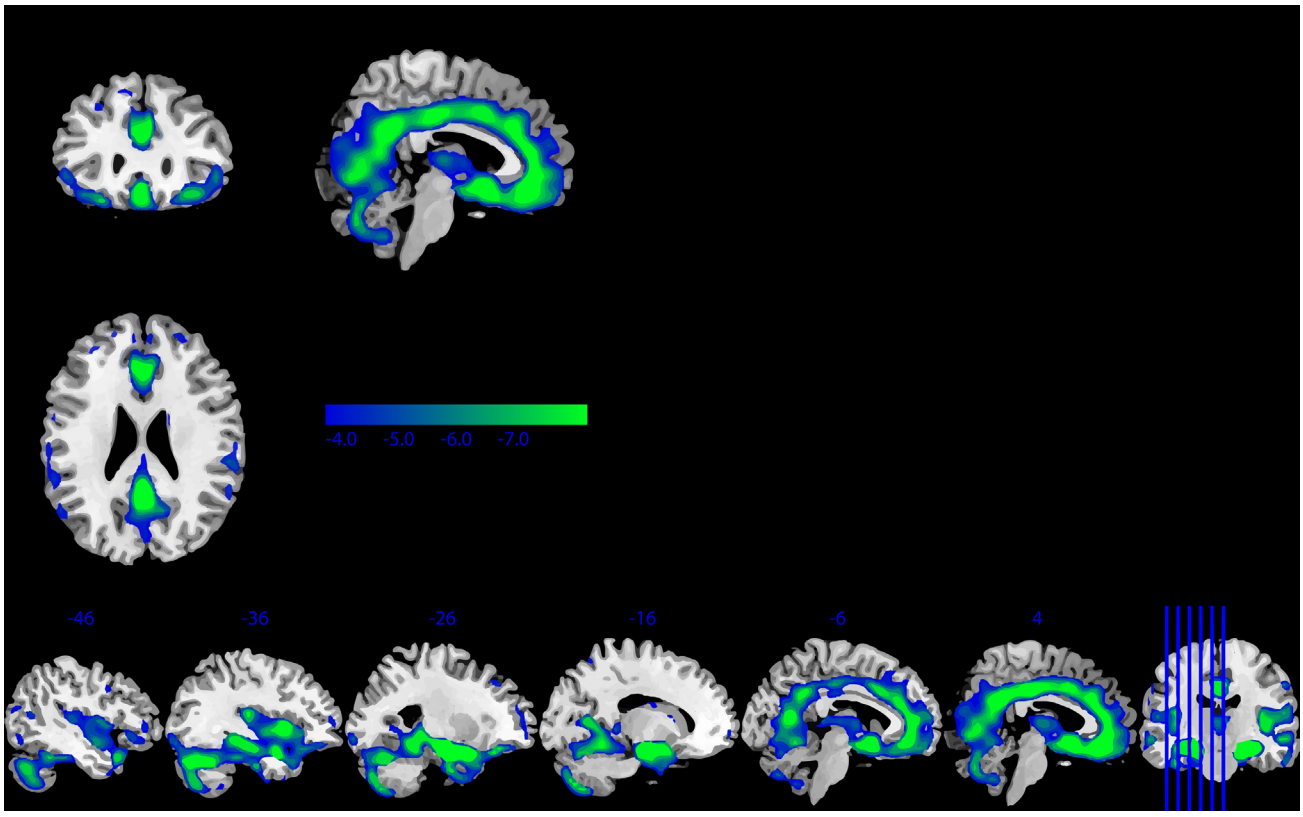

Figure 6. Gray matter alteration in mild cognitive impairment

Alterations in the gray matter of individuals with mild cognitive impairment when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

information about this category can be found in the supplemental experimental procedures), 88 individuals with ASD, 44 individuals diagnosed with MDD, 32 individuals with PTSD, and 2,743 HCs from the following datasets, many previously described in the literature: 1000 BRAINS study (1000BRAINS[88]), the Australian Schizophrenia Research Bank,[89] Emory University Grady Trauma Project,[90–92] Imaging Genetics in Psychosis,[93] Centre for Healthy Brain Aging-Sydney Memory and Aging Study,[94] Older Australian Twins Study,[95] Cognitive Genetics Collaborative Research Organization consortium,[96] and Bipolar Kids and Sibs-Sydney.[97] Diagnoses were confirmed by clinical physicians at each respective site as part of the study's protocol (note that in the population-based cohort 1000BRAINS, a dementia screening test was employed to detect individuals with suspected cognitive impairment [DemTect score < 12[98]]; please refer to the supplemental experimental procedures for more details). All data were collected under the approval of local institutional review boards, and all participants provided informed consent. The original study designs are described in previous publications (cited above). See Table 1 for more details on participant information including age, sex, and diagnostic breakdown from each site and see the supplemental experimental procedures for the participant inclusion and exclusion criteria for each site.

MRI dataset acquisition and preprocessing

T1-weighted scans were obtained at the eight sites with varying MRI field strength and vendors. Details regarding MRI acquisition and sample demographics can be found in Table 2. Individual sites obtained approval from local institutional review boards, and informed consent was obtained at the time of the original study. All preprocessing steps were completed within the COINSTAC (https://coinstac.org/)[99,100] federated analysis tool (see below for description). All T1-weighted images used the following preprocessing protocol for data harmonization. Images were coregistered and normalized to the standard Montreal Neurological Institute template using a 12-parameter affine model, resliced to a voxel size of 2 × 2 × 2 mm and segmented into GM, white matter, and cerebrospinal fluid using Statistical Parametric Mapping 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). All images were smoothed at 10 mm FWHM prior to analyses. The preprocessing resulted in a total of 4,102 GM concentration images.[76,101]

COINSTAC

In the current study, we examined the GM alterations using the COINSTAC tool.[52,99,100] Briefly, COINSTAC (https://coinstac.trendscenter.org) is an open-source, decentralized analysis application that provides a venue for analyses of neuroimaging datasets without sharing any individual-level data while maintaining granular control of privacy. COINSTAC has been utilized for multiple decentralized approaches, circumventing the need for pooling data. Instructions for installing the application and running analyses can be found online at https://github.com/trendscenter/coinstac-instructions. See Figure 11 for a breakdown of the COINSTAC architecture.

In this study, eight global sites contributed T1-weighted images (n = 4,102) for a VBM analysis within the COINSTAC platform. Data harmonization was completed using the COINSTAC software with all the sites using the same preprocessing pipeline, and then all scanning sites were added as covariates to the regression models. The regression models were also run in COINSTAC, allowing sites to perform all computations on their local data, and intermediate results were collected by a cloud-based "private aggregator," which synthesized the results and returned them to the sites. The -log(*p*) maps of each diagnostic GM image were compared to one another using spatial correlations to examine cross-diagnostic similarities and differences.

General linear regressions

We employed a general linear model on all normalized and smoothed GM images to associate each diagnosis with voxelwise GM concentration,

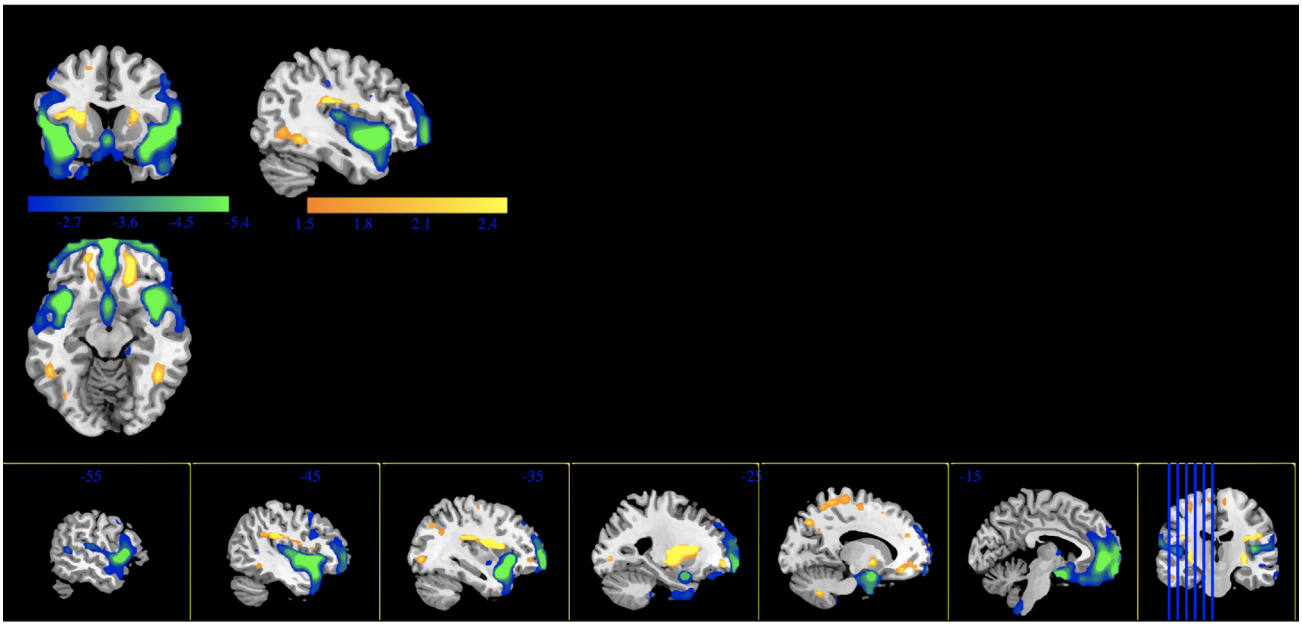

Figure 7. Gray matter alteration in spectrum

Alterations in the gray matter of individuals identified with a spectrum disorder when compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

controlling for age, sex, site, and apolipoprotein-E allele classification. Each diagnostic category was compared separately, resulting in eight separate regression models. Following the regressions, the -log(*p*) maps of each diagnostic GM image were compared using spatial correlations.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.patter.2024.100987.

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AUTHOR CONTRIBUTIONS

K.R.-M., S.M.P., A.D.S., and V.D.C. designed the study. S. Panta, J.R., R.K., and K.R.-M. acquired and analyzed the data. K.R.-M., S. Panta, and V.D.C. wrote the article, which all authors reviewed. All other authors contributed data, and all authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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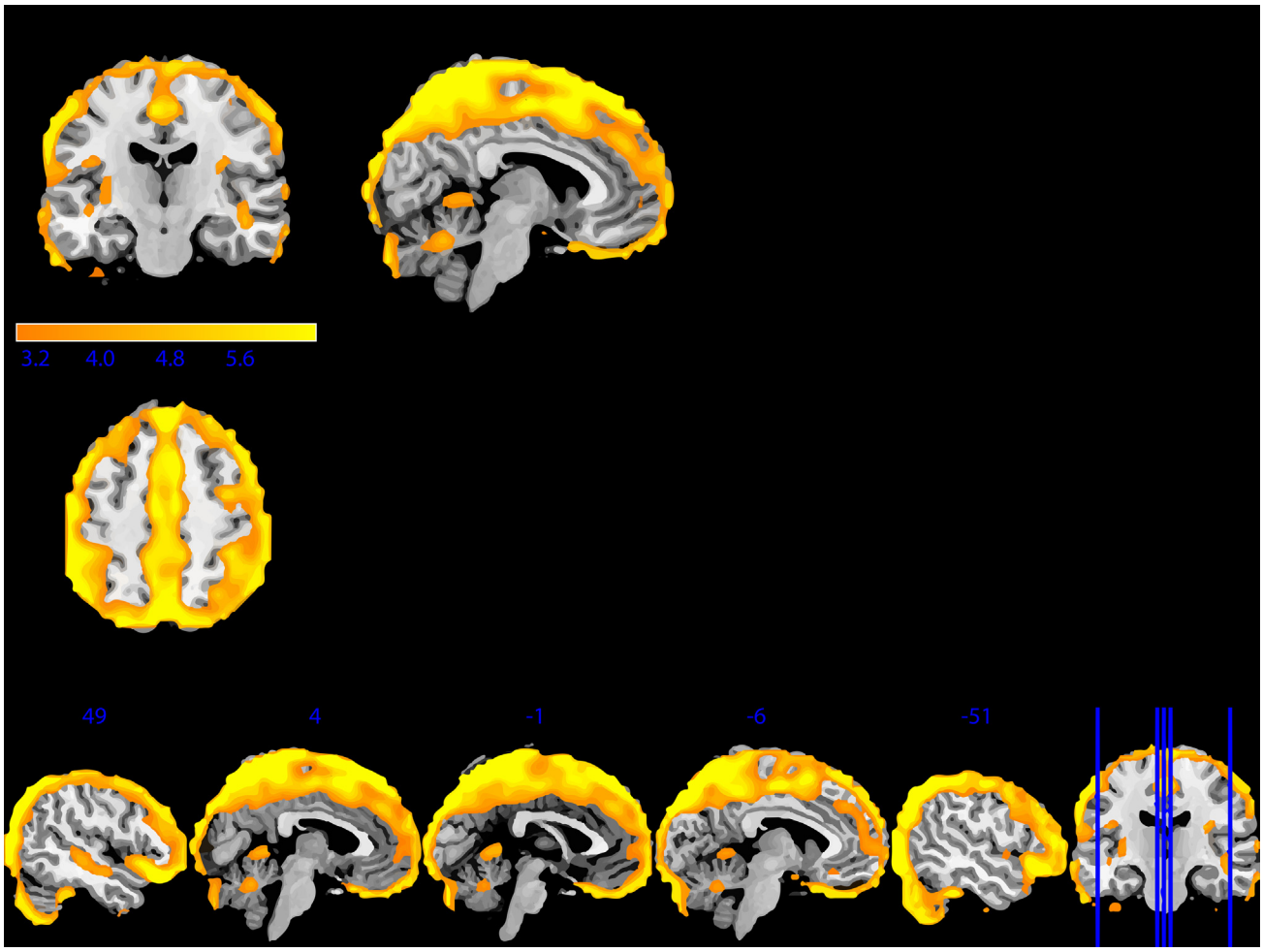

Figure 8. Gray matter alteration in unaffected first-degree relatives

Alterations in the gray matter of unaffected relatives compared to healthy volunteers. The colormap shows the -log(*p*) value; warm colors are used for positive values and cool colors for negative values.

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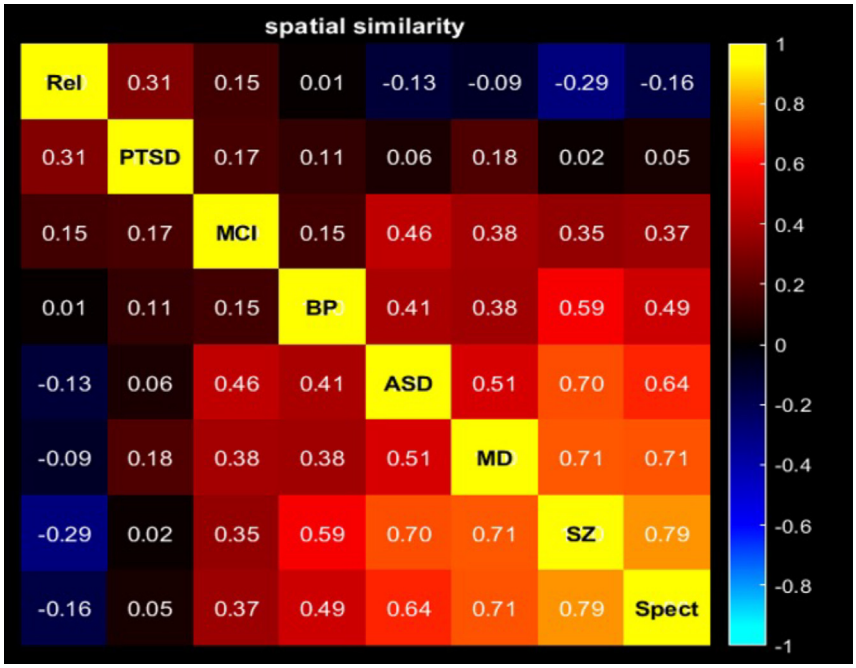

Figure 9. Heatmap of spatial correlations

Correlations for each pair of diagnostic group comparisons. Rel, unaffected relatives; PTSD, post-traumatic stress disorder; MCI, mild cognitive impairment; BP, bipolar disorder; ASD, autism spectrum disorder; MD, major depressive disorder; SZ, schizophrenia; Spect, spectrum.

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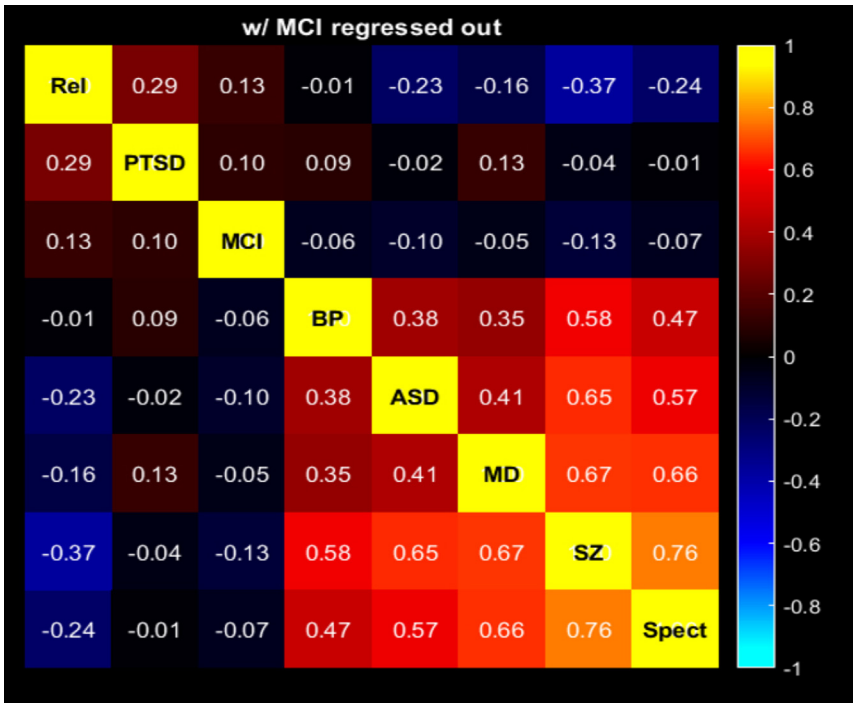

Figure 10. Heatmap of spatial correlations with MCI correlated out of comparisons

Correlations for each pair of diagnostic group comparisons. Rel, unaffected relatives; PTSD, post-traumatic stress disorder; MCI, mild cognitive impairment; BP, bipolar disorder; ASD, autism spectrum disorder; MD, major depressive disorder; SZ, schizophrenia; Spect, spectrum.

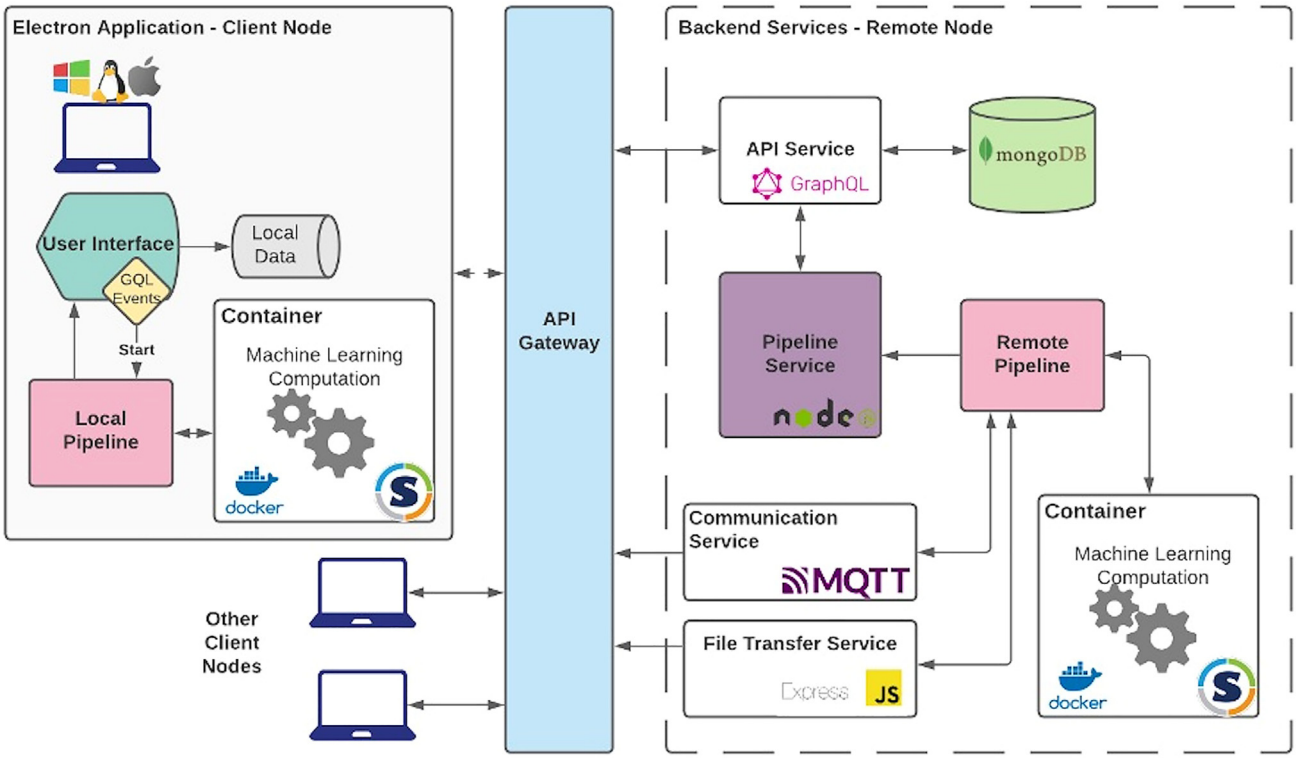

Figure 11. The COINSTAC architecture

A diagram of the COINSTAC architecture, including both client nodes and remote services. The COINSTAC application uses standard web communication protocols to transfer (meta-)data between each client node and a publicly accessible remote node via an API gateway. Client nodes and the remote node run computations in a pipeline, with client nodes sending meta-data derived from local data and the remote node aggregating and running required computations, sending results back to client nodes for either final output or iteration if required. Pipeline results are stored in a noSQL data store provided by MongoDB.

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Table 1. Participant information across sites

Site	*n*	Age (SD)	Sex (M%)	Diagnoses (*N*)	HCs
1000Brains	815	67.41 (6.79)	454 (55.71)	70 suspected cognitive impairment	745
ASRB	321	39.36 (11.72)	204 (63.55)	215 SZ; 14 spectrum	92
COCORO	1,719	33.89 (14.45)	891 (51.83)	305 SZ; 88 ASD; 82 spectrum; 44 MDD	1,200
Emory	105	38.23 (11.30)	0 (0)	32 PTSD	73
IGP	179	37.94 (11.85)	88 (49.16)	64 BP; 52 SZ	63
MAS	449	78.28 (4.69)	198 (44.10)	164 MCI	285
OATS	193	70.33 (5.17)	71 (36.79)	25 MCI	168
Sydney	321	21.64 (5.05)	134 (41.75)	147 unaffected relatives; 57 BP	117
Total	4,102	46.88 (10.28)	2,040 (49.73)	572 SZ; 259 MCI; 147 unaffected relatives; 121 BP; 96 spectrum; 88 ASD; 44 MDD; 32 PTSD	2,743

SD, standard deviation; M, male; HCs, healthy controls; SZ, schizophrenia; ASD, autism spectrum disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; BP, bipolar disorder; MCI, mild cognitive impairment; ASRB, Australian Schizophrenia Research Bank; Emory, Emory University Grady Trauma Project; IGP, Imaging Genetics in Psychosis; Centre for Healthy Brain Aging-Sydney Memory and Aging Study; OATS, Older Australian Twins Study; COCORO, Cognitive Genetics Collaborative Research Organization; Sydney, Bipolar Kids and Sibs-Sydney.

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Table 2. MRI scanner information across sites

Study	Size	Sites	Scanner (T)	Sequence	Voxel size (mm^3)	Orientation
1000Brains	815	1	Siemens TrioTrim (3)	MPRAGE	1 × 1 × 1	sagittal
ASRB	321	5	Siemens Avanto (1.5)	MPRAGE	0.98 × 0.98 × 1.0	sagittal
COCORO	1,719	3	GE Signa EXCITE (1.5)	IR fast SPGR	0.9375 × 0.9375 × 1.4	sagittal
			GE Signa HDxt 3.0T (3)	IR fast SPGR	0.9375 × 0.9375 × 1.0	sagittal
			GE DISCOVERY 750 (3)	IR fast SPGR	1.0156 × 1.0156 × 1.2	sagittal
Emory	105	2	Siemens TrioTrim (3)	MPRAGE	1 × 1 × 1	sagittal
IGP	179	1	Philips Achieva TX (3)	MPRAGE	1 × 1 × 1	sagittal
MAS	449	12	Philips Intera Quasar (3)	3D turbo field echo	1 × 1 × 1	coronal
			Philips Achieva Quasar Dual (3)	3D turbo field echo	1 × 1 × 1	coronal
OATS	193	3	Siemens Magnetom Avanto (1.5)	3D turbo field-echo	1 × 1 × 1	coronal
			Siemens Sonata (1.5)	3D turbo field-echo	1 × 1 × 1	coronal
			Philips Achieva Quasar Dual (3)	3D turbo field-echo	1 × 1 × 1	coronal
Sydney	321	1	Phillips Achieva (3)	3D turbo field-echo	1 × 1 × 1	sagittal

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