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Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders

Writing Committee for the Attention-Deficit/Hyperactivity Disorder; Autism Spectrum Disorder; Bipolar Disorder; Major Depressive Disorder; Obsessive-Compulsive Disorder; and Schizophrenia ENIGMA Working Groups

IMPORTANCE Large-scale neuroimaging studies have revealed group differences in cortical thickness across many psychiatric disorders. The underlying neurobiology behind these differences is not well understood.

OBJECTIVE To determine neurobiologic correlates of group differences in cortical thickness between cases and controls in 6 disorders: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS Profiles of group differences in cortical thickness between cases and controls were generated using T1-weighted magnetic resonance images. Similarity between interregional profiles of cell-specific gene expression and those in the group differences in cortical thickness were investigated in each disorder. Next, principal component analysis was used to reveal a shared profile of group difference in thickness across the disorders. Analysis for gene coexpression, clustering, and enrichment for genes associated with these disorders were conducted. Data analysis was conducted between June and December 2019. The analysis included 145 cohorts across 6 psychiatric disorders drawn from the ENIGMA consortium. The numbers of cases and controls in each of the 6 disorders were as follows: ADHD: 1814 and 1602; ASD: 1748 and 1770; BD: 1547 and 3405; MDD: 2658 and 3572; OCD: 2266 and 2007; and schizophrenia: 2688 and 3244.

MAIN OUTCOMES AND MEASURES Interregional profiles of group difference in cortical thickness between cases and controls.

RESULTS A total of 12 721 cases and 15 600 controls, ranging from ages 2 to 89 years, were included in this study. Interregional profiles of group differences in cortical thickness for each of the 6 psychiatric disorders were associated with profiles of gene expression specific to pyramidal (CA1) cells, astrocytes (except for BD), and microglia (except for OCD); collectively, gene-expression profiles of the 3 cell types explain between 25% and 54% of variance in interregional profiles of group differences in cortical thickness. Principal component analysis revealed a shared profile of difference in cortical thickness across the 6 disorders (48% variance explained); interregional profile of this principal component 1 was associated with that of the pyramidal-cell gene expression (explaining 56% of interregional variation). Coexpression analyses of these genes revealed 2 clusters: (1) a prenatal cluster enriched with genes involved in neurodevelopmental (axon guidance) processes and (2) a postnatal cluster enriched with genes involved in synaptic activity and plasticity-related processes. These clusters were enriched with genes associated with all 6 psychiatric disorders.

CONCLUSIONS AND RELEVANCE In this study, shared neurobiologic processes were associated with differences in cortical thickness across multiple psychiatric disorders. These processes implicate a common role of prenatal development and postnatal functioning of the cerebral cortex in these disorders.

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Supplemental content

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The advancement of large-scale magnetic resonance imaging (MRI) studies has enabled systematic investigations of cortical morphology, such as cortical thickness and surface area, across a variety of psychiatric disorders. In particular, the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium has conducted some of the largest MRI studies characterizing group differences between patients (cases) and control individuals in the cerebral cortex for a number of disorders, including attention-deficit/hyperactivity disorder (ADHD),[1] autism spectrum disorder (ASD),[2] bipolar disorder (BD),[3] major depressive disorder (MDD),[4] obsessive-compulsive disorder (OCD),[5] and schizophrenia.[6] Nonetheless, the neurobiology underlying these MRI-derived macroscopic features is not well understood.

As identified in postmortem studies, there are subtle differences in the cellular composition of the cerebral cortex of patients diagnosed as having various psychiatric disorders (vs controls) such as the density of neurons and/or glial cells and the extent of dendritic arborization.[7] Mostly lower neuronal density and/or neuronal size have been documented in ASD,[8] BD,[9] MDD,[10,11] OCD,[12] and schizophrenia.[13-15] Similar alterations in the density of glial cells (astrocytes, microglia, or oligodendrocytes) have been observed in ASD,[8] BD,[9] MDD,[10,11] and schizophrenia.[16]

Several MRI studies have demonstrated distinct interregional profiles of group differences in cortical thickness across the 34 regions of the Desikan-Killiany atlas.[17] We use the word *profile* to refer to interregional (spatial) variations in a measure, such as cortical thickness, across the cerebral cortex. Lower cortical thickness in temporal regions in cases (vs controls) is a common feature across ADHD, ASD, BD, MDD, OCD, and schizophrenia[1-6,18]; a 2019 report of the ENIGMA cohorts[19] showed cross-disorder correlations among disorders. Likewise, large-scale genome-wide association studies (GWAS) identify shared genetic architecture among these psychiatric disorders.[20]

To our knowledge, no studies have investigated systematically the association between microscopic ex vivo histology and macroscopic in vivo differences in cortical thickness across psychiatric disorders. This is required to facilitate our understanding of MRI-derived measures in a neurobiologic context as well as the usefulness of MRI for tracking of clinical progression of disorders and their treatment.

Here, we generate profiles of group differences in cortical thickness between cases and controls for ADHD, ASD, BD, MDD, OCD, and schizophrenia using an identical linear-modeling approach executed in each participating cohort. Next, we use a virtual histology approach whereby interregional profiles of cell-specific gene expression are correlated across the 34 cortical regions,[17] with interregional profiles of group differences in cortical thickness. Through a series of bioinformatic approaches, we then identify shared cellular correlates across the 6 psychiatric disorders.

Key Points

Question What are the neurobiologic underpinnings of group differences in cortical thickness in various psychiatric disorders?

Findings In this consortium analysis of data from 145 cohorts, regions of the cerebral cortex with greater expression of genes specific to pyramidal (CA1) cells were also regions with greater case-control group differences in cortical thickness in all 6 disorders: attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and schizophrenia. There was a common profile of group differences in cortical thickness shared among these disorders, which was associated with the expression of genes involved in neurodevelopmental processes (prenatally) and processes underlying synaptic activity and plasticity (postnatally).

Meaning There are shared neurobiologic and cellular mechanisms associated with differences in cortical thickness across multiple psychiatric disorders, implicating a common role of prenatal development and postnatal functioning of the cerebral cortex.

Methods

Group Differences in Cortical Thickness

T1-weighted MRI scans were acquired in 145 cohorts participating in the ENIGMA Consortium with varying MRI field strength and vendors. Details regarding MRI acquisition and sample demographics are found in eTable 1 and eTable 2 in the Supplement. FreeSurfer cortical reconstruction (several versions) was used to derive measures of cortical thickness in 34 regions (per hemisphere), as segmented using the Desikan-Killiany atlas.[17,21] Quality control was conducted by contributing cohorts, following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Individual ENIGMA groups performed multiple linear regression analyses in their respective cohorts, which modeled cortical thickness of each region, separately, as a function of diagnosis (eg, ADHD), age, age squared, sex, and site-specific covariates (eg, MR scanner). Individual cohorts obtained approval from local institutional ethics boards, and informed consent was obtained from study participants or their guardians. An inverse variance-weighted random-effects model from the "metafor" R package (The R Foundation) was used to generate meta-analytic profiles of group differences across the 34 regions for each disorder.[22] This report is an analysis of shared data in the ENIGMA consortium rather than existing literature.

Magnetic Resonance Imaging–Derived Similarity and Genetic Similarity

This analysis was carried out to evaluate similarity in pairwise correlations in interregional profiles of group differences in cortical thickness and corresponding pairwise correlations in genome-wide genetic architecture, described in the eMethods in the Supplement. Group differences in cortical thickness were first correlated across psychiatric disorders with a biweight midcorrelation using R package WGCNA (rationale in the eMethods in the Supplement).[23] Genetic correlations between psychiatric disorders were obtained from the Brainstorm consortium.[20] The similarity of the group differences in cortical thickness and genetic cross-disorder correlation matrices was tested for significance using Mantel test from the "vegan" R package.[24,25]

Virtual Histology

Virtual histology is an approach that correlates, across space, an MRI-derived profile, such as an interregional profile of group differences in cortical thickness, with interregional profiles of cell-specific gene expression.[26,27] As described previously, gene-expression data from the Allen Human Brain Atlas (AHBA; 6 donors, aged 24-57 years) were first mapped to the 34 regions of the Desikan-Killiany atlas.[28,29] To ensure similarity of interregional profiles in gene expression across donors, and across the life span, we applied a conservative 2-stage filtering process. First, a donor-to-median correlation in the AHBA was used to retain only genes whose profiles were consistent among the 6 donors (retaining 8216 of 20 737 genes present in AHBA). Second, the genes passing stage 1 were filtered based on interregional profile similarity with an independent atlas of gene expression, namely BrainSpan (retaining 2511 of 8216 genes; see eMethods in the Supplement for additional details). The final set of 2511 genes was used for analyses conducted in this report. Next, single-cell RNA sequencing data from the mouse hippocampus and S1 area of cerebral cortex were used to categorize the 2511 genes as specific to 9 cell types identified (CA1 pyramidal, S1 pyramidal, interneuron, astrocyte, microglia, oligodendrocyte, mural, endothelial, and ependymal cells).[30] Pyramidal cell types (CA1 and S1) were labeled based on their anatomic origin, but the molecular characteristics of these pyramidal cells, as indexed by gene expression, were not restricted to the brain regions in which these 2 types of pyramidal cells were found. The use of these panels is analogous to a data reduction technique driven by neurobiologically relevant clustering (see the eMethods in the Supplement for additional details). Interregional profiles of cell-specific gene expression were then correlated across the 34 regions with MRI-derived profiles to generate a distribution of correlation coefficients for each of the cell types. This distribution was then tested for significance using a resampling approach from 100 000 random samples. This analysis was restricted to MRI profiles from the left hemisphere only (owing to data availability in AHBA). In addition, we have estimated the collective variance explained by cell types identified from virtual histology in interregional profiles of group differences (see the eMethods in the Supplement).

Coexpression Analyses

Seed genes were defined by biweight midcorrelation between principal component 1 (PC1) profile (shared variance in group differences in cortical thickness across the 6 disorders) and cell-specific genes passing false discovery rate (FDR)–corrected threshold; 2-sided *P* less than .05.[31] For these analyses, we harmonized gene-expression data from human cerebral cortex across 5 data sets (AHBA,[29] BrainCloud,[32] Brain eQTL Almanac [Braineac],[33] Genotype Tissue Expression [GTEx],[34] and BrainSpan).[35] The curation of these 5 gene-expression databases has been described previously and is presented in the eMethods in the Supplement.[36,37] In total there were 534 donors (aged 0-102 years) with gene-expression data for 16 245 genes across all data sets. Coexpression analyses were generated using linear mixed-effects models where gene expression of each seed was modeled against other genes' expression, with age and sex as fixed effects and donor identifier as a random effect. The top 0.1% of positively coexpressed genes for each of the seed genes were used to construct our coexpressed network panels.

Gene Trajectory Clustering

Coexpressed genes were clustered based on their temporal pattern of gene expression using data from the BrainSpan atlas (http://www.brainspan.org). This data set was chosen for the gene trajectory clustering because it is the only one that includes gene expression across prenatal and postnatal developmental periods (42 donors, age range from 8 postconception weeks to age 40 years; 11 cortical regions). Genes were clustered using mixed-effects models with nonparametric smoothing spline fitting available in the "TMixClust" R package (the eMethods and eTables 12-17 in the Supplement for additional details).[38]

Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and Psychiatric Disorder Enrichment Analysis

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were conducted using the R package "clusterProfiler."[39] Gene ontology (biological process ontology only) and Kyoto Encyclopedia of Genes and Genomes terms with a minimum of 10 and a maximum of 500 genes were included in the analysis. Redundancy of GO terms was removed based on similarity cutoff of 0.90. Enrichment between coexpressed genes and genes associated with psychiatric disorder were conducted using a hypergeometric test. Genetic variants associated with psychiatric disorder were derived from the DisGeNet database (http://www.disgenet.org).[40] The background gene set for all of the aforementioned enrichment test included 16 245 genes that were present in our harmonized data set of gene expression for coexpression analyses. *P* values were corrected using the FDR procedure.[41]

Results

Meta-analysis

We characterized meta-analytic profiles of group differences in cortical thickness for each of the 6 disorders across the 34 regions of the cerebral cortex (**Figure 1**; eTables 3-8, eFigure 1 in the Supplement, left hemisphere only). In total, there were 12 721 cases and 15 600 controls contributing to these profiles (eTable 2 in the Supplement). Across the disorders, interregional variation in group differences of cortical thickness were positively correlated between schizophrenia and ADHD, ASD, BD, MDD, and OCD (**Figure 2**A). Overall, there was a general trend of positive correlations (biweight midcorrelation, $r > 0$) of group differences across all 6 psychiatric disorders (Figure 2A). Genetic correlations, as quantified by linkage disequilibrium score regression, also showed a number of pairwise positive correlations among these psychiatric disorders, in particular for schizophrenia (Figure 2B; reproduced using data from the Brainstorm consortium).[20] Cross-disorder similarity of differences in cortical thickness (derived from MRI; Figure 2A) was positively associated with cross-disorder

Figure 1. Profiles of Group Differences in Cortical Thickness (Left Hemisphere Only) Between Cases and Controls

Profiles of group differences in cortical thickness (left hemisphere only) between cases and controls across the 6 psychiatric disorders investigated. Group differences are adjusted for age, sex, and other site-specific variables.

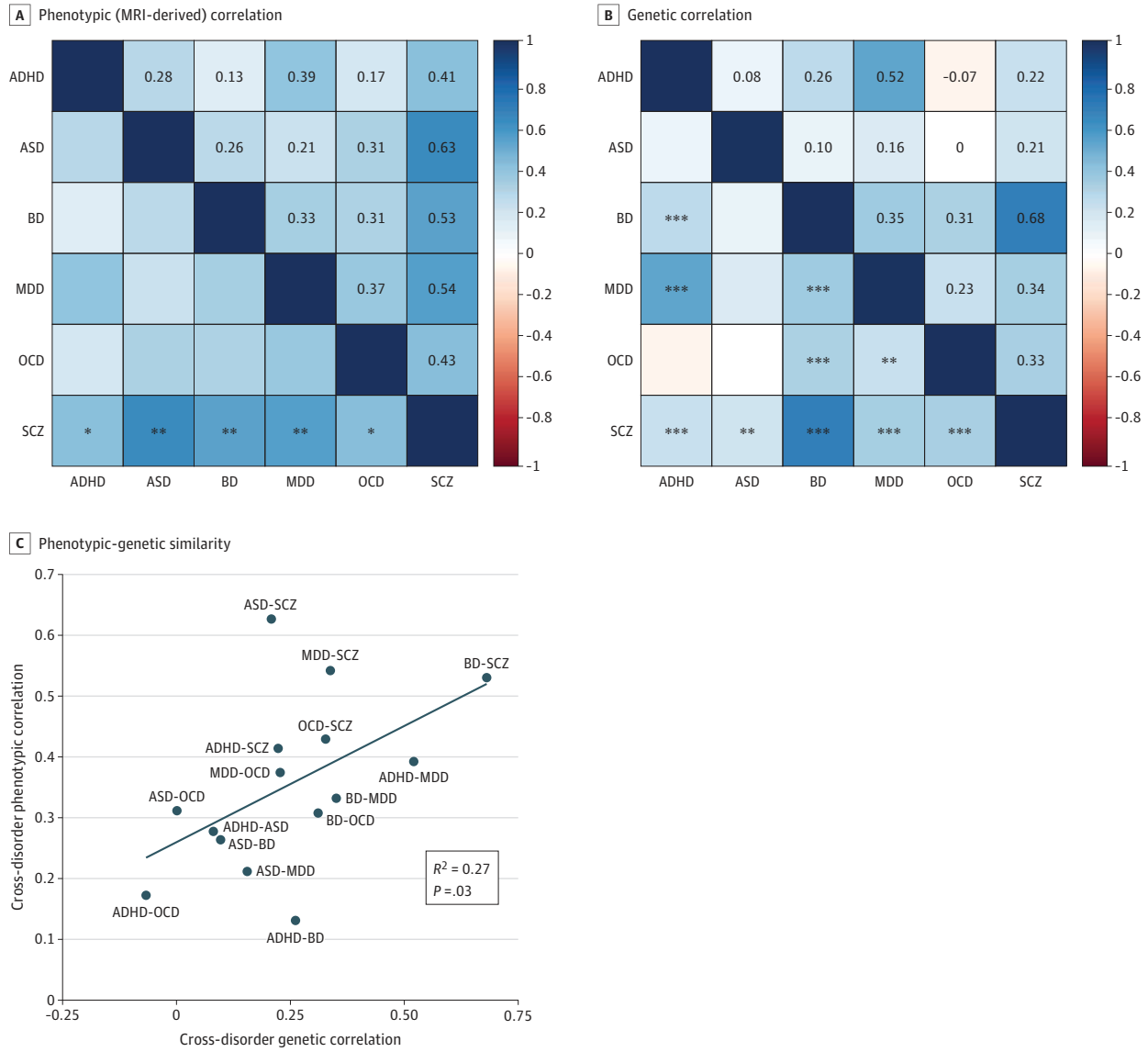
Error bars represent 95% confidence intervals. Estimates less than zero represent thinner cortex in cases as compared with controls.

genetic similarity (derived from GWAS; Figure 2B), explaining 27% of variance (r = 0.52; Mantel P = .034, Pearson P = .045).

Virtual Histology of Group Difference in Cortical Thickness

Interregional variation in the expression of genes specific to pyramidal (CA1) cells was negatively associated with the interregional profile of group differences in cortical thickness in each of the 6 psychiatric disorders ($-0.08 > r > -0.23$; FDR P value <.05, **Figure 3**; eTable 9, eFigure 2 in the Supplement). Thus, regions with greater expression of pyramidal (CA1)-specific genes showed greater differences in cortical thickness between cases and controls. We also observed this negative association with interregional profiles of expression of genes specific to astrocytes and microglia in all 6 disorders except BD (no correlation with astrocytes) and OCD (no cor-

Figure 2. Phenotypic and Genetic Similarity Between Psychiatric Disorders



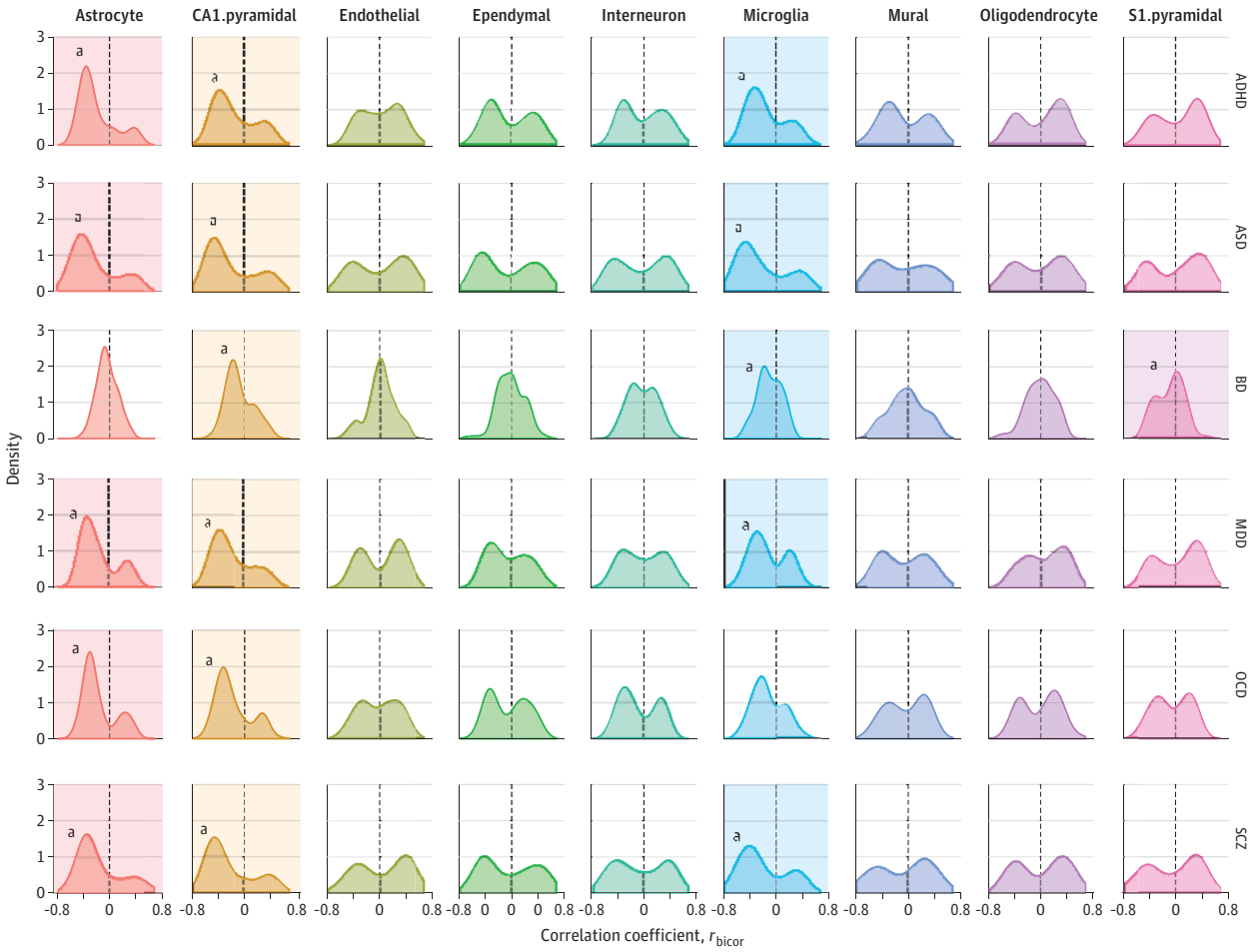
A, Cross-disorder correlation of group differences in cortical thickness (profiles from Figure 1). B, Cross-disorder genetic correlation (linkage disequilibrium score regression) derived from Brainstorm et al.[20] C, Plot of genetic correlation against phenotypic (magnetic resonance imaging [MRI]–derived difference in thickness) correlations between psychiatric disorders with a linear model fit (blue line, R^2 = 0.27; Mantels P = .03, Pearson P <.05). ADHD indicates attention-deficit/hyperactivity disorder, ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder, OCD, obsessive-compulsive disorder; SCZ, schizophrenia.

relation with microglia). Lastly, we observed a negative association between pyramidal (S1) specific expression and group differences in thickness in BD only. The amount of interregional variation in the group differences in cortical thickness explained collectively by the gene-expression profiles is presented in eTable 18 in the Supplement.

Principal Component Analysis

Given the similarity of findings across the 6 disorders vis à vis virtual histology, we used principal component analysis to reduce the dimensions of the data (**Figure 4**A). The first principal component (PC1) explained 48% of variation in group differences of thickness profiles across the 6 disorders (eFigure 3 in the Supplement). Principal component 1 was positively correlated with each of disorder's profiles (eFigure 3C in the Supplement), and its interregional profile was negatively associated with the interregional profiles of pyramidal (CA1), astrocyte, and microglia-specific gene expression (Figure 4B); regions with greater expression of cell-specific genes showed greater differences in cortical thickness between cases and controls. The amount of interregional variation in the shared group difference in cortical thickness explained by the gene-expression profiles is presented in eTable 18 in the Supplement.

Figure 3. Virtual Histology of Group Differences in Cortical Thickness



Results from virtual histology. Distribution of correlation coefficients between cell-specific gene expression profiles and group differences in cortical thickness for the 6 psychiatric disorders.

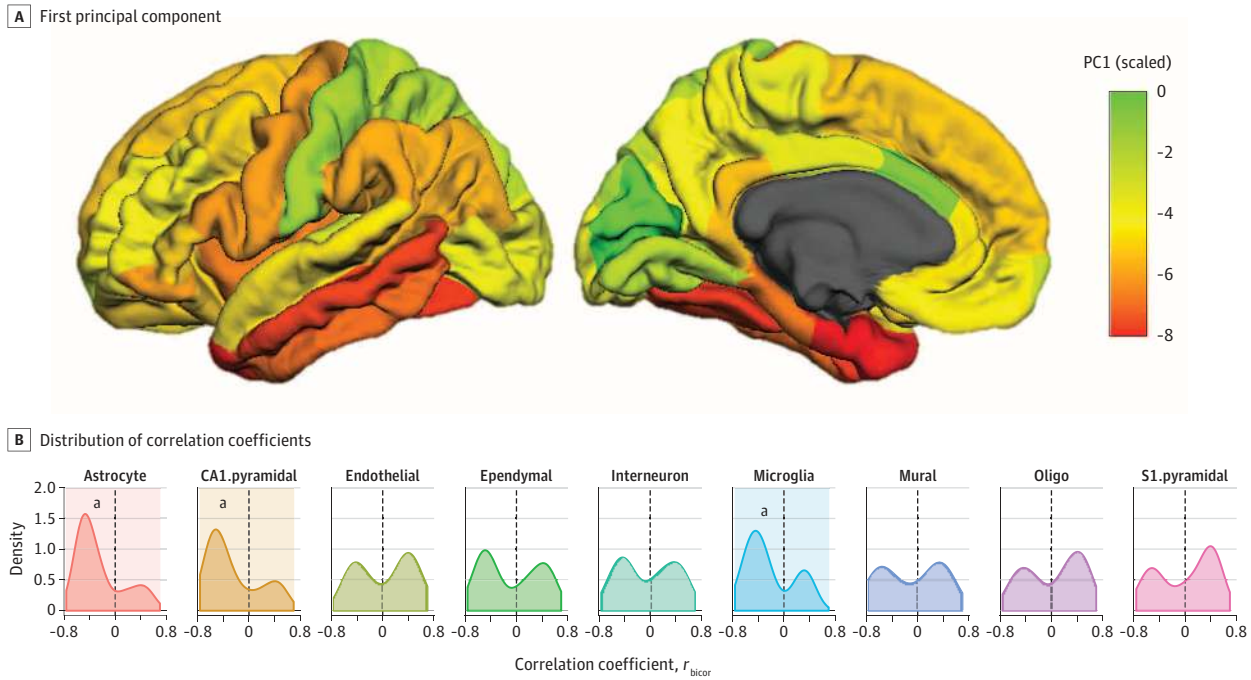
ADHD indicates attention-deficit/hyperactivity disorder, ASD, autism spectrum disorder; BD, bipolar disorder; bichor, biweight midcorrelation; MDD, major depressive disorder, OCD, obsessive-compulsive disorder; SCZ, schizophrenia.

[a] False discovery rate P <.05.

Shared Neurobiology Across Disorders

To investigate the association between PC1 and CA1 pyramidal specific genes, we used all CA1 genes associated significantly (FDR significance threshold $P < .05$) with PC1 as seed genes for coexpression analyses. Data from the AHBA, BrainEAC, BrainSpan, BrainCloud, and GTEx were harmonized to identify robust coexpression associations across the genome (eFigures 4 and 5 in the Supplement). These PC1-CA1 coexpressed genes (412 genes) were clustered based on their temporal pattern of expression using unsupervised nonparametric mixed modeling. This analysis yielded 2 clusters: cluster 1, which was upregulated during prenatal periods and downregulated in postnatal life, and cluster 2, which showed the opposite developmental trajectory (**Figure 5**A). Gene ontology enrichment analysis revealed involvement of neurodevelopmental processes (axon development; fold enrichment = 3.99; FDR $P = 5.15 \times 10^{-05}$) in the prenatal cluster (Figure 5B; eFigure 6 in the Supplement) and involvement of synaptic signaling/neurotransmission- and synaptic plasticity-related terms (Fold enrichment, 4.70 and 4.56, respectively; FDR P value = 5.11×10^{-09} and 2.31×10^{-03}, respectively) in the postnatal cluster (Figure 5C; eFigure 6 in the Supplement). Gene enrichment analysis showed that the prenatal cluster is enriched in genes associated with ASD, BD, MDD, and schizophrenia, while the postnatal cluster is enriched only in genes associated with ADHD and schizophrenia (FDR P value <.05; eFigure 7 in the Supplement). The entire coexpressed network (ie, genes from both clusters) is enriched for all 6 disorders, at varying levels of enrichment (eFigure 7 in the Supplement). Finally, with the aid of laminar gene-expression data from the developing human neocortex, we show that the prenatal cluster was upregulated in the cortical subplate zone and cortical plate (area under the receiver operating curve, 0.68; FDR P value = 2.35×10^{-15}), while downregulated in the ventricular zone (area under the receiver operating curve, 0.30; FDR P value = 1.30×10^{-17}; eFigure 8 and eTable 10 in the Supplement). This held true for the postnatal cluster as well (eFigure 8 and eTable 11 in the Supplement).

Figure 4. Principal Component 1 From the 6 Group Difference Profiles



Principal component analysis of profiles of group differences across 6 psychiatric disorders. A. First principal component (PC1) plotted across the 34 regions of the left hemisphere. First principal component values are scaled down to have a maximum of zero to facilitate interpretation; negative values reflect greater differences in cortical thickness between cases and controls shared by the 6 disorders. Unscaled values are presented in eFigure 3 in the Supplement. B. Distribution of correlation coefficients between cell-specific gene expression and PC1 profile. bicor indicates biweight midcorrelation; Oligo, oligodendrocyte.

[a] False discovery rate $P < .05$.

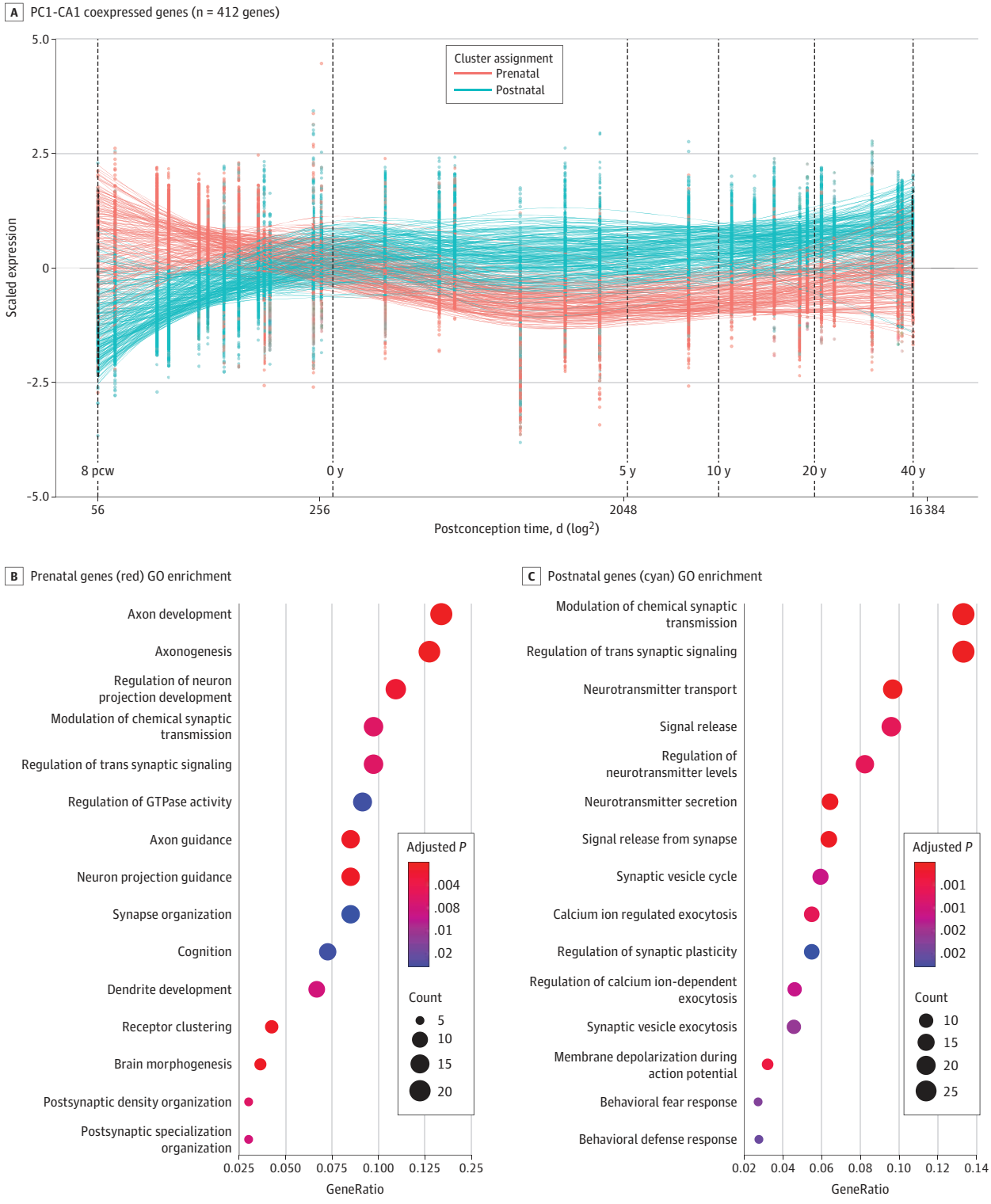
The analysis described previously was repeated for the astrocyte-specific and microglial-specific genes. Principal component 1-astrocyte coexpressed genes (168 genes) were enriched in metabolic processes, such as amino acid transport (Fold enrichment = 19.56; FDR P value = 2.09×10^{-03}), as well as enriched in genetic variants associated with BD and schizophrenia (Fold enrichment = 2.50 and 1.82; FDR P value = .01 and .01, respectively; eFigure 9 in the Supplement). Principal component 1-microglia coexpressed genes (118 genes) were enriched in immune-related processes (Fold enrichment = 11.93; FDR P value = 1.7×10^{-08}) and showed no enrichment with genetic variants associated with any of the 6 psychiatric disorders (eFigure 10 in the Supplement).

Discussion

We characterized robust interregional differences in cortical thickness between cases and controls across the cerebral cortex in 6 common psychiatric disorders, as done previously by the individual working groups of the ENIGMA consortium.[1-6,18] The interregional profiles presented in this report were generated using the same linear model (with the same covariates) in each of the 145 participating cohorts and, as such, allow for direct comparisons of these profiles across the 6 disorders. This also facilitated our observation of the similarity between shared differences in MRI-derived thickness and genetic architecture across these 6 disorders, an observation suggesting the presence of genetic variants that may be associated with vulnerable brain phenotypes in common for the 6 disorders investigated here (Figure 2).

Virtual histology identified common cell-specific associations between ex vivo gene expression and in vivo MRI-derived group differences in cortical thickness across the 34 cortical regions. In this analysis, all 6 disorders showed a negative association with expression profiles specific to CA1 pyramidal cells. Regions with greater group differences in cortical thickness are the regions with greater expression of pyramidal (CA1-like) specific genes within the normative human brain, potentially indicating vulnerability of these regions. Although the CA1 pyramidal-cell panel is labeled based on the source of these cells (CA1 region of the hippocampus), this does not mean that biologic processes implicated in CA1 genes are restricted to this region; in fact, similar molecular processes are present throughout the human cerebral cortex (see the eDiscussion in the Supplement for additional details). As such, we interpret the functional relevance of these genes being associated with differences in cortical thickness. It is important to state that the gene expression used throughout this report comes from individuals without any diagnoses of neurologic or psychiatric disorders. Studies linking cell-specific genes with psychiatric GWAS-associated genes

Figure 5. Trajectories of Expression for Genes Associated With the Shared Profile of Group Differences in Cortical Thickness



Life span trajectory in gene expression of first principal component (PC1)–CA1 coexpressed genes. Each line represents a fitted LOESS model for the expression of a given gene. Genes and their fitted models are colored based on clustering based on temporal trajectories. First principal component–CA1 coexpressed genes were generated using coexpression of seed genes, namely genes that associate with PC1 profile and the 103 CA1 pyramidal specific genes passing false discovery rate $P < .05$. Gene ontology (GO) enrichment analysis of the prenatal cluster (B) and postnatal cluster (C). Dot size (count) for enrichment analysis (B,C) represents the number of genes that are within the co-expression gene panels as well as a particular GO group (y-axis).

show similar enrichment of CA1 pyramidal cells in ASD, BD, and schizophrenia.[42] This is another line of evidence linking genetically identified enrichment of CA1 pyramidal cells (previous study[42]) with MRI-identified enrichment of CA1 pyramidal cells within psychiatric disorders as seen in this study.

Principal component analysis identified a common component of these cortical differences, indicating a shared interregional profile of case-control differences in cortical thickness among all 6 disorders. Although not the primary focus of this report, we also report other PCs (explaining less variance); these appear to capture mostly disease-specific variations in group differences in cortical thickness (eFigure 3 in the Supplement). As expected from the disease-specific analyses, this PC1 profile was associated with the same 3 cell types, namely CA1 pyramidal, astrocyte, and microglia. The CA1 pyramidal gene set is enriched with biologic processes related to dendritic arborization,[27] and extensive dendritic branching is a key morphologic phenotype of pyramidal neurons.[43] Similarly, our phenotype is derived from cortical thickness, a measure that is directly associated with ex vivo dendrite length across individuals (R^2 = 0.25).[44] Dendrites control the flow and integration of information within neurons and are a medium of structural plasticity within the cerebral cortex. Remodeling of dendritic trees and dendritic spines have been observed as a result of environmental (stress and sensory enrichment/deprivation) and genetic influences acting both early and later in life.[45,46] Alterations in dendritic morphology, such as reduction in size of dendritic arborization, have been described in postmortem samples from patients with ASD,[47,48] BD,[49] schizophrenia,[49] depression,[50] and anxiety.[50]

The network of genes coexpressed with the CA1 pyramidal genes associated with PC1 contained 2 clusters: one upregulated during the prenatal and the other during the postnatal period. Through a series of bioinformatic approaches we found evidence for 2 sets of processes involving cortical development and cortical functioning, and, based on the temporal profile, the influence of these processes prevails during prenatal (prenatal cluster) and postnatal (postnatal cluster) life, respectively. The emergence of these 2 clusters is highly convergent with the 2-hit hypothesis regarding the etiology psychiatric disorders, particularly with schizophrenia.[51] We speculate that the group differences in cortical thickness observed across the 6 psychiatric disorders are a summation of processes occurring throughout life (prenatal and postnatal) whereby atypical development and/or impaired cortical functioning leave a morphological signature in the cerebral cortex.

Prenatal/Neurodevelopmental Features of Psychiatric Disorders

The development of the cerebral cortex during gestation is a complex process with a high susceptibility to perturbations. It is hypothesized that the risk for psychiatric disorders increases owing to perturbations in normal neurodevelopment.[52,53] Cross-disorder GWAS studies of ADHD, affective disorder, anorexia, ASD, BD, and schizophrenia have all implicated genes involved in regulating neurodevelopmental processes within radial glia and interneurons of the developing neocortex.[54]

The prenatal (coexpression) cluster was enriched in neurodevelopmental processes such as axonogenesis/guidance, dendrite development, and, in general terms, neuron projection guidance. Axon guidance was also one of the key GO terms found in the aforementioned cross-disorder GWAS study.[54] Axon guidance is a process that directs growth cones to establish neuron pathways and cortical circuits. The strongest evidence in implicating axon-guidance proteins in psychiatric disorders is found in ASD whereby expression and GWAS studies converge on canonical axon-guidance proteins, such as slits, robos, and semaphorins, all of which are present in the PC1-CA1 coexpressed genes in our study (eFigure 11 in the Supplement).[55] See the eDiscussion in the Supplement regarding subplate enrichment. We speculate that early changes in neurodevelopmental processes may render certain regions and cell types (pyramidal cells and their dendrites) more vulnerable and, as such, more likely to be involved in the etiology of all psychiatric disorders. This may explain the shared profile of difference we observe.

Postnatal/Functional Features of Psychiatric Disorders

There is strong genetic, molecular, and histological evidence demonstrating synaptic dysfunction and pathological changes in spine density and morphology in psychiatric disorders (particularly ASD, schizophrenia, MDD, and BD).[56-59] Alterations in these processes are likely to influence structural plasticity and subsequent formation of complex and adaptable circuits. Both genetic and experience-dependent factors play a role in structural plasticity across life, and a summation of these factors may increase or decrease the risk of developing a psychiatric disorder. These structural (dendritic spine) changes are prominent during periods of maturation (childhood and youth), coinciding with the peak age in incidence of psychiatric disorders.[56,60] The postnatal cluster of coexpressed genes was enriched in synaptic transmission and regulation of synaptic plasticity. We hypothesize that this cluster of genes is indicative of plasticity-related morphological changes in the cerebral cortex that may in part reflect adverse experiences common across all psychiatric disorders. This interpretation is consistent with the fact that there are fewer disorder-associated gene variants enriched in the postnatal cluster as compared with the prenatal cluster, potentially indicating that the postnatal processes are associated with environmental rather than genetic components of risk for psychiatric disorders.

Limitations

There are several limitations to the approach used in this report. First, only 2511 genes determined as having representative interregional profiles of their expression are used for virtual histology. We chose this conservative approach given that interregional profiles in case-control differences and those in gene expression come from 2 different sets of brains (see the eDiscussion in the Supplement for additional details). This limitation may lower our ability to capture other relevant neurobiologic signals. In an attempt to mitigate this limitation, downstream analyses use coexpression to broaden the scope of the genes investigated, albeit indi-

rectly. Second, we are using single-cell data from mice, which have shown general conservation with human data. However, there are some species-specific differences that may not be accounted for in this report (see eMethods in the Supplement for details on single-cell vs single-nucleus data set).[61] Third, our analysis uses a relatively coarse parcellation allowing us to capture gross interregional patterns of group differences in cortical thickness. This might, however, increase the potential for missing subtle (vertex-level) variations. Lastly, when interpreting T1-weighted MRI, we assume that these estimates reflect true variations in brain phenotype rather than measurement error, artifacts, or other physiological sources of T1 signal.

Conclusions

In summary, we characterized shared neurobiology across 6 psychiatric disorders that implicates pyramidal cells (and dendrites) in representing a possible target of perturbations that may increase a general vulnerability to mental illness. Our bioinformatics-based analyses point toward involvement of neurodevelopmental (prenatal) and plasticity-related (postnatal) aspects underlying pathophysiology of psychiatric disorders and their brain correlates. These shared aspects of psychiatric disorders highlight the importance of transdiagnostic approaches in psychiatry.

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