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## A computational tool (H-MAGMA) for improved prediction of brain disorder risk genes by incorporating brain chromatin interaction profiles

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### Abstract

Most risk variants for brain disorders identified by genome-wide association studies (GWAS) reside in non-coding genome, which makes deciphering biological mechanisms difficult. A commonly used tool, MAGMA, addresses this issue by aggregating SNP associations to nearest genes. Here, we developed a platform, *Hi-C coupled MAGMA (H-MAGMA)*, that advances MAGMA by incorporating chromatin interaction profiles from human brain tissue across two developmental epochs and two brain cell types. By employing gene regulatory relationships in the disease-relevant tissue, H-MAGMA identifies neurobiologically-relevant target genes. We applied H-MAGMA to five psychiatric disorders and four neurodegenerative disorders to interrogate biological pathways, developmental windows, and cell types implicated for each disorder. Psychiatric disorder risk genes tended to be expressed during mid-gestation and in excitatory

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Author Contributions

H.W. designed the H-MAGMA framework. N.Y.A.S. and H.F. applied cMAGMA and H-MAGMA to nine brain disorders. J.C.M. compared H-MAGMA with cMAGMA. H.F. and W.M. performed LDSC and genetic correlation analyses. N.Y.A.S. conducted developmental trajectories analyses, RRHO, and functional characterization of pleiotropic genes. B.H. analyzed astrocyte RNA-seq data and compared H-MAGMA with eQTL-based tools. P.R., K.B., S.A. contributed the Hi-C data from iPSC-derived neurons and astrocytes. N.Y.A.S. and H.W. wrote the manuscript.

Competing Interests Statement

The authors declare no competing interests.

neurons, whereas degenerative disorder risk genes showed increasing expression over time and more diverse cell-type specificities. H-MAGMA adds to existing analytic frameworks to help identify the neurobiological consequences of brain disorder genetics.

## Introduction

Genome-wide association studies (GWAS) have provided insight into the genetic etiology of multiple brain disorders. However, extracting biological mechanisms from GWAS data is a challenge, largely because the majority of common risk variants reside in non-coding regions of the genome<sup>1</sup>.

Multi-marker Analysis of GenoMic Annotation (MAGMA) was initially developed to extract biological insights from GWAS by linking risk variants to their cognate genes<sup>2</sup>. It aggregates SNP associations to gene-level associations while correcting for confounding factors such as gene length, minor allele frequency, and gene density<sup>2</sup>. While MAGMA is a powerful tool and has been used broadly, there is room for improvement. MAGMA assigns SNPs to the nearest genes, which has two major pitfalls. First, it is becoming increasingly recognized that non-coding SNPs can regulate distal genes via long range (>10 kb) regulatory interactions, whereby distal enhancers are brought into contact with the gene promoter<sup>3,4</sup>. Second, MAGMA does not take into account tissue-specific regulatory relationships, whereas disease risk SNPs are enriched in regulatory elements of the disease-relevant tissue<sup>5,6</sup>.

To overcome the limitations in MAGMA, we modified MAGMA approach to create *Hi-C coupled MAGMA* or *H-MAGMA* to assign non-coding SNPs to their cognate genes based on long range interactions in disease-relevant tissues measured by Hi-C. H-MAGMA advances conventional MAGMA (hereafter referred to as cMAGMA) by incorporating relevant functional genomics evidence and allowing developmental stage and cell-type specific gene mapping. H-MAGMA also differs from traditional Hi-C guided gene mapping, as it employs the genome-wide mapping capability of MAGMA. While traditional Hi-C guided gene mapping restricts its analysis to genome-wide significant (GWS) loci<sup>7</sup>, H-MAGMA can leverage signals from sub-threshold loci that explain a significant proportion of heritability<sup>8</sup>.

H-MAGMA was constructed from four classes of brain-derived Hi-C datasets that include human cortical tissue across two developmental stages (prenatal and postnatal) and two brain cell types (neurons and astrocytes), enabling developmental and cell-type specific gene mapping. We applied H-MAGMA to five psychiatric disorders (Attention deficit hyperactivity disorders, ADHD; Autism spectrum disorders, ASD; Schizophrenia, SCZ; Bipolar disorder, BD; Major depressive disorders, MDD) and four neurodegenerative disorders (Amyotrophic lateral sclerosis, ALS, Multiple sclerosis, MS; Alzheimer's disease, AD, and Parkinson's disease, PD) to generate gene-level summary statistics (Fig. 1). By comparing H-MAGMA with cMAGMA, we found that non-coding SNPs often interact with distal genes, necessitating the use of functional genomic evidence in assigning SNPs to cognate genes. We also found a significant overlap between H-MAGMA and two widely used expression quantitative trait loci (eQTL)-based gene mapping tools, coloc<sup>9</sup> and

TWAS<sup>10</sup>. Gene-level association statistics from H-MAGMA closely resembled genetic relationships among brain disorders, which enabled subsequent analyses to identify biological pathways, developmental windows, and cell types critical for each brain disorder.

## Result

### Hi-C coupled MAGMA

Since our primary goal is to identify neurobiological mechanisms underlying brain disorders, we leveraged two Hi-C datasets obtained from human brain tissue, one from the developing cortex<sup>4</sup> and the other from the adult dorsolateral prefrontal cortex<sup>3</sup> (DLPFC), to generate gene-SNP pairs that serve as an input file for MAGMA (Fig. 1a, Methods). Exonic and promoter SNPs were directly assigned to their target genes based on their genomic location, while intronic and intergenic SNPs were assigned to their cognate genes based on chromatin interactions (Fig. 1a). We also generated a cMAGMA input file that utilizes the same set of genes and SNPs as H-MAGMA whereby all intronic and intergenic SNPs were annotated by positional mapping with a generous gene definition that includes 35kb upstream and 10kb downstream of each gene.

The major source of discrepancy between H-MAGMA and cMAGMA is non-coding variants because promoter and exonic SNPs were assigned to the same genes in both frameworks. We therefore tested how often intronic and intergenic SNPs can be mapped to the nearest genes as predicted by cMAGMA. We found that only 20% of intronic SNPs and 5% of intergenic SNPs interact with nearest genes based on Hi-C (Fig. 1b, Extended Data Fig. 1a, Methods). Because Hi-C based gene mapping cannot capture proximal interactions within 10kb<sup>4</sup>, we additionally used an eQTL resource from the human DLPFC<sup>3</sup>, from which we found 56% of intronic SNPs and 76% of intergenic SNPs did not show any association with nearest genes (Extended Data Fig. 1a, Methods). The majority of non-coding SNPs associated with nearest genes showed additional association with distal genes, as 80% of intronic SNPs and 87% of intergenic SNPs showed associations with distal genes (Fig. 1b). These results highlight the importance of using functional genomic evidence in assigning non-coding SNPs to genes.

We reasoned that H-MAGMA would provide neurobiologically relevant target genes for GWAS by accurately linking non-coding variants to their cognate genes via brain-derived chromatin interaction profiles. We therefore applied the framework to nine brain GWAS, including five neuropsychiatric disorders and four degenerative disorders (Fig. 1a). The number of brain disorder risk genes (FDR<0.05) was comparable between H-MAGMA and cMAGMA (Extended Data Fig. 1b, Supplementary Data 1–2), whereas the number of SNPs assigned per gene was three-fold higher for cMAGMA (~244 SNPs per gene) than H-MAGMA (~73 SNPs per gene, Extended Data Fig. 1c). In total, cMAGMA and H-MAGMA linked 7.4M and 3.9M SNPs to genes, respectively (Extended Data Fig. 1d).

Up to 60% of disorder risk genes were H-MAGMA selective (genes identified by H-MAGMA but not by cMAGMA), suggesting that functional genomics guided gene annotation can help identify novel genes and pathways (Extended Data Fig. 1b). H-MAGMA selective genes were significantly enriched for heritability in all nine brain

disorders, demonstrating the increase in power of H-MAGMA (Fig. 1c, Extended Data Fig. 1e, Methods).

Using SCZ GWAS as a representative example, we next compared H-MAGMA with eQTL-based gene annotation tools, coloc and TWAS (Methods). Coloc tests whether GWAS SNPs and eQTLs in a certain GWS locus share the same causal variant<sup>9</sup>, whereas TWAS imputes the genotype-expression relationship based on the eQTL association statistics and derives expression-trait associations by correlating the imputed gene expression to the trait<sup>11</sup>. We found that a significant proportion of genes identified by eQTL-based gene mapping were also detected by H-MAGMA (Fig. 1d, 74.9% of coloc genes, Fisher's exact test, OR=4.34, 95% CI=3.22–5.90, P=1.76x10<sup>-26</sup>; 72.6% of TWAS genes, Fisher's exact test, OR=12.14, 95% CI=10.20–14.49, P=3.94x10<sup>-206</sup>). H-MAGMA detected a much larger number of genes to be associated with SCZ, which explained a significant proportion of heritability (4.7% of SNPs explained 38.93% of heritability, Enrichment = 8.23, Enrichment P= 7.17x10<sup>-53</sup>, Methods).

### **Psychiatric disorders exhibit neurodevelopmental origin, while degenerative disorders exhibit adult origin.**

Since 3D chromatin loops are highly tissue-specific<sup>4</sup>, it is important to decide which Hi-C datasets are appropriate to identify target genes for each disorder. To address this, we first measured the heritability enrichment of each disorder using tissue-specific regulatory elements (Methods). Consistent with the previous findings<sup>6</sup>, psychiatric disorders showed strong enrichment in brain tissues, while degenerative disorders lacked brain-specific enrichment (Extended Data Fig. 2). Within brain tissue, psychiatric disorders showed stronger heritability enrichment in the fetal brain than in the adult brain, highlighting their neurodevelopmental origin (Fig. 2a). Fetal enrichment was more robust in neurodevelopmental disorders such as ADHD and ASD than in adult onset disorders including BD, SCZ, and MDD.

To confirm this result based entirely on regulatory enrichment, we also used an alternative gene-centric approach. Genes associated with each brain disorder were identified based on fetal and adult brain H-MAGMA, and their expression values were compared between prenatal and postnatal stages. There was a clear distinction between psychiatric and degenerative disorders. Genes associated with psychiatric disorders were highly expressed during prenatal stages, while genes associated with degenerative disorders were highly expressed postnatally (Fig. 2b–c, see Supplementary Data 3 for statistics). The only exception was MS, which displayed prenatal enrichment. This distinction between psychiatric and degenerative disorders was less clear in cMAGMA: ASD- and BD-associated genes were postnatally enriched, AD-associated genes did not display postnatal enrichment, and ALS-associated genes were prenatally enriched (Extended Data Fig. 3, Supplementary Data 3).

Next, we plotted the developmental expression trajectories of brain disorder risk genes (Fig. 2b–c). ASD-, SCZ-, and MDD-associated genes showed remarkably similar expression patterns with a peak at the developmental stage 5 (16–19 PCW). BD- and ADHD-associated genes were gradually increased during the prenatal stage with a peak at the developmental

stage 6 (19–22 PCW). Developmental stages 5 and 6 represent mid-gestation, the period during which upper layer neurons are generated and neuronal differentiation including axonogenesis and dendritic arborization takes place<sup>12,13</sup>. This result highlights mid-gestation as a critical window during neurodevelopment that may confer risk to multiple psychiatric disorders, consistent with recent results from cross-disorder GWAS<sup>14,15</sup>. On the contrary, degenerative disorders showed distinct expression trajectories. Genes associated with degenerative disorders except MS constantly and gradually increased during both prenatal and postnatal stages, suggesting that these genes may become more susceptible upon aging. This result is consistent with a strong neurodevelopmental predisposition for psychiatric disorders, in contrast with degenerative disorders which have a postnatal origin.

### **Pathways implicated for brain disorders.**

To identify biological pathways underlying psychiatric and degenerative disorder risk, we conducted a gene ontology (GO) analysis on gene-level association statistics from H-MAGMA. We ranked genes based on Z-scores so that genes with higher Z-scores (more significantly associated with a given disorder) are located at the top of the list. We then tested whether a given gene set is over-represented at the top of the list by performing an incremental enrichment analysis (Methods, see Supplementary Data 4–5 for a full GO result). This approach allows us to (1) identify biological pathways associated with a given trait regardless of the power of GWAS, and (2) characterize the biological pathways reflecting the gene set as a whole rather than using arbitrarily defined genes with a specific P-value threshold.

All brain disorders showed enrichment for pathways involved in transcriptional and translational regulation (e.g. transcriptional regulators, RNA splicing, and DNA damage and repair pathways; Table 1). This is in line with the previous finding that transcriptional dysregulation may mediate risk for brain disorders<sup>16</sup>. Neuronal differentiation and neuronal apoptotic pathways were also enriched in all brain disorders. Neurogenesis was enriched in the majority of disorders except ASD and BD, consistent with an increasing number of studies elucidating the role of neurogenesis, differentiation, and neuronal apoptosis in brain disorders<sup>17,18</sup>. Not surprisingly, neurotransmitter and synaptic pathways were implicated in multiple brain disorders, supporting decades of studies highlighting the importance of synaptic function in psychiatric disorders<sup>19</sup>.

There were interesting distinctions among brain disorders. For example, all brain disorders showed postsynaptic associations, while a selected set of disorders (ADHD, SCZ, MDD, and MS) also exhibited presynaptic associations. Further, while the majority of brain disorders displayed enrichment in glutamatergic signaling, ASD, SCZ, and ALS displayed enrichment in GABAergic signaling. ASD-associated genes were enriched for acetylcholinergic and serotonergic signaling, reflecting known biology of ASD<sup>20,21</sup>. SCZ and BD-associated genes were also enriched for acetylcholinergic signaling, supporting previous studies that altered cholinergic signaling contributes to SCZ and BD pathogenesis<sup>4,22</sup>. MS-associated genes were enriched for dopaminergic signaling, disruption of which has been associated with immune malfunction in MS<sup>23</sup>. These results collectively highlight synaptic dysfunction in

brain disorders, albeit we could detect distinctions among disorders based on neurotransmitters and pre/post synaptic associations.

We observed pronounced immune related processes for degenerative disorders in contrast to psychiatric disorders. In support of this finding, multiple aspects of glial development were also associated with brain disorders, with stronger enrichment in degenerative disorders (Table 1). Moreover, all degenerative disorders showed associations with genes involved in myelination and oligodendrocyte function, suggesting a potential role of oligodendrocytes in neurodegeneration. In line with this, single cell transcriptomic profiles in AD postmortem brains suggested altered molecular profiles in oligodendrocytes<sup>24</sup>. Together with heritability enrichment, this finding of enriched immune response in degenerative, but less so in psychiatric disorders hints a possible explanation for genetic distinctions between psychiatric and degenerative disorders<sup>25</sup>.

Additional interesting findings include amyloid beta enrichment for AD and PD, and tau enrichment for MS and PD (Table 1), supporting amyloid beta and tau pathology in degenerative disorders<sup>26,27</sup>. We also observed Wnt/ $\beta$ -catenin pathway enrichment for a number of brain disorders including ASD, SCZ, MDD, PD, MS and ALS. Wnt/ $\beta$ -catenin signaling is a key pathway for neurogenesis and cortical pattern specification, and its dysregulation has been observed in several psychiatric disorders<sup>28</sup>. Notably, genes involved in vocalization were associated with ASD, diagnostic criteria of which include impairment in vocalization<sup>29</sup>. We also identified brain regions (e.g. cortex, hippocampus, substantia nigra, and hypothalamus) associated with multiple brain disorders. This is intriguing as we used cortical Hi-C data.

### Cell-type specificity

Brain disorders often exhibit different cellular signatures and vulnerability, highlighting the need to identify critical cell types for brain disorders to develop proper therapeutic strategies. For example, ASD postmortem brains exhibit cell-type specific gene expression signatures such as upregulation of glial genes and downregulation of neuronal genes<sup>30</sup>. Common variation in SCZ maps onto specific groups of cells including pyramidal neurons and medium spiny neurons<sup>31</sup>. Microglia are increasingly recognized as a central cell type contributing to the etiology of AD<sup>32</sup>.

To address central cell types mediating risk for brain disorders, we next assessed cell-type specific expression profiles of brain disorder risk genes (Methods). One striking difference between psychiatric and degenerative disorders was that psychiatric disorder-associated genes coalesced in neurons, while degenerative disorder-associated genes were highly expressed in glia (microglia for AD and MS, astrocytes for ALS and PD, Extended Data Fig. 4a). Since psychiatric disorders showed neurodevelopmental origin, we also measured cell-type specific expression profiles of psychiatric disorder-associated genes in the developing cortex and found convergence onto outer radial glia and excitatory neurons (Extended Data Fig. 4b). This selective enrichment in excitatory neurons prevailed across development, as adult neuronal expression profiles for psychiatric disorder-associated genes also indicated excitatory neuronal enrichment (Extended Data Fig. 4b).

While cMAGMA gave a similar result to H-MAGMA, there were important discrepancies, which include astrocytic expression of ASD-associated genes, lack of astrocytic expression of PD- and ALS-associated genes, and lack of endothelial expression of MS-associated genes (Extended Data Fig. 4). Given the growing evidence of astrocyte-mediated neurodegeneration in ALS and PD<sup>33,34</sup>, the emerging role of blood-brain barrier in MS<sup>35</sup>, and lack of genetic association signals of an astrocytic co-expression network in ASD<sup>36</sup>, this result indicates that H-MAGMA can provide cellular etiology that can be missed by cMAGMA.

### Cell-type specific gene mapping

As we detected a remarkable cellular specificity for both psychiatric and degenerative disorders, we next sought to identify disorder risk genes in a cell-type specific manner. To this end, we built H-MAGMA framework based on Hi-C interactions from iPSC-derived neurons and astrocytes<sup>37</sup>. Neuronal and astrocytic H-MAGMA were subsequently used to decode psychiatric and degenerative disorder GWAS, respectively (Fig. 3a). We found that a significant proportion of genes (20–40%) were detected in a cell-type specific fashion (Extended Data Fig. 5).

Cell-type specific H-MAGMA recapitulated biological processes, cell-type specificities, and developmental trajectories of brain homogenate H-MAGMA. For example, brain disorder risk genes derived from cell-type specific H-MAGMA were involved in transcriptional regulation, neurogenesis, and synaptic transmission (Supplementary Data 6). Degenerative disorder risk genes showed pronounced enrichment for glial development and inflammatory responses.

Cell-type specific H-MAGMA further recapitulated cellular expression profiles of disease risk genes. For example, we observed excitatory neuronal expression of psychiatric disorder risk genes, microglial expression of AD- and MS-associated genes, and astrocytic expression of PD- and ALS-associated genes (Fig. 3a). As astrocytes gain inflammatory profiles with aging<sup>38</sup>, we further assessed age-associated astrocytic expression of degenerative disorder risk genes derived from astrocytic H-MAGMA. We found that AD- and PD-associated genes were expressed in mature astrocytes, while ALS-associated genes were highly expressed in fetal astrocytes. MS-associated genes were highly expressed in glioblastoma, consistent with the emerging view that astrocyte-mediated neuroinflammation is a key contributor to the MS pathogenesis<sup>39</sup>. Further, psychiatric disorder-associated genes showed prenatal enrichment with a peak during mid-gestation, while degenerative disorder-associated genes were postnatally enriched with a gradual increase in expression across a lifespan (Fig. 3b–c). One remarkable difference between cell-type specific and brain homogenate H-MAGMA was postnatal expression of MS-associated genes from astrocytic H-MAGMA, which was not detected in brain homogenate.

### Functional impact of genetic risk factors in transcriptomic signatures

We next hypothesized that brain disorder-associated genes are dysregulated in corresponding disorders. Therefore, we assessed whether brain disorder-associated genes are differentially regulated in postmortem brains with brain disorders (Methods)<sup>2</sup>.

We first compared our gene association statistics with postmortem brain gene expression profiles from individuals with three psychiatric disorders (ASD, BD, SCZ)<sup>40</sup>. We found a significant overlap between common variation affected genes and differentially expressed genes (DEG) in SCZ (Extended Data Fig. 6a). SCZ-associated genes were also enriched for ASD DEG. In addition, ADHD-associated genes were enriched for ASD DEGs, recapitulating a shared genetic relationship between these two neurodevelopmental disorders<sup>41</sup>.

Since gene co-expression networks may capture additional disease-associated signatures to DEG, we compared gene association statistics with gene co-expression modules in three psychiatric disorders (Extended Data Fig. 6b). We found that an interneuronal module (geneM23) downregulated in ASD were enriched for ADHD-associated genes. Further, SCZ-associated genes were enriched for a synaptic module (geneM7) upregulated in BD and SCZ. MDD-associated genes were enriched for a neurodevelopmental module (geneM16) upregulated in BD and SCZ.

However, the overlap between DEG and gene association statistics was nominal ( $\beta=0-0.04$ ), and ASD- and BD-associated genes were neither differentially regulated in psychiatric disorders nor enriched for any disease-associated co-expression modules (Extended Data Fig. 6). This can be due to multiple reasons. First, ASD and BD GWAS have relatively limited power compared to SCZ and MDD, hence a more comprehensive picture may arise once we obtain better powered GWAS. Second, transcriptomic signatures do not necessarily reflect early events in the disease process that are directly impacted by genetic risk factors, but result from complex gene-environment interactions throughout the disease progression. Third, given that brain disorder-associated genes show cell-type specific enrichment (Fig. 3, Extended Data Fig. 4), they may affect gene regulation in a specific cell type(s) that may be missed by the bulk expression datasets. To test the third hypothesis, we compared gene association statistics with cell-type specific molecular signatures in AD pathology<sup>24</sup>. We found that AD-associated genes were significantly enriched for DEGs in microglia and oligodendrocytes, but not in neurons (Fig. 4a). While we cannot completely rule out the first and second hypotheses, this result suggests that the cellular context in which risk variants influence gene expression needs to be carefully considered in understanding the molecular complexity of brain disorders.

### Interplay between common and rare variation

Not only common but also rare variation plays a role in brain disorders, highlighting the importance of studying risk variants across the allele frequency spectrum. Our previous work suggests a potential interplay between common and rare variation in the genetic architecture of brain disorders<sup>42</sup>. Therefore, we assessed how rare and common variation in brain disorders crosstalk with each other at a gene level (Fig. 4b, Methods).

We found that the same set of genes, including synaptic genes (*DLG2*, *SYNGAP1*, *SHANK1*) and genes that encode transcriptional regulators (*SETD1A*, *SMARCC2*), are affected by both common and rare variation in SCZ. Common and rare variation in ASD also converge onto the same set of genes. MDD-associated genes overlap with genes that harbor rare *de novo* variation in ASD and developmental disorders (DD), suggesting that a



recently reported genetic correlation between MDD and ASD GWAS<sup>43</sup> may also apply for rare variation. ADHD-associated genes also overlap with genes with rare *de novo* variation in ASD, supporting the shared genetic basis of neurodevelopmental disorders. These results collectively suggest that rare and common variation may impact same biological pathways<sup>42</sup>.

### Shared genetic architecture among brain disorders

We next assessed whether the gene-level association statistics obtained from H-MAGMA can be used to elucidate the shared genetic architecture among brain disorders. Since the number of genes significantly associated with a given disorder differs based on the sample size and power of GWAS, we used a rank-rank hypergeometric test of overlap (RRHO), which is a threshold-free algorithm for comparing two genomic datasets<sup>44</sup>. Genes were ranked based on Z-scores from the H-MAGMA output, and ranked lists between two disorders were compared to identify the gene-level overlap between two disorders (Methods). We then compared this gene-level overlap with genetic correlations calculated by linkage disequilibrium score regression (LDSC)<sup>45</sup>.

Gene-level overlaps recapitulated the previously reported genetic architecture of brain disorders<sup>25</sup>: psychiatric disorders exhibited strong overlaps in their ranked gene lists, whereas degenerative disorders did not display significant overlaps (Extended Data Fig. 7a). Among psychiatric disorders, neurodevelopmental disorders (ADHD and ASD) and adult-onset psychiatric disorders (BD, SCZ, and MDD) showed strong overlaps, indicating shared neurobiological bases. The correlation between RRHO and genetic correlation was 0.79 (Extended Data Fig. 7b,  $P\text{-value}=8.08\times 10^{-9}$ ), demonstrating that gene-level association statistics from H-MAGMA reflect shared genetic architecture, and hence can be further used to decipher the biological mechanisms underlying shared genetic architecture among psychiatric disorders.

### Biological pathways underlying pleiotropy

Cross-disorder GWAS of eight psychiatric disorders recently identified more than a hundred GWS loci increasing risk for multiple disorders, further providing evidence of widespread pleiotropy among psychiatric disorders<sup>14</sup>. Shared genetic etiology across psychiatric disorders may underlie concerted developmental expression trajectories and cellular expression profiles of psychiatric disorder-associated genes (Fig. 2–3). Therefore, we next examined genes shared in multiple psychiatric disorders ( $n = 4$ ) to identify common molecular mechanisms of psychiatric disorders (see Methods for gene selection).

In total, we found 1,841 genes (hereby referred to as pleiotropic genes) that are shared in more than four psychiatric disorders (Supplementary Data 7). Notably, pleiotropic genes showed higher enrichment for genes mapped to pleiotropic cross-disorder GWS loci than those mapped to non-pleiotropic (disease-specific) GWS loci<sup>14</sup> (Fig. 5a).

Pleiotropic genes were involved in gene regulation, synaptic function, and neuronal and dendritic development (Fig. 5b). They showed a distinct peak at mid-gestation, consistent with the overall developmental expression patterns of psychiatric disorder-associated genes (Fig. 5c). Finally, pleiotropic genes showed strong excitatory neuronal enrichment for

cortical projection neurons in cortical layers 2/3 (excitatory neuronal subtypes 1) and corticothalamic projection neurons in cortical layers 5/6 (excitatory neuronal subtype 7) (Fig. 5d).

## Discussion

Here we present a refined framework for gene pathway analysis, H-MAGMA, that aggregates SNP-level summary statistics into the gene-level association statistics. Compared with cMAGMA, H-MAGMA (1) links non-coding SNPs to their target genes based on functional genomic evidence, and (2) adds relevant cellular context to gene mapping by using chromatin interaction data from disease-relevant tissue and cell types. While the basic concept of mapping SNPs to genes using functional genomic resources is similar to FUMA<sup>7</sup>, H-MAGMA leverages the MAGMA framework to obtain gene-level association statistics in a genome-wide fashion, while FUMA maps a selected set of genomic loci to target genes. Therefore, H-MAGMA can provide an attractive framework to identify genes and biological pathways for low powered GWAS. It also allows comparing different GWAS to elucidate shared biological pathways.

H-MAGMA can be expanded into many different forms. For example, while we decided to use MAGMA among many other tools as it is most widely used, this framework is applicable to any other tools that convert SNP-level P-values into gene-level association statistics<sup>16</sup>. Moreover, H-MAGMA can be built on Hi-C datasets from multiple tissue- and cell-types to distill biological mechanisms of any GWAS (e.g. Hi-C datasets from immune cells for rheumatoid arthritis GWAS). Finally, while we primarily used Hi-C datasets to link SNPs to target genes, other functional genomics tools such as chromatin accessibility correlations and machine learning-based enhancer-promoter predictions can be used to generate SNP-gene pairs. In fact, a similar approach using eQTLs (eMAGMA) has been recently reported<sup>46</sup>.

To further examine the interrelationship between Hi-C and eQTLs, we compared H-MAGMA-derived outputs with two eQTL-based gene mapping tools, coloc and TWAS. Consistent with the previous finding<sup>3,11</sup>, we detected a substantial overlap. While eQTL-based gene mapping is in no doubt a powerful approach, H-MAGMA can provide a complementary platform to understand the mechanism of GWAS for the following reasons. First, Hi-C can provide comprehensive genome-wide maps for tissues or cell-types with limited access. One example is Hi-C datasets from iPSC-derived neurons and astrocytes that allow GWAS annotation in a cell-type specific manner<sup>37</sup>, which is currently not available with eQTL. Second, it has been recently shown that the variants associated with chromatin accessibility capture stimulus-sensitive signals and explain a significant proportion of heritability, even more so than eQTLs<sup>47,48</sup>. Supporting this claim, we found that H-MAGMA derived genes explain a significant proportion of heritability in addition to eQTL derived genes. These results collectively suggest that chromatin architecture such as Hi-C and chromatin accessibility may provide complementary regulatory phenotypes that can be missed by eQTLs. It is of note that H-MAGMA also has its shortcoming, as it does not capture gene regulatory mechanisms such as altered RNA splicing or the allelic effect (Hi-C cannot predict whether the SNPs will downregulate or upregulate the cognate genes).

Leveraging multiple genomic resources, such as eQTL, spliceQTLs, caQTLs, and Hi-C, is therefore critical for annotating and interpreting GWAS.

An application of H-MAGMA to nine brain disorder GWAS enabled systematic delineation of pathogenic mechanisms of brain disorders. For example, one important question in psychiatry is whether a critical window exists for treatment of psychiatric disorders. Moreover, there is an ongoing debate whether adult onset disorders such as schizophrenia and depression have a neurodevelopmental origin. By comparing prenatal and postnatal expression trajectories, we found that genes associated with psychiatric disorders show remarkable developmental convergence onto mid-gestation, while genes associated with degenerative disorders were gradually increased across the life span, reflecting their increased burden upon aging.

Another layer of convergence among psychiatric disorders was hinted by cellular expression profiles. Psychiatric disorder-associated genes were selectively expressed in excitatory neurons, while degenerative disorder-associated genes show more diverse cellular enrichment profiles. Similar cell-type specificity was reported by the interactome study, demonstrating the robustness of the result using an orthogonal approach<sup>49</sup>.

These results demonstrate that the shared genetic basis of psychiatric disorders translates into shared neurobiological mechanisms. To further identify shared neurobiological basis among psychiatric disorders, we defined a set of pleiotropic genes that are associated with more than four psychiatric disorders. Pleiotropic genes were associated with neuronal development and synaptic plasticity, suggesting that inappropriate neuronal activity and regulation may act as key components in the pathogenesis of psychiatric disorders. Pleiotropic genes also displayed mid-gestational and excitatory neuronal enrichment, summarizing the overall pattern of psychiatric disorder-associated genes. Importantly, this characteristic was also observed for pleiotropic genes identified by meta-analysis of eight psychiatric disorders<sup>14</sup>.

Finally, we found intricate relationships among genes impacted by common and rare variation. For example, common and rare variation in SCZ and ASD coalesce to the same set of genes, highlighting the importance of studying risk variation across the allele frequency spectrum to comprehensively understand the complex interplay between common and rare variation in psychiatric disorders.

## Accession codes

Hi-C data from the developing cortex is available through dbGaP under the accession number phs001190.v1.p1; Hi-C data from the adult DLPFC is available through the PsychENCODE resource site ([resource.psychencode.org](https://resource.psychencode.org)); Hi-C data from neuron and astrocyte is available through PsychENCODE knowledge portal under the accession number syn4921369.

## Methods

### Hi-C

Fetal brain Hi-C data was obtained from the paracentral cortex of three individuals of gestation week (GW) 17–18<sup>4</sup>. Adult brain Hi-C data was obtained from the dorsolateral prefrontal cortex (DLPFC) of three individuals (36, 44, 64 years)<sup>3</sup>. Neuronal and astrocytic Hi-C data were derived from human induced pluripotent stem cells (hiPSC) obtained from two individuals (15 and 31 years)<sup>37</sup>.

### GWAS

We used the following GWAS summary datasets: attention deficit/hyperactivity disorder (ADHD) (n = 20,183 cases; 35,191 controls)<sup>50</sup>, autism spectrum disorder (ASD) (n = 18,381 cases; 27,969 controls)<sup>41</sup>, bipolar disorder (BD) (n = 20,352 cases; 31,538 controls)<sup>51</sup>, schizophrenia (SCZ) (n = 11,260; 24,542 controls)<sup>52</sup>, major depressive disorder (MDD) (n = 246,363 cases; 561,190 controls)<sup>53</sup>, Alzheimer's disease (AD) (n = 71,880 cases; 383,378 controls)<sup>54</sup>, Parkinson's disease (PD) (n = 37,700 cases; 1,400,000 controls)<sup>55</sup>, multiple sclerosis (MS) (n = 4,888; 10,395 controls)<sup>56</sup>, amyotrophic lateral sclerosis (ALS) (n = 12,577; 23,475 controls)<sup>57</sup>. Since we used publicly available GWAS summary statistics, (1) no data points were excluded from analysis, (2) no statistical methods were used to pre-determine the sample size, and (3) data collection and analysis were not performed blind to the conditions of the experiments.

### Development of Hi-C coupled MAGMA (H-MAGMA)

Exonic and promoter SNPs were directly assigned to their target genes based on their genomic location using a gene model Gencode v26 ([https://www.gencodegenes.org/human/release\\_26lift37.html](https://www.gencodegenes.org/human/release_26lift37.html)), and promoter definition as 2kb upstream of transcription start sites (TSS) of each gene isoform. Intronic and intergenic SNPs were assigned to their cognate genes based on chromatin interactions with promoters and exons as previously described<sup>3,4</sup>. Briefly, we generated a background Hi-C interaction profile by pooling 9 million imputed SNPs from schizophrenia GWAS summary statistics<sup>58</sup>. Using this background Hi-C interaction profile, we fit the distribution of Hi-C contacts at each distance from each chromosome using the `fitdistrplus` package (<https://cran.r-project.org/web/packages/fitdistrplus/index.html>). Significance for a given Hi-C contact was calculated as the probability of observing a stronger contact under the fitted Weibull distribution matched by chromosome and distance. Hi-C contacts with  $FDR < 0.01$  were selected as significant interactions. Significant Hi-C interacting regions were overlapped with Gencode v26 exon and promoter coordinates to identify exon- and promoter-based interactions. We used exon- and promoter-based interactions, because our previous study comparing Hi-C data with eQTLs have demonstrated the gene regulatory potential of exon-level interactions<sup>3</sup>. Hi-C data from brain homogenate (fetal and adult human brain) and brain cells (hiPSC-derived neurons and astrocytes) were used to generate MAGMA input files that describe gene-SNP pairs. Input files can be found in the github repository: <https://github.com/thewonlab/H-MAGMA>.

## Gene annotation for conventional MAGMA (cMAGMA)

We generated an input file for cMAGMA that is comparable to H-MAGMA. We used the same gene model (Gencode v26) and a SNP list used for H-MAGMA, and allowed a window of 35kb upstream and 10kb downstream of each gene as previously described<sup>16,52</sup>. Subsequently, any intronic and nearby intergenic SNPs were assigned to the genes based on positional mapping. This input file can be found in the github repository: <https://github.com/thewonlab/H-MAGMA>.

## Non-coding SNP annotation

We first grouped non-coding SNPs into intronic and intergenic SNPs. Proximal genes were defined by positional mapping: for intronic SNPs, genes in which SNPs are located were defined as proximal genes; for intergenic SNPs, nearest genes were defined as proximal genes. Intronic and intergenic SNPs were then overlapped with the SNPs annotated by Hi-C (Hi-C non-coding SNPs: SNPs that interact with gene promoters and exons) and eQTLs (eQTL non-coding SNPs: SNPs that have associations with gene expression). For Hi-C non-coding SNPs, we compared proximal genes with genes that physically interact with the SNPs. For eQTL non-coding SNPs, we compared proximal genes with e-genes (genes that show eQTL associations). We assessed how often (1) physically interacting genes and/or e-genes for a given SNP contain proximal (nearest) genes (Extended Data Fig. 1a), and (2) SNPs show any interactions/associations with distal (non-nearest) genes (Fig. 1b).

## Running MAGMA

For both H-MAGMA and cMAGMA, we used the MAGMA analysis pipeline as the default setting:

```
magma_v1.07b/magma --bfile g1000_eur -pval <GWAS summary statistics>  
use=rsid,p ncol=N --gene-annot <MAGMA input annotation file> --out <output  
file>
```

Here, `g1000_eur` denotes the reference data file for European ancestry population. This file can be downloaded from: <https://ctg.cncr.nl/software/magma>. Detailed instructions can be found in the github repository: <https://github.com/thewonlab>.

## Comparison between H-MAGMA and cMAGMA

We compared disorder risk genes identified by H-MAGMA with those identified by cMAGMA using a `vennerable` package in `R`. We reported the proportion of H-MAGMA selective genes by calculating the number of genes only identified by H-MAGMA divided by the total number of genes identified by H-MAGMA. Since H-MAGMA results were available from the fetal and adult brain Hi-C data, we used genes that are significantly associated in either fetal or adult dataset using a `union` function in `R` (hereby referred to as union disorder risk genes).

We next obtained SNPs mapped to H-MAGMA selective genes using H-MAGMA input files from the fetal and adult brain (H-MAGMA SNPs) and the cMAGMA input file (cMAGMA SNPs). We also obtained H-MAGMA selective SNPs by excluding cMAGMA

SNPs from H-MAGMA SNPs to ensure that heritability enrichment we observed is not due to the exonal and promoter SNPs that are shared between H-MAGMA and cMAGMA. We then measured heritability explained by H-MAGMA SNPs and H-MAGMA selective SNPs using stratified linkage disequilibrium score regression with the baseline-LD model ( $s$ -LDSC)<sup>6</sup>.

### Comparison between H-MAGMA and eQTL-based gene mapping algorithms

To compare H-MAGMA with eQTL-based tools, we used previously reported schizophrenia (SCZ) risk genes obtained through the transcriptome-wide association study (TWAS)<sup>40</sup> and coloc<sup>3</sup>. Both TWAS and coloc were performed on SCZ GWAS<sup>52</sup> using the largest eQTL resource obtained from the adult human DLPFC<sup>3</sup>. We restricted our H-MAGMA results to those derived from the adult brain so that we can match the developmental period (adult) and brain region (DLPFC) with the eQTL database. TWAS identified 708 SCZ-associated genes (TWAS SCZ genes) whose imputed expression values are correlated with SCZ (FDR<0.05). Coloc identified 255 SCZ-associated genes (coloc SCZ genes) whose eQTLs co-localize with SCZ genome-wide significant (GWS) loci (PP4>(PP0+PP1+PP2+PP3)).

While H-MAGMA uses the whole genome as genetic background, coloc and TWAS require a more carefully defined background. Because coloc is a GWS loci-centric approach, e-genes within GWS loci  $\pm$  1Mb were considered as background (3,632 genes). On the other hand, TWAS is a genome-wide approach and uses cis-heritable genes as background (13,396 genes). We therefore intersected H-MAGMA SCZ association results with coloc and TWAS background, from which 1,576 and 2,801 H-MAGMA SCZ genes (FDR<0.05) were selected and compared with coloc and TWAS SCZ genes, respectively. By comparing H-MAGMA SCZ genes and coloc/TWAS SCZ genes, we obtained 3,004 H-MAGMA selective genes (genes identified by H-MAGMA but not by TWAS and/or coloc). SNPs mapped to H-MAGMA selective genes were subsequently identified via H-MAGMA input file from the adult brain (H-MAGMA SNPs). Finally, heritability enrichment of H-MAGMA SNPs was calculated by  $s$ -LDSC to demonstrate that H-MAGMA genes without eQTL support still explain a significant proportion of heritability.

### Heritability enrichment for tissue-specific regulatory elements

To measure heritability enrichment of eight brain disorder GWAS in active genomic regions in each cell/tissue-type, we used  $s$ -LDSC<sup>6</sup> with chromHMM-defined chromatin states<sup>5</sup>. Since chromatin profiling hasn't been performed in all cell/tissue-types (e.g. DNase hypersensitivity was missing for fetal brains, while H3K27ac ChIP-seq was not performed in the adult DLPFC), we instead used genomic regions that are active in each cell/tissue type using chromatin states defined by chromHMM<sup>59</sup>. We defined active genomic elements by the regions marked as Active transcription start sites (TSS, state 1), Flanking active TSS (state 2), Genic enhancers (state 6), and Enhancers (state 7), and repressive genomic elements marked as Heterochromatin (state 9), Repressed polycomb (state 13), Weak repressed polycomb (state 14), and Quiescent (state 15) in the core 15-state model ([https://egg2.wustl.edu/roadmap/web\\_portal/chr\\_state\\_learning.html](https://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html)). To further assess developmental stage specific heritability enrichment in the human brain tissue, we defined fetal active elements (elements that are active in the fetal brain and become repressive in the

adult brain) and adult active elements (elements that are repressive in the fetal brain then become active in the adult brain). The SNP annotation file can be downloaded from the github repository: <https://github.com/thewonlab/H-MAGMA>. Heritability enrichment values in different cell/tissue types resulting from *S*-LDSC were then scaled to allow tissue-level comparison of enrichment values.

### Gene selection

For assessing (1) developmental expression profiles, (2) cell-type specific expression profiles, and (3) gene ontology enrichment of disorder-associated genes, we used following strategies to select genes. We restricted our analysis only on protein-coding genes, because (1) the majority of genes detected in the spatiotemporal transcriptomic atlas<sup>12</sup>, single cell expression datasets<sup>60-62</sup>, and gene ontologies were protein-coding genes, and (2) non-coding genes have much lower expression values compared with protein-coding genes, which can dilute the signals. We also excluded genes within the MHC region due to the complexity of LD, which can override the overall pattern. Finally, we removed genes within chromosome X (chrX), as only a subset of GWAS had association statistics available in chrX.

### Developmental and Cellular Expression Profiles

Analyzing developmental and cell-type specific expression levels required selection of significantly associated genes for each disorder. We calculated adjusted P-values based on the Benjamini and Hochberg (BH) procedure using `p.adjust` function in R. We then selected genes with two FDR thresholds (FDR<0.01 for GWAS with >20 GWS hits, SCZ, BD, MDD, AD; FDR<0.1 for GWAS with < 20 GWS hits, ADHD, ASD, PD, MS, ALS) for as significantly associated brain disorder genes.

Spatiotemporal transcriptomic atlas from Kang et al., 2011<sup>12</sup> was used to obtain cortical expression profiles across multiple developmental stages. Developmental stages were defined as follows: stage 1, 4 PCW Age < 8 PCW; stage 2, 8 PCW Age < 10 PCW; stage 3, 10 PCW Age < 13 PCW; stage 4, 13 PCW Age < 16 PCW; stage 5, 16 PCW Age < 19 PCW; stage 6, 19 PCW Age < 24 PCW; stage 7, 24 PCW Age < Birth; stage 8, Birth Age < 6 M; stage 9, 6M Age < 1 Y; stage 10, 1 Y Age < 6 Y; stage 11, 6 Y Age < 12 Y; stage 12, 12 Y Age < 20 Y; stage 13, 20 Y Age < 60 Y; stage 14, Age > 60 Y.

Log-transformed expression values were centered to the mean expression level per sample using a `scale(center=T, scale=F)` function in R. Genes associated with brain disorders were selected for each brain sample and their average centered expression values were calculated for each brain sample. To ensure that developmental expression trajectories are not dictated by the developmental stage from which Hi-C data was obtained, we used union disorder risk genes. To further verify the developmental trajectories in a cell-type specific fashion, we used neuronal Hi-C for psychiatric disorders and astrocytic Hi-C for degenerative disorders. Prenatal versus postnatal expression values were compared using `lm` function in R (e.g. for a given disorder, `lm(Expression values ~ stages)`).

We also used single cell transcriptomic data from the adult brain<sup>60,62</sup> and fetal brains<sup>61</sup> to identify cell-type specific expression profiles of brain disorder-associated genes. To measure

astrocytic expression profiles across developmental stages, we used transcriptomic data from purified human astrocytes<sup>63</sup>. H-MAGMA results derived from fetal and adult brain Hi-C were used to assess cell-type specific expression values in the fetal and adult brain, respectively. Furthermore, neuronal H-MAGMA was used to assess cell-type and neuronal subtype enrichment of psychiatric disorder risk genes, whereas astrocytic H-MAGMA was used to assess cellular expression profiles and age-associated expression changes in astrocytes for degenerative disorders. We processed log-transformed expression values per cell or sample using a `scale(center=T, scale=F)` function in R. Average centered expression values of genes associated with brain disorders were calculated for each cell type.

### Gene ontology analysis

We used an R package `gProfileR` (<https://biit.cs.ut.ee/gprofiler/gost>) for running gene ontology analysis, as it allows a ranked gene list, which resembles Gene Set Enrichment Analysis (GSEA). Because it does not require a P-value threshold to select significantly associated genes, it allows comparing gene ontologies for differently powered GWAS in a non-bias fashion. After ranking genes based on Z-scores generated by H-MAGMA, we ran gene ontology analysis using this command line:

```
gprofiler(<Ranked gene list>, organism="hsapiens", ordered_query=T,
significant=T, max_p_value=0.05, min_set_size=15, max_set_size=600,
min_isect_size=5, correction_method="fdr", hier_filtering="moderate",
custom_bg=background gene set, include_graph=T, src_filter="GO")
```

### Gene-set analysis

Genes that harbor *de novo* protein disrupting variation in developmental disorders (DD) were obtained from the Deciphering Developmental Disorders Study (93 DD risk genes with genome-wide significance)<sup>64</sup>. We also obtained 102 ASD risk genes (rare variation burden, FDR<0.1) from the Autism Sequencing Consortium (ASC) study<sup>65</sup>. Schizophrenia risk genes with elevated burden of rare variation were obtained from Singh et al., 2016<sup>66</sup> (110 genes with FDR<0.3). Differentially expressed genes (DEG) in postmortem brains with psychiatric disorders were obtained from Gandal et al., 2018<sup>40</sup> (FDR<0.05). Cell-type specific DEG in AD postmortem brains was obtained from Mathys et al., 2019<sup>24</sup>.

Since different brain disorders have different numbers of significantly associated genes, we tried to avoid selecting genes based on a P-value threshold. In comparing H-MAGMA outputs with DEG, we used the gene-set analysis embedded in MAGMA, which utilizes the whole gene-level association statistics while controlling for covariates such as gene size and LD<sup>2</sup>. In comparing H-MAGMA outputs (common variation) with the gene lists that harbor protein disrupting variation (rare variation), we used a generalized linear model controlling for the exome length (controlling for rare variation) and the number of SNPs mapped to each gene (controlling for common variation).

```
glm(<MAGMA Z-scores> ~ <Rare variation annotation file> + <Exome length> +
<The number of SNPs mapped to genes>)
```



We took this alternative approach than using MAGMA gene-set analysis because protein disrupting variation in brain disorders was detected by exome-sequencing and is dependent on the exon, but not gene length.

### Rank-rank hypergeometric overlap (RRHO)

We assessed genetic relationship between two disorders ( $r_g$ ) by using genetic correlation analysis of LDSC<sup>45</sup>. To provide similar metrics based on gene-level association statistics, we compared ranks between two datasets (e.g. H-MAGMA outcomes from two disorders) using an R package RRHO (<https://www.bioconductor.org/packages/release/bioc/html/RRHO.html>) with the following command line:

```
RRHO(<Ranked gene list 1>, <Ranked gene list 2>, outputdir=<output
directory>, alternative="enrichment", BY=TRUE, log10.ind=TRUE)
```

To compare gene-level overlaps (RRHO output) with genetic correlations (calculated by LDSC), P-values from RRHO was converted into Z-scores using the following command line:

```
Zscore = qnorm(10^(-Pvalues), lower.tail=FALSE)
```

We then compared resulting RRHO Z-scores with  $r_g$  values from the genetic correlation analysis using Pearson's correlation. This correlation coefficient provides a metric to compare a genetic relationship between two disorders measured at the SNP level ( $r_g$ ) vs. gene-level (RRHO Z).

### Identification of pleiotropic genes

RRHO outputs two gene sets consisting of most up and downregulated genes, with most upregulated genes referring to a list of genes that are associated with both conditions, and most downregulated genes referring to a list of genes that are not associated with both conditions. Therefore, we employed most upregulated genes as a gene list that is shared between two disorders, hence representing pleiotropic genes. We then generated pleiotropic genes shared in at least four disorders by intersecting RRHO most upregulated genes between the following disorder pairs (ADHD vs. ASD/BD/SCZ/MDD; ASD vs. BD/SCZ/MDD; BD vs. SCZ/MDD; and SCZ vs. MDD). Since psychiatric disorder-associated genes showed neurodevelopmental and neuronal enrichment, we used fetal brain and neuronal H-MAGMA results. We merged the gene sets by a union function in R and obtained uniquely identified genes. The code is provided in the github repository: <https://github.com/thewonlab/H-MAGMA>. In the end, we obtained 1,841 genes that are shared in more than four disorders, and defined them as pleiotropic genes. These genes were compared with the genes mapped to pleiotropic versus non-pleiotropic GWS loci from the meta-analysis of 8 psychiatric disorders<sup>14</sup>. We next performed the gene ontology, developmental expression, and cell-type expression analyses on the pleiotropic genes as described above.

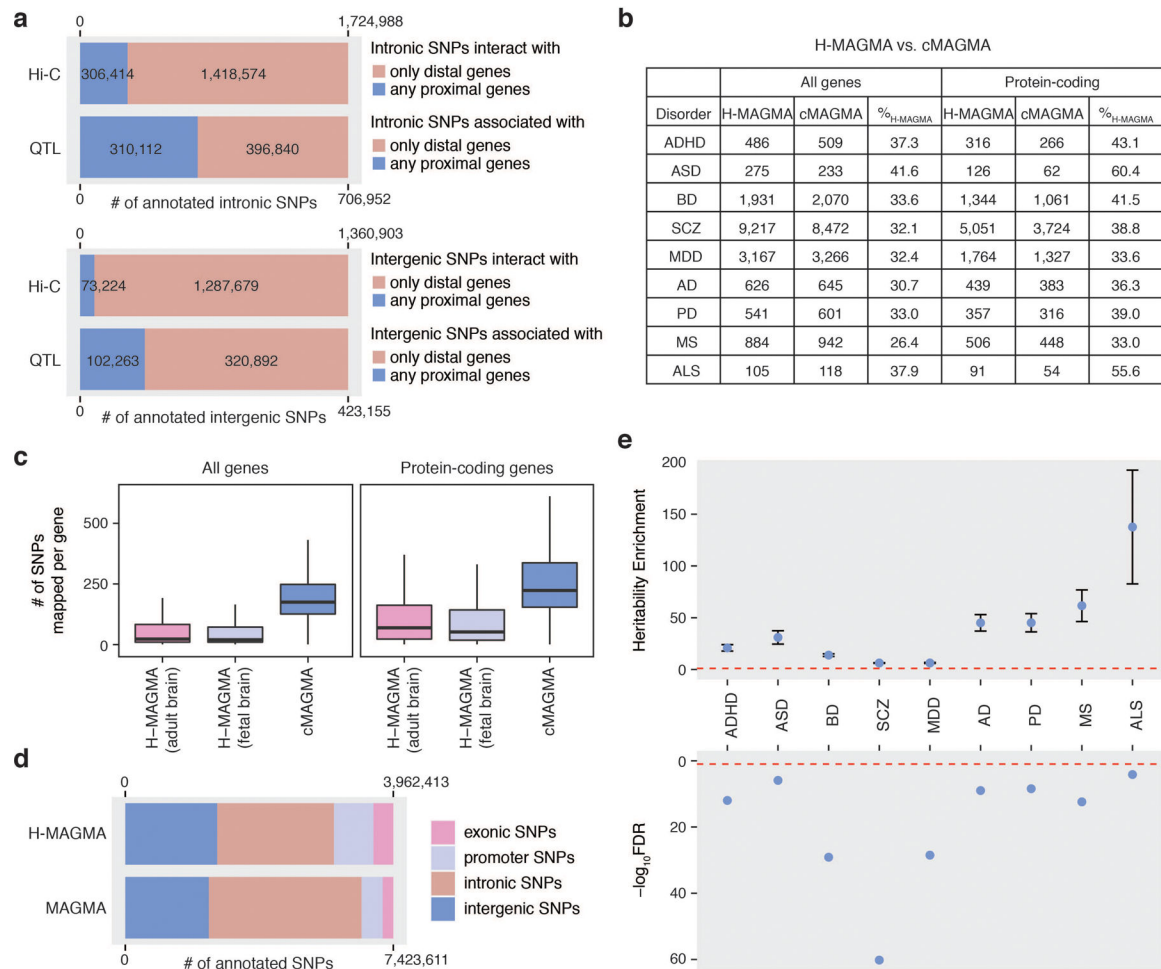
**Data availability**

All GWAS summary statistics used in this study are publicly available. We deposited (1) H-MAGMA input files derived from the fetal and adult brain, and neuronal and astrocytic Hi-C data, and (2) H-MAGMA output files for nine brain disorders in the github repository <https://github.com/thewonlab/H-MAGMA>.

**Code availability**

Codes used in this study are provided in the github repository: <https://github.com/thewonlab/H-MAGMA>.

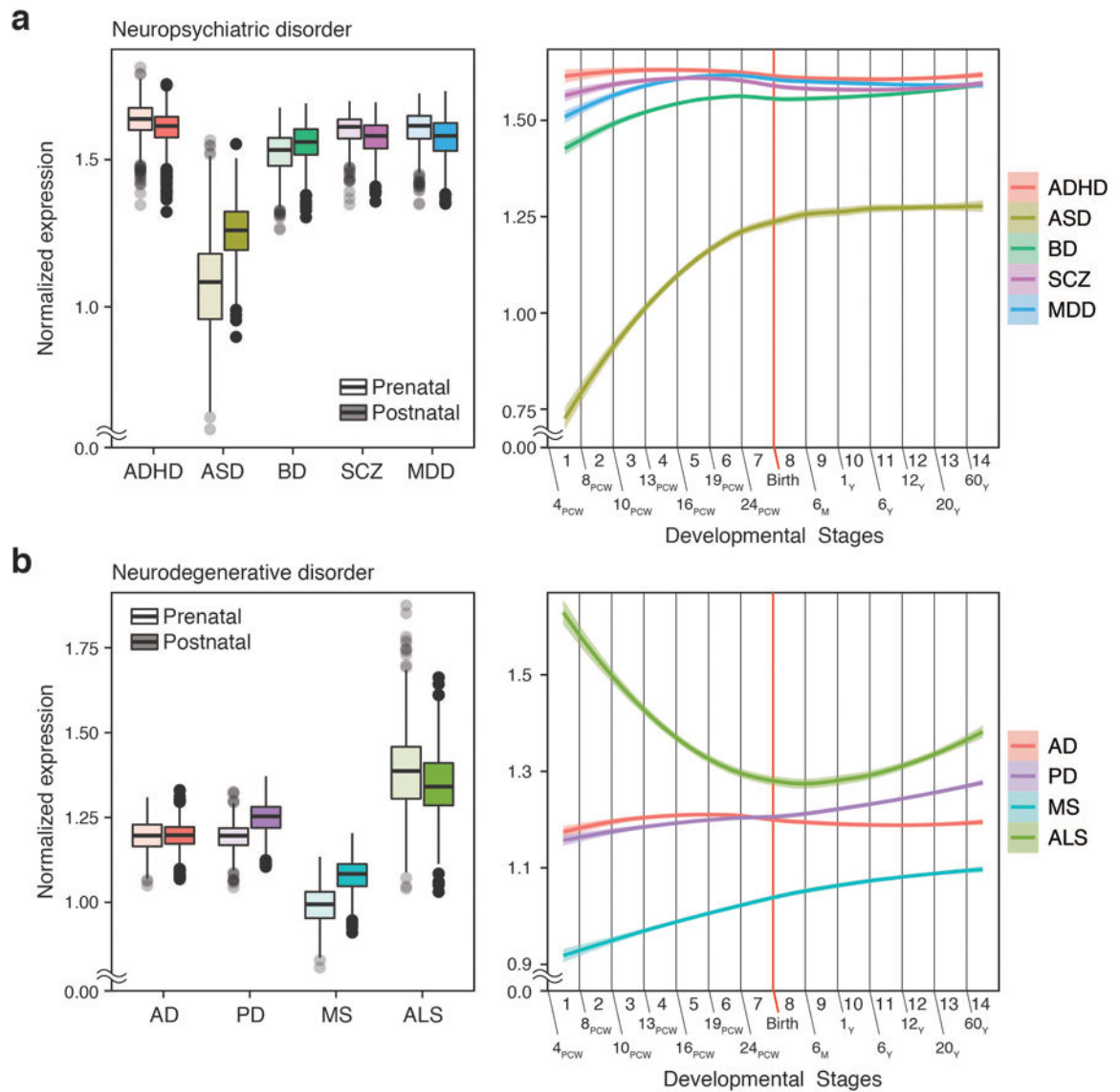
**Extended Data**



### Extended Data Fig. 1. Comparison between H-MAGMA and cMAGMA

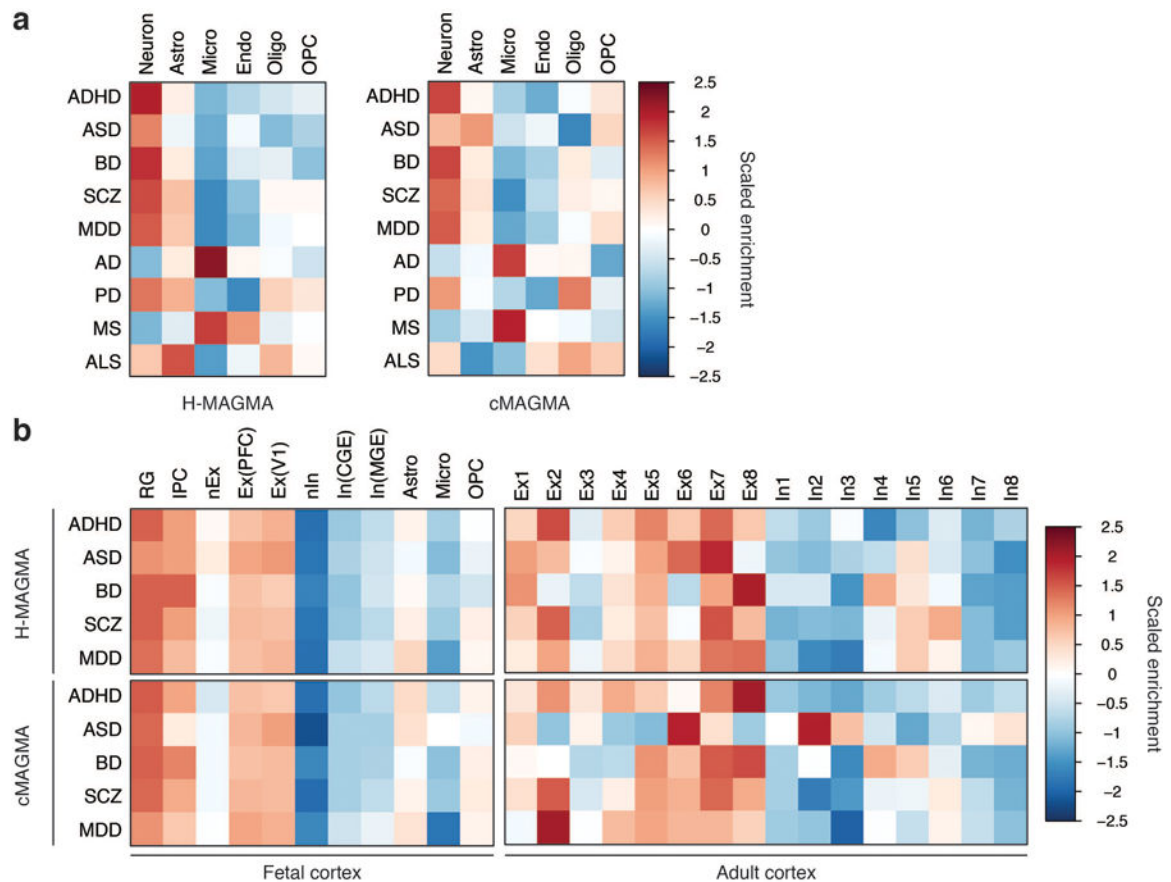
**a.** The number and proportion of intronic and intergenic SNPs annotated to proximal and distal genes. SNPs mapped to proximal genes may also have distal associations, while SNPs mapped to distal genes do not have any association with proximal genes. **b.** The number of brain disorder risk genes (genes that are significantly associated with each brain disorder at a threshold of  $FDR < 0.05$ ) predicted by H-MAGMA and cMAGMA. % H-MAGMA denotes the percentage of H-MAGMA selective genes (genes that were identified by H-MAGMA but not by cMAGMA). **c.** The number of SNPs assigned to each gene for H-MAGMA and cMAGMA. Center, median; box=1st-3rd quartiles (Q); minima,  $Q1 - 1.5 \times \text{interquartile range (IQR)}$ ; maxima,  $Q3 + 1.5 \times \text{IQR}$ . **d.** The number and proportion of SNPs annotated to the cognate genes by H-MAGMA and cMAGMA. **e.** H-MAGMA selective SNPs (SNPs assigned to H-MAGMA selective genes in H-MAGMA – SNPs assigned to H-MAGMA selective genes in cMAGMA) explain a significant proportion of heritability. Top graph: Heritability enrichment  $\pm$  standard error; enrichment denotes proportion of heritability/proportion of SNPs; red dotted line, enrichment=1. Bottom graph: false discovery rate (FDR) of heritability enrichment: red dotted line,  $FDR = 0.05$ .





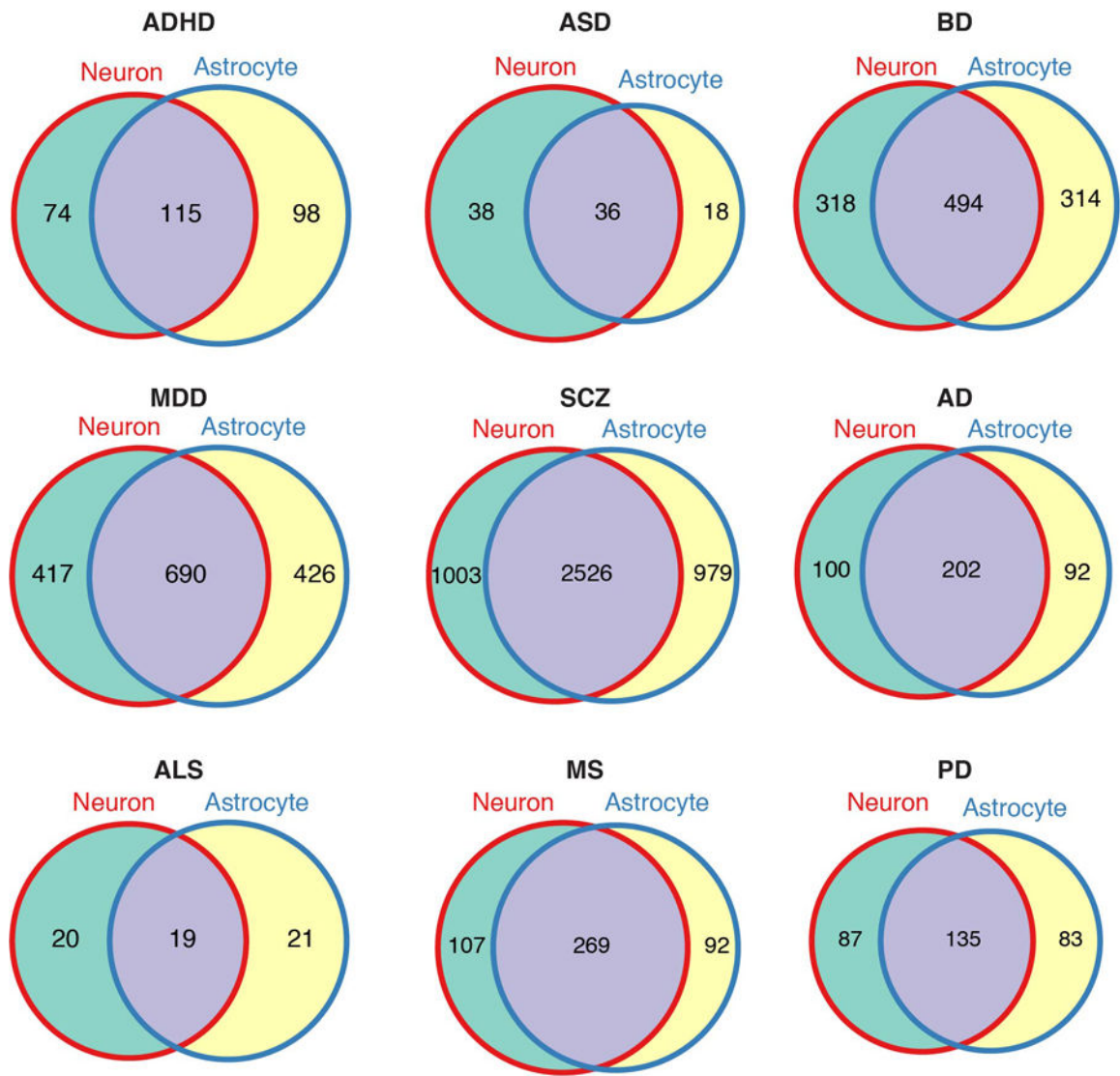
**Extended Data Fig. 3. Developmental expression trajectories of brain disorder risk genes derived from cMAGMA**

PCW, post-conception week; M, month; Y, year. (Left)  $N = 410$  and  $453$  for prenatal and postnatal samples, respectively. Center, median; box=Q1-Q3; lower whisker,  $Q1 - 1.5 \times IQR$ ; upper whisker,  $Q3 + 1.5 \times IQR$ . (Right) LOESS smooth curve with 95% confidence bands.



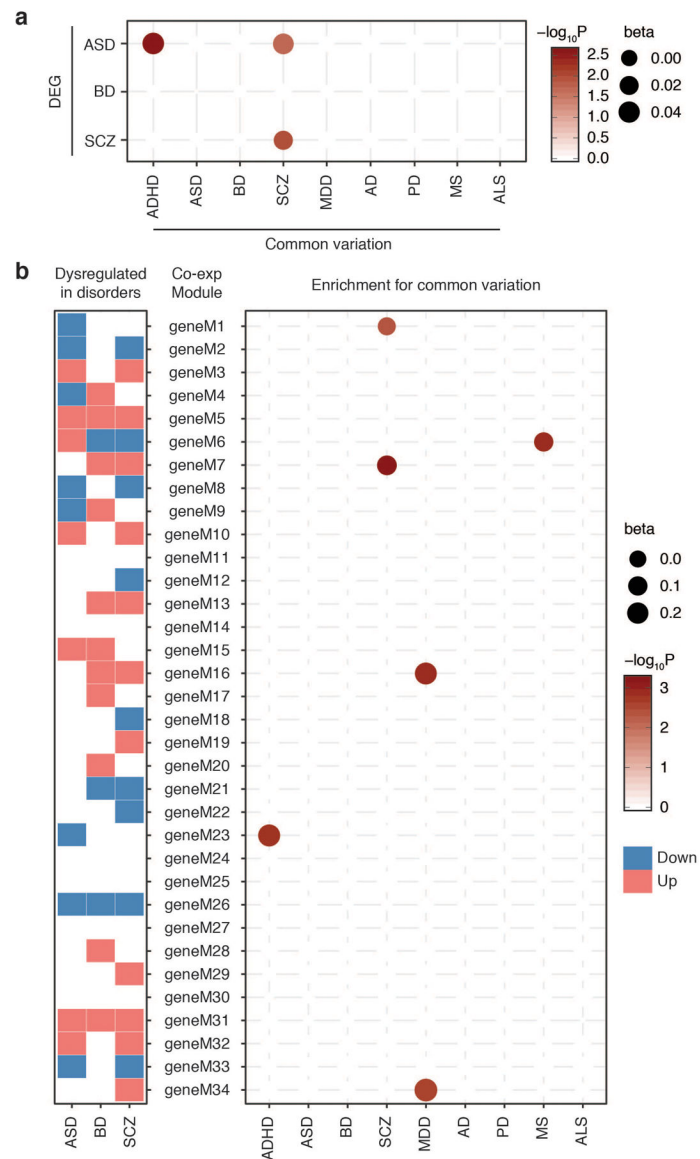
**Extended Data Fig. 4. Cellular expression profiles of brain disorder risk genes.**

**a.** Cellular expression profiles of brain disorder risk genes derived from H-MAGMA and cMAGMA. Psychiatric disorder-associated genes are highly expressed in neurons, while neurogenerative disorder-associated genes show glial signatures. Astro, astrocytes; Micro, microglia; Endo, endothelial cells; Oligo, oligodendrocytes; OPC, oligodendrocytes progenitor cells. **b.** Psychiatric disorder-associated genes are highly expressed in radial glia and excitatory neurons in the developing cortex. RG, radial glia, vRG; ventricular RG; oRG, outer RG; tRG, truncated RG; IPC, intermediate progenitor cells; Ex, excitatory neurons; In, inhibitory neurons; nEx/nIn, newly born excitatory/inhibitor neurons; PFC, prefrontal cortex; V1, visual cortex; CGE, caudal ganglionic eminence; MGE, medial ganglionic eminence.



**Extended Data Fig. 5. Overlap between brain disorder risk genes derived from neuronal and astrocytic H-MAGMA**

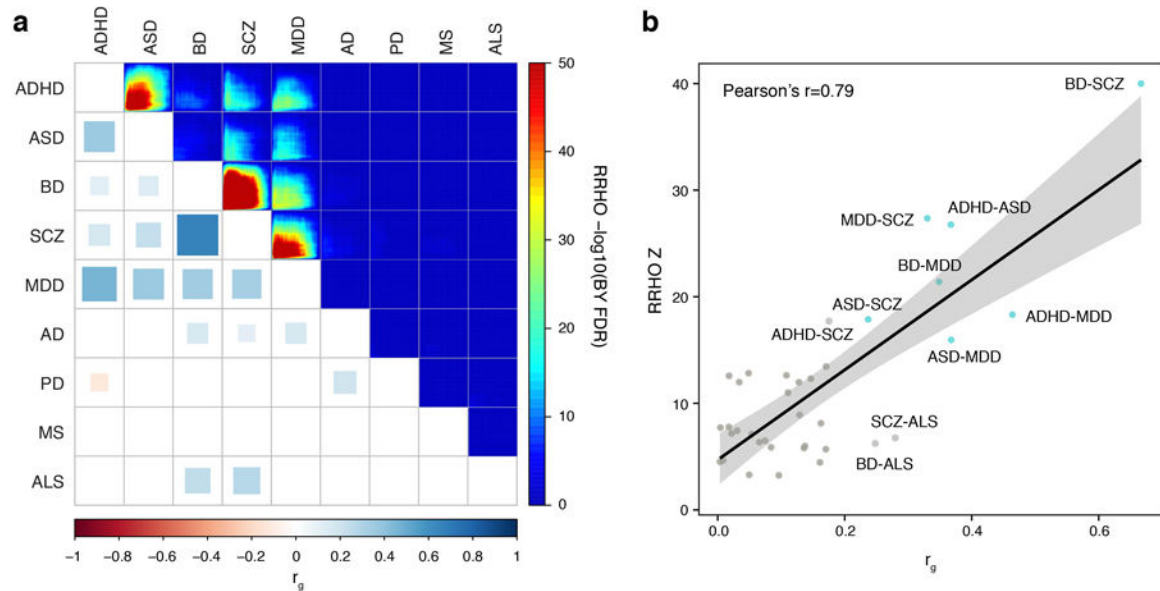
Brain disorder risk genes (FDR<0.05) were compared between neuronal and astrocytic H-MAGMA results.



**Extended Data Fig. 6. Psychiatric disorder risk genes predicted by H-MAGMA are dysregulated in postmortem brains of individuals with psychiatric disorders.**

**a.** Overlap between common variation associated genes and genes differentially expressed (DEG) in postmortem brains with psychiatric disorders. **b.** Overlap between common variation associated genes and co-expression (co-exp) modules differentially regulated in psychiatric disorders. Down, modules are downregulated in disorders; Up, modules are upregulated in disorders.





**Extended Data Fig. 7. Genetic relationships among brain disorders.**

**a.** Psychiatric disorders show strong genetic relationships both at the level of genetic correlations (bottom left,  $r_g$ ) and gene-level overlaps (top right, RRHO). BY FDR, P-values adjusted by the Benjamini and Yekutieli procedure. **b.** Genetic correlations measured with Pearson's correlation ( $r_g$ ) and gene-level overlaps (RRHO Z) are highly correlated, indicating that gene-level overlaps obtained by H-MAGMA recapitulate genetic correlations. Brain disorders that show strong genetic correlations ( $r_g > 0.2$ ) and gene-level overlaps (RRHO Z > 15) are marked in blue. Linear regression line with 95% confidence bands.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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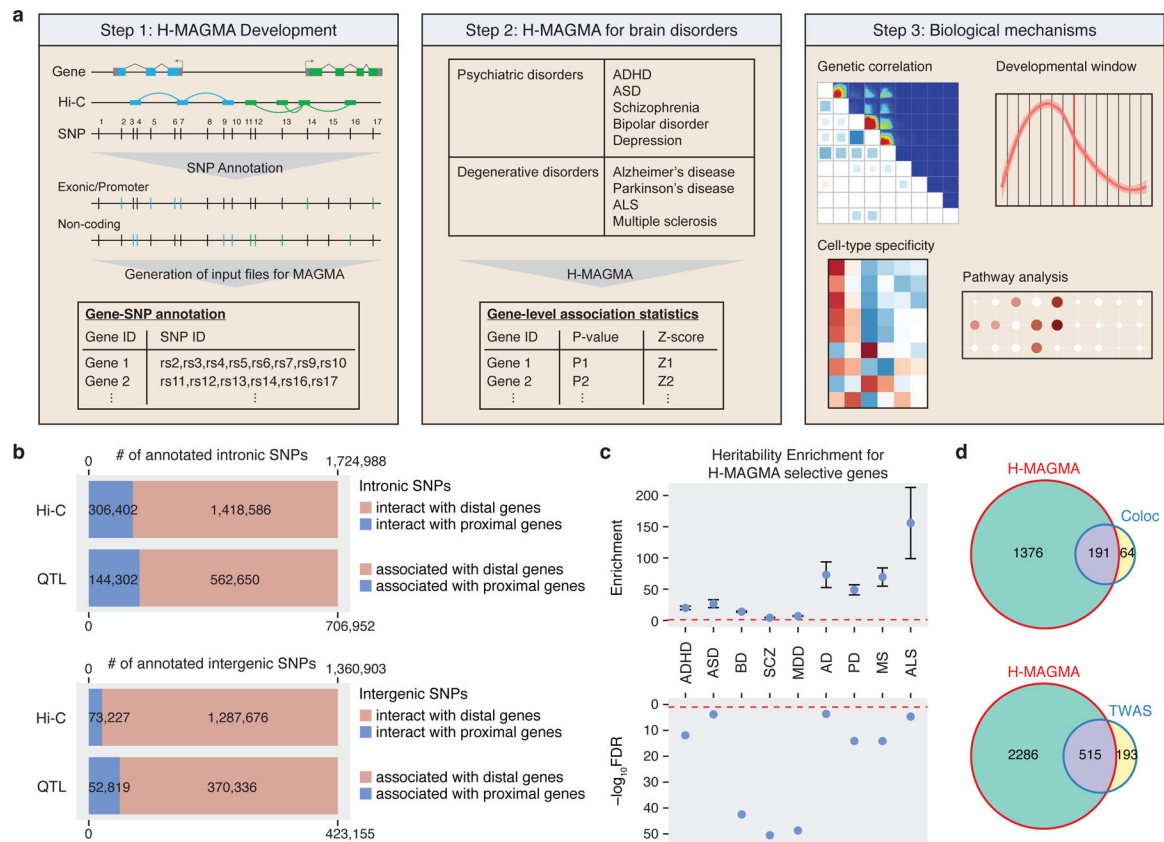
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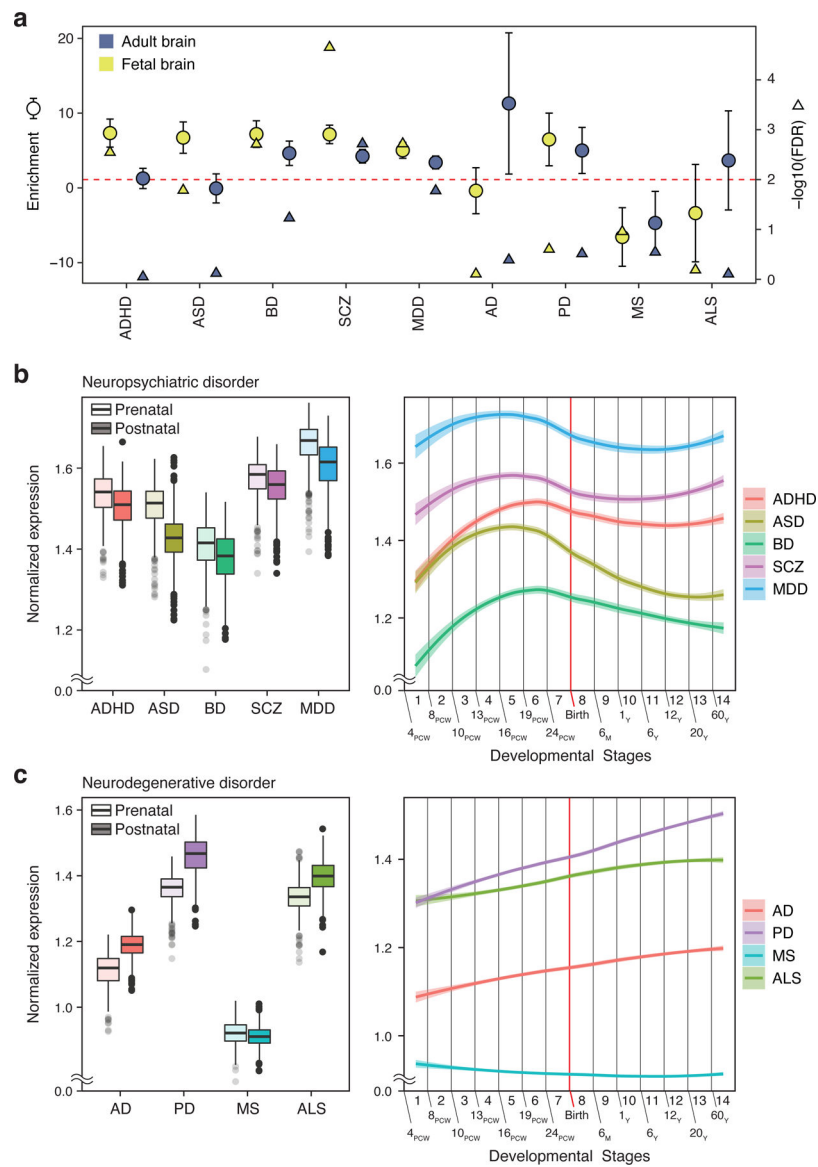
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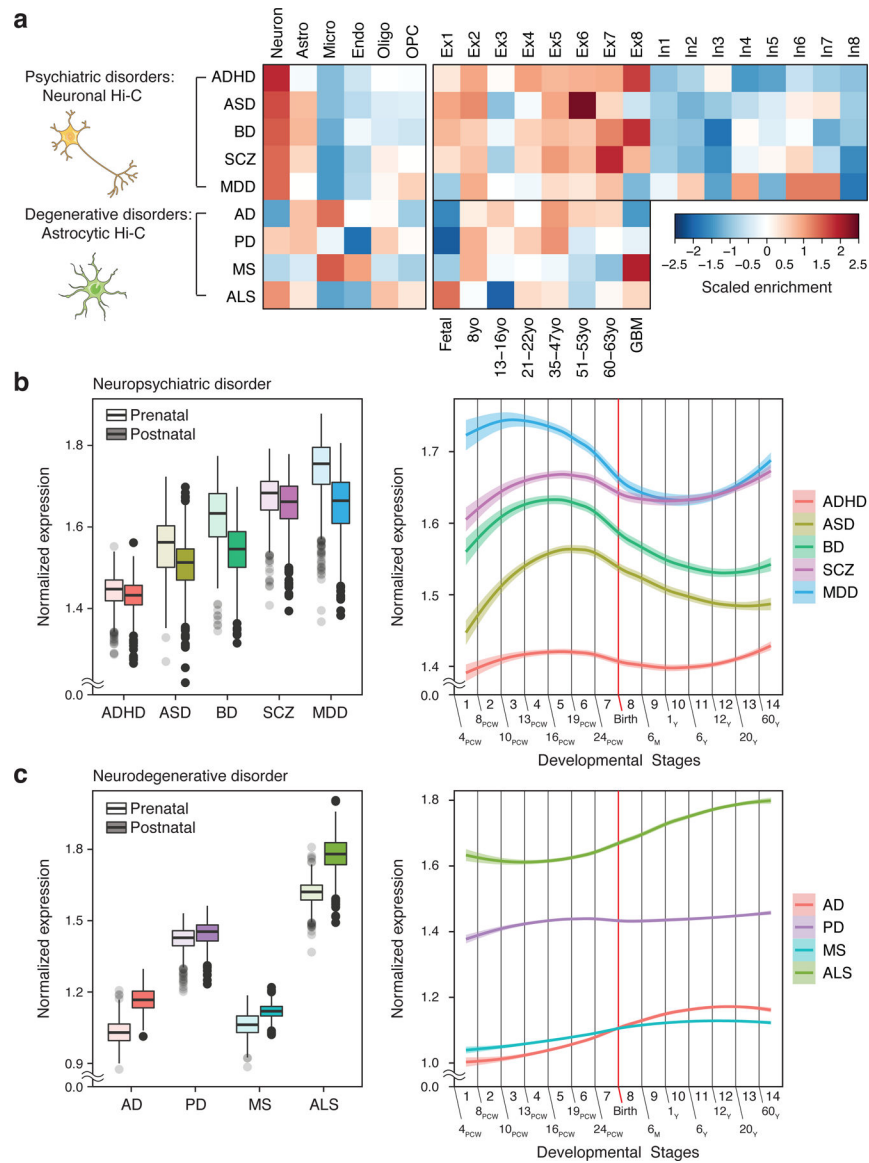
**Fig. 1. Schematics of H-MAGMA approach.**

**a.** H-MAGMA leverages chromatin interaction profiles (Hi-C) to assign intergenic and intronic SNPs to cognate genes. We have applied this framework to five psychiatric disorders and four degenerative disorders using Hi-C datasets from the fetal and adult brain. In return, H-MAGMA provides gene-level association statistics, which can be used to elucidate biological mechanisms underlying brain disorders. **b.** Intronic and intergenic SNPs are often annotated to distal genes. **c.** SNPs mapped to H-MAGMA selective genes explain a significant proportion of heritability. Top graph: Heritability enrichment  $\pm$  standard error; enrichment denotes proportion of heritability/proportion of SNPs; red dotted line, enrichment=1. Bottom graph: false discovery rate (FDR) of heritability enrichment; red dotted line, FDR=0.05. **d.** Overlap between SCZ-associated genes identified by H-MAGMA, TWAS, and coloc.



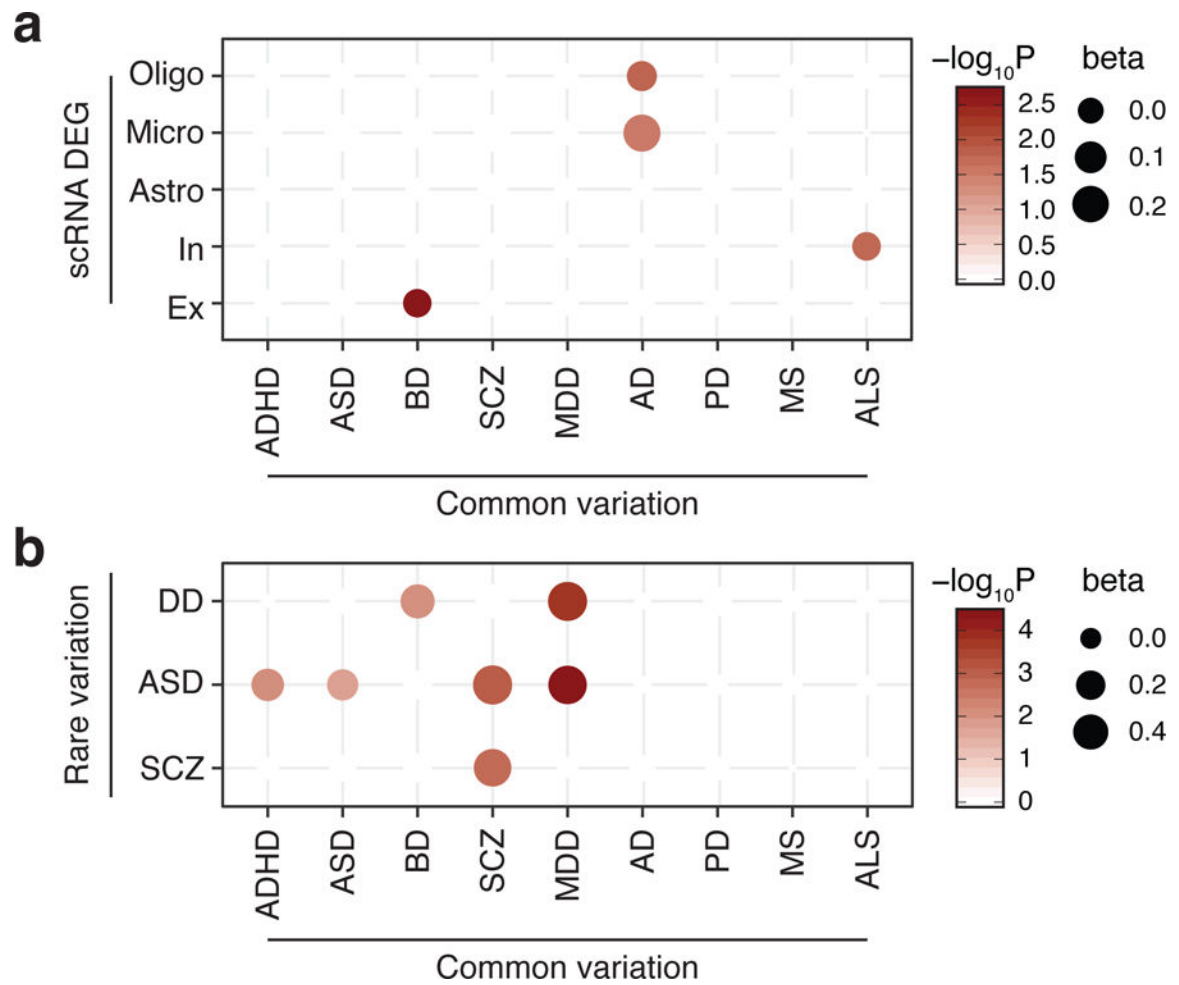
**Fig. 2. Spatiotemporal dynamics of brain disorder risk genes.**

**a.** Heritability enrichment of brain disorders in active regulatory elements of the fetal and adult brain. Enrichment  $\pm$  standard error (circle) and significance of heritability enrichment (triangle) are depicted. **b-c.** Developmental expression trajectories of brain disorder risk genes. PCW, post-conception week; M, month; Y, year. (Left)  $N = 410$  and  $453$  for prenatal and postnatal samples, respectively. Center, median; box = 1st-3rd quartiles (Q); minima,  $Q1 - 1.5 \times$  interquartile range (IQR); maxima,  $Q3 + 1.5 \times$  IQR. (Right) LOESS smooth curve with 95% confidence bands.



**Fig. 3. Cellular expression profiles of brain disorder risk genes.**

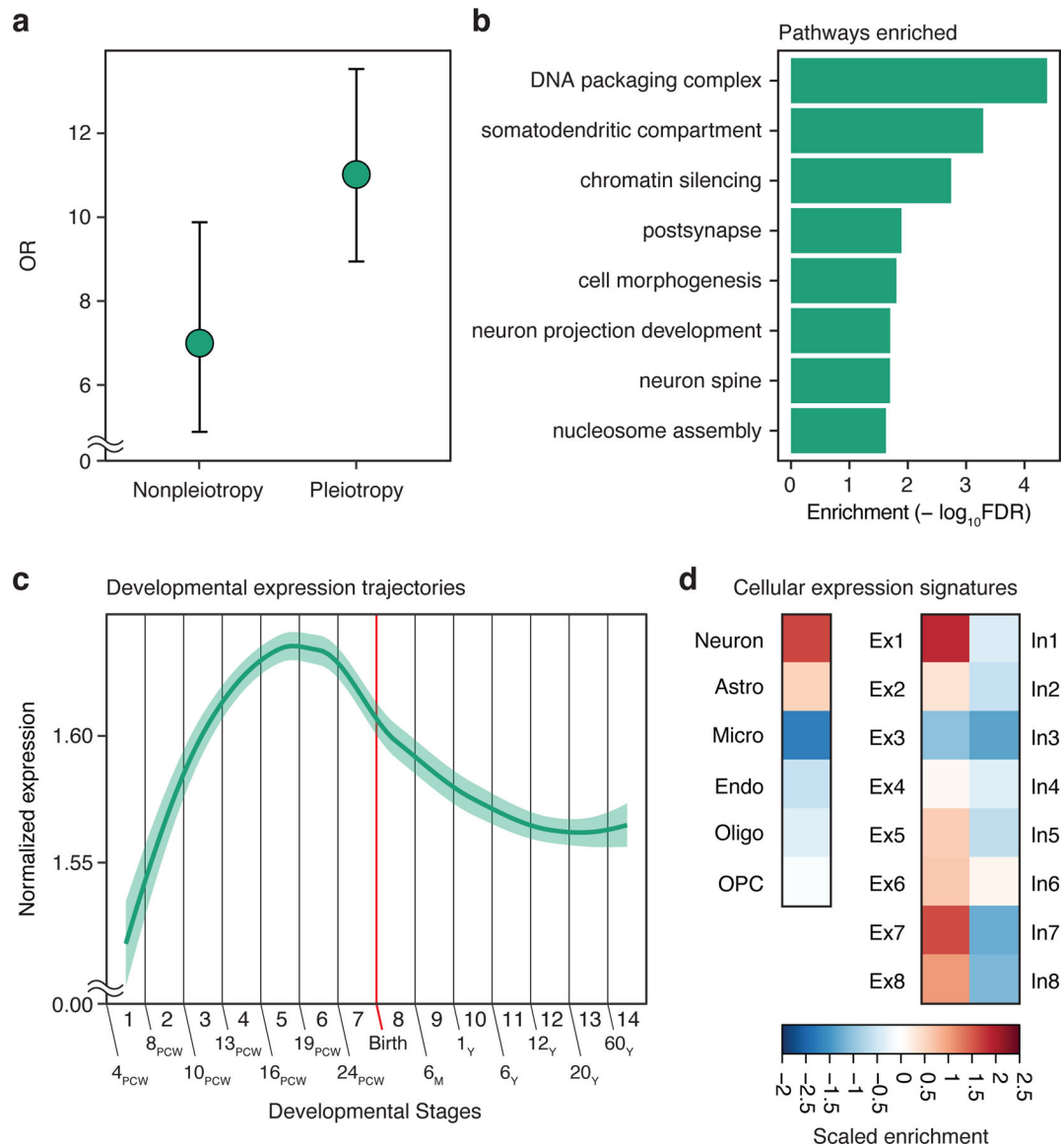
**a.** We used neuronal and astrocytic H-MAGMA to annotate psychiatric disorder and degenerative disorder GWAS, respectively. Psychiatric disorder-associated genes are highly expressed in neurons, while neurodegenerative disorder-associated genes exhibit glial signatures. Astro, astrocytes; Micro, microglia; Endo, endothelial cells; Oligo, oligodendrocytes; OPC, oligodendrocytes progenitor cells; Ex, excitatory neurons; In, inhibitory neurons; GBM, glioblastoma multiforme tumor. **b-c.** Developmental expression trajectories of psychiatric disorder-associated genes (**b**) and degenerative disorder-associated genes (**c**). PCW, post-conception week; M, month; Y, year. (Left)  $N = 410$  and  $453$  for prenatal and postnatal samples, respectively. Center, median; box=Q1-Q3; minima,  $Q1 - 1.5 \times IQR$ ; maxima,  $Q3 + 1.5 \times IQR$ . (Right) LOESS smooth curve with 95% confidence bands.



**Fig. 4. Characteristics of brain disorder risk genes.**

**a.** AD-associated genes are dysregulated in oligodendrocytes and microglia from AD postmortem brains (single-cell RNA-seq DEG). **b.** Comparison of brain disorder risk genes with common and rare variation. Only significant associations ( $FDR < 0.1$ ) were depicted.





**Fig. 5. Pleiotropic genes reveal shared molecular mechanisms of psychiatric disorders.**

**a.** Comparison between pleiotropic genes and genes mapped to non-pleiotropic and pleiotropic GWS loci. Odds ratio (OR) and 95% confidence intervals (CI). **b.** Gene ontology enrichment of pleiotropic genes. **c.** A developmental expression trajectory of pleiotropic genes. LOESS smooth curve with 95% confidence bands. **d.** Cell-type specific expression profiles of pleiotropic genes.

**Table 1.** Biological processes enriched for brain disorders. Gene ontologies detected in H-MAGMA but not in cMAGMA are marked in bold.

	ADHD	ASD	BD	SCZ	MDD	AD	PD	MS	ALS
Transcriptional regulators	✓	✓	✓	✓	✓	✓	✓	✓	✓
DNA damage/repair	✓	✓	✓	✓	✓	✓	✓	-	✓
RNA splicing	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neurogenesis	✓	-	-	✓	✓	✓	✓	✓	✓
Neuronal differentiation	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neuronal apoptosis	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glutamatergic	✓	✓	✓	✓	✓	✓	✓	✓	✓
GABAergic	-	✓	✓	✓	-	-	-	-	✓
Synaptic	Pre/Post	Post	Post	Pre/Post	Pre/Post	Post	Post	Pre/Post	Post
Neurotransmitter	Dopamine Serotonin Acetylcholine Monoamine Nitric oxide	Acetylcholine Nitric oxide Serotonin	Acetylcholine Nitric oxide	Dopamine Acetylcholine Nitric oxide	Monoamine	-	Nitric oxide Norepinephrine	Dopamine	-
Glial/Astrocytes	Differentiation	Development Gliogenesis	Gliogenesis	-	Astrocyte development Glial guided migration	Differentiation Migration Proliferation	Differentiation Proliferation	Projection Migration Proliferation	Migration
Oligodendrocytes	-	✓	-	✓	✓	✓Myelination	✓Myelination	✓Myelination	✓Myelination
Brain development	Cerebral cortex	Telencephalon	Hippocampus Substantia Nigra Telencephalon	-	Cerebral cortex Telencephalon Substantia nigra	Forebrain Cerebral cortex	Forebrain Limbic system Midbrain Telencephalon	Cerebral cortex Hypothalamus Forebrain	Hindbrain Forebrain Substantia nigra
Interferon	✓	-	✓	✓	✓	✓	✓	✓	✓
Antigen processing	✓	✓	✓	✓	-	✓	✓	✓	✓
Interleukin	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cytokine	-	✓	-	✓	✓	✓	✓	✓	-
T cell	✓	✓	✓	✓	✓	✓	✓	✓	✓
B cell	-	✓	-	✓	-	✓	-	-	-
TLR	✓	✓	✓	✓	✓	-	✓	-	✓

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	ADHD	ASD	BD	SCZ	MDD	AD	PD	MS	ALS
Aging	✓	✓	-	-	-	✓	-	-	✓
Ischemia	-	-	-	-	-	-	-	✓	✓
Others	ERBB	Vocalization Wnt BAF APP	Glucocorticoid APP Synaptic plasticity	Amyloid beta BAF Beta- catenin/Wnt ERBB	Beta-catenin ERBB	Amyloid beta ERBB Glucocorticoid	Wnt Amyloid beta ERBB Tau	ERBB2 Beta- catenin/Wnt Tau	Wnt