ARTICLE

Psychiatric disorders and brain white matter exhibit genetic overlap implicating developmental and neural cell biology

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Improved understanding of the shared genetic architecture between psychiatric disorders and brain white matter may provide mechanistic insights for observed phenotypic associations. Our objective is to characterize the shared genetic architecture of bipolar disorder (BD), major depression (MD), and schizophrenia (SZ) with white matter fractional anisotropy (FA) and identify shared genetic loci to uncover biological underpinnings. We used genome-wide association study (GWAS) summary statistics for BD ($n = 413{,}466$), MD ($n = 420{,}359$), SZ ($n = 320{,}404$), and white matter FA ($n = 33{,}292$) to uncover the genetic architecture (i.e., polygenicity and discoverability) of each phenotype and their genetic overlap (i.e., genetic correlations, overlapping trait-influencing variants, and shared loci). This revealed that BD, MD, and SZ are at least 7-times more polygenic and less genetically discoverable than average FA. Even in the presence of weak genetic correlations (range = −0.05 to −0.09), average FA shared an estimated 42.5%, 43.0%, and 90.7% of trait-influencing variants as well as 12, 4, and 28 shared loci with BD, MD, and SZ, respectively. Shared variants were mapped to genes and tested for enrichment among gene-sets which implicated neurodevelopmental expression, neural cell types, myelin, and cell adhesion molecules. For BD and SZ, case vs control tract-level differences in FA associated with genetic correlations between those same tracts and the respective disorder ($r_{BD} = 0.83$, $p = 4.99e\text{-}7$ and $r_{SZ} = 0.65$, $p = 5.79e\text{-}4$). Genetic overlap at the tract-level was consistent with average FA results. Overall, these findings suggest a genetic basis for the involvement of brain white matter aberrations in the pathophysiology of psychiatric disorders.

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INTRODUCTION

Optimal brain function relies on the complex organization of interconnected brain regions. Brain white matter, composed of over one hundred thousand kilometers of bundled axons [1], facilitates neuronal communication within and across brain regions as well as with peripheral organ systems. This complexity provides considerable opportunity for perturbations, potentially during neurodevelopment, which may manifest as atypical cognitive, emotional, or behavioural functioning [2–5]. Indeed, abnormal structural connectivity has been revealed by many neuroimaging studies of psychiatric disorders and is associated with psychiatric symptoms and traits [2, 5–8].

Diffusion tensor imaging (DTI) derived measures aid in making inferences about microstructural variations in brain white matter that may contribute to altered connectivity. One of the commonly studied measures is fractional anisotropy (FA) which captures the ordered (or directional) displacement of water molecules, a robust property of white matter pathways [9]. Variations in FA, predominantly reductions, have been observed in many psychiatric disorders including bipolar disorder (BD), major depressive disorder (MD), and schizophrenia (SZ) [10–12]. These variations are often widespread across numerous white matter tracts and may reflect various microstructural properties including, but not exclusive to: the size, density and organized packing of axons, crossing fibers, degree of myelination, and integrity of axonal and myelin membranes [9, 13]. Therefore, while studies of FA provide some evidence supporting disconnectivity theories of psychiatric disorders [2], ambiguity regarding potential cellular and molecular mechanisms remain.

Understanding the shared genetic architecture between psychiatric disorders and white matter FA may provide new insights into the underlying pathobiology. Major psychiatric disorders such as BD, MD, and SZ are heritable (twin-heritability ranging from 41–80%) and highly polygenic [14–17]. Additionally,

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averaged FA across all white matter tracts, is typically reported as the most heritable among average DTI metrics (twin-heritability estimates as high as 0.88) and exhibits widespread genetic associations across the genome [18, 19]. Genetic correlations between psychiatric disorders and white matter FA tend to be weak to moderate [19, 20]. However, there has been limited investigation of the polygenic overlap beyond genetic correlations.

Genome-wide genetic correlations have and will continue to be a useful measure of genetic overlap. However, this approach averages effects across the genome, which means it does not capture genetic overlap in the presence of a mixture of variants with effects that are concordant (e.g., increasing effects on both traits) and discordant (i.e., increasing effects in one trait but decreasing effects in the other trait) [17]. A balanced mixture of concordant and discordant genetic effects can result in a near zero genetic correlation even if the pair of traits share many causal genetic variants. Moreover, genetic overlap can be assessed at varying levels of granularity including single genetic variants, individual loci, and genome-wide summary metrics. Methods that are agnostic to effect direction can capture overlapping genetic architecture between traits even in the presence of low or absent genetic correlation. Non-correlative genetic overlap can be important for identifying shared biological pathways between traits.

Here, we leverage recent large-scale genome-wide association studies (GWAS) to investigate genetic overlap between three psychiatric disorders (BD, MD, and SZ) and white matter FA. First, we characterize genetic architecture estimating heritability, polygenicity, and discoverability of each disorder and average FA. Then both correlative and non-correlative genetic overlap is estimated with genetic correlations, the number of overlapping trait-influencing variants, and identification of shared genetic loci. After mapping genes to shared loci, enrichment analyses are performed to investigate potential neurodevelopmental, molecular, and cellular mechanisms contributing to the shared genetic architecture. Finally, additional analyses assess genetic overlap for each psychiatric disorder with individual white matter tracts.

METHODS

Sources of data

GWAS summary statistics were acquired from the Psychiatric Genomics Consortium for BD, MD, and SZ. This included studies of 413,466 participants for BD [21], 420,359 participants for MD (including participants from 23andMe, Inc) [22, 23], and 320,404 participants for SZ [24]. For average and tract-level FA, GWAS summary statistics were acquired from the study of 33,292 participants from the UK Biobank by Zhao et al. (2021) [19]. To avoid sample overlap for conjunctional false discovery rate analyses (conjFDR, see below), we acquired summary statistics for MD and BD that excluded UK Biobank participants. To validate lead SNPs discovered using conjFDR, summary statistics from independent GWAS for each psychiatric disorder were leveraged (Supplementray Methods). Given the utility of glucose as a major energy source for the brain, we used summary statistics for blood glucose levels from 361,194 UK biobank participants (http://www.nealelab.is/blog/2019/9/16/biomarkers-gwas-results) as a comparator for MiXeR analyses (see below). Standardized effect sizes (Cohen's D) for case vs control differences in white matter tracts' FA were obtained for BD [12], MD [11], and SZ [10] studies conducted by the ENIGMA consortium. These Cohen's D values were then correlated at the tract-level with genetic correlations for each disorder.

Statistical analyses

MiXeR. To characterize genetic architecture and estimate polygenic overlap we used MiXeR v1.3 (https://github.com/precimed/mixer) [25, 26]. Univariate MiXeR analysis rests on the assumption that the genetic architecture of a given trait is a mixture of variants that are trait-influencing and those that are not trait-influencing. Polygenicity is estimated as the number of trait-influencing variants that explain 90% of the estimated SNP-heritability [25]. Traits which are more polygenic have a greater number of trait-influencing variants than less polygenic traits. Discoverability is estimated as the average magnitude of additive genetic effects among trait-influencing variants. That is, for more discoverable traits, the average effect size of associated variants is larger than less discoverable traits. Beyond this, power-plots display the estimated proportion of variance in heritability explained by various sample sizes for each trait. More genetically discoverable traits require smaller sample sizes to explain a given proportion of variance. Heritability is estimated as a function of the product of polygenicity and discoverability. The more heritable a trait the greater the proportion of variance explained by genetic variations in a given population.

To estimate the number of overlapping trait-influencing variants between pairs of traits we used bivariate MiXeR [25]. Bivariate MiXeR models the number of trait-influencing variants unique to each trait (non-overlapping) as well as the number of shared trait-influencing variants (overlapping), irrespective of effect direction. Details are provided in the Supplementary Methods.

Genetic correlations. Pairwise genetic correlations were estimated using LD score regression [27]. Adjustments for multiple comparisons were conducted using the Benjamini-Hochberg method.

Conjunctional false discovery rate (conjFDR) analyses. For a pair of traits, conditional quantile-quantile plots (QQ-plots) were constructed such that one trait is assigned the primary trait and the other the secondary trait. SNPs in the primary trait were filtered based on *p*-value thresholds in the secondary trait ($p < 1$, <0.1, <0.001). Cross-trait enrichment is observed when smaller *p*-value thresholds result in a leftward deflection in the primary traits conditional QQ-plot. For a valid conjFDR analysis, both traits must exhibit cross-trait enrichment for each other.

Next, for those pair of traits that exhibit cross-trait enrichment with each other, we performed conjFDR analyses. The cross-trait enrichment was transformed into conditional FDR values for each SNP (Supplementary Methods). By using FDR values the condFDR analysis is agnostic to effect direction. The condFDR estimation is performed twice switching the role of primary and secondary trait for each pair of traits.

Finally, the conjFDR value is estimated as the maximum of the two condFDR values for a given pair of traits. A threshold of conjFDR < 0.05 was applied for all analyses. The resulting SNPs that surpass this threshold are considered to exhibit shared associations with the pair of traits analysed. More details are provided in the Supplementary Methods including definitions of loci, candidate and lead SNP, measuring loci overlap, and validation of lead SNP sign concordance in independent samples.

Gene mapping and enrichment analyses. For loci shared by average FA and each of the psychiatric disorders, all candidate SNPs were mapped to genes using FUMA default parameters for positional mapping. We used data from the Human Brain Transcriptome project (www.hbtatlas.org) [28] to determine lifespan expression profiles of the mapped genes. This included a total of 57 donors aged 5.7 weeks post conception to 82 years old with samples from regions across the brain. Linear mixed models were used to assess group differences in gene expression (Supplementary Methods). Additionally, mapped genes were then tested for enrichment among gene ontology terms, differentially expressed genes in the brain at different ages [29], neural cell-type genes [30–32], and genes associated with neural cell components [33, 34]. Details are provided in the Supplementary Methods.

RESULTS

Characterizing the genetic architecture of each phenotype

SNP-heritability ranged from 0.07 (sd = 1.06e-3) for MD to 0.38 (sd = 4.14e-3) for SZ (Fig. 1a, Supplementary Table 1). The polygenicity of the psychiatric disorders were more than seven times larger than average FA (Fig. 1b, Supplementary Table 1). Meanwhile, average FA was more discoverable than the psychiatric disorders with a smaller sample size estimated to explain 100% of variance (Fig. 1c, Supplementary Table 1).

Characterizing genetic overlap between psychiatric disorders and average FA

Genetic overlap was estimated among the trait-influencing variants for each psychiatric disorder and average FA (Fig. 2a)

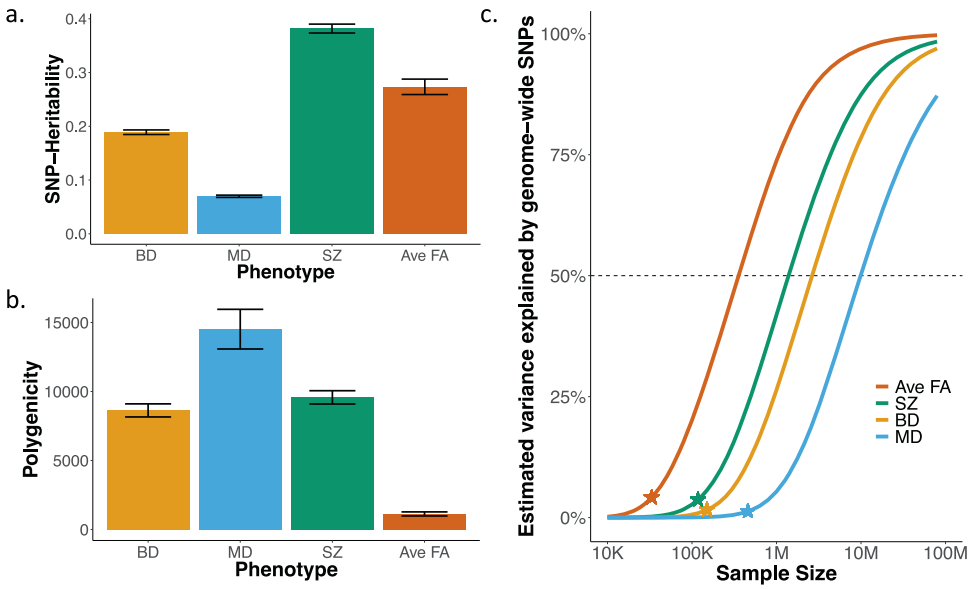


Fig. 1 Genetic architecture of psychiatric disorders and average FA. a SNP-heritability for each phenotype. **b** Polygenicity for each phenotype. Error bars in plots A and B represent two standard deviations. **c** Power-plot displaying the effective sample size required to capture 0–100% of SNP-heritability. More genetically discoverable traits require smaller sample sizes for a given proportion of variance explained. The stars represent current effective sample size from included GWAS. SNP single nucleotide polymorphism, BD bipolar disorder, MD major depression, SZ schizophrenia, Ave FA average fractional anisotropy across all tracts.

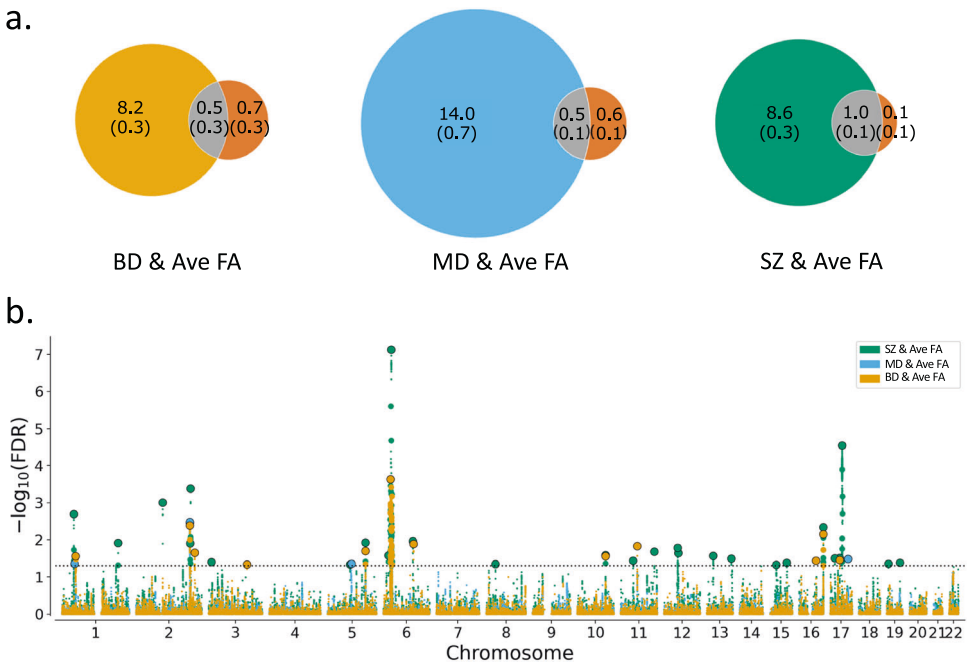


Fig. 2 Genetic overlap between psychiatric disorders and average FA. a Venn diagrams representing the genetic overlap (grey) between each psychiatric disorder and average FA (dark orange). The size of the circles depicts the polygenicity of the phenotype. Also depicted are the estimated number of trait-influencing variants and the standard deviations (below in brackets) for trait specific and shared components of the Venn diagrams. The number of variants is expressed in thousands rounded to the nearest tenth (e.g., 8.2 = 8200 variants). **b** A Manhattan plot displaying conjunctional loci shared by each psychiatric trait and average FA. Larger circles represent independent significant SNPs while those outlined in black represent lead SNPs. BD bipolar disorder, MD major depressive disorder, SZ schizophrenia, Ave FA average fractional anisotropy across all tracts, FDR false discovery rate.

after establishing good model fit (Supplementary Table 2, Supplementary Fig. 1). Average FA shared an estimated 42.5%, 43.0%, 90.7% of its trait-influencing variants with BD, MD, and SZ, respectively. Conversely, BD, MD, and SZ, respectively shared 5.8%, 3.5%, 11.9% of their trait-influencing variants with average FA. This overlap was observed in the presence of weak genetic correlations for average FA with MD ($r_g = -0.09$, $p = 1.72e\text{-}3$) and SZ ($r_g = -0.07$, $p = 4.64e\text{-}2$) and no correlation with BD ($r_g = -0.05$, $p = 1.15e\text{-}1$). As a comparator, average FA trait-influencing variants only showed 7.8% overlap with blood glucose levels

and 25.8% of glucose trait-influencing variants overlapped with average FA (Supplementary Table 2, Supplementary Fig. 1). Additionally, there was no genetic correlation between average FA and glucose ($r_g = -0.02$, $p = 0.58$).

Cross trait enrichment was observed for each psychiatric disorder and average FA (Supplementary Figure 2). Average FA shared a total of 12, 4, and 28 genetic loci with BD, MD, and SZ, respectively (Fig. 2b, Supplementary Table 3). When combined across disorders this resulted in a total of 35 unique loci. For example, one locus on chromosome two overlapped between average FA and each of the psychiatric disorders (Supplementary Table 4). While 6 of the 12 loci shared between average FA and BD also overlapped with loci shared between FA and SZ.

Gene-level analyses

A total of 98, 33, and 235 genes were mapped to variants shared between average FA and BD MD, and SZ, respectively (Supplementary Table 5). These genes will hereafter be referred to as BD-shared-genes, MD-shared-genes, and SZ-shared-genes. Gene expression data were available for 46, 18, and 126 of the BD-, MD-, and SZ- shared-genes. Peaks in expression were observed during fetal development compared to the profile of all genes (Fig. 3a; BD-shared-genes: beta = 0.11, $p = 1.16e\text{-}68$; MD-shared-genes: beta = 0.22, $p = 9.65e\text{-}110$; SZ-shared-genes: beta = 0.02, $p = 3.79e\text{-}7$). MD- and BD- shared-genes had larger peaks in fetal gene-expression than SZ-shared-genes (BD vs SZ shared-genes: beta = 0.09, $p = 3.05e\text{-}35$; MD vs SZ shared-genes: beta = 0.20, $p = 3.04e\text{-}80$). Meanwhile, SZ-shared-genes had greater expression postnatally than the other two disorders with a secondary peak in expression during adulthood. Only BD-shared-genes were enriched for genes that are differentially expressed in early to mid-gestation (Fig. 3b, Supplementary Table 6).

BD- and MD- shared-genes were enriched for astrocyte, microglia, and neuron genes (Fig. 3c, Supplementary Table 7). Notably, this enrichment was predominantly observed in tissue sampled from the fetal brain. SZ-shared-genes were enriched for myelin ($n_{genes} = 5$, $p_{adj} = 0.03$) with nominally significant enrichment for axons, neurons, and various glia including oligodendrocytes (Fig. 3c, d, Supplementary Table 7-8). Moreover, gene ontology terms related to cell-adhesion molecules, mitochondria, and calcium binding were enriched among BD- and SZ- shared-genes (Fig. 3e, Supplementary Table 9).

White matter tract-level analyses

There were few significant correlations observed between tract-level FA and each of the psychiatric disorders (Fig. 4a, Supplementary Table 10). BD had the strongest genetic correlation with FA within the uncinate fascicules ($r_g = -0.16$, $p_{fdr} = 5.04e\text{-}3$). Significant genetic correlations between MD and six tracts were observed, half of which were commissural pathways. The profile of genetic correlations between disorder and each tract was compared to the profile of case *vs*. control differences in tract level FA (Fig. 4b). This resulted in a substantial cross-tract correlations between genetic and phenotypic associations for BD ($r = 0.83$, $p = 4.99e\text{-}7$) and SZ ($r = 0.65$, $p = 5.79e\text{-}4$) but not MD ($r = 0.25$, $p = 2.48e\text{-}1$).

Of the 21 tracts investigated, 18, 6, and 14 had good model fit for MiXeR analyses with BD, MD, and SZ, respectively (Supplementary Table 11 and Supplementary Figs. 3–5). An average of 49.1%, 46.2%, and 66.4% trait-influencing variants for a given tract was estimated to overlap with BD, MD, and SZ trait-influencing variants (Fig. 5a). Cross-trait enrichment was observed for 19, 16, and all 21 tracts with BD, MD, and SZ, respectively (Supplementary Figs. 6–8). Of those tract-disorder pairs which showed enrichment, 169, 76, and 346 loci were shared with BD, MD, and SZ, respectively (Supplementary Table 12) with variability observed across tracts (Fig. 5b).

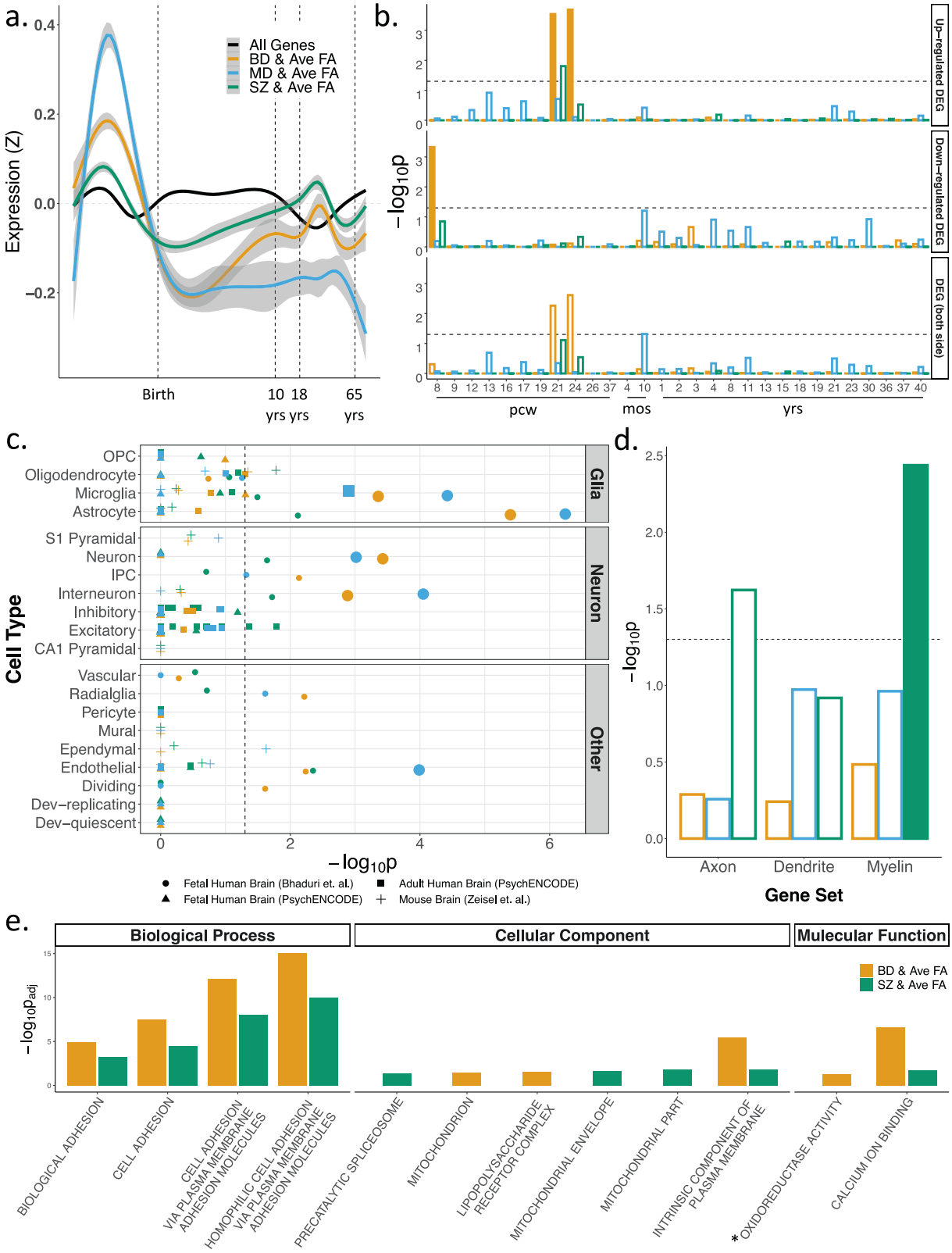
Notably, the genu of the corpus callosum (GCC) had the greatest number of shared loci with BD ($n = 25$) while the cingulate gyrus (cingulum) had the largest overlap for MD ($n = 8$; tied with the external capsule) and SZ ($n = 36$). Of those loci shared across each tract with BD, MD, and SZ, there were 113 (66.86%), 28 (36.84%), and 162 (46.82%) that overlapped with loci also found to be shared with average FA and the same disorder (Supplementary Table 13). Moreover, BD MD, and SZ respectively had 73, 38, and 137 unique loci identified across all 21 tracts. Of these disorder-specific unique loci, 70.7% ($p = 2.25e\text{-}4$), 84.2% ($p = 1.22e\text{-}5$), and 75.8% ($p = 9.33e\text{-}11$) of lead SNPs showed concordant effect directions in independent samples for BD, MD, and SZ, respectively (Supplementary Table 14). A substantial amount of loci overlap was observed across each of the tract-disorder pairings predominantly between BD and SZ shared loci (Supplementary Fig. 9) which resulted in a total of 199 unique loci identified across all disorder-tract pairings.

DISCUSSION

Leveraging data from large GWAS of BD, MD, SZ, and white matter FA we show that the psychiatric disorders were more polygenic and less genetically discoverable than average FA despite variable heritability. Investigation of genetic overlap suggests that average FA has less overlap with BD and MD than with SZ. Moreover, the shared genetic architecture between each of the psychiatric disorders and average FA implicated differing developmental, cellular, and molecular biological underpinnings through gene-level analyses. Overall, these results provide a genetic basis for the involvement of impaired white matter connections in the pathophysiology of psychiatric disorders.

Our genetic characterization of each phenotype supports the concept that brain imaging metrics, such as white matter FA, may be intermediate phenotypes (e.g., endophenotypes) for psychiatric disorders [35, 36]. That is, average FA is a less heterogeneous phenotype than psychiatric disorders that likely lies closer to the underlying disorder pathobiology. We find that the psychiatric disorders, which are likely more distal from their genetic underpinnings, were at least seven times more polygenic than average FA, which is likely more proximal to its genetic underpinnings. The estimated polygenicity for the psychiatric disorders is consistent with previous estimates [17, 37] and supports the idea that psychiatric disorders are more heterogenous traits. To our knowledge, the polygenicity of white matter FA has not previously been estimated but the relatively smaller polygenicity, compared to psychiatric disorders, coincides with other brain imaging metrics [37, 38]. Average FA was more genetically discoverable than the psychiatric disorders, therefore, FA requires a smaller estimated sample size to uncover its complete genetic architecture. The observed correlative genetic overlap provides the directional association necessary to support FA as an endophenotype. Although, recent studies illustrate that genetic correlations within smaller genomic regions are informative and a mixture of effect directions in these local genetic correlations could result in attenuated or non-significant genome-wide genetic correlations [17, 39–41]. Whether the non-correlative genetic overlap observed in this study may be indicative of these local associations and supportive of FA as an endophenotype for psychiatric disorders remains a topic for future investigations. The combined results for polygenicity and discoverability with the observed genetic correlations supports the idea that white matter variations in FA may be an intermediary from genetic variations to psychiatric disorders.

Although genetic correlations between each psychiatric disorder and FA were weak, consistent with previous findings [19, 20], analyses beyond correlation revealed substantial genetic overlap. Recent imaging genetics studies observe the same phenomenon where a mixture of positive and negative genetic



effects across the genome weaken genetic correlation estimates, even in the presence of strong genetic overlap [37, 38]. By using methods agnostic to effect direction, we uncovered an extensive shared genetic architecture between each psychiatric disorder and FA. Although the observed shared genetic architecture is a mixture of concordant and discordant effects, this implicates shared biology between FA and psychiatric disorders. Therefore, the same biological mechanisms may be involved but in potentially consistent or opposing directions. SZ had the largest portion of overlapping trait-influencing variants and shared loci

Fig. 3 Gene-level analyses. a Lifespan gene expression profiles for genes shared by average FA and each of the psychiatric disorders. Additionally, the lifespan gene expression profile across all genes is displayed as a reference. The y-axis represents the normalized expression values as z-scores while the x-axis represents age on a log2 scale. All other plots (**b**–**e**) display results of gene enrichment analyses. **b** Enrichment for differentially expressed genes at various ages from fetal development to 40 years postnatally. The top plot displays enrichment for genes that are upregulated at each age on the x-axis. The middle plot displays enrichment for genes that are downregulated at each age on the x-axis. The bottom plot displays enrichment for genes that exhibit differential expression irrespective of direction at each age on the x-axis. The y-axis displays the significance of enrichment at each age. Significant enrichment surviving correction for multiple comparisons are represented by bars with a solid color while bars not filled in represent non-significant associations. **c** Cell-type enrichment analyses performed for four sources of cell-type gene sets. Larger points represent association that surpass correction for multiple comparisons. **d** Specific cell compartment enrichment analysis that uses genes associated with axons, dendrites, and myelin. Dashed lines in plot **b**–**d** represent the nominal significance threshold at $p = 0.05$. **e** Gene ontology group enrichment analyses displaying only those groups which survive correction for multiple comparison. *full gene ontology term = oxidoreductase activity acting on paired donors with oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water. BD bipolar disorder, MD major depressive disorder, SZ schizophrenia, Ave FA average fractional anisotropy, yrs years (since birth), pcw post-conception weeks, mos months (since birth), DEG differentially expressed gene, OPC oligodendrocyte progenitor cell, S1 Pyramidal: primary sensory cortex pyramidal cell, IPC intermediate progenitor cell, CA1 Pyramidal: pyramidal cell of the first cornu Ammonis region of hippocampus, Dev developmental.

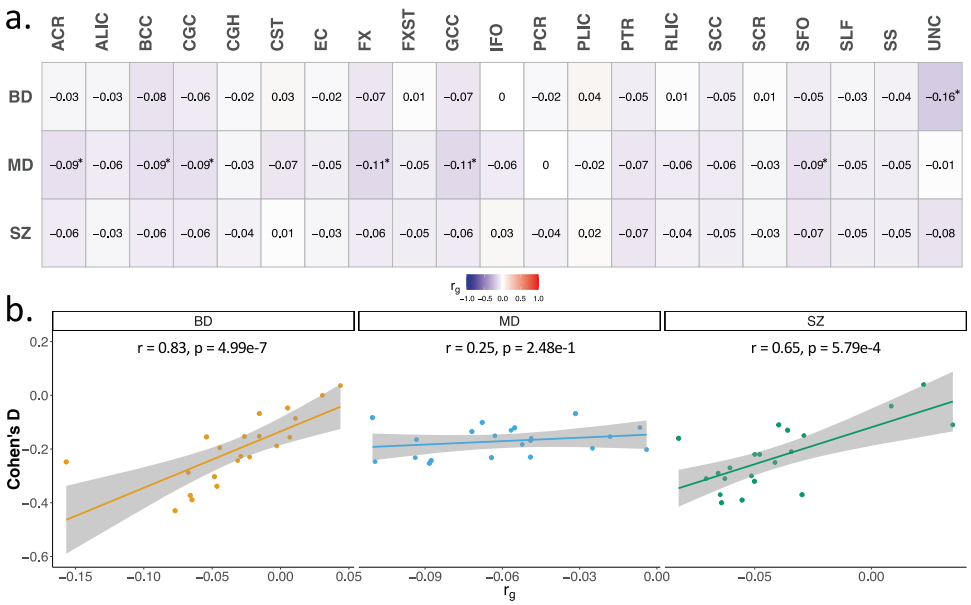


Fig. 4 Tract-level FA genetic associations with psychiatric disorders. a The genetic correlation (r_g) between fractional anisotropy for 21 white matter tracts and each of the psychiatric disorders. The value of the correlation coefficient is printed within each cell. The more negative the correlation the more intense the blue colour of the cell while the more positive the correlation the more intense the red colour of the cell. The presence of an asterisk above the correlation coefficient represents a significant association after correction for multiple comparisons. **b** A depiction, for each disorder, of the association between case-control differences in fractional anisotropy for each tract (Cohen's D) and genetic correlation between disorder and fractional anisotropy for each tract (r_g). A robust bi-weight mid-correlation was performed to adjust for any influence due to potential outliers. BD bipolar disorder, MD major depressive disorder, SZ schizophrenia, ACR anterior corona radiata, ALIC anterior limb of internal capsule, BCC body of corpus callosum, CGC cingulate gyrus cingulum, CGH cingulate gyrus hippocampus, CST corticospinal tract, EC external capsule, FX fornix, FXST fornix stria terminalis, GCC genu of corpus callosum, IFO inferior fronto-occipital fasciculus, PCR posterior corona radiata, PLIC posterior limb of internal capsule, PTR posterior thalamic radiation, RLIC retrolenticular part of internal capsule, SCC splenium of corpus callosum, SCR superior corona radiata, SFO superior fronto-occipital fasciculus, SLF superior longitudinal fasciculus, SS sagittal stratum, UNC uncinate fasciculus.

with average and tract-level FA. The strong genetic overlap between SZ and FA is in line with phenotypic associations where SZ on average has larger case *vs* control differences in average and tract level FA than BD and MD [10–12]. Many shared loci between BD and FA tended to overlap with shared loci between SZ and FA. These two disorders have extensive genetic and symptom overlap [17, 42]. Moreover, for BD and SZ, the pattern of tract-level differences in FA between cases and controls correlated strongly with genetic correlations between those same tracts and the respective disorder. This suggests phenotypic case-control differences in white matter FA may be more genetically driven for BD and SZ than for MD.

The present analyses link genes overlapping between FA and the psychiatric disorders with fetal brain development. Shared genes for all disorders exhibited a peak in gene expression during fetal development, and BD-shared-genes demonstrated enrichment for genes differentially expressed during fetal development. Although neurodevelopmental theories of SZ are more common, there is also evidence for a neurodevelopmental component for the etiology of BD and MD [43, 44]. We also observe that BD- and MD- shared-genes were enriched for astrocyte, microglia, and neuron cell-type genes identified from fetal brain tissue. Astrocytes and microglia are involved in development and maintenance of white matter including axon guidance in the fetal brain [45–47]. The two cell types also play a role in central immunity providing a potential mechanism connecting fetal exposure to immune factors, white matter, and psychiatric disorders. Moreover, BD-shared-genes were enriched for cell adhesion molecules and lipopolysaccharide receptor complex genes which both implicate immune activity. Although speculative, our findings

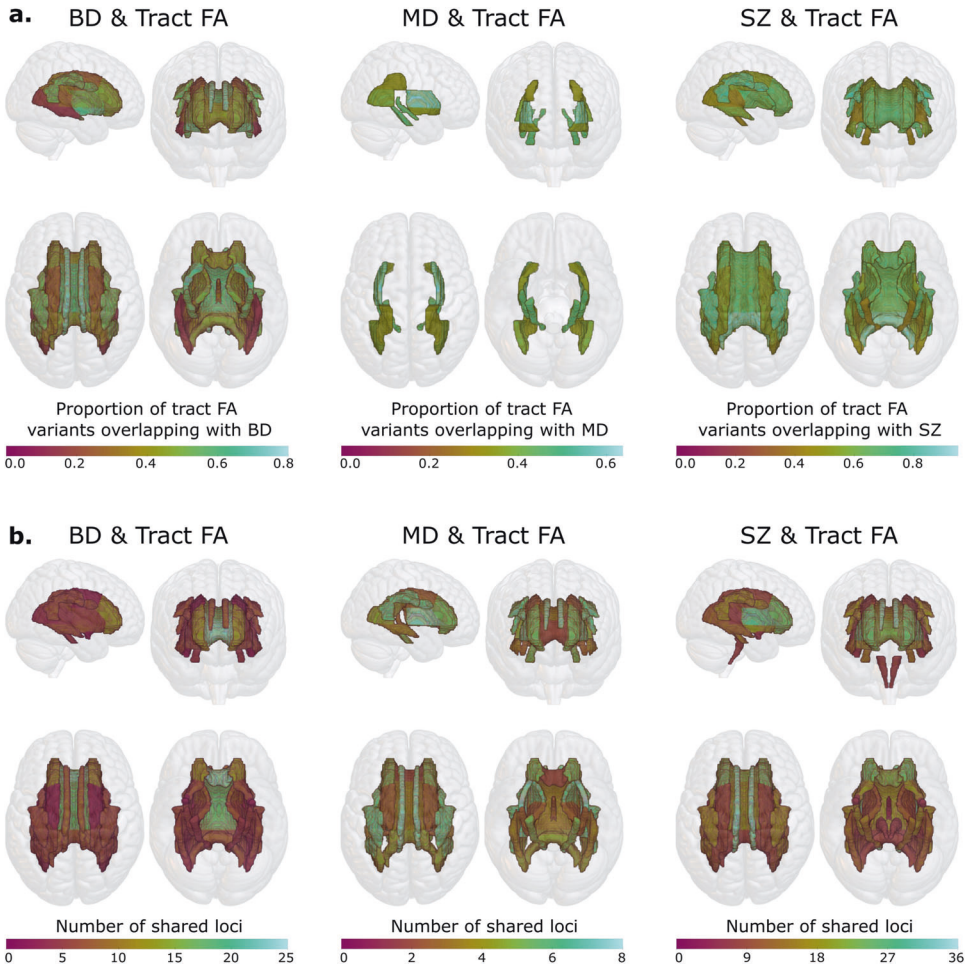


Fig. 5 Tract-level genetic overlap beyond genetic correlation. a Brain maps displaying the proportion of trait-influencing variants for each white matter tract that overlap with trait-influencing variants for each psychiatric disorder, as estimated by MiXeR. **b** Brain maps displaying the number of shared genetic loci between each disorder and each white matter tract, as estimated by conjFDR. For all figures, disorder-tract comparisons with poor model fit are not visualized.

suggest BD, and to some extent MD, have a neurodevelopmental connection to brain white matter potentially mediated by glial cells and immune-related factors.

SZ-shared-genes exhibit a more dynamic neurodevelopmental relationship while implicating differing biological mechanisms. These genes showed small peaks in expression prenatally and in adulthood. The postnatal expression trajectory coincides with myelin development occurring predominantly after birth and into the third decade of life [48]. This is consistent with the SZ-shared-genes enrichment for myelin and oligodendrocyte genes. Post-mortem studies of brain tissue have revealed that SZ patients exhibit differential expression of myelin and oligodendrocyte genes compared to controls [49, 50]. Additionally, SZ-shared-genes were also enriched for cell adhesion molecule genes potentially related to membrane interactions necessary for myelination. In general, SZ may have a unique association with white matter compared with BD and MD.

There are some study limitations to consider. The main analyses are restricted to European samples which may limit the generalizability of these findings. However, replication of effect directions in lead SNPs involved an east Asian sample. The power of each phenotype's GWAS affects the original loci discovery, the results of MiXeR model fit, conjFDR analyses, and subsequent enrichment results. Larger GWAS may provide further discoveries while, equally powered GWAS would improve the validity of cross-disorder comparisons. Shared genes were currently mapped from the most strongly associated joint loci for disorders and average FA. Since SCZ and BIP are highly genetically overlapped, future GWAS for BIP with larger sample sizes will likely see more convergent results with SCZ at the gene level. We focus on average white matter FA rather than individual tracts to understand global white matter associations with each disorder. It is plausible that psychiatric disorders are associated with widespread disruption to the integration of brain regions.

To conclude, we characterized the shared genetic architecture between three major psychiatric disorders and white matter FA. While BD, MD, and SZ were more polygenic, average FA was estimated to be a more genetically discoverable trait. The genetic overlap with FA was strongest for SZ, followed by BD, and then MD. Gene-level results provided plausible neurodevelopmental, cellular, and molecular mechanisms derived from the observed genetic overlap. Ultimately, these findings provide a genetic basis for the relationship between brain white matter and psychiatric disorders.

CODE AVAILABILITY

All tools used in this study are publicly available including: MiXeR v1.3 (https://github.com/precimed/mixer), cond/conjFDR (https://github.com/precimed/pleiofdr), LD score regression (https://github.com/bulik/ldsc), bedtools (bedtools.readthedocs.io), FUMA GWAS (https://fuma.ctglab.nl/).

REFERENCES

1. Marner L, Pakkenberg B. Total length of nerve fibers in prefrontal and global white matter of chronic schizophrenics. J Psych Res. 2003;37:539–47.
2. Catani M, ffytche DH. The rises and falls of disconnection syndromes. Brain. 2005;128:2224–39.
3. Thiebaut de Schotten M, Forkel SJ. The emergent properties of the connected brain. Science. 2022;378:505–10.
4. Fields RD. White matter in learning, cognition and psychiatric disorders. Trends Neurosci. 2008;31:361–70.
5. Alnæs D, Kaufmann T, Doan NT, Córdova-Palomera A, Wang Y, Bettella F, et al. Association of Heritable Cognitive Ability and Psychopathology With White Matter Properties in Children and Adolescents. JAMA Psych. 2018;75:287–95.
6. Zalesky A, Fornito A, Seal ML, Cocchi L, Westin C-F, Bullmore ET, et al. Disrupted Axonal Fiber Connectivity in Schizophrenia. Biol Psych. 2011;69:80–89.
7. Korgaonkar MS, Fornito A, Williams LM, Grieve SM. Abnormal Structural Networks Characterize Major Depressive Disorder: A Connectome Analysis. Biol Psych. 2014;76:567–74.
8. Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev. 2010;34:533–54.
9. Beaulieu C Chapter 8 - The Biological Basis of Diffusion Anisotropy. In: Johansen-Berg H, Behrens TEJ, editors. Diffusion MRI (Second Edition), San Diego: Academic Press; 2014. p. 155–83.
10. Kelly S, Jahanshad N, Zalesky A, Kochunov P, Agartz I, Alloza C, et al. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. Mol Psych. 2018;23:1261–9.
11. van Velzen LS, Kelly S, Isaev D, Aleman A, Aftanas LI, Bauer J, et al. White matter disturbances in major depressive disorder: a coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. Mol Psych. 2020;25:1511–25.
12. Favre P, Pauling M, Stout J, Hozer F, Sarrazin S, Abé C, et al. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals. Neuropsychopharmacol. 2019;44:2285–93.
13. Beaulieu C. The basis of anisotropic water diffusion in the nervous system – a technical review. NMR Biomed. 2002;15:435–55.
14. Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, Hedman AM. A population-based heritability estimate of bipolar disorder – In a Swedish twin sample. Psych Res. 2019;278:180–7.
15. Smeland OB, Frei O, Dale AM, Andreassen OA. The polygenic architecture of schizophrenia — rethinking pathogenesis and nosology. Nat Rev Neurol. 2020;16:366–79.
16. Kendler KS, Ohlsson H, Lichtenstein P, Sundquist J, Sundquist K. The Genetic Epidemiology of Treated Major Depression in Sweden. AJP. 2018;175:1137–44.
17. Hindley G, Frei O, Shadrin AA, Cheng W, O'Connell KS, Icick R, et al. Charting the Landscape of Genetic Overlap Between Mental Disorders and Related Traits Beyond Genetic Correlation. AJP. 2022;179:833–43.
18. Vuoksimaa E, Panizzon MS, Hagler DJ Jr, Hatton SN, Fennema-Notestine C, Rinker D, et al. Heritability of white matter microstructure in late middle age: A twin study of tract-based fractional anisotropy and absolute diffusivity indices. Hum Brain Mapp. 2017;38:2026–36.
19. Zhao B, Li T, Yang Y, Wang X, Luo T, Shan Y, et al. Common genetic variation influencing human white matter microstructure. Science. 2021;372:eabf3736.
20. Zhao B, Zhang J, Ibrahim JG, Luo T, Santelli RC, Li Y, et al. Large-scale GWAS reveals genetic architecture of brain white matter microstructure and genetic overlap with cognitive and mental health traits (n = 17,706). Mol Psyc. 2019;26:3943–55.
21. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53:817–29.
22. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50:668–81.
23. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet. 2016;48:1031–6.
24. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604:502–8.
25. Frei O, Holland D, Smeland OB, Shadrin AA, Fan CC, Maeland S, et al. Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. Nat Commun. 2019;10:2417.
26. Holland D, Frei O, Desikan R, Fan C-C, Shadrin AA, Smeland OB, et al. Beyond SNP heritability: Polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. PLoS Genet. 2020;16:e1008612.
27. Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47:291–5.
28. Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, et al. Spatio-temporal transcriptome of the human brain. Nature 2011;478:483–9.
29. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun. 2017;8:1826.
30. Bhaduri A, Sandoval-Espinosa C, Otero-Garcia M, Oh I, Yin R, Eze UC, et al. An Atlas of Cortical Arealization Identifies Dynamic Molecular Signatures. 2021;598:200–204.
31. Li M, Santpere G, Kawasawa YI, Evgrafov OV, Gulden FO, Pochareddy S, et al. Integrative functional genomic analysis of human brain development and neuropsychiatric risks. Science 2018;362:eaat7615–eaat7615.
32. Zeisel A, M̂oz-Manchado AB, Codeluppi S, Lönnerberg P, Manno GL, Juréus A, et al. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science 2015;347:1138–42.
33. Parker N, Patel Y, Jackowski AP, Pan PM, Salum GA, Pausova Z, et al. Assessment of Neurobiological Mechanisms of Cortical Thinning during Childhood and Adolescence and Their Implications for Psychiatric Disorders. JAMA Psych. 2020. 2020. https://doi.org/10.1001/jamapsychiatry.2020.1495.
34. Liao Z, Patel Y, Khairullah A, Parker N, Paus T. Pubertal Testosterone and the Structure of the Cerebral Cortex in Young Men. Cereb Cortex. 2021;31:2812–21.
35. Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci. 2006;7:818–27.
36. Gottesman II, Gould TD. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. AJP. 2003;160:636–45.
37. Cheng W, van der Meer D, Parker N, Hindley G, O'Connell KS, Wang Y, et al. Shared genetic architecture between schizophrenia and subcortical brain volumes implicates early neurodevelopmental processes and brain development in childhood. Mol Psych. 2022:1–10.
38. Cheng W, Frei O, van der Meer D, Wang Y, O'Connell KS, Chu Y, et al. Genetic Association Between Schizophrenia and Cortical Brain Surface Area and Thickness. JAMA Psych. 2021;78:1020–30.
39. Werme J, van der Sluis S, Posthuma D, de Leeuw CA. An integrated framework for local genetic correlation analysis. Nat Genet. 2022;54:274–82.
40. Parker N, Cheng W, Hindley GFL, O'Connell KS, Karthikeyan S, Holen B, et al. Genetic Overlap Between Global Cortical Brain Structure, C-Reactive Protein, and White Blood Cell Counts. Biol Psych. 2023. 20 June 2023. https://doi.org/10.1016/j.biopsych.2023.06.008.
41. Cheng W, Parker N, Karadag N, Koch E, Hindley G, Icick R, et al. The relationship between cannabis use, schizophrenia, and bipolar disorder: a genetically informed study. Lancet Psych. 2023;10:441–51.
42. DeRosse P, Karlsgodt KH. Examining the Psychosis Continuum. Curr Behav Neurosci Rep. 2015;2:80–89.
43. Kloiber S, Rosenblat JD, Husain MI, Ortiz A, Berk M, Quevedo J, et al. Neurodevelopmental pathways in bipolar disorder. Neurosci Biobehav Rev. 2020;112:213–26.
44. al-Haddad BJS, Oler E, Armistead B, Elsayed NA, Weinberger DR, Bernier R, et al. The fetal origins of mental illness. Am J Obstet Gynecol. 2019;221:549–62.
45. Lundgaard I, Osório MJ, Kress BT, Sanggaard S, Nedergaard M. White matter astrocytes in health and disease. Neuroscience 2014;276:161–73.
46. Galatro TF, Holtman IR, Lerario AM, Vainchtein ID, Brouwer N, Sola PR, et al. Transcriptomic analysis of purified human cortical microglia reveals age-associated changes. Nat Neurosci. 2017;20:1162–71.
47. Reemst K, Noctor SC, Lucassen PJ, Hol EM. The Indispensable Roles of Microglia and Astrocytes during Brain Development. Front Hum Neurosci. 2016;10:566.
48. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, Mcarthur MJ. Prolonged myelination in human neocortical evolution. Proc Natl Acad Sci USA. 2012;109:16480–5.
49. Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci. 2001;98:4746–51.
50. Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet. 2003;362:798–805.

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AUTHOR CONTRIBUTIONS

NP and OAA conceived the study. NP conducted analyses and wrote the initial draft of the manuscript. NP, WC, GFLH, PP, OF, and OAA were involved in study design and provided analytical input. All authors contributed to data interpretation and editing of the manuscript.

COMPETING INTERESTS

OAA reported personal fees from Lundbeck, Janssen, Sunovion (speaker's honorarium), Biogen (consultant) outside the submitted work and is a consultant to Cortechs.ai (stock options). AMD is a founder of and holds equity interest in Cortechs.ai and serves on its scientific advisory board. He also receives research funding from General Electric Healthcare (GEHC).

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