

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

 Supplemental content

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.

Group Information: The Writing Committee for the Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive-Compulsive Disorder and Schizophrenia ENIGMA Working Group is listed at the end of this article.

Corresponding Author: Tomas Paus, MD, PhD, Bloorview Research Institute, 150 Kilgour Rd, East York, ON M4G 1R8, Canada (tpaus@hollandbloorview.ca).

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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 cohorts¹⁹ 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.

Methods

Group Differences in Cortical Thickness

T1-weighted MRI scans were acquired in 145 cohorts participating in the ENIGMA Consortium with varying MRI field

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.

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' ex-

pression, 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 2A**). 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.

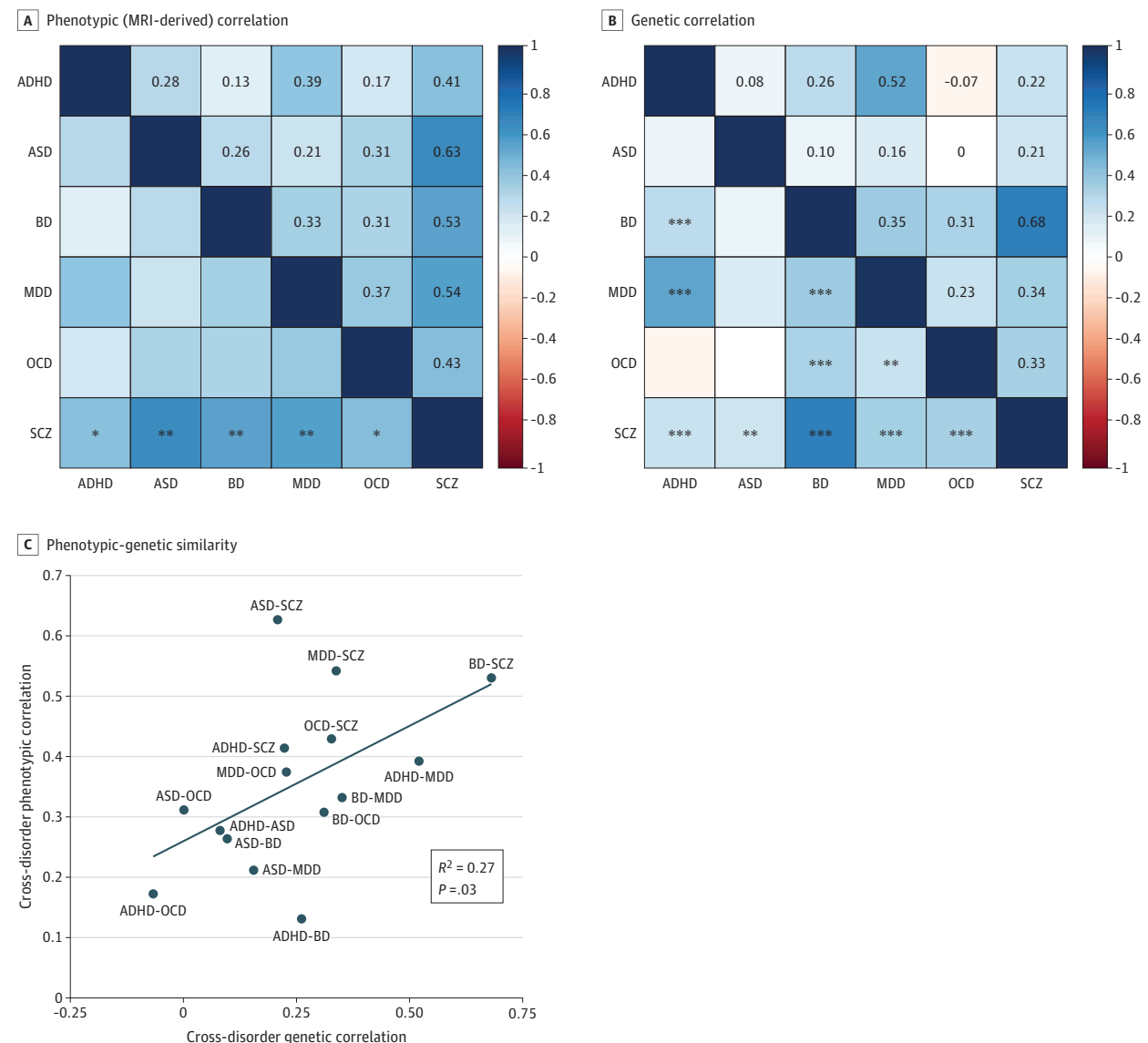
genetic similarity (derived from GWAS; Figure 2B), explaining 27% of variance ($r = 0.52$; Mantel $P = .034$, Pearson $P = .045$).

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 thick-

ness 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, $R^2 = 0.27$; Mantel's $P = .03$, 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.

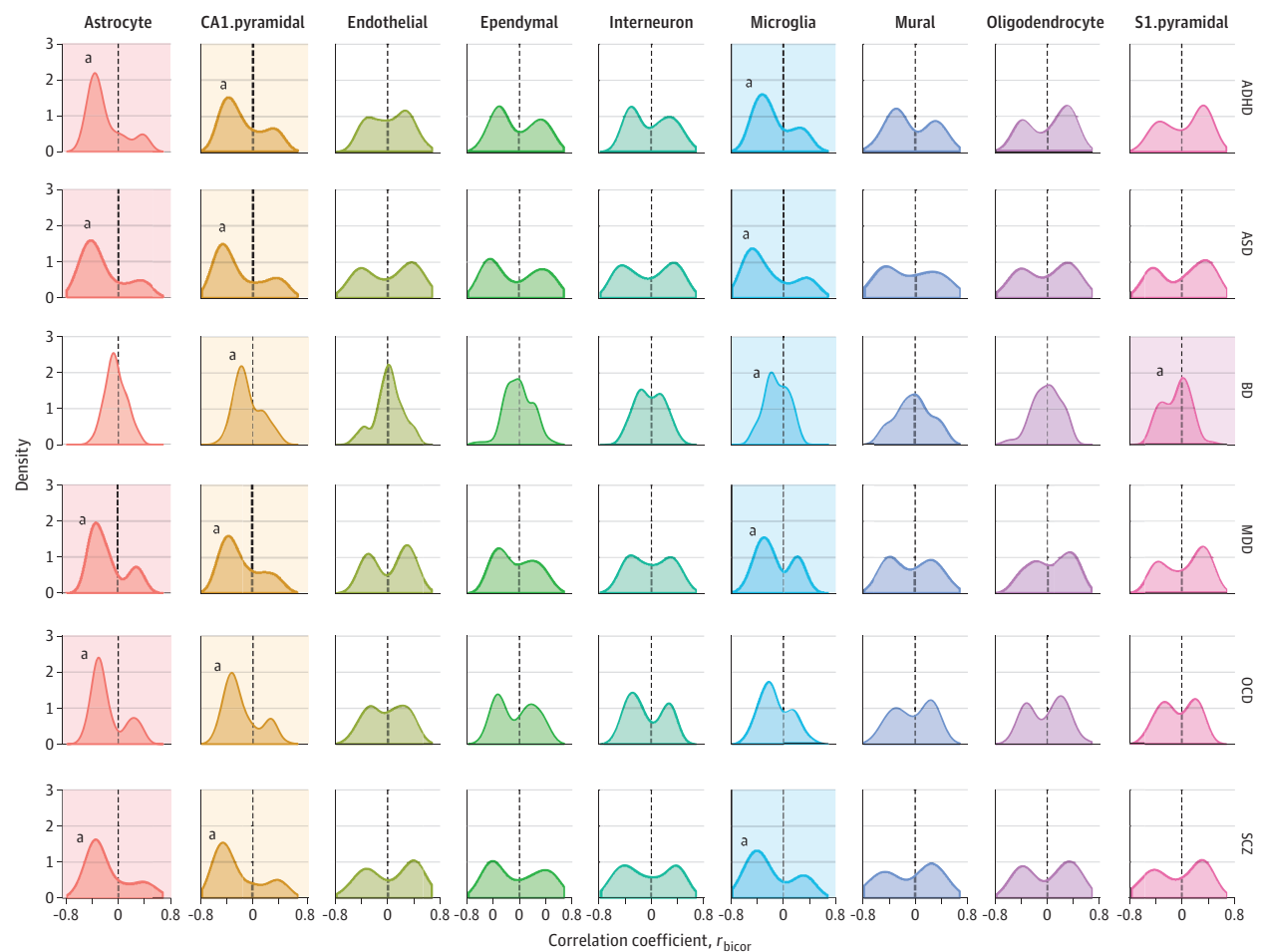
relation with microglia). Lastly, we observed a negative association between pyramidal (S1) specific expression and group differences in thickness in BD only. The amount of interregional variation in the group differences in cortical thickness explained collectively by the gene-expression profiles is 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 4A). 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; bicor, biweight midcorrelation; MDD, major depressive disorder, OCD, obsessive-compulsive disorder; SCZ, schizophrenia.

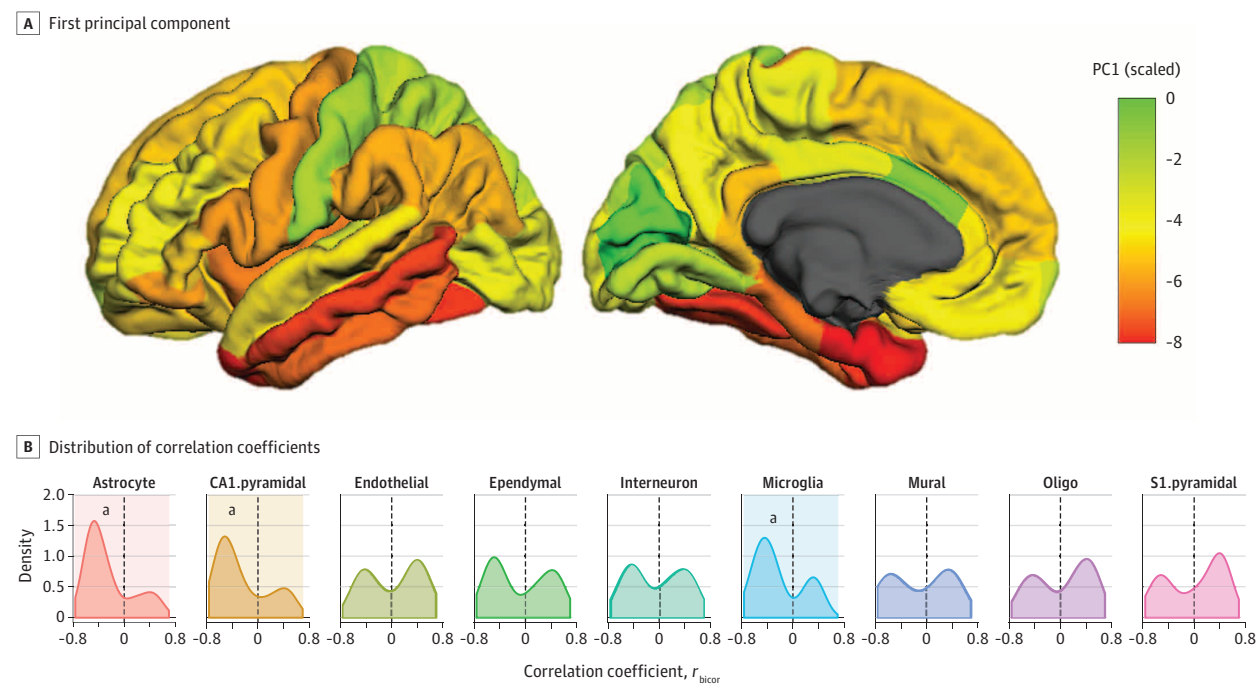
^a False discovery rate $P < .05$.

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 5A](#)). 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).

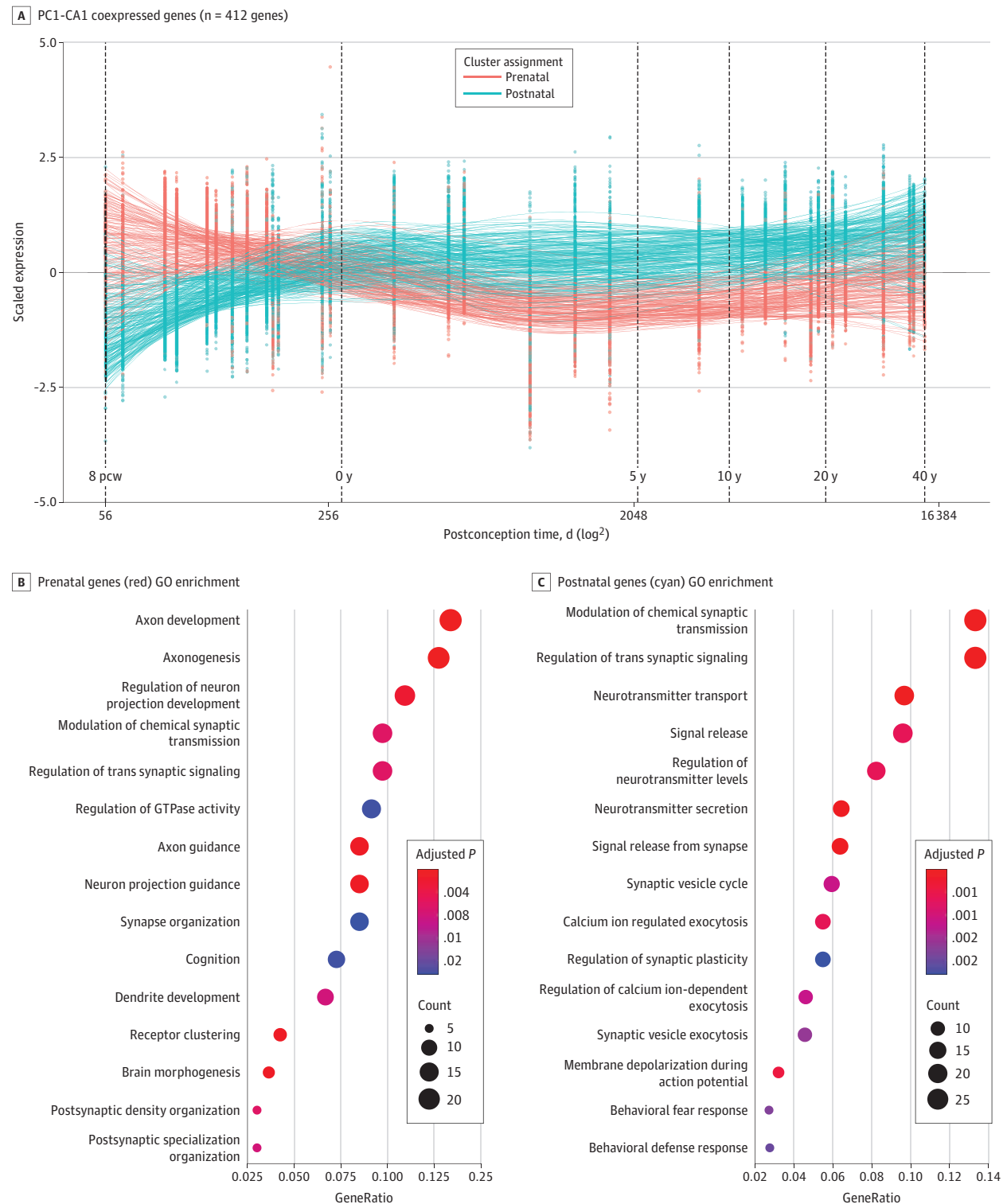
Discussion

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



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 study⁴²) 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*, *robo*s, 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.

ARTICLE INFORMATION

The Writing Committee for the Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive-Compulsive Disorder, and Schizophrenia ENIGMA Working Group:

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Affiliations of The Writing Committee for the Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive-Compulsive Disorder, and Schizophrenia ENIGMA Working Group: Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada (Patel, Parker, Paus); Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada (Patel, Parker, Paus); The Hospital for Sick Children, Toronto, Ontario, Canada (Shin, Pausova); Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

(Howard, French); Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles (Thomopoulos, Jahanshad, Ching, Thompson); Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia (Pozzi, Schmaal); Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan (Abe, Nakamae); Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Abé); Department of Psychiatry, Yale University, New Haven, Connecticut (Anticevic, Gruner); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (Alda, Hajek); University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells and Systems, Cognitive Neuroscience Center, Groningen, the Netherlands (Aleman); Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, CIBERSAM, Spain (Alloza, Janssen); FIDMAG Germanes Hospitalàries Research Foundation, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Catalonia, Spain (Alonso-Lana, Canales-Rodríguez, Fatjó-Vilas, Pomarol-Clotet, Salvador, Sarró); The Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute, University of Toronto, Toronto, Ontario, Canada (Ameis); Department of Pediatrics University of Toronto, Ontario, Canada (Anagnostou); Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, Scotland (McIntosh, Whalley, Lawrie); Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, School of Medicine, Universidad Complutense, CIBERSAM (Arango, Moreno, Parellada); The Mathison Centre for Mental Health Research & Education, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada (Arnold); Social, Genetic and Developmental Psychiatry Centre; Institute of Psychiatry, Psychology and Neuroscience; King's College London, London, England (Asherson, Kuntsi); Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy (Assogna, Banaj, Fabrizio Piras, Federica Piras, Spalletta, Vecchio); INT UMR 7289, Aix-Marseille Université, CNRS, Aix-en-Provence, France (Auzias, Deruelle); Department of Psychiatry, Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria; Centro de Investigación Biomédica en Red de Salud Mental, Santander, Spain (Ayesa-Arriola, Setién-Suero, Vázquez-Bourgon); Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, Maastricht University, the Netherlands (Bakker); Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany (Banaschewski, Baumeister, Brandeis, Hohmann); Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil (Bandeira, Bau, Cupertino); The Research Institute of Pediatrics and Child Health of the Central Clinical Hospital of the Russian Academy of Sciences of the

Ministry of Science and Higher Education of the Russian Federation, Moscow, Russia (Baranov, Namazova); Magnetic Resonance Image Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain (Bargalló); University of Münster, Department of Psychiatry, Münster, Germany (Baune, Borgers, Dannowski, Dohm, Grotegerd, Hahn, Leehr, Meinert, Opel, Redlich, Repple, Sarink); Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Melbourne, Australia (Bellgrove); Psychiatry and Clinical Psychobiology, Division of Neuroscience, Scientific Institute Ospedale San Raffaele, Milano, Italy (Benedetti, Bollettini); Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy (Bertolino); Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Department of Anatomy & Neuroscience, Amsterdam Neuroscience, Amsterdam, the Netherlands (Boedhoe, van den Heuvel); Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, Utrecht, the Netherlands (Boks); Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona Bipolar Disorders and Depressive Unit, Hospital Clinic, Institute of Neurosciences, University of Barcelona, Barcelona, Spain (del Mar Bonnin, Goikolea, Radua, Vieta); Department of Psychiatry, University of Basel, Basel, Switzerland (Borgwardt); McLean Hospital, Harvard Medical School, Belmont, Massachusetts (Brennan); School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia (Bruggemann, T. W. Weickert, C. S. Weickert); Institute for Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany (Bülow); Laboratory of Psychiatric Neuroimaging (LIM-21), Departamento e Instituto de Psiquiatria, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil (Busatto, Chaim-Avancini, Rosa, Serpa, Zanetti); Department of Developmental Neuroscience – IRCCS Fondazione Stella Maris, Pisa, Italy (Calderoni, Muratori); Department of Clinical and Experimental Medicine, University of Pisa, (Calderoni, Muratori); Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TREND), Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, Georgia (Calhoun); Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, Barcelona, Spain (Calvo, Lazaro, Puig); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); University of Barcelona, Spain (Calvo, Lazaro, Puig); Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, H91 TK33 Galway, Ireland (Cannon, Martyn, McDonald, McPhilemy, Nabulsi); School of Psychiatry, University of New South Wales, Randwick, New South Wales, Australia (Carr, Green, Mitchell, Quidé); Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland (Casella, Sawa, K. Yang); Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex, Brighton, England (Cercignani, N. A. Harrison); Centre for Integrative Neuroscience

and Neurodynamics, School of Psychology and Clinical Language Sciences, University of Reading, Reading, England (Christakou); Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, Australia (Coghill); Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Tübingen, Tübingen, Germany (Conzelmann); Department of Psychiatry, Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Departamento de Psiquiatria, Universidad de Sevilla, Instituto de Biomedicina de Sevilla (IBIS), Sevilla, Spain (Crespo-Facorro); Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London UK; Zurich Center for Neuroeconomics, University of Zurich, Zurich, Switzerland (Cubillo); Department of Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis, Minnesota (Cullen); Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, Sackler Institute for Translational Neurodevelopment, London, London, England (Daly); Orygen, Melbourne, Australia (Davey); Department of Psychiatry, Amsterdam UMC, Amsterdam, the Netherlands (Denys); IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy (Di Giorgio); Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada (Dickie, Voineskos); Department of Psychology, School of Arts and Social Sciences, City, University of London, Northampton Square, Clerkenwell, London, England (Dima); Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Dresden, Germany (Ehrlich, King); Department of Psychiatry and Biological Sciences, Albert Einstein College of Medicine, the Bronx, New York (Ely); University Medical Center Goettingen, Department of Psychiatry and Psychotherapy, Systems Neuroscience and Imaging in Psychiatry, Goettingen, Germany (Erwin-Grabner, Goya-Maldonado, Singh); Department of Psychiatry, University of Tuebingen, Tuebingen, Germany (Ethofer, Fallgatter); Behavioral Neuroscience Department, Oregon Health & Science University, Portland (Fair); Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, New York (Faraone); Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Fedor); Child OCD and Anxiety Disorders Program, Department of Psychiatry, University of Michigan Medical School, Ann Arbor (Fitzgerald); San Francisco VA Medical Center, San Francisco, California (Ford); Department of Psychiatry, Trinity College Dublin, Dublin, Ireland (Frodl, McCarthy); University of East London, School of Psychology, London, England (Fu); Neuroscience Research Australia (NeuRA), Sydney, New South Wales, Australia (Fullerton, Quidé); Department of Neuroscience, Brighton and Sussex Medical School, Brighton, England (Gabel); Tommy Fuss Center for Neuropsychiatric Disease Research, Department of Psychiatry, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Glahn);

School of Psychiatry, University of New South Wales, Randwick, New South Wales, Australia (Roberts); Central Clinical Hospital of the Russian Academy Sciences, Moscow, Russia (Gogberashvili); Department of Psychology, Stanford University, Stanford, California (Gotlib); Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany (Grabe); Department of Psychiatry, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil (Grevet, Picon); Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa (Groenewold, Temmingh, Uhlmann); Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University Hospital, Heidelberg, Germany (Gruber, Krämer, Rauer, Richter); FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain (Guerrero-Pedraza); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (R. E. Gur, R. C. Gur, Satterthwaite, Wolf); Department of Bioengineering, Imperial College London, London, England (Haar); Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Haarman); Department of Biomedicine, University of Bergen, Bergen, Norway (Haavik); Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia (B. J. Harrison); University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Groningen, the Netherlands (Hartman); Department of Experimental Psychology, Vrije Universiteit, Amsterdam, Netherlands (Heslenfeld); Genentech Inc, South San Francisco, California (Hibar); Department of Psychology, University of Oslo, Oslo, Norway (Hilland, Jonassen, Landrø); Research Center for Child Mental Development, Chiba University, Chiba, Japan (Hirano, Nakagawa); Department of Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco (Ho); University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Groningen, the Netherlands (P. J. Hoekstra); Radboud University Medical Center, Karakter University Center of Child and Adolescent Psychiatry, Nijmegen, the Netherlands (L. Hoekstra); Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland (Hong, Kochunov); National Institute of Mental Health, Klecany, Czech Republic (Höschl, Skoch, Spaniel, Tomecek); Department of Clinical Medicine, University of Bergen, Bergen, Norway (Høvik); Neuroscience Institute, University of Cape Town, Cape Town, South Africa (Howells); Department of Psychiatry and Psychotherapy, Philipps University Marburg, Marburg, Germany (Nenadic, Simon); Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Jalbrzikowski, Luna); University of Oxford, Oxford, England (James); Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada (Jaspers-Fayer, Stewart); Department of Internal Medicine, First Affiliated Hospital of Kunming Medical University, Kunming, China (Xu); Research Institute of Pediatrics and child health of the Central clinical hospital of the

Ministry of Science and Education, Moscow, Russia (Karkashadze); Department of Psychiatry, Philipps-University Marburg, Marburg, Germany (Kircher, Krug); Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada (Kirschner); Department of Neuroradiology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany (Koch); Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, University Hospital RWTH Aachen, Aachen, Germany (Kohls); Child Neuropsychology Section, University Hospital RWTH Aachen, Germany; JARA-Brain Institute II Molecular Neuroscience and Neuroimaging, Research Centre Juelich, Juelich, Germany (Konrad); Department of Psychiatry and Psychotherapy, University of Bonn, Germany (Krug); Department of Psychiatry, Seoul National University College of Medicine, Seoul, Korea (Kwon); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Landén); Mental Health Research Center, Moscow, Russia (Lebedeva); Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, Barcelona, Spain (Lera-Miguel); Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg, Würzburg, Germany (Lesch, Ziegler); SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, Stellenbosch, South Africa (Lochner); Institute of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil (Louza); Department of Biological and Medical psychology, University of Bergen, Bergen, Norway (Lundervold); Departments of Psychiatry and Pediatrics, University of Calgary, Calgary, Alberta, Canada (MacMaster); University Centre for Information Technology, University of Oslo, Oslo, Norway (Maglanoc); Developmental Imaging, Murdoch Children's Research Institute, Melbourne, Australia (Malpas); Group of Research in Mental Health, Institut d'Investigació Biomèdica Sant Pau, IIBSant Pau; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain (Portella); Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York (Marsh); Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Mataix-Cols); Department of Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco (Mathalon); Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain (Menchón, Soriano-Mas); McMaster University, Mood Disorders Program, SJH Hamilton, Hamilton, Ontario, Canada (Minuzzi); Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal (Morgado, Picó-Pérez); Department of Forensic and Neurodevelopmental Science, King's College London, London, England (C. M. Murphy); Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry Psychology and Neuroscience, King's College, London, England (D. Murphy); Louis A. Failace, MD, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston (Mwangi, Soares, Wu); OCD clinic, Department of Psychiatry, National Institute of Mental Health and

Neurosciences (NIMHANS), Bangalore, India (Narayanaswamy, Reddy, Venkatasubramanian); Department of Pediatrics, University of California, Irvine (Nguyen); Department of Child and Adolescent Psychiatry and Psychology, Hospital Clinic, Barcelona, Spain (Nicolau); Center for MR Research, University Children's Hospital, Zürich, Switzerland (O'Gorman Tuura); Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, North Carolina (O'Hearn); Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, department of Pediatrics, Amsterdam Reproduction and Development, Amsterdam, the Netherlands (Oosterlaan); Center for Neurobehavioral Genetics, University of California Los Angeles (Ophoff); Department of Psychiatry, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (Oranje, Shook); Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain (García de la Foz, Tordesillas-Gutiérrez); Neuroscience Research Australia, Sydney, Australia (Overs); Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, England (Paloyelis); Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, Australia (Pantelis); Department of Psychology (Biological Psychiatry, Clinical Psychology, and Psychotherapy), and Center of Mental Health, University of Würzburg, Würzburg, Germany (Pauli); Division of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland; Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Denmark (Plessen); Department of Psychiatry and Human Behavior, University of California, Irvine (Preda); Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute, Barcelona, Catalonia, Spain; Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain (Ramos-Quiroga, Richarte); Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain (Ramos-Quiroga, Richarte); Priority Centre for Brain & Mental Health Research, The University of Newcastle, Callaghan, New South Wales, Australia (Rasser, Schall); Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt (Reif); Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands (Reneman, Schranter); National Institute for Nuclear Physics, Pisa Division, Pisa, Italy (Retico); Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England (Rubia); Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan (Hashimoto); Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School, Belmont, Massachusetts (Sacchet); Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario

Gregorio Marañón, IISGM, Facultad de Psicología, Universidad Autónoma de Madrid (Santónja); Neuroscience Research Australia, Sydney, New South Wales, Australia (Schofield); Department of Child and Adolescent Psychiatry, RWTH Aachen University Hospital, Aachen, Germany (Seitz); National Human Genome Research Institute and National Institute of Mental Health, Bethesda, Maryland (Shaw); School of Psychology, Deakin University, Geelong, Melbourne, Australia (Silk); West Region, Institute of Mental Health, Singapore (Sim); Columbia University Irving Medical Center, New York, New York (Simpson); Center for Child and Adolescent Mental Health, Institute of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway (Skokauskas); Pediatric OCD Consultation Clinic, Anxiety Treatment and Research Center, SJH Hamilton, Ontario, Canada (Soreni); Department of Psychiatry, New York University School of Medicine, Nathan Kline Institute, New York (Stern); Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan (Takayanagi); Anxiety Disorders Center, The Institute of Living, Hartford, Connecticut (Tolin); Laboratory of Medical Physics and Magnetic Resonance - IRCCS Fondazione Stella Maris, Pisa, Italy (Tosetti); Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands (van Amelsvoort); Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands (van der Wee, van der Werff); Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre, Rotterdam, the Netherlands (van Haren); Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam Neuroscience, Amsterdam, the Netherlands (van Wingen); Academic Child Psychiatry Unit, Department of Pediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia (Vance); Hospital Clinic, University of Barcelona, Spain (Vieta); Department of Psychiatry and Forensic Medicine, Autonomous University of Barcelona, Cerdanyola del Vallès, Barcelona, Spain (Vilarroya); Instituto ITACA, Universitat Politècnica de València, Valencia, Spain (Vives-Gilabert); Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany (Völzke); Department for Child and Adolescent Psychiatry, University Hospital RWTH Aachen, Aachen, Germany (von Polier); Department of Psychology, University of Bath, Bath, England (Walton); Clinical Translational Neuroscience Laboratory, University of California Irvine, Irvine, CA; Center for the Neurobiology of Learning and Memory, University of California, Irvine (Weideman, van Erp); German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Germany (Wittfeld); University of California San Francisco, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of California, San Francisco, Weill Institute for Neurosciences (T. T. Yang); Department of Child and Adolescent Psychiatry, New York University Child Study Center, Hassenfeld Children's Hospital at NYU Langone, New York (Yoncheva); Seoul National University Hospital, Seoul, Republic of Korea (Yun); Department of Psychiatry, First Affiliated Hospital of Kunming Medical University, Kunming, China (Cheng); Departments of Human Genetics and Psychiatry, Radboud University

Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands (Franke); Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands (Hoogman); Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud UMC, Nijmegen, the Netherlands (Buitelaar); Donders Centre for Cognitive Neuroimaging, Radboud University Medical Centre, Nijmegen, the Netherlands (van Rooij); Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway (Andreassen); Department of Psychiatry, Amsterdam UMC, location VUMC, Amsterdam, the Netherlands (Veltman); Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia (Schmaal); SAMRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa (Stein); Psychology Department and Neuroscience Institute, Georgia State University, Atlanta, Georgia (Turner); Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, Canada (Paus).

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Concept and design: Patel, Bau, Boedhoe, Christakou, R. C. Gur, Hibar, Kirschner, Kochunov, Menchon, Mwangi, Richarte, Rubia, Sawa, Soreni, van der Werff, Vieta, Ching, Thompson, Paus.
Acquisition, analysis, or interpretation of data: Patel, Parker, Shin, Howard, French, Thomopoulos, Pozzi, Y. Abe, C. Abé, Anticevic, Alda, Aleman, Alloza, Alonso-Lana, Ameis, Anagnostou, McIntosh, Arango, Arnold, Asherson, Assogna, Auzias, Ayesa-Arriola, Bakker, Banaj, Banaschewski, Edom Bandeira, Bargallo, Baumeister, Baune, Bellgrove, Benedetti, Bertolino, PM Boks, Bollettini, Bonnin, Borgers, Borgwardt, Brandeis, Brennan, Bruggemann, Buelow, Busatto, Calderoni, Calhoun, Canales-Rodriguez, Cannon, Carr, Cascella, Cercignani, Chaim-Avincini, Christakou, Coghill, Conzelmann, Crespo-Facorro, Cubillo, Cullen, Basso Cupertino, Daly, Dannlowski, Davey, Denys, Deruelle, Di Giorgio, Dickie, Dima, Dohm, Ehrlich, Ely, Erwin-Grabner, Ethofer, Fair, Fallgatter, Faraone, Fatjo-Vilas, Fedor, Fitzgerald, Ford, Frodl, Fu, Fullerton, Gabel, Glahn, Roberts, Gogberashvili, Goikolea, Gotlib, Goya-Maldonado, Grabe, Green, Grevet, Groenewold, Grotegerd, Gruber, Gruner, Janssen, Jaspers-Fayer, Xu, Jonassen, Karkashadze, King, Kircher, Kirschner, Koch, Kochunov, Kohls, Konrad, Kraemer, Krug, Kuntsi, Kwon, Landen, Landrø, Lazaro, Lebedeva, Leehr, Lera-Miguel, Lesch, Lochner, Louza, Luna, Lundervold, MacMaster, Maglanoc, Malpas,

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Drafting of the manuscript: Patel, Alloza, Baranov, Baune, Bruggemann, Crespo-Facorro, Basso Cupertino, Fair, Glahn, Gogberashvili, Guerrero-Pedraza, Hajek, B. Harrison, Howells, Jonassen, Karkashadze, Kochunov, Kwon, Landrø, Lebedeva, Maglanoc, Marsh, Mwangi, O'Hearn, Oranje, Fabrizio Piras, Salvador, Silk, Stern, Vieta, K. Yang, Yoncheva, Ching, Paus.
Critical revision of the manuscript for important intellectual content: Patel, Parker, Shin, Howard, French, Thomopoulos, Pozzi, Y. Abe, C. Abé, Anticevic, Alda, Aleman, Alonso-Lana, Ameis, Anagnostou, McIntosh, Arango, Arnold, Asherson, Assogna, Auzias, Ayesa-Arriola, Bakker, Banaj, Banaschewski, Edom Bandeira, Bargallo, Baumeister, Baune, Bellgrove, Benedetti, Bertolino, PM Boks, Bollettini, Bonnin, Borgers, Borgwardt, Brandeis, Brennan, Bruggemann, Buelow, Busatto, Calderoni, Calhoun, Calvo, Canales-Rodriguez, Cannon, Carr, Cascella, Cercignani, Chaim-Avincini, Christakou, Coghill, Conzelmann, Crespo-Facorro, Cubillo, Cullen, Daly, Dannlowski, Davey, Denys, Deruelle, Di Giorgio, Dickie, Dima, Dohm, Ehrlich, Ely, Erwin-Grabner, Ethofer, Fallgatter, Faraone, Fatjo-Vilas, Fedor, Fitzgerald, Ford, Frodl, Fu, Fullerton, Gabel, Roberts, Goikolea, Gotlib, Goya-Maldonado, Grabe, Green, Grevet, Groenewold, Grotegerd, Gruber, Gruner, R. E. Gur, R. C. Gur, Haar, Haaran, Haavik, Hahn, N. Harrison, Hartman, Whalley, Heslenfeld, Hibar, Hilland, Hirano, Ho, P. Hoekstra, L. Hoekstra, Hohmann, Hong, Hoschl, Hovik, Nenadic, Jalbrzikowski, James, Janssen, Jaspers-Fayer, Xu, King, Kircher, Kirschner, Koch, Kochunov, Kohls, Konrad, Kraemer, Krug, Kuntsi, Landen, Lazaro, Leehr, Lera-Miguel, Lesch, Lochner, Louza, Luna, Lundervold, MacMaster, Malpas, Portella, Martyn, Mataix-Cols, Mathalon, McCarthy, McDonald, McPhilemy, Meinert, Menchon, Minuzzi, Mitchell, Moreno, Morgado, Muratori, C. Murphy, D. Murphy, Mwangi, Nabulsi, Nakagawa, Nakamae, Namazova-Baranova, Narayanaswamy, Jahanshad, Nguyen, Nicolau, O'Gorman Tuura, Oosterlaan,

Opel, Ophoff, Oranje, Ortiz-Garcia de la Foz, Overs, PALOVELIS, Pantelis, Parellada, Pauli, Pico-Perez, Picon, Fabrizio Piras, Federica Piras, Plessen, Pomarol-Clotet, Preda, Puig, Quide, Radua, Ramos-Quiroga, Rasser, Rauer, Reddy, Redlich, Reif, Reneman, Repple, Retico, Richarte, Richter, Rosa, Rubia, Hashimoto, Sacchet, Santonja, Sarink, Sarro, Satterthwaite, Sawa, Schall, Schofield, Schrantee, Seitz, Serpa, Setien-Suero, Shaw, Shook, Sim, Schmitt, Simpson, Singh, Skoch, Skokauskas, Soares, Soreni, Soriano-Mas, Spalletta, Spaniel, Lawrie, Stewart, Takayanagi, Temmingh, Tolin, Tomecek, Tordesillas-Gutierrez, Tosetti, Uhlmann, van Amelsvoort, van der Wee, van der Werff, van Haren, van Wingen, Vance, Vazquez-Bourgon, Vecchio, Venkatasubramanian, Vieta, Vilarroya, Vives-Gilabert, Voineskos, Voelke, von Polier, Walton, T. Weickert, C. Weickert, Weideman, Wittfeld, Wolf, Wu, T. Yang, Yun, Cheng, Zanetti, Ziegler, Franke, Hoogman, Buitelaar, van Rooij, Andreassen, Ching, J. Veltman, Schmaal, Stein, van den Heuvel, Turner, van Erp, Pausova, Thompson.

Statistical analysis: Patel, Parker, Shin, Howard, French, Alloza, Banaj, Baranov, Calderoni, Di Giorgio, Dima, Faraone, Frodl, Glahn, Hovik, James, Karkashadze, King, Kirschner, Kraemer, Lesch, Maglanoc, Malpas, Minuzzi, Mwangi, Fabrizio Piras, Pomarol-Clotet, Quide, Redlich, Retico, Richter, Stern, Tomecek, Vecchio, von Polier, Walton, Wittfeld, Wu, Hoogman, van Rooij, Ching. **Obtained funding:** Patel, Alda, Ameis, Anagnostou, McIntosh, Arango, Asherson, Bellgrove, Benedetti, Calhoun, Calvo, Canales-Rodriguez, Cannon, Dannlowski, Davey, Fair, Fitzgerald, Ford, Frodl, Fu, Fullerton, Gotlib, Grabe, Green, Groenewold, Gruner, Guerrero-Pedraza, R. E. Gur, Haarman, Haavik, Hajek, B. Harrison, Ho, Hong, Hoschl, Nenadic, James, Kircher, Kochunov, Krug, Kuntsi, Landen, Landrø, Lesch, Lochner, MacMaster, Portella, Marsh, Mataix-Cols, Mathalon, Mitchell, Morgado, C. Murphy, D. Murphy, Narayanaswamy, Oosterlaan, Ophoff, Pantelis, Parellada, Pomarol-Clotet, Ramos-Quiroga, Reddy, Rubia, Schall, Schofield, Shaw, Silk, Sim, Soreni, Spalletta, van der Wee, Voelke, T. Weickert, C. Weickert, T. Yang, Zanetti, Franke, Hoogman, Buitelaar, Turner, Thompson.

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Vazquez-Bourgon, Venkatasubramanian, Vieta, Weideman, K. Yang, Yun, Cheng, Zanetti, Franke, Buitelaar, van Rooij, Ching, Turner, van Erp. **Supervision:** Baune, Bertolino, PM Boks, Borgwardt, Brandeis, Calvo, Denys, Ehrlich, Fallgatter, Frodl, Fu, Goikolea, Grabe, Green, B. Harrison, Hibar, Ho, Hoschl, Kircher, Koch, Lazaro, Lesch, Mathalon, Menchon, Oosterlaan, Ophoff, Oranje, Pantelis, Parellada, Pico-Perez, Pomarol-Clotet, Preda, Puig, Ramos-Quiroga, Reddy, Redlich, Rubia, Sarro, Schofield, van der Wee, Vance, Vieta, Vilarroya, Zanetti, Buitelaar, Andreassen, Ching, J. Veltman, Schmaal, Pausova, Thompson, Paus.

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