Virtual histology of cortical thickness reveals shared neurobiology underlying six psychiatric disorders

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Key Points

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

Findings: In this meta-analysis, regions of the cerebral cortex with greater expression of genes specific to pyramidal (CA1) cells are also regions with greater case-control group differences in cortical thickness in all six studied disorders, namely attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder and schizophrenia. There is a common profile of the group difference in cortical thickness shared amongst all these disorders (48% of the variance explained). A bioinformatics analysis of co-expression of genes associated with this shared profile suggests that these genes are involved in neurodevelopmental processes (prenatally), and processes underlying synaptic activity & plasticity (postnatally).

Meaning: There are shared neurobiological and cellular mechanisms underlying differences in cortical thickness across multiple psychiatric disorders - implicating a common role of prenatal development and postnatal functioning of the cerebral cortex.

Abstract (350 words maximum)

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

Design: Meta-analytic profiles of group differences in cortical thickness between cases and controls were generated using T1-weighted magnetic resonance images. Similarity between inter-regional 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. Gene co-expression, clustering and enrichment for genes associated with these disorders were conducted. Data analysis was conducted between June and December 2019.

Setting: A meta-analysis including 145 cohorts across 6 psychiatric disorders drawn from the ENIGMA Consortium.

Participants: The number of cases/controls in each of the six disorders were as follows: ADHD: 1,814/1,602; ASD: 1,748/1,770; BD: 1,547/3,405; MDD: 2,658/3,572; OCD: 2,266/2,007; and SCZ: 2,688/3,244.

Main outcomes and measures: Inter-regional profiles of group difference in cortical thickness between cases and controls.

Results: Inter-regional profiles of group differences in cortical thickness for each of the six psychiatric disorders were associated with profiles of gene expression specific to pyramidal (CA1) cells, astrocytes (except for BD) and microglia (except for OCD). Principal component analysis revealed a shared profile of difference in cortical thickness across the six disorders (48% variance explained); inter-regional profile of this principal component 1 was related to that of the pyramidal-cell gene expression. Co-expression analyses of these genes revealed two clusters: (1) a prenatal cluster enriched with genes involved in neurodevelopmental (axon guidance) processes; and (2) a post-natal cluster enriched with genes involved in synaptic activity & plasticity-related processes. These clusters were enriched with genes associated with all six psychiatric disorders.

Conclusion: There are shared neurobiological processes underlying 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.

Introduction

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 ENIGMA (Enhanced Neuroimaging Genetics Through Meta-Analysis) Consortium has conducted some of the largest MRI studies characterizing group differences between patients (cases) and controls 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 (SCZ).[6] Nonetheless, the neurobiology underlying these MRI-derived macroscopic features is not well understood.

As identified in *post-mortem* studies, there are subtle differences in the cellular composition of the cerebral cortex of patients diagnosed with 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 SCZ.[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 SCZ.[16]

Several MRI studies have demonstrated distinct inter-regional 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 inter-regional (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 SCZ[1–6,18]; a recent report of the ENIGMA cohorts showed cross-disorder correlations among disorders.[19] Likewise, large scale genome-wide association studies (GWAS) identify shared genetic architecture amongst these psychiatric disorders.[20]

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

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

Methods

Meta-analytic 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**. 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 on their respective cohorts, which modelled cortical thickness of each region, separately, as a function of diagnosis (e.g., ADHD), age, age^2, sex, and site-specific covariates (e.g., 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 was used to generate meta-analytic profiles of group differences across the 34 regions for each disorder.[22] This report is a meta-analysis of shared data in the ENIGMA consortium rather than existing literature.

MRI-derived similarity and genetic similarity

This analysis was carried out to evaluate similarity in pair-wise correlations in inter-regional profiles of group differences in cortical thickness and corresponding pair-wise correlations in genome-wide genetic architecture; described in eMethods. Group differences in cortical thickness were first correlated across psychiatric disorders with a biweight midcorrelation using R package WGCNA (rationale in eMethods).[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's 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 inter-regional profile of group differences in cortical thickness, with inter-regional profiles of cell-specific gene expression.[26,27] As described previously, gene-expression data from the Allen Human Brain Atlas (AHBA; 6 donors, 24 to 57 years of age) were first mapped to the 34 regions of the Desikan-Killiany atlas.[28,29] To ensure similarity of inter-regional profiles in gene expression across donors, and across the lifespan, we apply a conservative two-stage filtering process. First, a donor-to-median correlation in the AHBA was used to retain only genes whose profiles are consistent among the six donors (retaining 8,216 out of 20,737 genes present in AHBA). Second, the genes passing stage one are filtered based on inter-regional profile similarity with an independent atlas of gene expression, namely BrainSpan (retaining 2,511 out of 8,216 genes; see **eMethods** for additional details). The final set of 2,511 genes was used for

analyses conducted in this report. Next, single-cell RNA sequencing data from the mouse hippocampus and S1 cerebral cortex were used to categorize the 2,511 genes specific to nine cell types identified (CA1 pyramidal, S1 pyramidal, interneuron, astrocyte, microglia, oligodendrocyte, mural, endothelial and ependymal cells).[30] Pyramidal cell types (CA1 and S1) are labeled based on their anatomic origin. But the molecular characteristics of these pyramidal cells, as indexed by gene expression, are not restricted to the brain regions in which these two types of pyramidal cells were found. The use of these panels is analogous to a data reduction technique driven by neurobiologically relevant clustering (see **eMethods** for additional details). Inter-regional 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 (due to data availability in AHBA).

Co-expression analyses

Seed genes were defined by biweight midcorrelation between principal component 1 (PC1) profile (shared variance in group differences in cortical thickness across the six disorders) and cell-specific genes passing false discovery rate (FDR) corrected threshold $p<0.05$.[31] For these analyses, we harmonized gene-expression data from human cerebral cortex across five datasets (AHBA,[29] BrainCloud,[32] Brain eQTL Almanac [Braineac],[33] Genotype Tissue Expression [GTEx],[34] and BrainSpan)[35]. The curation of these five gene-expression databases has been described previously and presented in eMethods.[36,37] In total there were 534 donors (ages 0 - 102 years old) with gene-expression data for 16,245 genes across all datasets. Co-expression analyses were generated using linear mixed-effects models where gene expression of each seed is modelled against other genes' expression with age and sex as fixed effects and donor identifier as a random effect. The top 0.1% of positively co-expressed genes for each of the seed genes were used to construct our co-expressed network panels.

Gene trajectory clustering

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

Gene ontology, KEGG, and psychiatric disorder enrichment analysis

Gene ontology and KEGG pathway enrichment analysis were conducted using the R package "clusterProfiler".[39] GO (biological process ontology only) and KEGG 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 cut-off of 0.90. Enrichment between co-expressed 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 (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 dataset of gene expression for co-expression analyses. P-values were corrected using FDR procedure.[41]

Results

Meta-analysis We characterized meta-analytic profiles of group differences in cortical thickness for each of the six disorders across the 34 regions of the cerebral cortex (**Figure 1**, **eTable 3-8**, **eFigure 1,** left hemisphere only). In total, there were 12,721 cases and more than 15,000 controls contributing to these profiles (**eTable 2**). Across the disorders, inter-regional variation in group differences of cortical thickness were positively correlated between SCZ and ADHD, ASD, BD, MDD & OCD (**Figure 2A**). Overall, there was a general trend of positive correlations ($r_{bicor} > 0$) of group differences across all six psychiatric disorders (**Figure 2A**). Genetic correlations, as quantified by linkage-disequilibrium score regression, also showed a number of pair-wise positive correlations among these psychiatric disorders, in particular for SCZ (**Figure 2B,** reproduced using data from the Brainstorm consortium).[20] Cross-disorder similarity of differences in cortical thickness (derived from MRI, **Figure 2A**) was correlated positively with cross-disorder genetic similarity (derived from GWAS, **Figure 2B**), explaining 27% of variance (Mantel's p value = 0.034, Pearson p value = 0.045).

Virtual histology of group difference in cortical thickness Inter-regional variation in the expression of genes specific to pyramidal (CA1) cells correlated negatively with the inter-regional profile of group differences in cortical thickness in each of the six psychiatric disorders (-0.08>r>-0.23, FDR-p-value<0.05, **Figure 3**, **eTable 9, eFigure 2**). 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 relationship with inter-regional profiles of expression of genes specific to astrocytes and microglia in all six disorders except BD (no correlation with astrocytes) and OCD (no correlation with microglia). Lastly, we observed a negative relationship between pyramidal (S1) specific expression and group differences in thickness in BD only.

Principal component analysis Given the similarity of findings across the six 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 six disorders (**eFigure 3**). PC1 was positively correlated with each of disorder's profiles (**eFigure 3C**), and its inter-regional profile was negatively associated with the inter-regional 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.

Shared neurobiology across disorders To investigate the relationship between PC1 and CA1 pyramidal specific genes, we used all CA1 genes associated significantly (FDR p<0.05) with PC1 as seed genes for co-expression analyses. Data from the AHBA, BrainEAC, BrainSpan, BrainCloud, and GTEx were harmonized to identify robust co-expression associations across the genome (**eFigure 4&5**). These "PC1-CA1" co-expressed genes (n = 412 genes) were clustered based on their temporal pattern of expression using unsupervised nonparametric mixed modelling. This analysis yielded two clusters: Cluster 1 was upregulated during prenatal time periods and down regulated in postnatal life; and Cluster 2 that showed the opposite developmental trajectory (**Figure 5A**). GO enrichment analysis revealed involvement of neurodevelopmental processes (axon development; FDR-pvalue=5.15E-05) in the "prenatal" cluster (**Figure 5B, eFigure 6**) and involvement of synaptic signalling/neurotransmission and synaptic plasticity related terms (FDR-pvalue=5.11E-09, and 2.31E-03, respectively) in the "postnatal" cluster (**Figure 5C, eFigure 6**). Gene-enrichment analysis showed that the prenatal cluster is enriched in genes associated with ASD, BD, MDD and SCZ, while the postnatal cluster is enriched only in genes associated with ADHD and SCZ (FDR-pvalue < 0.05, **eFigure** 7). The entire co-expressed network (i.e., genes from both clusters) is enriched for all six disorders, at varying levels of enrichment (**eFigure 7**). 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 (AUROC=0.68, FDR-pvalue = 2.35E-15), while down-regulated in the ventricular zone (AUROC=0.30, FDDR-pvalue = 1.30E-17; **eFigure 8; eTable 10**). This held true for the post-natal cluster as well (**eFigure 8, eTable 11**).

The analysis described above was repeated for the astrocyte- and microglial-specific genes. PC1-Astrocyte co-expressed genes (n = 168 genes) were enriched in metabolic processes such as amino acid transport (FDR-p-value=2.09E-03), as well as enriched in genetic variants associated with BD and SCZ (FDR-p-value=0.013 & 0.014, respectively, **eFigure 9**). PC1-Microglia co-expressed genes (n = 118 genes) were enriched in immune-related processes (FDR-p-value=1.7E-08) and showed no enrichment with genetic variants associated with any of the six psychiatric disorders (**eFigure 10**).

Discussion

We characterized robust inter-regional differences in cortical thickness between cases and controls across the cerebral cortex in six common psychiatric disorders, as done previously by the individual Working Groups of the ENIGMA Consortium.[1–6,18] The inter-regional 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 six disorders. This also facilitated our observation of the similarity between shared differences in MRI-derived thickness and

genetic architecture across these six disorders, an observation suggesting the presence of genetic variants that may be associated with “vulnerable” brain phenotypes in common for the six 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 six 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 labelled based on the source of these cells (CA1 region of the hippocampus), this does not mean that biological processes implicated in “CA1” genes are restricted to this region; in fact, similar molecular processes are present throughout the human cerebral cortex (see Supplement for additional details). As such, we interpret the functional relevance of these genes being related to differences in cortical thickness. It is important to state that the gene expression used throughout this report comes from individuals without any diagnoses of neurological or psychiatric disorders. Studies linking cell-specific genes with psychiatric GWAS-associated genes show similar enrichment of CA1 pyramidal cells in ASD, BD, MDD, and SCZ.[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 (this report).

Principal component analysis identified a common component of these cortical differences, indicating a shared inter-regional profile of case-control differences in cortical thickness among all six 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 (see **eFigure 3** for more details). As expected from the disease-specific analyses, this PC1 profile was associated with the same three cell types, namely CA1 pyramidal, astrocyte, and microglia. The CA1 pyramidal geneset is enriched with biological processes related to dendritic arborization[27], and extensive dendritic branching is a key morphological phenotype of pyramidal neurons.[43] Similarly, our phenotype is derived from cortical thickness, a measure that is directly correlated 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, 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 *post mortem* samples from the cerebral cortex of patients with ASD[47,48], BD[49], SCZ[49], depression[50], and anxiety.[50]

The network of genes co-expressed with the (CA1) pyramidal genes associated with PC1 contained two clusters: one upregulated during the prenatal and the other during the postnatal period. Through a series of bioinformatic approaches we found evidence for two 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 two clusters is highly convergent with the two-hit hypothesis regarding the etiology psychiatric disorders, particularly with schizophrenia.[51] We speculate that the group differences in cortical thickness observed across the six psychiatric disorders are a summation of processes occurring throughout life (pre- 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 due to perturbations in normal neurodevelopment.[52,53] Cross-disorder GWAS studies of ADHD, affective disorder, anorexia, ASD, BD, and SCZ have all implicated genes involved in regulating neurodevelopmental processes within radial glia and interneurons of the developing neocortex.[54]

The prenatal (co-expression) 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 as to establish the correct 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 our PC1-CA1 co-expressed genes (**eFigure 11***).*[55] See supplemental discussion 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, SCZ, 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 co-expressed 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 related to environmental rather than genetic components of risk for psychiatric disorders.

Limitations

There are several limitations to the approach used in this report. First, only 2,511 genes determined as having 'representative' inter-regional profiles of their expression are used for virtual histology. We chose this conservative approach given that inter-regional profiles in case-control differences and those in gene expression come from two different sets of brains (see Supplement for additional details). This limitation may lower our ability to capture other relevant neurobiological signals. In an attempt to mitigate this limitation, downstream analyses use co-expression to broaden the scope of the genes investigated, albeit indirectly. Secondly, we are using single-cell data from mice, which have shown general conservation with human data. There are, however, some species-specific differences that may not be accounted for in this report (see **eMethods** for details on single-**cell** vs. single-**nucleus** dataset).[61] Thirdly, our analysis uses a relatively coarse parcellation allowing us to capture gross inter-regional patterns of group differences in cortical thickness. This might, however, increase the potential for false positives (reduced number of comparisons) and for missing subtle (vertex-level) variations. Lastly, when interpreting T1-weighted MRI, we assume that these estimates reflect true variations in brain phenotype rather measurement error, artifacts, or other physiological sources of T1 signal.

Conclusion

In summary, we characterized shared neurobiology across six 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 towards 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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Figure legend

Figure 1: Meta-analytic profiles of group differences in cortical thickness (left hemisphere only) between cases and controls across the six psychiatric disorders investigated. Group differences are adjusted for age, sex and other site-specific variables. Error bars represent 95% confidence intervals. Estimates below zero represent thinner cortex in cases as compared with controls.

Figure 2 A. Cross disorder correlation of group differences in cortical thickness (profiles from Figure 1). B). Cross disorder genetic correlation (LD score regression) derived from Brainstorm et al. *Science* 2018. C. Plot of genetic correlation against phenotypic (MRI-derived difference in thickness) correlations between psychiatric disorders with a linear model fit (blue line, R2=0.27, Mantels p value = 0.034, Pearson p value < 0.05). * FDR-pvalue < 0.05, ** < 0.01, *** < 0.001.

Figure 3. Results from virtual histology. Distribution of correlation coefficients between cell-specific gene expression profiles and group differences in cortical thickness for the six psychiatric disorders. *represents FDR p < 0.05.

Figure 4. Principal components analysis of profiles of group differences across six psychiatric disorders. A. First principal component, PC1, plotted across the 34 regions of the left hemisphere. PC1 values are scaled down to have a max of zero in order to facilitate interpretation: negative values reflect greater differences in cortical thickness between cases and controls. Unscaled values presented in eFigure 3. B. Distribution of correlation coefficients between cell specific gene expression and PC1 profile. * indicates FDR-p-value < 0.05.

Figure 5. Lifespan trajectory in gene expression of PC1-CA1 co-expressed genes. Each line represents a fitted loess model for the expression of a given gene. Genes and their fitted models are coloured based on clustering based on temporal trajectories. PC1-CA1 co-expressed genes were generated using co-expression of seed genes, namely genes that correlate with PC1 profile and the 103 CA1 pyramidal specific genes passing FDR < 0.05. Gene ontology (GO) enrichment analysis of the prenatal cluster (B), and postnatal cluster (C).

Figure titles

Figure 1: Meta-analytic profiles of group differences in cortical thickness (left hemisphere only) between cases and controls

Figure 2: Phenotypic and genetic similarity between psychiatric disorders

Figure 3: Virtual histology correlations between psychiatric group differences in thickness and cell specific gene expression

Figure 4: Principal component 1 from the six psychiatric disorder profiles

Figure 5: Psychiatric disorder implicated PC1-CA1 Pyramidal gene co-expression and enrichment analysis