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ABSTRACT

BACKGROUND: Morphology of the human cerebral cortex differs across psychiatric disorders, with neurobiology and developmental origins mostly undetermined. Deviations in the tangential growth of the cerebral cortex during pre/perinatal periods may be reflected in individual variations in cortical surface area later in life.

METHODS: Interregional profiles of group differences in surface area between cases and controls were generated using T1-weighted magnetic resonance imaging from 27,359 individuals including those with attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, schizophrenia, and high general psychopathology (through the Child Behavior Checklist). Similarity of interregional profiles of group differences in surface area and prenatal cell-specific gene expression was assessed.

RESULTS: Across the 11 cortical regions, group differences in cortical area for attention-deficit/hyperactivity disorder, schizophrenia, and Child Behavior Checklist were dominant in multimodal association cortices. The same interregional profiles were also associated with interregional profiles of (prenatal) gene expression specific to proliferative cells, namely radial glia and intermediate progenitor cells (greater expression, larger difference), as well as differentiated cells, namely excitatory neurons and endothelial and mural cells (greater expression, smaller difference). Finally, these cell types were implicated in known pre/perinatal risk factors for psychosis. Genes coexpressed with radial glia were enriched with genes implicated in congenital abnormalities, birth weight, hypoxia, and starvation. Genes coexpressed with endothelial and mural genes were enriched with genes associated with maternal hypertension and preterm birth.

CONCLUSIONS: Our findings support a neurodevelopmental model of vulnerability to mental illness whereby prenatal risk factors acting through cell-specific processes lead to deviations from typical brain development during pregnancy.

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The majority of symptoms of mental illness, from hallucinations and delusions in psychosis to the impaired attention and cognitive control in attention-deficit/hyperactivity disorder (ADHD), are rooted in disturbances of perceptual, cognitive, and affective processes subserved by the cerebral cortex. The human cerebral cortex is a highly folded sheath of tissue (~1800 cm^2 of surface area) containing approximately 12 billion neurons and 17 billion non-neuronal cells (1). Both global and regional expansion of the primate cerebral cortex are driven by biological events taking place during fetal development; the phase of symmetrical division of progenitor cells in the proliferative zones during the first trimester is particularly important for tangential growth through addition of ontogenetic columns (2). Although neurogenesis—and related additions of ontogenetic columns—ends before birth, the surface area of the cerebral cortex continues to increase during the first 2 to 4 years of human life (3). But subsequent changes in the surface area of the human cerebral cortex, as estimated with magnetic resonance imaging (MRI), are comparatively minimal (4–6). Quantitively, a majority of the cortical expansion occurs prenatally and perinatally, with the most prominent rate in cortical expansion occurring during prenatal development (Figure S1) (7–10). Moreover, cortical surface area in children, adolescents, and young adults is correlated with birth weight, a common indicator for healthy neurodevelopment (11,12). The genetics of cortical surface area also implicates neurodevelopmental proliferative cells as compared with adult cell types (13,14). Therefore, in the adult brain, measures of cortical surface area provide a window into events shaping prenatal and early postnatal growth of the cerebral cortex that predate a broad array of mental illnesses (13,15–17).

To gain insights into the neurodevelopmental events that may underlie differential growth of the cerebral cortex in individuals with mental illness and/or the presence of clinically significant psychopathology (vs. healthy individuals) and the influence of external risk factors, we first estimated the extent of such group differences between cases[1] and controls in the surface areas of 11 cortical regions (due to corresponding availability of fetal gene expression data). We then identified cellular elements underlying interregional variations in these group differences using virtual ontogeny, through which interregional profiles of group differences in surface area were correlated with interregional profiles of gene expression. The latter were restricted to transcripts expressed during 12 to 22 postconception weeks (PCWs) and to the following cell types: radial glia, intermediate progenitor cells (IPCs), excitatory neurons, interneurons, oligodendrocyte progenitor cells, microglia, and endothelial and mural cells. Finally, we asked which of these cell types might mediate the impact on cortical growth of prenatal factors reported to increase the risk of developing psychosis—risk factors applicable to many mental illnesses in general.

[1]Cases are defined as individuals with a diagnosis of the following conditions: schizophrenia, autism spectrum disorder, attention-deficit/hyperactivity disorder, bipolar disorder, and major depressive disorder, or by the presence of symptoms of psychopathology as assessed with the Child Behavior Checklist in a large community-based sample of children (the ABCD Study).

METHODS AND MATERIALS

Meta-analytic Group Differences in Cortical Surface Area

T1-weighted MRI scans were acquired in 89 cohorts participating in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Consortium. The ENIGMA Consortium is a collaborative initiative in global neuroscience and focuses on studying the human brain in health and disease through genetics and imaging (18). Sample demographics and MRI acquisition details per cohort are provided in Tables S1–S7. FreeSurfer cortical reconstruction software was used to extract surface area according to a parcellation scheme that intersects with tissue sampling from the PsychENCODE Consortium, described in Supplemental Methods and presented in Figure S2. Individual ENIGMA cohorts performed multiple linear regression analysis, modeling surface area of each cortical region separately as a function of diagnosis status, age, age squared, sex, and site-specific covariates (such as MR scanner, multiple sites). Cohort-specific information regarding diagnostic and sampling criteria are described in previously published ENIGMA reports (19–23). Individual cohorts obtained institutional ethics approval, and informed consent was obtained from study participants or guardians. Cohort-level summary statistics were then meta-analyzed using an inverse variance–weighted random effects model from the "metafor" R package (24). Meta-analytic estimates are provided in Tables S8–S12.

The ABCD (Adolescent Brain Cognitive Development) Study is a longitudinal cohort study of brain development on roughly ~11,500 children sampled across the United States from the general community (25). T1-weighted MRI data from the ABCD Study were processed with FreeSurfer version 7.1 on the Compute Canada Niagara server (26). MRI and sample recruitment procedures for the ABCD Study have been described previously (25,27). Psychopathology was indexed by the total problem score from the parent-completed Child Behavior Checklist (CBCL)—a simple index of global psychopathology (28). The top and bottom 20% of the CBCL total score distribution (stratified by sex and ethnicity) was used to classify cases and controls, respectively (Figure S2B). Note that this extremes-only approach minimizes possible noise in CBCL data resulting from the known discrepancies between parental reports (used here) and self-reports. Linear mixed-effects models for each cortical region were run as a function of high/low psychopathology, age, age squared, sex, ethnicity, and random effects (family structure and MRI machine). The "lme4" R package was used to run mixed-effects models (29).

Virtual Ontogeny

To gain insights into the relationship between prenatal development and postnatal group differences in cortical surface area, we proceeded by following three steps (depicted in Figure 1). First, we identified gene-expression markers specific to a set of cells present in the human cerebral cortex toward the end of the first and throughout the second trimester (30–32). To do so, we used publicly available single-cell data from the developing cerebral cortex of 5 donors, with postconception age ranging from 5 to 22 PCWs (30) (Figures S4 and S5). Second, we used these cell-specific genes and calculated the median value of their expression (200 genes per cell type) for each of the 11 cortical regions for which group differences in surface area were examined (steps 2 and 3 from Figure 1). These expression values were derived from the PsychENCODE bulk RNA sequencing dataset (14 donors, 12–22 PCWs) (33). The processing of single-cell and bulk RNA sequencing data is described in the Supplement. Third, the interregional profiles of the (median) expression of these marker genes were correlated with the interregional profiles of group differences in cortical surface area from Figure 2A (step 4 from Figure 1). The average MRI-expression correlation was tested for significance using a permutation-based approach with 10,000 resamplings of random gene lists, as described in detail in the Supplement (step 5 from Figure 1). We also performed two additional sensitivity analyses 1) to estimate the distribution of the average correlation coefficient between MRI and cell-specific gene expression by bootstrapping the 200 gene expression profiles per cell type and 2) to use gene set enrichment analysis as a test of over-representation of cell-specific genes within the rank-ordered list of MRI–gene expression correlations (34,35).

Gene Coexpression and Enrichment Analyses

The virtual ontogeny analysis focused exclusively on the limited set of cell-specific genes. To expand the focus of genes investigated while simultaneously interjecting findings from our cell-specific approach, we used genome-wide coexpression analysis including all prenatal donors from the PsychENCODE dataset. Modeling of coexpression is presented in the Supplement. Next, coexpressed gene panels for cell types that showed significance from virtual ontogeny were used as inputs for several enrichment analyses, including 1) gene ontology enrichment, 2) disorder-related gene set enrichment, 3) cortical surface area gene enrichment from prior ENIGMA genome-wide association study data, and 4) enrichment with genes associated with risk factors for psychosis. The details for each analysis are presented in the Supplement.

RESULTS

Case-Control Differences in Surface Area and Expression of Proliferative-Cell Genes

Meta-analytic profiles of group differences in cortical surface area were quantified using structural T1-weighted brain MRI scans. Cohorts from the ENIGMA Consortium contributed MRI scans of individuals diagnosed with schizophrenia (SCZ), ADHD, autism spectrum disorder (ASD), bipolar disorder, and major depressive disorder. In addition, children from the ABCD Study were classified into two groups with high or low psychopathology, defined as the top and bottom 20%, respectively, of the CBCL total problem score (Figure S2). This cohort of children allowed us to extend findings obtained in patients with an established clinical diagnosis to young people with emerging psychopathology from the general community (25). In total, 27,359 individuals contributed to group differences in cortical surface area across 11 cortical regions (Figure 2A, B; Tables S2–S6). These specific regions (and time period) were

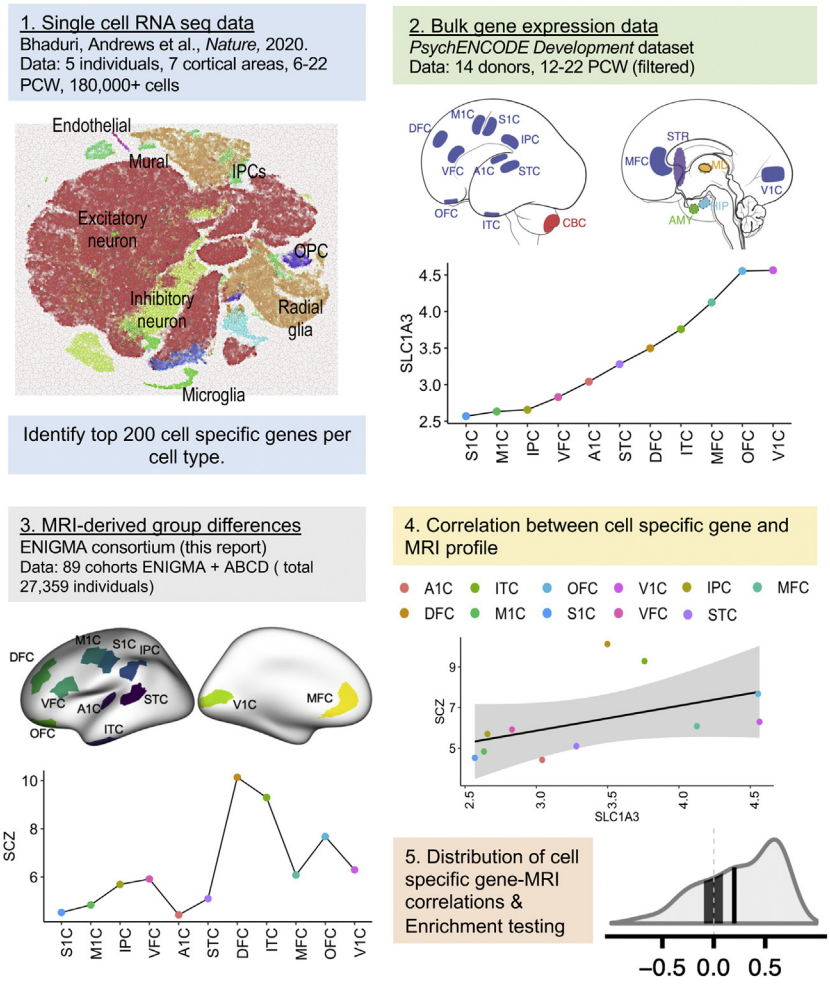

Figure 1. Methodological workflow for virtual ontogeny. Step 1 (top left): identify top 200 cell-specific genes from single-cell RNA sequencing data of the developing neocortex (30). Step 2 (top right): quantify median gene expression (bulk RNA) across donors for each of 11 cortical regions sampled from the PsychENCODE dataset (33). Cell specificity was defined as the ratio of expression of a gene in a given cell type divided by the expression across all cells. For instance, the gene *SLC1A3* was in the top 200 specific genes for the radial-glia panel. The expression of this gene is plotted in step 2 (top right). Step 3 (bottom left): quantify meta-analytic group differences in surface area between cases and controls across the 11 cortical regions sampled in the PsychENCODE dataset. Group differences for SCZ are plotted as an example. Step 4 (bottom right, top half): correlation between cell-specific gene expression and an MRI-derived profile, in this case, *SLC1A3* expression and case-control differences for SCZ. This is repeated for all 200 genes specific to a cell type (in this case, radial glia) to create a distribution of correlation coefficients in step 5 (bottom right, bottom half). A1C, primary auditory cortex; ABCD, Adolescent Brain Cognitive Development; AMY, amygdala; CBC, cerebral cortex; DFC, dorsal frontal cortex; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; HIP, hippocampus; IPC, inferior parietal cortex; IPCs, intermediate progenitor cells; ITC, inferior temporal cortex; M1C, primary motor cortex; MD, mediodorsal nucleus of thalamus; MDD, major depressive disorder; MFC, medial frontal cortex; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; OPC, oligodendrocyte progenitor cell; PCW, postconception week; S1C, primary somatosensory cortex; SCZ, schizophrenia; STC, superior temporal cortex; STR, striatum; V1C, primary visual cortex; VFC, ventral frontal cortex.

selected based on the availability of gene expression data during gestation (Figures S3 and S4) (33).

Case-control differences in surface area were greatest in patients with SCZ and ADHD, and in the community sample of children with high CBCL psychopathology scores (Figure 2A; Tables S7–S12). Interregional profiles across the 11 cortical regions were highly correlated between SCZ and ADHD (Figure 2C). At the nominal level of significance ($p < .05$), we also observed correlations between the CBCL profile and both the ADHD and SCZ profiles (Figure 2C).

What neurodevelopmental processes might underlie these group differences? To answer this, we related interregional profiles of cell-specific gene expression in the developing cerebral cortex (12–22 PCWs) with interregional profiles of group differences in cortical area across the same 11 regions. These case-control group differences were used as input to the analytic framework depicted in Figure 1. This "virtual ontogeny" analysis revealed positive associations between prenatal expression profiles of proliferative cells, namely radial glia and IPCs, and postnatal profiles of group differences in SCZ, ADHD, CBCL, and ASD (Figure 3A, B; Table S13). Likewise, these group contrasts showed negative associations with a number of differentiated cells, namely excitatory neurons and endothelial and mural cells[2]. We tested the sensitivity of these findings using two different statistical approaches: 1) bootstrapped estimation of the correlation-coefficient distribution and 2) gene-set enrichment analysis (Figures S6 and S7, respectively). These somewhat more conservative analyses confirm the general opposing pattern of enrichment with radial glia/IPCs and excitatory neurons with ADHD, SCZ, and ASD. This association was nominally significant for CBCL. In the next steps, we focused on results specific to SCZ, ADHD, and CBCL because these profiles presented robust group differences in surface area (Figure 2A).

Multimodal Associative Versus Primary/Unimodal Cortex

Unsupervised hierarchical clustering of interregional profiles of group differences in surface area revealed two distinct sets of

[2]Undifferentiated (radial glia, intermediate progenitor cells); differentiated (neurons, microglia, oligodendrocytes, and mural and endothelial cells). Oligodendrocyte progenitor cells are a hybrid state.

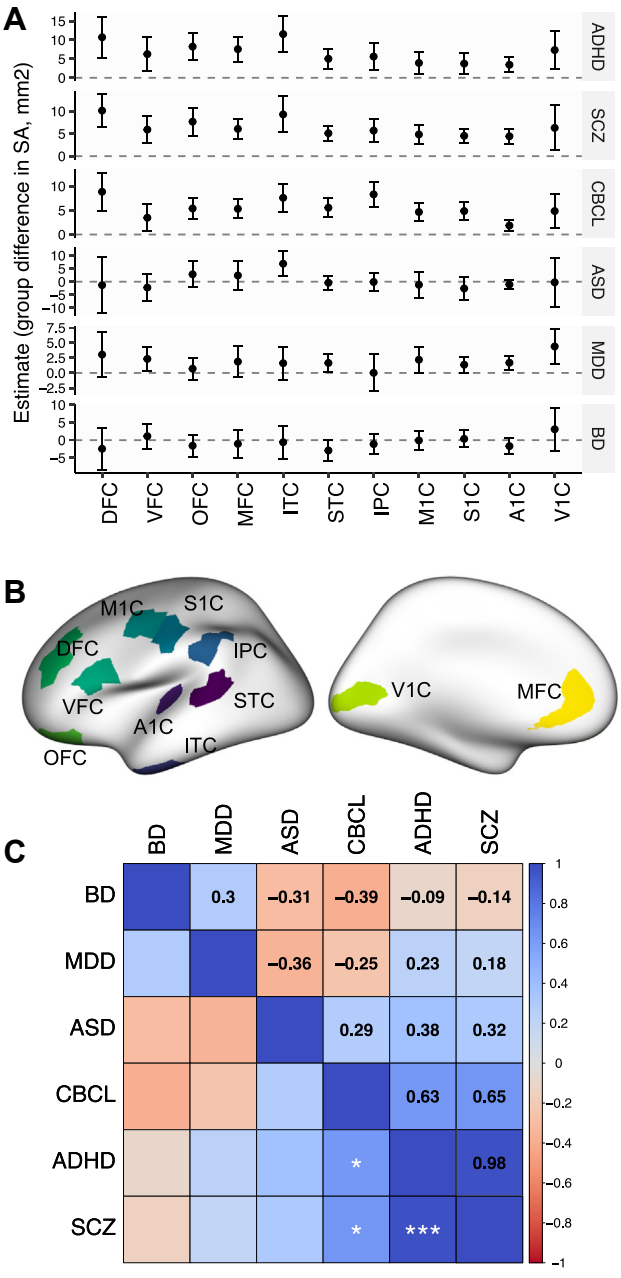

Figure 2. Regional differences in cortical surface area across multiple psychiatric conditions. **(A)** Meta-analytic estimates of group differences in cortical surface between cases and controls. Contrast shown as controls minus cases, where positive values indicate smaller surface area in cases. **(B)** Schematic location of regions of interest from which surface area was quantified. **(C)** Cross-disorder correlation matrix of profiles from panel **(A)**. *Nominal $p < .05$; ***false discovery rate–corrected $p < .05$. A1C, primary auditory cortex; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CBCL, Child Behavior Checklist; DFC, dorsal frontal cortex; IPC, inferior parietal cortex; ITC, inferior temporal cortex; M1C, primary motor cortex; MDD, major depressive disorder; MFC, medial frontal cortex; OFC, orbitofrontal cortex; SA, surface area; S1C, primary somatosensory cortex; SCZ, schizophrenia; STC, superior temporal cortex; V1C, primary visual cortex; VFC, ventral frontal cortex.

cortical regions (Figure 4A). Cluster 1 consisted of multimodal associative cortices[3] while cluster 2 contained mostly primary and unimodal cortices[4]. The group differences in cortical surface area for SCZ, ADHD, and CBCL were greater in multimodal versus primary/unimodal cortices (Figure 4B; Figure S8). Cell-specific gene expression trajectories during gestation also revealed remarkable differences between these two clusters: proliferative (i.e., undifferentiated) cells have greater cell-specific expression in the multimodal cortices while differentiated cells have greater expression in primary/unimodal cortices (Figure 4C; Table S14).

Genetics of Psychiatric Conditions and Cortical Growth: Intersection With Cell-Specific Gene Coexpression Networks

As described above, we observed a certain degree of similarity in interregional profiles of group differences in the cortical surface area among the different mental health conditions (particularly with SCZ, ADHD and CBCL) (Figure 2C). To capture these similarities, we carried out principal component (PC) analysis of the interregional profiles. This analysis revealed clear demarcation between the multimodal and primary/unimodal clusters, respectively (Figure 5A), with PC1 explaining 50% of the variance and PC1 correlating highly with SCZ, ADHD, and CBCL (Figure 5B). As expected from the condition-specific analyses (Figure 3), virtual ontogeny of the PC1 loadings showed positive associations with radial glia and IPCs and showed negative associations with excitatory neurons and endothelial and mural cells (Figure 5C; Figure S9). Sensitivity analyses confirmed significant associations with radial glia, IPCs, and excitatory neurons, with a weaker finding for the mural cells (Figure S10). To investigate further the processes underlying the association between PC1 and cell-specific genes, we generated coexpression panels of genes for each cell type associated with PC1, expanding the scope of our work from cell-specific genes to all related genes. Gene Ontology enrichment analysis revealed a number of specific biological processes associated with each cell type–specific coexpressed panel. Thus, radial glia and IPC genes were highly enriched for biological processes relating to cell division, while vasculature-forming endothelial and mural cells as well as excitatory neurons were enriched, respectively, for blood vessel morphogenesis and synaptic signaling/organization (Figure 5D–F). Genes associated with schizophrenia, as derived from genetic variant studies (36), were enriched in coexpression networks of the radial glia and excitatory neurons (Figure 5G). Genes associated with the cortical expansion of multimodal cortices, as derived from genome-wide association studies (14), were enriched in coexpression networks of the radial glia and IPCs (Figure 5H; Table S14). Note that the latter enrichment was not found in the case of unimodal cortices, pointing again at the distinction of the two types of

[3]Multimodal associative cortices in cluster 1 (intermediate progenitor cell, orbital frontal cortex, medial frontal cortex, dorsal frontal cortex).

[4]Primary/unimodal cortices in cluster 2 (primary visual cortex, ventral frontal cortex, primary motor cortex, primary somatosensory cortex, primary auditory cortex, superior temporal cortex).

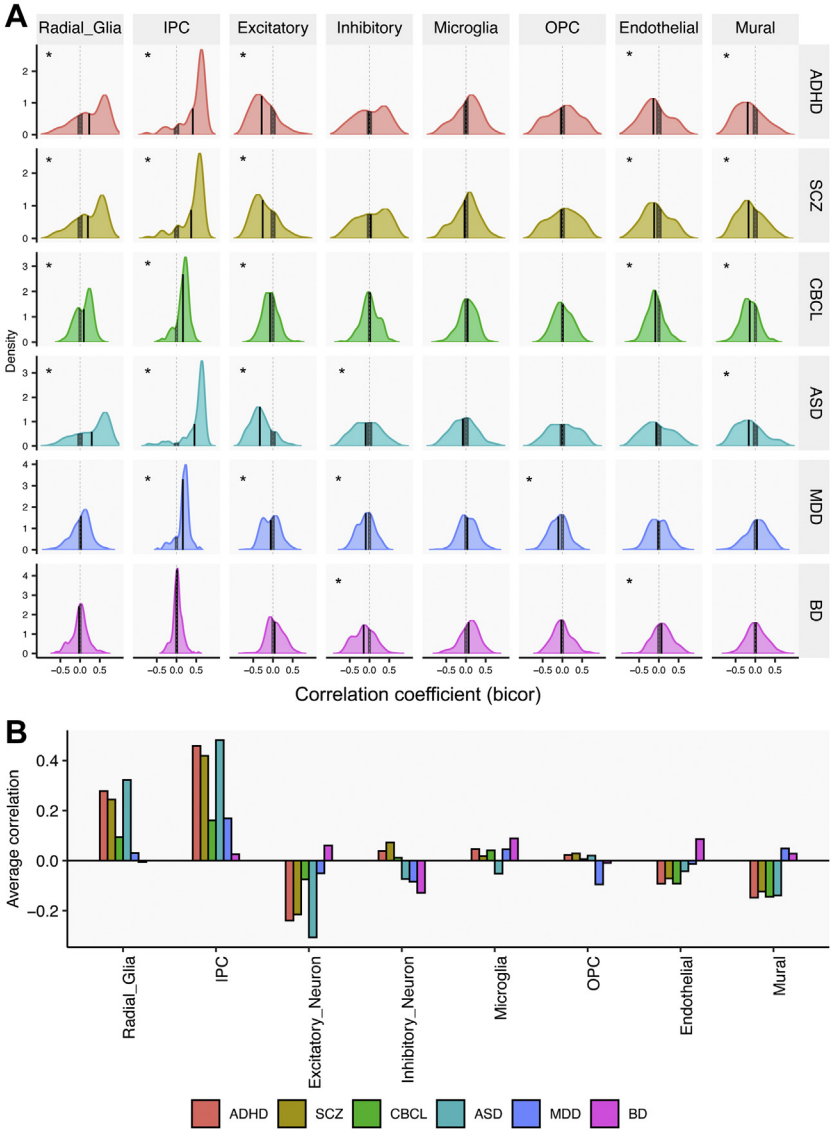

Figure 3. Virtual ontogeny. **(A)** Distribution of correlation coefficients between prenatal cell-specific gene expression and postnatal group differences in cortical surface area. Gray box around zero represents 99% confidence intervals from the null distribution generated through 10,000 resamplings of gene expression and group-difference profiles. Black vertical line represents the mean correlation coefficient (biweight midcorrelation) of the distribution, also plotted in panel **(B)**. *False discovery rate–corrected p value $<$ .01. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; bicor, biweight midcorrelation; CBCL, Child Behavior Checklist; IPC, intermediate progenitor cell; MDD, major depressive disorder; OPC, oligodendrocyte progenitor cell; SCZ, schizophrenia.

cerebral cortices with respect to their neurodevelopmental characteristics and/or developmental timing.

Cell Types and Prenatal Risk for Psychosis

Experimental studies have pointed to a number of external factors that may interfere with typical development of the cerebral cortex in nonhuman primates (37,38). Similarly, epidemiological studies have identified a number of pre/perinatal risk factors associated with later emergence of psychosis (such as low birth weight and preterm birth) (39). These risk factors can be generalizable to most neurodevelopmental disorders.

Here, we tested which of the cell types associated with the PC1 profile of group differences in surface area might mediate the impact of risk factors for psychosis on prenatal growth of the human cerebral cortex. Prenatal risk factors for psychosis were identified from a systematic review and meta-analysis that included 152 studies (Figure 6A) (39). We selected, a priori, sets of genes linked to each of these risk factors using either relevant Gene Ontology terms (40) or genes associated with a particular condition (e.g., congenital abnormalities), as identified in curated datasets based on genome-wide association study catalogs, animal models, and the greater scientific literature (Table S15) (36,41). The results showed that genes implicated in congenital abnormalities were enriched with the radial glia, IPCs, and mural cell–specific coexpressed panels (Figure 6B; Table S17). Genes pertaining to birth weight, hypoxia, and famine were also enriched in the radial glia panel. In contrast, genes pertaining to the regulation of blood pressure (and, therefore, relevant to maternal hypertension during pregnancy), as well as genes associated with preterm birth,

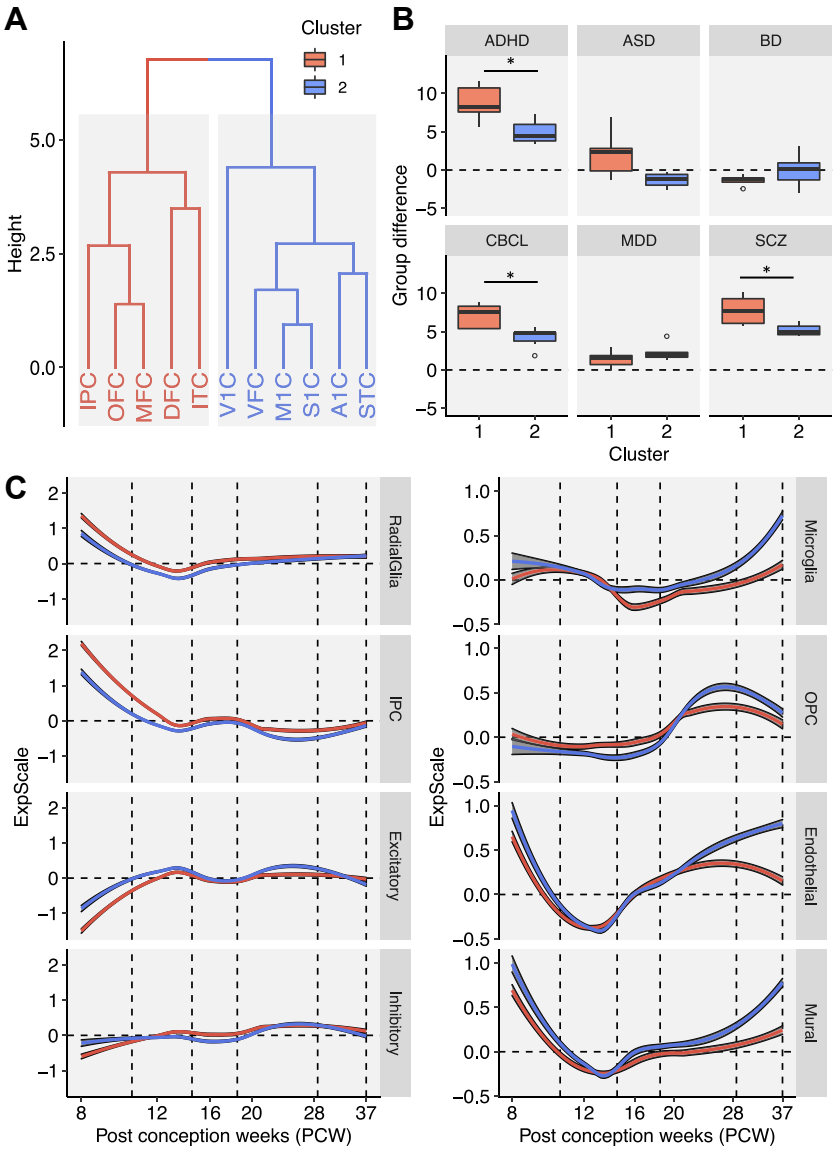

Figure 4. Differences in cortical surface area cluster into associative and primary/unimodal cortex. **(A)** Hierarchical clustering dendrogram of group differences in cortical surface area with $k = 2$ clusters. **(B)** Boxplot depicting group differences between clusters for each of the six profiles investigated. **(C)** LOESS model fits of cell-specific gene expression trajectories stratified by cortical cluster. Expression (y-axis) is unit scaled. Shaded gray region around the model fit represents 95% confidence intervals. Vertical black dashed lines represent prominent windows of neurodevelopment reported previously (33). A1C, primary auditory cortex; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CBCL, Child Behavior Checklist; DFC, dorsal frontal cortex; IPC, intermediate progenitor cell; IPC, inferior parietal cortex; ITC, inferior temporal cortex; M1C, primary motor cortex; MDD, major depressive disorder; MFC, medial frontal cortex; OFC, orbitofrontal cortex; OPC, oligodendrocyte progenitor cell; PCW, postconception week; S1C, primary somatosensory cortex; SCZ, schizophrenia; STC, superior temporal cortex; V1C, primary visual cortex; VFC, ventral frontal cortex.

were enriched in the mural panel. Although preeclampsia was not a significant risk factor for psychosis [odds ratio = 1.32, p = .059 from (39)], genes associated with this condition intersected with those included in the endothelial and mural panels (Figure S11).

DISCUSSION

It appears that the differential growth of the cerebral cortex preceding mental illness and general psychopathology in childhood 1) is more pronounced in multimodal (vs. primary/unimodal) cortical regions, 2) is related to the spatial pattern of prenatal expression of genes underlying neuro- and angiogenesis, and 3) might be reflective of influences of known risk factors acting on these cellular processes during prenatal development.

Cortical regions that show the largest case-control group differences in surface area are regions with greater prenatal expression of proliferative cells (radial glia, IPCs) and lower expression of differentiated cells such as excitatory neurons and endothelial and mural cells during the first trimester. This implies potential disruption in processes of progenitor expansion and subsequent differentiation, with possible cascading effects in later (postnatal) developmental periods. Radial glia serve as a key progenitor population driving neurogenesis and creating a vertical scaffold for neuronal migration from proliferative zones to the cortical plate (2). According to the radial unit hypothesis, the cortical surface area of a given region depends on the number of contributing proliferative units (2); experimental enhancement of the neural progenitor population results in greater surface expansion and folding (42). Subtle deviations in progenitor cell division may have a profound

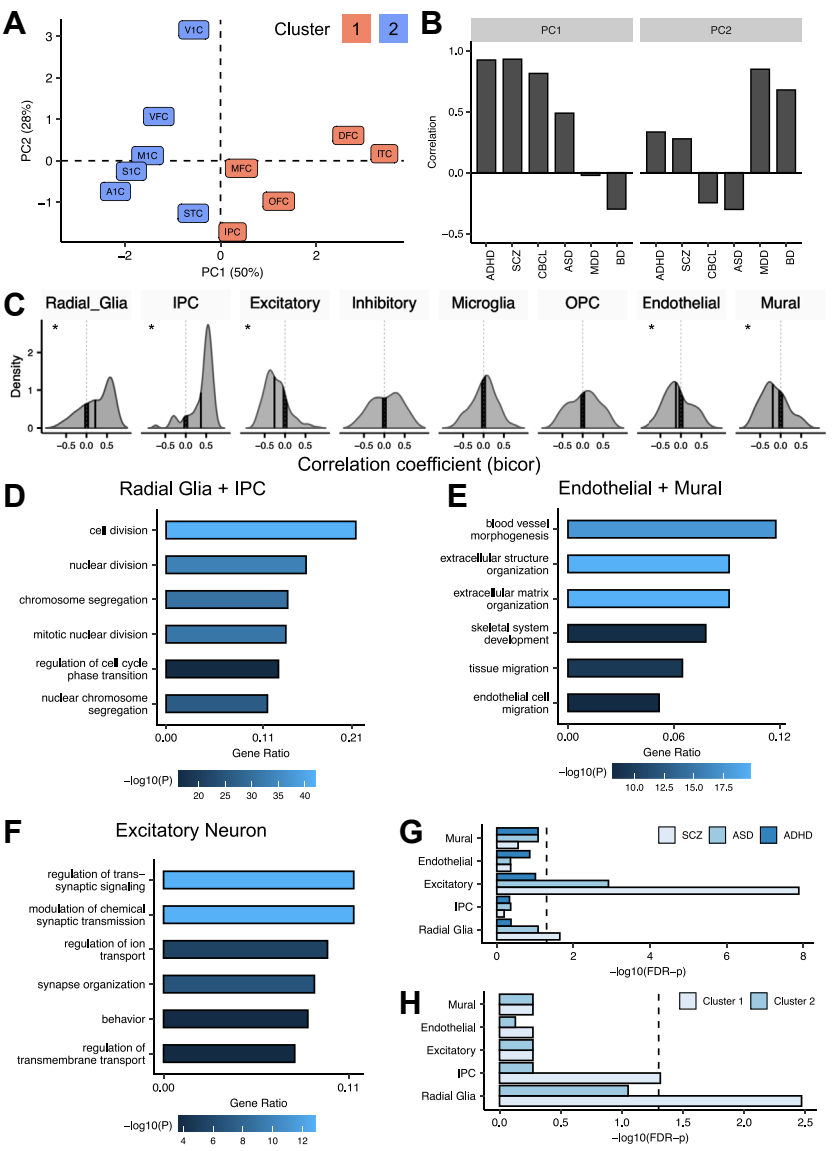

Figure 5. Enrichment of cell-specific gene panels. **(A)** Principal component analysis plot of regional loadings of PC1 and PC2. **(B)** Correlation between disorder-specific profiles and PC1/PC2 loadings. **(C)** Virtual ontogeny analysis depicting distributions of correlation between interregional variation in cell-specific gene expression and PC1 loadings (across the 11 regions). *FDR $p < .01$. **(D–F)** Gene Ontology enrichment analysis of coexpressed cell-specific gene panels. Gene ratio represents the proportion of genes in the cell-specific panel that intersect with a Gene Ontology term with the total size of the gene set. **(G)** Enrichment analysis for disorder-associated genes for the three disorders loading strongest on PC1 (SCZ, ADHD, and ASD) and for **(H)** cortical surface area–associated genes of clusters 1 and 2. A1C, primary auditory cortex; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CBCL, Child Behavior Checklist; DFC, dorsal frontal cortex; FDR, false discovery rate; IPC, intermediate progenitor cell; IPC, inferior parietal cortex; ITC, inferior temporal cortex; M1C, primary motor cortex; MDD, major depressive disorder; MFC, medial frontal cortex; OFC, orbitofrontal cortex; OPC, oligodendrocyte progenitor cell; PC, principal component; S1C, primary somatosensory cortex; SCZ, schizophrenia; STC, superior temporal cortex; V1C, primary visual cortex; VFC, ventral frontal cortex.

impact on the resulting neuronal population owing to the self-renewing (amplifying) nature of radial glia and IPCs: two radial glia cells may generate more than 80 neurons following eight rounds of cellular division (43). For instance, loss of the *DISC1* gene, a genetic locus of relevance for schizophrenia among other mental illnesses, reduces neural-progenitor proliferation, leading to premature differentiation (44). This parallels the observed intersection between genes associated with SCZ and genes in the radial glia coexpression network associated with group differences in cortical surface area between patients with SCZ and healthy control subjects (Figures 2A and 4H). We also observed associations with endothelial and mural cells, components of the developing cortical blood vessels. The development, growth, and maturation of cerebral vasculature and neural structures occurs simultaneously with bidirectional signaling and influences [reviewed in (45)]. Neural-derived signals control angiogenesis and blood vessel patterning, while vascularization modulates the extent of neurogenesis and progenitor differentiation. Given that neurogenic niches require hypoxic conditions for progenitor cell expansion, a spatiotemporal balance between expansion and differentiation is controlled, in part, by blood vessel formation and subsequent oxygenation (45,46).

Multimodal (association) cortices appear to stand out, with regard to both the observed group differences in their surface area and the spatiotemporal pattern of prenatal expression of genes specific to undifferentiated (proliferative) and differentiated (neurons, vasculature) cells. Generally speaking, these cortical regions subserve complex perceptual and cognitive processes, building on information received from unimodal cortices. Previous studies have pointed to a prolonged developmental time course as one of the characteristics

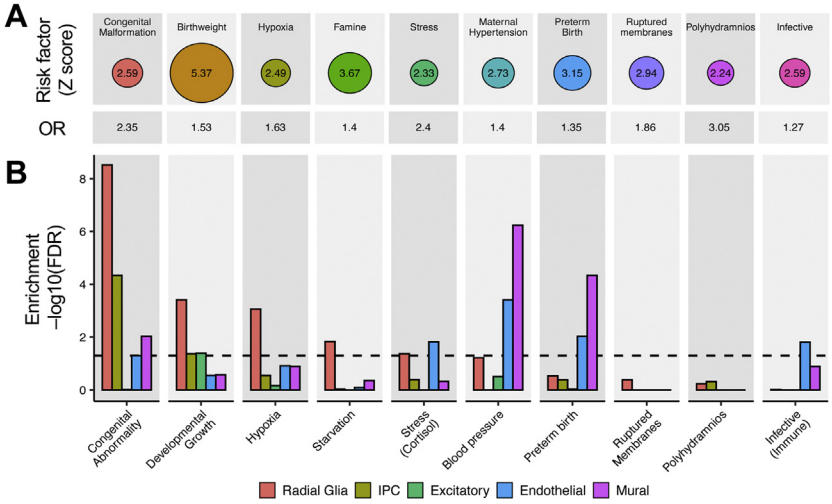

Figure 6. Risk factors of psychosis with implicated cell types. **(A)** *Z* scores for pre/perinatal risk factors for psychosis from Davies *et al.* (39) are represented by the size of the circle, and the corresponding odds ratio is in the text below. **(B)** Enrichment between genes implicated in risk factors for psychosis and coexpressed cell-specific gene panels identified to be related to group differences in cortical surface area. Horizontal dashed line represents FDR $<$ .05. FDR, false discovery rate; IPC, intermediate progenitor cell; OR, odds ratio.

distinguishing multimodal and primary cortices. Evidence supporting this view includes a prolonged existence of the transient associative subplate as compared with primary cortices (47), less dendritic shaft/spine growth at birth (48), and a delayed maturation of projection fibers in associative white matter (49). The prolonged existence of the associative subplate may be of particular importance for disorders characterized by alterations in complex perceptual and cognitive processes because these neurons play key roles in axonal pathfinding, cell survival, and guiding cortical circuitry maturation and, as such, in the development of corticocortical associative fibers [see review in (50)]. Postnatally, functional MRI and structural (tract tracing) studies in humans and macaques, respectively, have shown a principal gradient in cortical connectivity of multimodal regions distinct from the primary cortex (51). These regions are also situated in key nodes of the default mode network, in which aberrant activity is implicated in many, if not all, psychiatric conditions (51,52). Taken together, delayed maturation of association cortices correlates with greater vulnerability to genetic or environmental perturbations.

The neurodevelopmental theory of schizophrenia, as per Murray (53) and Weinberger (54,55), has sparked intense interest in early events that may increase the risk of developing this mental illness later in life. As summarized recently, a number of prenatal and perinatal factors appear to increase the risk to developing psychosis (39). Here, we provide initial evidence that links, albeit indirectly, such risk factors to SCZ via cellular processes underpinning cortical growth during prenatal development (Figure 5). We have identified two possible—mutually nonexclusive—pathways. The first one—at play in cases of low birth weight, hypoxia, and famine—involves radial glia (i.e., proliferation). The other one—at play in cases of maternal hypertension, preeclampsia, and preterm birth—involves endothelial and mural cells (i.e., vasculature). Nutrient restriction in animal models (nonhuman primates and other vertebrates) produces impaired function of progenitor cells, cell-cycle arrest, and increased cell death (38,56). Likewise, rat models of hypoxia-ischemia–related injury in the developing cortex show marked reduction in the population of neural stem cells (57). In contrast, experimental models of preeclampsia (a hypertensive syndrome) have shown abnormal cerebrovascular morphology and permeability/growth [reviewed in (58)]. The latter parallels our intersection between maternal hypertension (and preeclampsia) and endothelial and mural cells. Finally, the broad classification of congenital malformations was strongly associated with radial glia/IPC genes as well as endothelial and mural cells, hinting at the close (likely bidirectional) relationship between corticogenesis and developing blood vessels [reviewed in (45)].

Limitations and Considerations

It is important to qualify the findings from this report, given the nature of the comparisons between different datasets and periods in time. Group differences in cortical surface area likely indicate a general vulnerability to developing psychopathology, but it is not a feature that distinguishes what kind of disorder an individual may manifest later in postnatal life.

These findings allow us and others to formulate follow-up hypotheses to be tested experimentally, possibly with the advancement in cortical organoid modeling (59). The findings were limited by the availability of prenatal gene-expression data given the limited sampling of cortical regions (only 11 regions) and the limited number of donors from various periods of gestation (missing data from very early and later stages of prenatal development). Statistically, it would be most straightforward to relate the spatial profile of group differences in surface area with the average gene-expression profile specific to cell types; with only 11 regions, however, there is little statistical power. To address this limitation, we have used resampling-based approaches along with sensitivity analyses to test for cell-specific associations. Likewise, the gene-expression dataset was sampled from the cortical plate, while cellular division, differentiation, and maturation take place within the ventricular, subventricular, and intermediate zones of the developing cerebral cortex. This necessitates the

assumption of similar interregional expression profiles reflected across developing lamina, as postulated in the protomap hypothesis (2).

We investigated exclusively the prenatal period in relation to group differences in cortical surface area for several reasons: 1) the dominance of prenatal period vis-a-vis the tangential growth of the cerebral cortex (surface area) as shown from experimental (37,60) and genetic (13,14) studies, 2) epidemiologic evidence implicating birth weight (an index of healthy brain growth) and risk for psychiatric disorder diagnosis (16), and 3) enrichment of neurodevelopmental cell types/processes in genetic variants associated with multiple psychiatric disorders (13,15,17). Even so, this is not to say that developmental disturbances during postnatal life, especially during infancy, may not contribute to the surface area sampled later in life. There are three key periods of cortical expansion: 1) greatest expansion during gestation, 2) expansion from birth to the first 2 years of life, and 3) subtle increases until the end of childhood (depicted in Figure S1) (7–10). It is very likely, however, that different processes underly cortical expansion in these different stages of brain development. Prenatally (before birth), expansion is determined through addition of ontogenetic columns (2,43). Between birth and the first 2 years of life, cortical growth may be a consequence of the expansion in neuropil and cortical minicolumns (61–63). Following 2 years of age, cortical expansion may be related to the growth of underlying white matter (64). The processes governing cortical expansion after birth have not been systematically evaluated. Nonetheless, we observe signals relevant to neurodevelopmental cells (radial glia/IPCs) in cohorts with vastly different age ranges such as those in the ENIGMA ASD, ENIGMA ADHD, and ABCD CBCL groups, which were predominately younger, as compared with the (older) ENIGMA SCZ group. This supports our assumption about the importance of the pre/perinatal environment and cortical surface area. Taken together, it is likely that perturbations of early development may have a sizable impact on cortical surface area measured later in life, primarily through neurogenesis and subsequent expansion of neuropil.

Conclusions

In summary, we show that a simple in vivo measure of brain structure, namely surface area of a set of cortical regions, acquired many years after birth provides an anchor for identifying developmental processes at play before birth and for suggesting cellular mechanisms that may mediate the known associations between common pre- and perinatal risk factors and severe mental illness.

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