Abundant pleiotropy across neuroimaging modalities identified through a multivariate genome-wide association study

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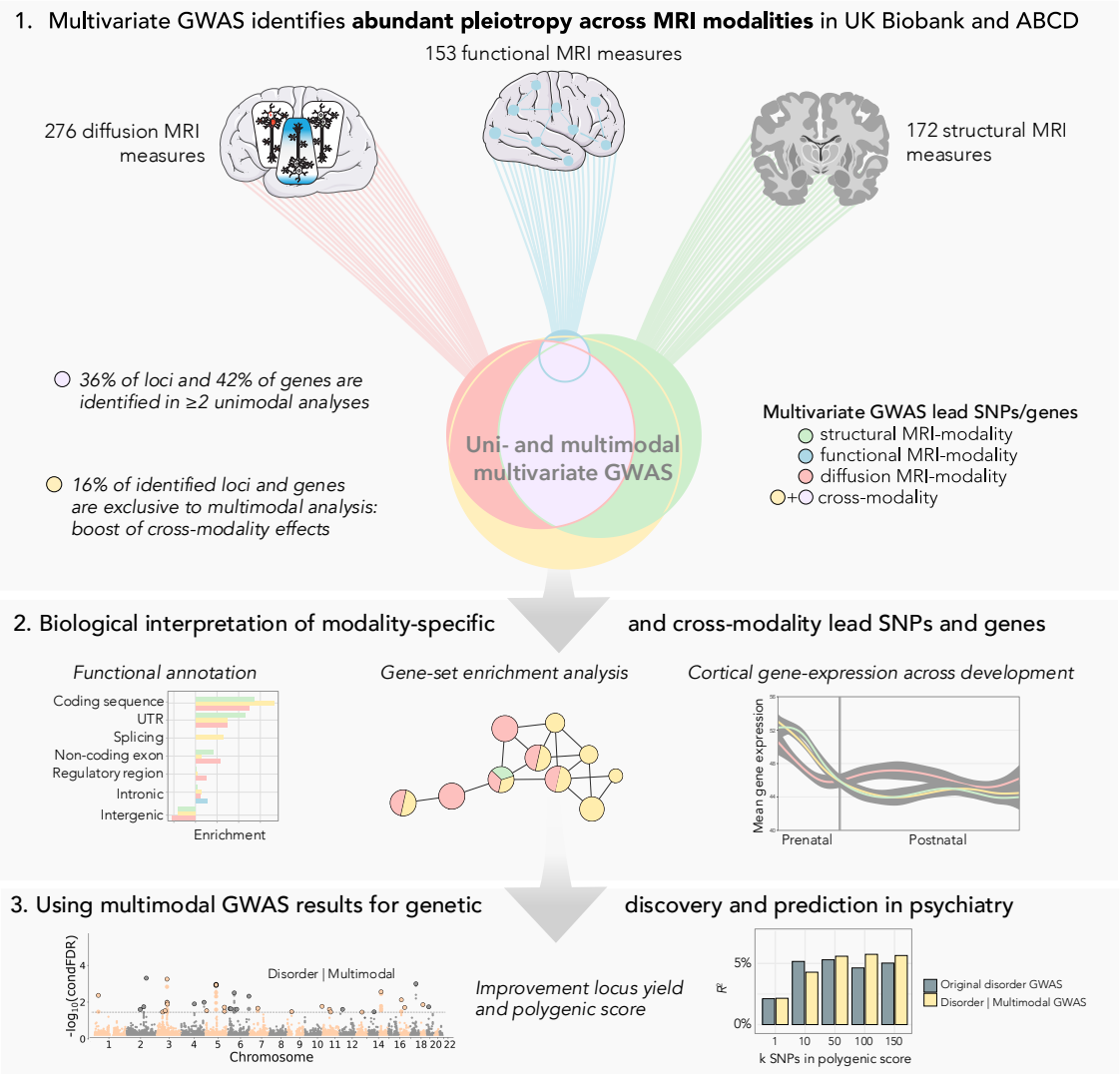
Abstract

Genetic pleiotropy is abundant across spatially distributed brain characteristics derived from one neuroimaging modality (e.g. structural, functional or diffusion MRI). A better understanding of pleiotropy across modalities could inform us on the integration of brain function, micro- and macrostructure. Here we show extensive genetic overlap across neuroimaging modalities at a locus and gene level in the UK Biobank (N=34,029) and ABCD Study (N=8,607). When jointly analysing phenotypes derived from structural, functional and diffusion MRI with the Multivariate Omnibus Statistical Test (MOSTest), we boost the discovery of loci and genes beyond previously identified effects for each modality individually. Cross-modality genes are involved in fundamental biological processes and predominantly expressed during prenatal brain development. We additionally boost genetic discovery and prediction of psychiatric disorders by conditioning independent GWAS on our multimodal multivariate GWAS. These findings shed light on the shared genetic mechanisms underlying variation in brain morphology, functional connectivity, and tissue composition.

Graphical abstract



Introduction

The brain is our most complex organ, rapidly integrating information from many different sources[1], with strong genetic influences[2]. Studying genetic influences through genome-wide association studies (GWAS) has shown that most loci and genes show association with multiple traits[3], a phenomenon known as "statistical pleiotropy" (e.g. one gene influences multiple phenotypes directly, or indirectly via a causal pathway or common factor)[4]. Recently, numerous loci and genes with pleiotropic effects across brain characteristics derived from a single neuroimaging modality (e.g. structural, functional or diffusion MRI) have been discovered[5–9]. Yet the majority of pleiotropic loci act across rather than within phenotype domains[3], indicating that the genes associated within these loci may show pleiotropic effects across neuroimaging modalities, but the extent of this is underexplored. Investigating how genes influence a wide variety of brain imaging phenotypes may shed light on the mechanisms underlying alterations in brain morphology, activity, connectivity, and tissue composition that often co-occur in heritable psychiatric disorders[10,11].

Complex traits are affected by thousands of genetic variants scattered throughout the genome which makes pleiotropy between them inevitable[12]. In presence of such abundant pleiotropy, multivariate GWAS models have greater statistical power than univariate GWAS models[13]. This is because the cumulative evidence from different phenotypes leads to more sensitive detection of genetic associations and reduces the burden of multiple testing[7]. Previous studies have investigated either structural MRI-derived (sub)cortical volumes, surface area, and thickness[5–7], functional MRI-derived brain connectivity[8], or diffusion MRI-derived brain tissue composition[9] in a multivariate GWAS framework. The identified loci and genes inform us about the biological signal that is picked up by MRI, such as linking genetic effects of diffusion MRI to synaptic pruning, neuroinflammation, and axonal growth[9], structural MRI to neurogenesis and cell differentiation[5], and functional MRI to mental health[14] and psychiatric disorders[8]. Yet the modality specificity of these links remains unclear. Moreover, many loci are currently not discoverable in unimodal analyses: a multimodal multivariate GWAS could identify those loci that can improve our understanding of the interplay of biological processes contributing to brain structural organisation on multiple scales and reveal underpinnings of the structure-function relationship from a genetics viewpoint.

A large body of neuroimaging research established associations between psychiatric disorders and brain structure[15–20], function[21,22] and diffusion metrics[23,24]. However, previous studies were not able to detect non-null genetic correlations[25–27], possibly due to mixed effect directions[28] and differential polygenicity between neuroimaging phenotypes and psychiatric disorders[29]. Alternative methods that leverage the shared genetic signal between brain morphology and psychiatric disorders have been more fruitful[28] allowing improved prediction of disease liability[30]. Given that alterations of brain morphology, activity, connectivity, and tissue composition often co-occur in heritable psychiatric disorders[10,11], using multimodal GWAS associations may potentially further aid in leveraging the shared genetic signal between neuroimaging traits and psychiatric conditions.

88 Here, we demonstrate evidence of extensive pleiotropy across neuroimaging modalities using
89 583 structural (sMRI), resting-state functional (fMRI) or diffusion (dMRI) MRI-derived phenotypes in
90 the UK Biobank and the Adolescent Brain Cognitive Development (ABCD) Study®. We do so by
91 performing unimodal and multimodal multivariate GWAS with the Multivariate Omnibus Statistical
92 Test (MOSTest), which was designed to boost statistical power by capitalizing on the distributed nature
93 of genetic influences across imaging-derived phenotypes[7]. Specifically, we 1) overlap the previously
94 described multivariate effects for each modality and 2) combine all MRI-derived phenotypes into one
95 multimodal multivariate GWAS, obtaining an additional boost for discovery of cross-modality
96 pleiotropic loci and genes. Next, we functionally annotate single-modality (identified in only one
97 unimodal analysis) and cross-modality (identified in ≥ 2 unimodal analyses or unique to multimodal
98 analysis) loci and genes to describe the biological signal across MRI modalities. Last, we improve locus
99 discovery of five major psychiatric disorders by using the multimodal, multivariate, genetic signal of
100 brain morphology, functional connectivity, and tissue composition and observe improved polygenic
101 prediction for depression, autism, ADHD, and bipolar disorder. Thereby the current study provides
102 insight into pleiotropic effects across neuroimaging modalities and their relevance for understanding
103 the neurobiology of the human brain and mental health conditions.
104

105 ## Results

106 **Abundant pleiotropy of loci and genes across neuroimaging modalities**

107 We used data from three previous studies that applied MOSTest on single neuroimaging modality
108 phenotypes: 172 sMRI-derived brain morphology measures (68 regional surface area and 68 regional
109 thickness of the cerebral cortex, and 36 volumes of subcortical structures)[7], 153 fMRI-derived BOLD
110 signal and connectivity measures (17 network variances and 136 network correlations)[8], and 276 dMRI-
111 derived brain tissue composition principal components (65 restricted isotropic diffusion PCs, 124
112 restricted directional diffusion PCs, 87 normalized free water diffusion PCs)[9]. We investigated white
113 British UK Biobank samples (as derived from both self-declared ethnic background and genetic
114 principal component analysis) with quality-controlled genotypes and neuroimaging available (N_{sMRI} =
115 34,029, N_{fMRI}=31,023, N_{dMRI} = 30,106). We also included the ABCD cohort which had identical sMRI-
116 and dMRI-derived measures and similar fMRI-derived measures (see Methods). The ABCD sample
117 has a heterogeneous and admixed ancestral background. We created a replication sample within ABCD
118 similar to our UKB discovery sample by selecting the subset of European individuals (N_{sMRI} = 4,794,
119 N_{fMRI} = 4,132, N_{dMRI} = 4,418) assigned based on genetic ancestry factor[31] as defined in Methods. All
120 quality controlled ABCD samples (N_{sMRI} = 8,607, N_{fMRI} = 7,277, N_{dMRI} = 7,853) served as an additional
121 (ad)mixed ancestral replication sample. Next to genetic ancestry, ABCD samples were used to test the
122 generalizability of our results across age.

Heritability estimates obtained in UK Biobank with linkage disequilibrium (LD) Score Regression[32] ranged from median = 5.80% (IQR = 3.09%) for fMRI-derived network variances to 28.00% (IQR = 6.92%) for sMRI-derived subcortical volumes (Supplementary Fig. 1 and Supplementary Data 1), with dMRI-derived measures ranking in-between (median = 13.70%, IQR = 9.63%). Genetic and phenotypic correlations were generally similar ($\rho(r_g,r_p) = 0.53$, $p = 2.2\times10^{-16}$), and stronger within modalities than between modalities (Supplementary Fig. 2).

First, we combined all heritable (nominal $p < 0.05$) phenotypes derived from the same modality in multivariate GWAS analyses using MOSTest (Manhattan plots in Supplementary Fig. 4). This heritability filter was applied (as previously by Roelfs *et al*[8]) because including non-heritable phenotypes into MOSTest analyses have been shown to reduce statistical power[7]. MOSTest estimates the correlation between measures from univariate GWAS (on randomly permuted genotype data) and sums the squared decorrelated *z*-values across univariate GWAS summary statistics (from the original genotype data) to integrate the effects across the measures into a multivariate test statistic[7]. These unimodal multivariate analyses identified 590, 42 and 512 genome-wide significant loci associated with sMRI, fMRI and dMRI respectively ($p < 5\times10^{-8}/3$; Supplementary Data 2). These results are in line with earlier research (Supplementary Results 1). The number of genome-wide significant lead SNPs from UK Biobank that replicated at nominal significance ($p < 0.05$) in ABCD-based MOSTest summary statistics differed across modalities (EUR: 24.46% sMRI, 8.70% fMRI, 23.63% dMRI), and were higher for the larger sample with (ad)mixed ancestries (42.12% sMRI, 15.38% fMRI, 35.39% dMRI). Replication rates after correcting for the number of lead SNPs tested are provided in Supplementary Data 3. Applying MAGMA[33] gene-level analyses to unimodal multivariate summary statistics identified 1,620, 39 and 1,453 genome-wide significant genes ($p < ((0.05/18{,}877)/3 =) 8.83\times10^{-7}$) for sMRI, fMRI and dMRI respectively (Supplementary Data 4).

When overlapping the identified loci ($p < 5\times10^{-8}/3$) and genes ($p < 8.83\times10^{-7}$) from each modality (Methods), we observed 326 loci (36.18% of total) and 1,021 genes (41.79% of total) associated with at least two out of three modalities (Fig. 1a). This indicates pleiotropy across neuroimaging modalities both at the genome-wide significant locus and gene level. We replicated this pattern of overlap between sMRI and dMRI genome-wide significant loci and genes from UK Biobank in the ABCD cohort, though fMRI genome-wide significant loci did not overlap and fMRI genome-wide significant genes were not identified in ABCD (Supplementary Fig. 5, Supplementary Data 5-6). Replication patterns were similar across ancestries, with all of the sMRI and dMRI loci identified in the European ABCD sample overlapping with the loci identified within the (ad)mixed ancestry ABCD sample. Locus definition parameters (LD cut-off and window size) did not affect on the observed locus overlap (Fig. 1a), as was apparent from sensitivity analyses presented in Supplementary Fig. 3.

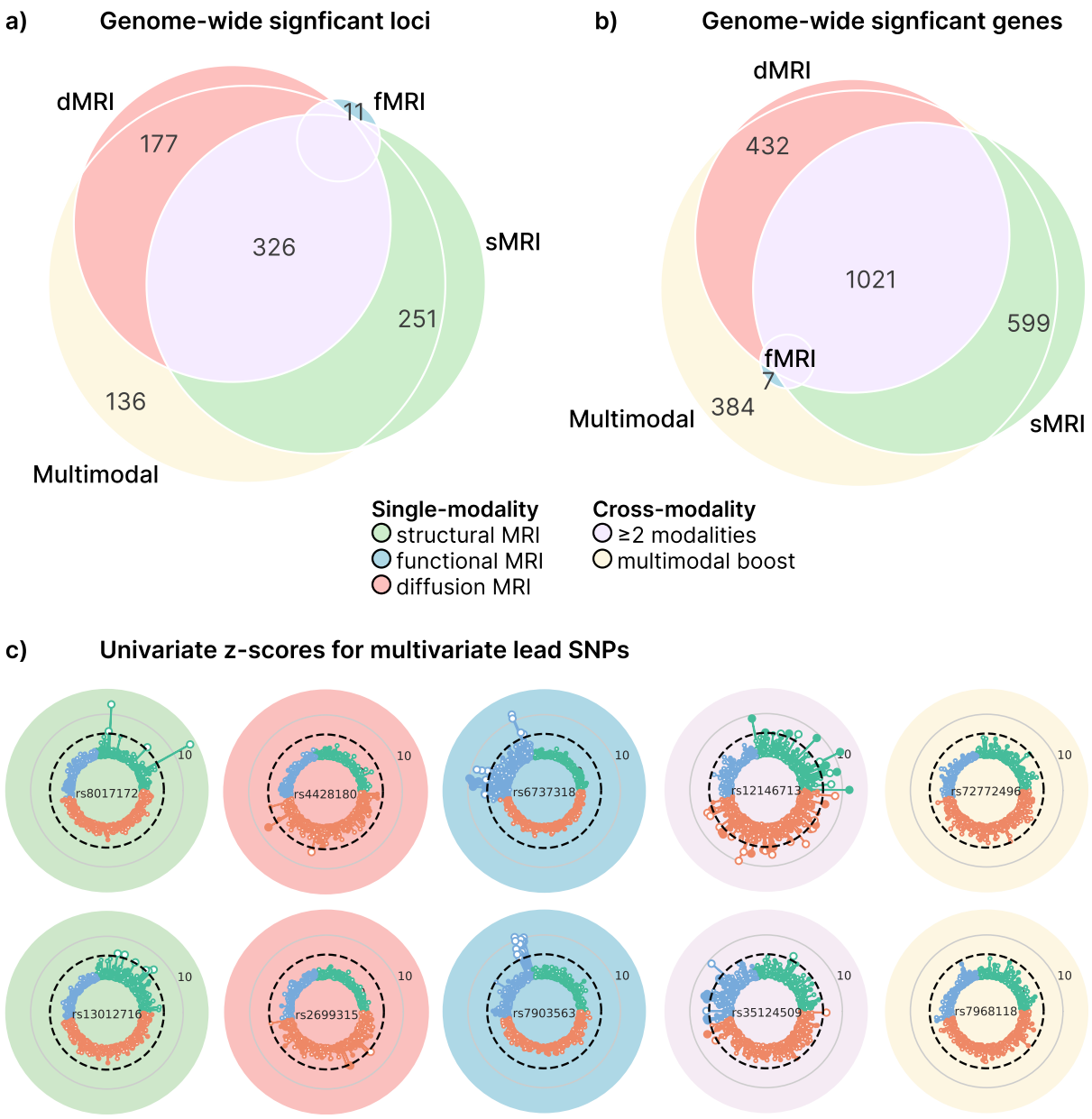


Figure 1. **Abundant pleiotropy of loci and genes across neuroimaging modalities.** Overlap of genome-wide significant a) loci and b) genes observed across neuroimaging modalities in single-modality and joint multimodal analyses ($p < 5\times10^{-8}/3$). When sMRI, fMRI and dMRI-derived phenotypes are jointly analysed in MOSTest (multimodal analysis), a boost in discovery of pleiotropic loci and genes is observed (yellow). This pattern partially replicates in the ABCD cohort (Supplementary Fig. 5). For 10 example lead SNPs from different parts of a) the univariate *z*-scores of all phenotypes used in this study (sMRI-derived phenotypes in green, dMRI-derived phenotypes in red, fMRI-derived phenotypes in blue) are plotted in c) as the distance from the centre of each circular plot. The dashed black line corresponds to $p = 5\times10^{-8}$ ($z = 5.45$) and *z*-scores that pass this threshold are depicted larger. Positive effect direction is shown as a filled circle and negative effect direction as a white circle.

169 **Multimodal GWAS boosts discovery of cross-modality loci and genes**

170 We next investigated whether combining all sMRI, fMRI, and dMRI-derived measures in one
171 multivariate analysis generated greater statistical power to identify significant pleiotropic loci and genes
172 which show sub-threshold associations in each unimodal multivariate analysis (Manhattan plot in
173 Supplementary Fig. 4). We therefore applied MOSTest across neuroimaging modalities, combining 583
174 phenotypes, identifying 794 genetic loci (Supplementary Data 2). The LD Score Regression intercept
175 (1.04, SE=0.04) indicated that the inflation in these multimodal MOSTest *p*-values (lambdaGC = 2.83)
176 was driven by polygenicity and not population stratification or cryptic relatedness. Replication rates at
177 nominal significance were comparable to previous MOSTest studies: EUR 26.45%, 37.55% (ad)mixed
178 ancestries (see Supplementary Data 3 for rates after correction for the number of lead SNPs). One-
179 hundred-thirty-six (15.09%) of these loci did not overlap with any of the loci identified in the unimodal
180 multivariate analyses, suggesting that MOSTest leveraged the shared genetic signal across imaging
181 modalities to boost the discovery of pleiotropic loci. Gene-based GWAS from MAGMA showed that
182 of the 2,242 genome-wide significant multimodal genes, 384 (15.72%) were not discovered for
183 unimodal gene-based GWAS (Supplementary Data 4). We used the ABCD cohort to investigate the
184 generalizability of our findings and observed a similar boost in multimodal discovery on a genome-
185 wide significant locus and gene level (Supplementary Fig. 5, Supplementary Data 5-6). Additionally,
186 81.82% of multimodal loci identified in the European ABCD sample were overlapping with the loci
187 identified in the (ad)mixed ancestry ABCD sample.

188 We examined the univariate associations underlying multivariate associations from different
189 parts of the Venn diagram (Fig. 1a). Fig. 1c shows the univariate *z*-scores across sMRI-, fMRI-, and
190 dMRI-derived phenotypes for ten lead SNPs representing different parts of the Venn diagram (Fig. 1a).
191 Cluster map of univariate *z*-scores for all multimodal MOSTest lead SNPs is displayed in
192 Supplementary Fig. 6. Alternatively, for every lead SNP identified in the MOSTest analyses presented
193 in the Venn diagram (Fig. 1a) we extracted the minimum univariate *p*-value across all analysed
194 phenotypes. A lead SNP with a relatively high minimum univariate *p*-value would indicate that the
195 signal should have been highly distributed across other measures for the variant to become genome-
196 wide significant in the multivariate analysis. Supplementary Fig. 7 shows that lead SNPs boosted by
197 the multimodal analysis had relatively high minimum univariate *p*-values ($0.05 > p > 5\times10^{-5}$) more
198 frequently (87%) than lead SNPs of loci identified in one unimodal analysis only (sMRI-modality 72%;
199 fMRI-modality 25%; dMRI-modality 78%), indicating that the discovery of these lead SNPs is driven
200 by pleiotropic signals across modalities.

201

202 **Comparing characteristics of single- and cross-modality loci and genes**

203 We investigated to what extent single-modality (identified in only one unimodal analysis) and cross-
204 modality (identified in ≥ 2 unimodal analyses or boosted by the multimodal analysis) loci and genes
205 (Supplementary Data 7-8) differ in their biological effects compared to other complex traits. To this

206 end, we annotated 251 sMRI-, 11 fMRI-, 177 dMRI-modality, and 462 cross-modality lead SNPs using
207 ANNOVAR[34] (Supplementary Data 9). We used the annotations of 43,492 (unique) lead SNPs derived
208 from 558 traits (with reasonable power, i.e. N > 50,000) across 24 trait domains from Watanabe et al.[3]
209 as a reference. Fig. 3b demonstrates that cross-modality and single-modality lead SNPs were very
210 similarly located in genomic regions as other complex traits[3,35]. Notably, cross-modality lead SNPs
211 showed unique enrichment of exonic variants (6.58%, OR = 2.17, 95% CI = 1.43-3.17, $p = 2.91\times10^{-4}$).
212 Watanabe et al. already demonstrated that the contribution of exonic SNPs increases from ~1% (SNPs
213 associated to 1 trait domain) to ~5% (associated to ≥10 trait domain) with increasing pleiotropy[3]. The
214 enrichment we observed therefore emphasizes the strong pleiotropic nature of the cross-modality lead
215 SNPs.

216 Next, we tested whether any difference in results from gene-set enrichment analyses with Gene
217 Ontology (GO) biological processes, cellular components and molecular functions could be observed
218 using the 599 sMRI-, 7 fMRI-, 432 dMRI-modality, or 1,405 cross-modality genes (Fig. 3a). We
219 identified four networks of gene-sets that consisted of both single-modality and cross-modality subsets
220 of genes and showed significant enrichment after Bonferroni correction (Supplementary Data 10).
221 These processes were mostly related to nervous system development and neuronal growth and
222 differentiation. However, most gene-sets were significantly enriched of cross-modality genes only and
223 highlight the genes' involvement in fundamental biological processes, such as cell cycle processes,
224 cellular structure (chromatin, cytoskeleton, cell junction), and vesicle transport.

225 To investigate potential differential temporal patterns of cortical gene expression between
226 single-modality and cross-modality genes, we investigated transcriptome data of post-mortem brain
227 tissue (N=56) representing males and females of multiple ethnicities across the life span (Fig. 3c)[36]. The
228 number of fMRI-modality genes in the data (n=5) was too low to generate a reliable expression pattern
229 (Supplementary Fig. 8). Prenatal gene expression was high for both sMRI-, dMRI-modality and cross-
230 modality genes compared to all genes in the data. In (early) childhood until adolescence, a differential
231 dMRI-modality expression pattern was not apparent (compared to all genes in the data), whereas sMRI-
232 modality and cross-modality genes were generally lower expressed. This matches a large body of
233 research showing that pre- and postnatal cortical transcriptomes differ largely and pronounced prenatal
234 expression matches the course of cortical development[37].

235 Given the predominant prenatal gene-expression pattern, we investigated whether single-
236 modality and cross-modality genes were enriched for any cell-type identified by Bhaduri et al.[38] using
237 single-cell RNA sequencing analyses of the fetal brain (Fig. 2d). We observed that cross-modality genes
238 were enriched across all cell-types, confirming their importance in fetal brain tissue and suggesting
239 their expression pattern is not cell-specific and more general in nature (Supplementary Data 11).

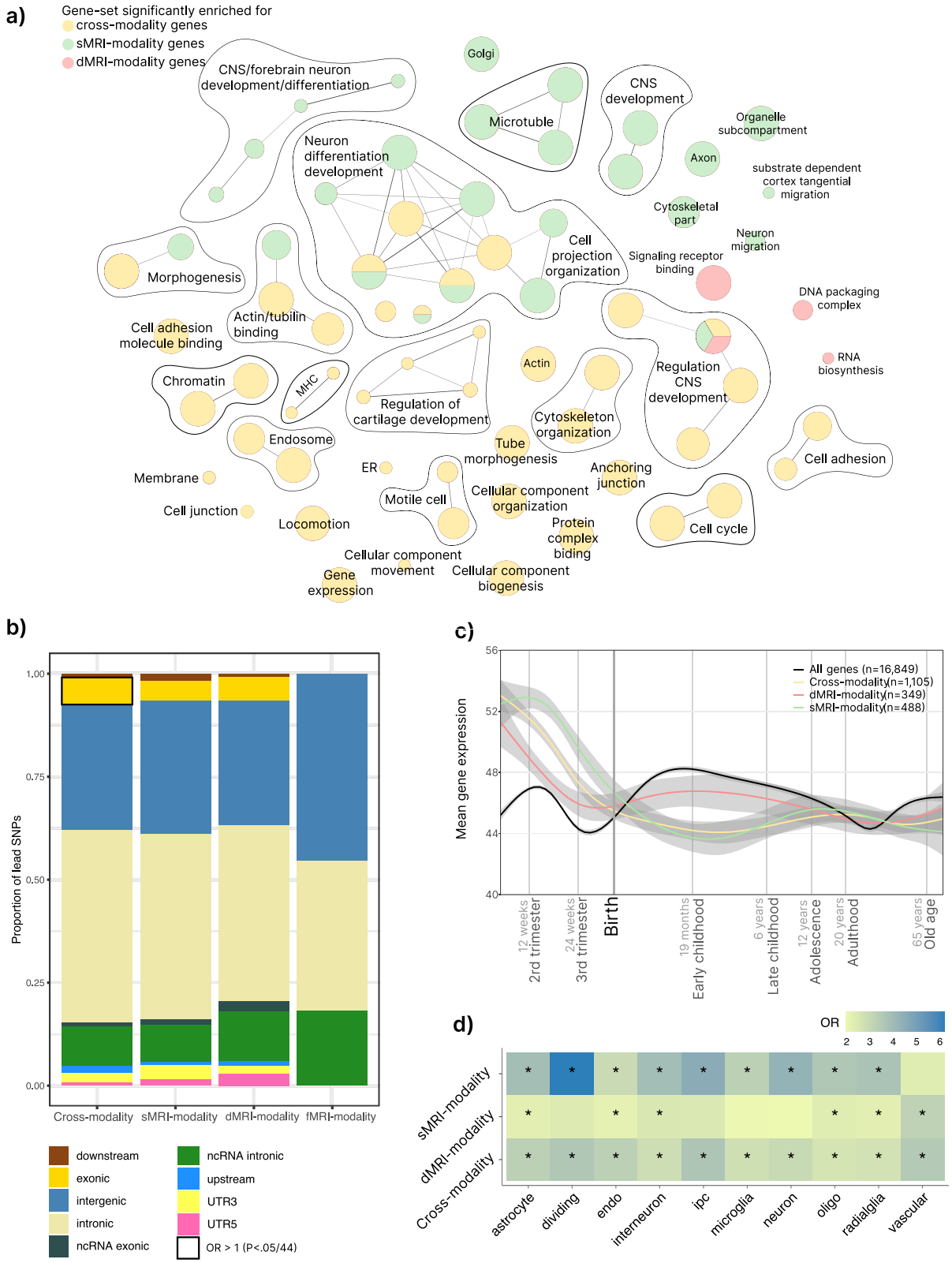


Figure 2. **Comparing properties of single-modality and cross-modality lead SNPs and genes.** a) Gene-ontology biological processes, molecular functions and cellular components that were (Bonferroni-corrected) significantly enriched for cross-modality, sMRI-modality and/or dMRI-modality genes (none of the GO terms tested showed enrichment for the 6 fMRI-modality genes). Node size reflects gene-set size, edges reflect pathway similarity scores (Methods). b) Functional consequences of single-modality and cross-modality lead SNPs as

245 annotated with ANNOVAR[34]. When the null hypothesis (OR=1) could be rejected after Bonferroni correction (p
246 $< 1.14\times10^{-3}$), the solid line indicates significant enrichment of the annotation. Annotations of 43,492 (unique)
247 lead SNPs derived from 558 traits across 24 trait domains from Watanabe et al. were used as reference for Fisher
248 Exact Test (Supplementary Data 9). ncRNA = non-coding RNA. c) Mean-normalized expression (y-axis) of
249 cross-modality and single-modality genes over developmental timepoints (x-axis; log10 scale). Gray shading
250 indicates 95% confidence intervals. The mean-normalized expression of fMRI-modality genes is displayed in
251 Supplementary Fig. 8, since the number of genes (n=5) was low and therefore created an unreliable pattern. d)
252 Cell-type enrichment analysis for fetal brain tissue from Bhaduri et al.[38]. Bonferroni corrected significant results
253 (p < (0.05 / 30 =) 1.67×10^{-3}) are indicated by an asterisk (*). ipc = intermediate progenitor cells, oligo =
254 oligodendrocytes.
255
256 **Leveraging shared genetics with psychiatric disorders for discovery**
257 Alterations in brain morphology, connectivity, and tissue composition often co-occur in heritable
258 psychiatric disorders[11], suggesting that our multimodal, multivariate genetic signal may have relevance
259 for genetic discovery and prediction of psychiatric disorders. It is possible to boost locus discovery and
260 polygenic prediction by re-ranking the test-statistics from a given GWAS based on a genetically related
261 secondary GWAS[39]. We therefore conditioned five major psychiatric disorder GWAS summary
262 statistics from the Psychiatric Genomics Consortium (Supplementary Data 12) on our multimodal
263 MOSTest summary statistics using the conditional false discovery rate approach (condFDR)[40] to
264 identify loci associated with schizophrenia (SCZ)[41], bipolar disorder (BD)[42], major depressive disorder
265 (MDD)[43,44], attention-deficit hyperactivity disorder (ADHD)[45], and autism spectrum disorder (ASD)[46].
266 The rationale behind condFDR is that, in the presence of cross-trait enrichment, a variant with strong
267 associations with both traits is more likely to represent a true association[30].
268 Compared to the number of genome-wide significant loci identified in the original GWAS (Fig. 3a), we
269 observed a 5-19 fold increase in locus yield in the condFDR summary statistics (Supplementary Data
270 13). Note that the locus yield from the original GWAS may be lower than the number presented in the
271 original articles, since we relied on publicly available data (e.g. excluding 23andMe) and exclude some
272 additional cohorts to prevent sample overlap (with e.g. UKB, see Supplementary Results 2). We
273 calculated the sign concordance of the condFDR lead SNPs using independent disorder GWAS
274 summary statistics[47–49] (Supplementary Data 12) and observed higher and more significant sign
275 concordance across all disorders compared to the lead SNPs identified in the original GWAS
276 (Supplementary Data 14). We positionally mapped condFDR loci to genes (528 genes for MDD, 2,416
277 for SCZ, 116 for ASD, 1,162 for BD, 122 for ADHD; Supplementary Data 15) and subsequently used
278 these genes as input for hypergeometric test-based tissue enrichment analyses, both as implemented in
279 FUMA. The SCZ and BD genes were significantly enriched in gene-sets with upregulated gene
280 expression in brain tissue, but not in other body tissues (Supplementary Data 16, Fig. 3c). This contrasts
281 with the sets of genes mapped from the original GWAS loci (60 genes for MDD, 498 for SCZ, 5 for

ASD, 186 for BD, 14 for ADHD; Supplementary Data 15), which showed no enrichment of upregulated gene expression in brain tissues. This illustrates that genetic overlap may be used to identify genetic variants that may play a role in psychiatric disorders with a specific relevance for brain traits.

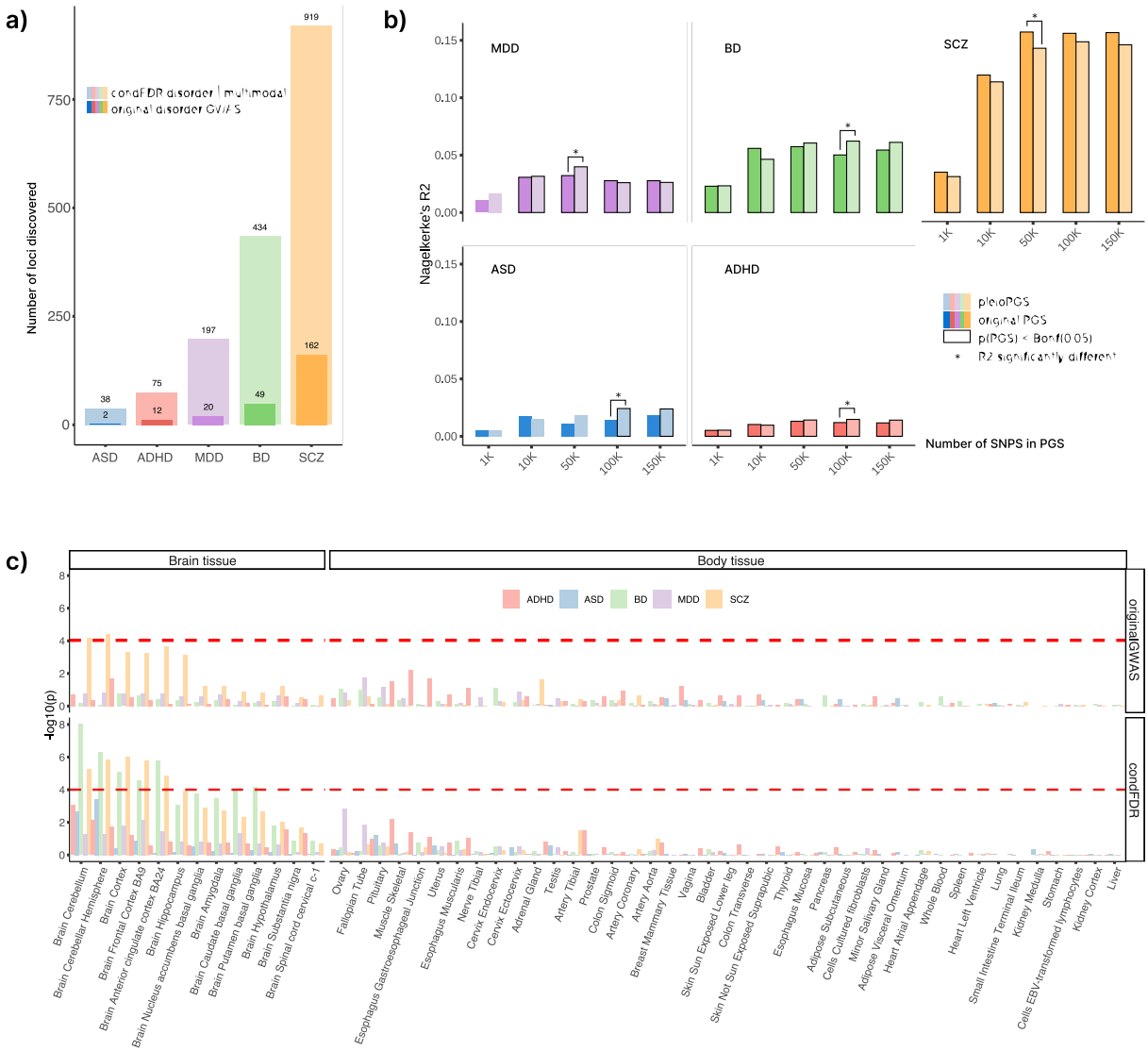


Figure 3. **Leveraging multimodal analysis to boost discovery and polygenic prediction of psychiatric disorders**. a) Loci discovered in the publicly available summary statistics of each disorder GWAS ($p < 5\times10^{-8}$), and after conditioning the disorder on multimodal MOSTest summary statistics with conditional FDR (FDR < 0.05). b) Phenotypic variance explained for five psychiatric disorders explained by polygenic scores based on original disorder GWAS summary statistics (original PGS) and conditional disorder-multimodal GWAS summary statistics (pleioPGS). Note that PGS using top 10 and top 100 SNPs had too low R^2 values to be visible and are therefore not plotted, but can be found in Supplementary Data 17. Independent target samples were used for prediction (see Methods). A random sampling procedure and *t*-test were applied per disorder to test if the observed difference in R^2 was significant (Supplementary Fig. 9). c) Enrichment of disorder genes (positionally mapped from the original disorder GWAS loci *vs* conditional FDR loci) in tissue-specific gene-sets with upregulated expression (Supplementary Data 16). The red line indicates Bonferroni correction for the number of tests ($\alpha = 0.05/540 = 9.26\times10^{-5}$).

298 We followed-up by testing whether our disorder-multimodal condFDR summary statistics
299 could improve polygenic prediction of the disorders in independent samples using a pleiotropy-
300 informed polygenic scoring method[30] (pleioPGS; see Methods). For that purpose, we constructed
301 polygenic scores with PRSice2 in two independent clinical datasets (TOP and MoBa, see
302 Supplementary Data 12) based on the top 10-150,000 original disorder GWAS ordered SNPs and
303 condFDR-based ordered SNPs (Fig. 3b). We observed a 1.24-fold increase in variance explained (R^2 =
304 6.22%, $p = 2.28\times10^{-15}$) for BD in the TOP sample (N_{case} = 463; $N_{control}$ = 1,073) using the pleioPGS with
305 100,000 SNPs, compared with the original GWAS-based PGS (R^2 = 5.02%, $p = 2.28\times10^{-15}$). We
306 employed a random sampling procedure to show that this was a significant improvement (t = 42.16, p
307 $= 3.64\times10^{-101}$; Supplementary Fig. 9). Also for MDD (N_{case} = 135, $N_{control}$ = 1,073), the pleioPGS (R^2 =
308 3.98%, $p = 2.16\times10^{-6}$) significantly outperformed (t = 14.57, $p = 7.43\times10^{-33}$) the original GWAS-based
309 PGS (R^2 = 3.22%, $p = 1.92\times10^{-5}$). The phenotypic variance explained by PGS in ASD and ADHD was
310 low (R^2 < 2.43%) when using either the original PGS or pleioPGS (Supplementary Data 17), though a
311 significant improvement of the pleioPGS over the original PGS could be observed for both ASD (ΔR^2
312 = 0.99%, t = 30.99, $p = 4.16\times10^{-78}$) and ADHD (ΔR^2 = 0.28%, t = 46.44, $p = 9.68\times10^{-109}$). When
313 predicting SCZ in TOP (N_{case} = 735; $N_{control}$ = 1,073), the original GWAS-based PGS explained
314 significantly ($p = 1.44\times10^{-34}$) more variance in SCZ liability.
315

316 **Discussion**

317 Our findings demonstrated that many loci and genes show pleiotropic effects across brain characteristics
318 derived from three distinct MRI modalities. We found evidence of extensive pleiotropy across
319 structural, functional and diffusion MRI from genetic overlap (loci and genes being associated with at
320 least two out of three modalities), and a boost in discovery of loci (n=136) and genes (n=384) when all
321 MRI-derived phenotypes are jointly analysed using MOSTest. The results in the ABCD cohort show
322 generalizability of structural and diffusion MRI pleiotropic loci from adulthood to childhood, and from
323 European ancestry to (ad)mixed ancestries. Genes with cross-modality pleiotropic effects were highly
324 prenatally expressed, though not cell-type specific and mostly enriched in gene-sets of general
325 biological functions. Moreover, we showed how these results can be leveraged to improve locus
326 discovery for and prediction of major psychiatric disorders.

327 The human brain is a highly complex and inter-connected structure for which "the whole is
328 more than the sum of its parts"[50]. This complexity emerges from tight interplay between different units
329 and processes, where disturbance of any part may change the state of the whole system. With this in
330 mind, pervasive effects of genetic variants on brain-related traits are inevitable, resulting in abundant
331 pleiotropy not only across phenotypically linked traits such as brain morphology measures[37], but also
332 in widespread genetic overlap between distinct aspects of brain functioning such as personality and
333 cognition[39]. Our results implicate that the multivariate genetic signals of structural, functional, or

334 diffusion MRI are not only composed of pleiotropic effects within modalities as previously shown[5–9],
335 but also of a component that is shared across brain traits measured with different MRI modalities. This
336 provides a new conceptual insight into the integration of human brain functional connectivity (fMRI),
337 microstructure (dMRI) and macrostructure (sMRI) and highlights the importance of characterizing
338 patterns of specificity and pleiotropy to improve our understanding of molecular neurobiological
339 mechanisms. It is expected from theoretical analysis that rare variants would follow this pattern of
340 pleiotropy under assumption of the infinitesimal model[51], which would be an interesting direction of
341 future research given the recent availability of multivariate tools for gene-based rare-variant association
342 studies[52,53].

343 We observed genetic overlap across all three modalities in our discovery sample from UK
344 Biobank. Even though the heritability and number of loci and genes for fMRI was lower than in dMRI
345 and sMRI, the proportions of genome-wide significant loci and genes that did and did not overlap with
346 other modalities was generally equal across modalities. The results in the ABCD cohort showed
347 generalizability of structural-diffusion MRI pleiotropy from old age to late childhood, and from
348 European ancestry to (ad)mixed ancestries. Note that more sophisticated methods for analyses with
349 admixed individuals are becoming available[54], that allow to model individuals' local ancestry. A lack
350 of power in the smaller ABCD cohort most likely limited the robust estimation of genetic associations
351 for the relatively low heritable functional MRI-derived phenotypes, which complicated examining the
352 generalizability of structural-functional-diffusion MRI pleiotropy beyond structural-diffusion MRI
353 pleiotropy. The necessary future samples size to uncover the heritability of neuroimaging-derived
354 phenotypes depends on genetic architecture and varies across modalities or the brain trait of interest[6].
355 For example, researchers expect that multivariate analyses of the prospective UK Biobank
356 neuroimaging sample of 100,000 individuals will explain 32% and 24% of the additive genetic variance
357 in cortical surface area and thickness respectively[5]. This highlights that both larger neuroimaging-
358 genetic datasets and novel statistical approaches are required to delineate the genetic background of
359 neuroimaging phenotypes.

360 Our enrichment analyses showed that the biological processes and molecular components only
361 enriched for cross-modality genes include more general functions such as cell cycle processes,
362 regulation of gene expression, cell junctions. That gene-sets implicated by cross-modality genes alone
363 are involved in fundamental biological processes is consistent with previous findings that genes
364 associated with multiple trait domains are more likely to be involved in general biological functions[3].
365 This is in line with our finding that, although cross-modality genes were highly expressed in fetal brain
366 tissue, those genes were not necessarily cell-specific – suggesting they may serve in cellular functions
367 taking place in all cell-types. Future research may explore this putative relationship between the degree
368 of pleiotropy and the specificity of biological functions. The functional enrichment of cross-modality
369 lead SNPs investigated here can hint towards the mechanisms through which pleiotropic effects could
370 be exerted. Cross-modality pleiotropic lead SNPs were enriched for exonic variants as found previously

371 for pleiotropic SNPs[3,12]. There is previous evidence to suggest that pleiotropy emerges from the
372 variants' effect on total expression of functional protein, for example by the selective exclusion of
373 missense exons from the gene transcript[55]. However, identification of the (unmeasured) causal SNPs
374 tagged by these multivariate GWAS lead SNPs is necessary in future studies to uncover the mechanisms
375 through which variants exerts their pleiotropic effect.

376 When conditioning GWAS summary statistics for five major psychiatric disorders on our
377 multimodal multivariate analysis, we discovered new loci including genes with increased brain-specific
378 gene expression. The validity of these boosted loci needs to be replicated in independent samples in
379 future research. Nevertheless, prioritizing these variants already showed enhanced polygenic prediction
380 for MDD, BD, ASD, and ADHD. This highlights that future diagnostic strategies targeting psychiatric
381 disorders may benefit from aligning the PGSs to a relevant endophenotype. This rationale is similar to
382 a previously published study that showed improved prediction of SCZ after filtering on genetic variants
383 expressed in the placenta[56]. Exploring which disorders benefit from either a more specific or broader
384 range of neuroimaging phenotypes could also be an intriguing area for future research.

385 Some limitations are worth noting when interpreting our results. First, despite our efforts to
386 harmonize the three sets of phenotypes to the greatest degree, the differential spatial granularity and
387 number of features across modalities can result in differential representation of certain brain regions or
388 brain characteristics in the multivariate signal. Second, our definition of single-modality loci and genes
389 is inherent to two factors: 1) the grouping of phenotypes in unimodal and multimodal analyses –
390 MOSTest may miss a small number of hits when genetic signal is sparse across the jointly analyzed
391 phenotypes[7], and 2) the currently available data limits our statistical power – loci that are now associated
392 with one modality could become genome-wide significant in another modality once sample sizes
393 increase. Third, one should keep in mind that the presence of statistical pleiotropy as indicated in this
394 study can include instances of pleiotropy where multiple traits are affected by one gene but different
395 causal SNPs[4] or one locus with distinct gene effects that are in linkage disequilibrium[3]. Fourth,
396 MOSTest does not provide effect directions due to its multivariate nature and requires the use of
397 individual level data. This restricted access to certain post GWAS analyses that require direction of
398 effect, but these limitations were outweighed by MOSTest's ability to boost identification of variants
399 with shared effects across phenotypes and handle hundreds of phenotypes with sample size differences
400 in a computationally efficient manner[7]. Fifth, the temporal gene-expression patterns of single-modality
401 and cross-modality genes are based on a *postmortem* dataset with a limited number of donors per
402 timepoint[36]. A study that was recently released compared gene-expression between *postmortem* and
403 living brain samples and found a significant difference in 80% of the genes[57]. Although living postnatal
404 gene-expression samples may become available in the future for validation of our findings, prenatal
405 gene-expression will remain to rely on *postmortem* brain tissue.

406 In conclusion, we identified extensive cross-modality pleiotropy and demonstrated that
407 combining different neuroimaging modalities in multivariate analysis substantially increases genetic

variant and gene discovery compared to multivariate analyses within single modalities. The results presented improve our understanding of the biology implicated by single-modality and cross-modality genetic effects, and provide insights into the mechanistic pathways linking common genetic variation, brain structure and function, and psychiatric disorders.

Methods

Samples

UK Biobank

The primary analyses of this study were conducted using data from UK Biobank participants who provided written informed consent. This population-based resource obtained ethical approval from the National Research Ethics Service Committee North West–Haydock (reference 11/NW/0382) and the current study was conducted under application number 27412. We included participants that passed quality control for functional[8] or diffusion[9] MRI-derived phenotypes as described in previous publications (N_{fMRI} = 39,951; N_{dMRI} = 31,306). We increased our sample size for participants with structural MRI-derived phenotypes compared to the original MOSTest publication[7], since new data had been released (N_{sMRI} = 42,068). For all three subsamples, we excluded participants based on relatedness (kinship coefficient > 0.05 as estimated in PLINK), non-European ancestry (UKB field 22006), a genotype missing rate > 10%, and bad scan quality as indicated by an (age- and sex-adjusted) Euler number > 3 SDs lower than the scanner site mean. This resulted in the sample characteristics described in Supplementary Data 18.

Adolescent Brain Cognitive Development (ABCD) Study

Baseline data from ABCD participants from release 3.0 [NIMH Data Archive (NDA) DOI:10.151.54/ 1519007] were used for the replication efforts in this study. All children in this cohort assented before participation and their parents or guardians provided written informed consent. The procedures were approved by a central Institutional Review Board (IRB) at the University of California, San Diego, and, in some cases, by individual site Institutional Review Boards. We included participants with data for the structural or functional MRI-derived phenotypes of interest (N_{sMRI} = 11,760; N_{fMRI} = 11,801) or quality controlled diffusion MRI-derived phenotypes as previously described[9] (N_{dMRI} = 11,904). For all three subsamples, we excluded participants based on recommended criteria for either modality as provided by ABCD (e.g. imgincl_t1w_include), relatedness (first cousin), a genotype missing rate > 10%, and bad scan quality as indicated by an (age- and sex-adjusted) Euler number < 3 SDs lower than the scanner site mean. This resulted in a sample with (ad)mixed ancestries (Table 1), as described by Fan et al. recently[58]. We additionally excluded participants with a genetic ancestry factor[31] of European ancestry < 90% (as provided by ABCD and applied previously in Loughnan *et al*[59]) to create a replication sample that matched the ancestry characteristics of the discovery sample more specifically (Supplementary Data 18).

445 **Genotype data**

446 *UK Biobank*

447 UK Biobank samples were genotyped from whole blood either using the UK BiLEVE or the UK
448 Biobank axiom array and subsequently quality controlled and imputed by the UK Biobank Team[60].
449 Additional quality control was performed in-house and included SNP filters on minor allele frequency
450 (MAF > 0.1%), imputation information score (INFO > 0.5), Hardy-Weinberg equilibrium (HWE; $p <$
451 1×10^{-9}) and missingness (< 10%). This resulted in 9,061,587 SNPs used for association testing.
452 Ancestral principal components were computed within European samples by UK Biobank and used to
453 control for population stratification.

454

455 *ABCD*

456 Release 3.0 genotype data from ABCD participants was obtained through the Affymetric NIDA
457 SmokeScreen Array, using either saliva or whole blood based on higher successful calls, higher non-
458 missingness, matched genetic sex and less excessive identity by state. Initial quality control was
459 performed by ABCD based on calling signals and variant call rates and subsequently following pre-
460 imputation RICOPILI (Rapid Imputation and Computational Pipeline). We complemented ABCD
461 quality control after creating two subsamples (European and (ad)mixed ancestries as described above)
462 by further filtering pre-imputed variants on call rates (<5% missingness), MAF > 0.01, passing the
463 HWE test ($p < 1\times10^{-9}$) and heterozygosity rate (deviating >6SD from the mean value) in PLINK2[61]. A
464 pruned set of SNPs (r^2=0.1) was used to estimate 20 genetic principal components within each
465 subsample to use downstream as covariates in multivariate GWAS. Genetic data was phased and
466 imputed using the TOPMed imputation server and only SNPs with high imputation quality were
467 retained (INFO > 0.9).

468

469 **Neuroimaging data**

470 *Structural MRI-derived phenotypes*

471 Three previous publications have used MOSTest on sMRI-derived phenotypes. These included either
472 region-of-interest (ROI)-based cortical thickness, surface area, and subcortical volume[7] or vertex-based
473 cortical thickness, surface area[5], and sulcal depth[6]. Given that the aim of this study was to combine
474 phenotypes derived from three modalities and MOSTest can currently analyse a few thousand of
475 phenotypes simultaneously, we opted to use the ROI-based cortical thickness, surface area, and
476 subcortical volume[7] phenotypes given their relative low dimensionality. Supplementary Data 1 contains
477 all the regional morphology measures included in the current study and indicates which measures were
478 analysed for the left and right hemisphere separately. The respective publication by Van Der Meer &
479 Frei *et al*[7] describes how the sets of 36 regional subcortical volumes, 68 cortical thickness and 68 surface
480 area, as well as estimated intracranial volume (for covariate use downstream), were extracted from T1-
481 weighted MRI using FreeSurfer v5.3[62,63] in UK Biobank samples. A similar procedure was performed

482 by the ABCD Data Acquisition and Integration Core and were readily available. As the importance of
483 normally distributed phenotypes for MOSTest was demonstrated in the original publication[7], we applied
484 rank-based inverse-normal transformation to each measure.
485
486 *Functional MRI-derived phenotypes*
487 We used functional MRI (fMRI)-derived phenotypes as previously described by Roelfs *et al*[8]. The UK
488 Biobank resting-state fMRI scans were processed into 1,000 Schaefer parcels[64] and mapped onto 17
489 large-scale brain networks defined by Yeo & Krienen *et al*[65]. The averaged time series within each Yeo-
490 defined network were Pearson correlated and represented 136 brain connectivity measures next to the
491 17 network variances (Supplementary Data 1). Rank-based inverse-normal transformation was applied
492 to each measure.
493 The ABCD Data Acquisition and Integration Core provided similar, but not identical, resting-
494 state fMRI-derived phenotypes for replication purposes. Instead of the 17 Yeo & Krienen networks
495 based on 1,000 parcels, temporal variance in 333 Gordon-defined parcels and 66 average correlations
496 between 12 Gordon-defined networks were available[66]. We averaged the parcel variances belonging to
497 the same network to achieve comparability to our discovery phenotypes. Subsequently, we rank-based
498 inverse-normal transformed the 12 network variances and 66 network connectivity phenotypes.
499
500 *Diffusion MRI-derived phenotypes*
501 We used diffusion MRI-derived phenotypes from UK Biobank and ABCD based on a voxel-wise
502 restriction spectrum imaging (RSI) model (as in Fan *et al*[9]). In short, RSI estimates the signal volume
503 fractions of separable pools of water in the human brain (i.e. intracellular, extracellular, and unhindered
504 free water) and their corresponding spherical harmonic coefficients[67,68]. Three RSI features were used:
505 1) restricted isotropic diffusion (N0) is most sensitive to isotropically diffusing water in the restricted
506 compartment (within cell bodies), restricted directional diffusion (ND) is sensitive to anisotropically
507 diffusing water in the restricted compartment (within oriented structures such as axons and dendrites),
508 and 3) normalized free water diffusion (NF) is sensitive to cerebrospinal fluid or intravascular spaces[69].
509 Fan *et al*[9] calculated the principal components (PCs) across all voxels and extracted the first 5,000 PCs
510 explaining more than 70% of the total variance of each feature. Here, due to dimensionality constraints,
511 we reduced the number of PCs for each feature by estimating the "elbow" of each scree plot of
512 eigenvalues using the nScree function of the nFactors R package (Supplementary Fig. 10). This resulted
513 in the first 124 ND-PCs, 87 NF-PCs and 65 N0-PCs used in our multivariate GWAS.

514 **Statistical analyses**

515 *SNP-based GWAS*

516 We performed discovery and replication SNP-based GWAS in PLINK2[61] for every MRI-derived
517 phenotype separately while controlling for sex, age, age^2, genotype array (UKB only), scanner, 20
518 genetic principal components, and modality specific covariates. The latter included Euler number, and
519 total surface area, mean thickness or intracranial volume (sMRI), signal to noise ratio and motion
520 (fMRI), and intracranial volume (dMRI). A linear regression model with additive allelic effects was
521 fitted for each SNP. Subsequently, SNP-based heritability (h^2_{SNP}) was estimated for each phenotype
522 using Linkage Disequilibrium Score Regression (LDSC)[32]. Univariate GWAS summary statistics from
523 non-heritable phenotypes (nominal significance threshold $\frac{h^2_{SNP}}{h^2_{SNP_{SE}}} > 1.96$ as used by Roelfs *et al*[8]) were
524 dropped from further multivariate analyses, since including them may reduce statistical power[7]. This
525 led to the exclusion of 3 dMRI-derived NF-PCs and 14 fMRI-derived connectivity phenotypes GWAS
526 summary statistics (Supplementary Data 1). Then, variant *z*-scores from univariate GWAS were
527 combined in the MOSTest framework to construct multivariate *p*-values as described by Shadrin *et al*[5].
528 This approach selects a regularization parameter optimized to the maximum yield of genetic loci
529 (Supplementary Data 19). The alpha level for SNPs reaching genome-wide significance in the
530 multivariate GWAS was $\alpha = 5\times10^{-8}$.

531

532 *Locus definition*

533 We defined genome-wide significant loci from MOSTest and conditional FDR summary statistics
534 following a protocol as implemented in FUMA. First, independent genome-wide significant SNPs ($p <$
535 $5\times10^{-8}/3$) were obtained by clumping ($r^2 < 0.6$) and SNPs in linkage disequilibrium (LD) with them (r^2
536 ≥ 0.6) were defined as candidate SNPs. LD was estimated using reference genotypes, using 5,000
537 random participants from the UK Biobank sample for UKB-based summary statistics and 1000
538 Genomes Phase 3 EUR for the European as well as (ad)mixed ancestry ABCD-based summary
539 statistics. Second, independent significant SNPs with $r^2 < 0.1$ were defined as lead SNPs and the
540 minimum and maximum positional coordinates of the corresponding candidate variants defined the
541 locus start and end position. Loci in <250kb proximity were merged into a single locus. We excluded
542 loci with a single SNP as these are more likely to be false positives. To test the robustness of our findings
543 we performed sensitivity analyses for the locus definition parameters LD cut-off and merging proximity
544 window, leading to twelve scenarios with different locus definition settings (Supplementary Fig. 3).

545

546 *Multivariate gene-based GWAS*

547 We explored the overlap between modalities and multimodal MOSTest on a gene-level by applying a
548 SNP-wise mean model for 18,877 genes with MAGMA (Multi-marker Analysis of GenoMic
549 Annotation) v1.08[33] in FUMA. The SNP-based MOSTest summary statistics from sMRI, dMRI, fMRI

550 and multimodal served as input with default settings and the UKB European population was used as
551 reference. The alpha level for genes reaching genome-wide significance was adjusted from $\alpha = 0.05$ to
552 $\alpha = (0.05/18{,}877)/3 = 8.83\times10^{-7}$ according to Bonferroni correction for multiple testing.
553
554 *Definition of single-modality and cross-modality loci and genes*
555 Locus overlap between the three MOSTest summary statistics (sMRI, fMRI, dMRI) was defined as
556 physically overlapping genome-wide significant loci after clumping (see above). We used the
557 GenomicRanges R-package[70] to compare the chromosome and start and end base pair positions of all
558 loci between any pair of summary statistics. A locus was considered single-modality when it did not
559 overlap with any of the loci identified for other modalities. All loci that were found to overlap between
560 two or more modalities also overlapped with the multimodal loci, hence we decided to represent these
561 cross-modality loci with the association statistics of the multimodal locus' lead SNP(s) in downstream
562 analyses. All univariate statistics that laid the basis of these single-modality and cross-modality lead
563 SNPs were plotted in a heatmap with the hierarchical clustering algorithm as implemented in
564 seaborn.clustermap (https://seaborn.pydata.org/generated/seaborn.clustermap.html) applied to the
565 phenotypes using (Pearson's) correlation as a distance metric and method='average' clustering. The
566 sMRI, fMRI, dMRI and multimodal MOSTest genes that were found to be genome-wide significant in
567 MAGMA were compared to provide a similar overview. The overlapping patterns were then plotted
568 with the eulerr R-package. This procedure was repeated for both discovery (UKB) and replication
569 (ABCD) MOSTest summary statistics, to investigate whether a similar overlapping pattern could be
570 observed.
571
572 *Comparison of single-modality and cross-modality lead SNPs*
573 We were interested in potential differences between single-modality and cross-modality loci compared
574 to other complex traits. Therefore we selected the lead SNPs within the respective loci (see *Locus*
575 *definition*) and annotated them with ANNOVAR[34]. As reference, we used the annotations of 43,492
576 (unique) lead SNPs derived from 558 traits (with reasonable power, i.e. $N > 50{,}000$) across 24 trait
577 domains (Table 2 from Watanabe et al.[3]). Enrichment of the single-modality and cross-modality lead
578 SNPs in positional annotation categories was then tested using Fisher's Exact test. The alpha level for
579 significant enrichment was Bonferroni corrected ($\alpha = 0.05 / 44 = 1.14\times10^{-3}$).
580
581 *Comparison of single-modality and cross-modality gene properties*
582 In order to interpret the biological processes, cellular components or molecular functions our single-
583 modality and cross-modality genes are involved in, Gene Ontology (GO)[71,72] gene-sets were tested for
584 enrichment of genes in these four lists using hypergeometric testing as implemented in FUMA[73]. Protein
585 coding genes were used as background genes and Bonferroni correction was applied to adjust for the
586 multiple comparisons. The significant single-modality and cross-modality GO terms were visualized as

587 a graph using Cytoscape, EnrichmentMap[74] and AutoAnnotate[75] following the Nature Protocol
588 by Reimand & Isserlin *et al*[76]. Stringent pathway similarity scores (Jaccard and overlap combined
589 coefficient = 0.6 as used in Paczkowska, Barenboim *et al*[77]) were used as edges.
590 To visualize the temporal gene expression pattern of the sets of single-modality and cross-
591 modality genes, we made use of gene expression data derived from brain tissue from 56 donors[36]. This
592 dataset ranges from 5 weeks post conception to 82 years of age and we used the data as pre-processed
593 in Kang *et al*[36]. We selected the probe with the highest differential stability for each gene (n = 16,849).
594 A number of single-modality ($n_{sMRI\text{-}modality}$ = 111, $n_{dMRI\text{-}modality}$ = 83, $n_{fMRI\text{-}modality}$ = 2) and cross-modality
595 genes (n=300) were not available in the data. Given the relatively high homogeneity of expression
596 patterns across cortical brain samples[78], we subsequently averaged over 13 cortical regions, within
597 donor, and normalized the expression values, within probe, across donors, to a range between 0 and
598 100. Mean expression over time per set of genes was plotted with ggplot2 in R v4.0.3., with
599 geom_smooth(method="gam") using default settings.
600 Lastly, we explored cell-type enrichment of single-modality and cross-modality genes by
601 performing Fisher Exact Tests for each cell-type identified by Bhaduri et al.[38] using single-cell RNA
602 sequencing analyses of the fetal brain. The minimum number of genes overlapping was set to >2.
603 Bonferroni correction was applied for the number of tests performed ($\alpha = 0.05 / 30 = 1.67\times10^{-3}$).
604
605 *Conditioning major psychiatric disorder GWAS on multimodal MOSTest*
606 We explored whether the multimodal multivariate summary statistics could be leveraged to improve
607 locus discovery for major psychiatric disorders (schizophrenia[41], bipolar disorder[42], major depressive
608 disorder[43], attention-deficit hyperactivity disorder[45], and autism spectrum disorder[46]). For that purpose,
609 we applied Conditional False Discovery Rate (cFDR)[40] on Psychiatric Genomics Consortium GWAS
610 summary statistics (listed in Supplementary Data 12) by conditioning on multimodal MOSTest
611 summary statistics. We obtained disorder summary statistics excluding UK Biobank to prevent sample
612 overlap. In cFDR analyses, original *p*-values are replaced by FDR values that reflect the posterior
613 probability that a SNP is null for the disorder given that the *p*-values for both phenotypes are as small
614 or smaller as the observed *p*-values:
615 (1) $$FDR(p_{disorder}|p_{multimodal}) = \frac{\pi_0(p_{multimodal})p_{disorder}}{F(p_{disorder}|p_{multimodal})}$$
616 with F = the conditional empirical cumulative distribution function and $\pi_0(p_{multimodal})$ = the
617 conditional proportion of null SNPs for the disorder given that *p*-values for the multimodal phenotype
618 are as small or smaller. We subsequently defined genome-wide significant loci (see *Locus definition*)
619 for the original ($p < 5\times10^{-8}$) and conditioned (FDR < 0.05) summary statistics and compared the results.
620 Since the probability of replicating these original and conditioned loci at genome-wide
621 significance is low due to the limited statistical power of replication GWAS, we first tested for en masse
622 sign concordance of effect direction in independent summary statistics, as is in line with previous

623 literature[79,80]. All summary statistics that were used to look up lead SNPs and test for sign concordance
624 are listed in Supplementary Data 12. An exact binomial test was used to test the null hypothesis that
625 directions of effect were randomly distributed (*prob.*=0.5), given the total number of variants and the
626 number of variants with concordant effects.
627
628 *Tissue enrichment of condFDR genes and original disorder genes*
629 Using the genome-wide significant loci from the condFDR and original summary statistics, we used
630 FUMA[73] (https://fuma. ctglab.nl/) to positionally map SNPs to genes. The resulting gene lists were used
631 for hypergeometric test-based tissue enrichment analyses (as implemented in FUMA), to test the tissue-
632 specificity of the input genes for differentially expressed (upregulated) genes in each of the 54 tissues
633 available in GTEx (v8)[81]. Bonferroni correction was applied for the number of tests performed (α =
634 0.05 / (54 tissues × 2 gene lists × 5 disorders) = 9.26×10^{-5}).
635
636 *PleioPGS*
637 We then computed the prediction power of the original and conditioned summary statistics by
638 constructing polygenic scores (PGS) in independent case-control samples for the five major psychiatric
639 disorders described above in independent samples. The TOP, BUPGEN and MoBa[82] samples are
640 described in the Supplementary Methods (and Supplementary Data 12). We applied two different set-
641 ups, both based on the C+T (clumping + thresholding) approach[83] using different strategies for ranking
642 SNPs: 1) original GWAS *p*-value-based ranking and original GWAS effect sizes (standard PGS); 2)
643 cFDR-based ranking (described above) and original GWAS effect sizes (pleioPGS as introduced by
644 Van der Meer *et al*[30]; https://github.com/precimed/pleiofdr). For these two setups PGS were calculated
645 across five sets of LD-independent SNPs (n_{SNP} = 1,000, 10,000, 50,000, 100,000, 150,000) using
646 PRSice-2 (v2.3.3)[84] with no additional clumping (--no-clump option). Sets of LD-independent SNPs
647 were obtained using plink v1.90b6.1[61] based on the setup-defined SNP ranking with --clump-kb 250, -
648 -clump-r2 0.1 parameters and in-sample LD estimates. In both setups the phenotypic variance explained
649 by the PGS (R^2) was estimated as the difference between the R^2 of the full regression model and the R^2
650 of the null model only including the covariates (age, sex and the first 10 genetic PCs), also known as
651 Nagelkerke's pseudo-R^2. Bonferroni correction was applied for the number of tests (p < (0.05 / (7 n_{SNP}
652 cut-offs × 2 PRS models × 5 disorders) =) 7.14×10^{-4}.
653 We applied random sampling without replacement procedure and *t*-test per disorder to test if
654 the highest R^2 (MDD pleioPGS/SCZ original PGS with n_{SNP} = 50,000 SNPs; ADHD/ASD/BD pleioPGS
655 with n_{SNP} = 100,000 SNPs) significantly higher than the R^2 of the alternative PGS (MDD original
656 PGS/SCZ pleioPGS with n_{SNP} = 50,000 SNPs; ADHD/ASD/BD original PGS with n_{SNP} = 100,000
657 SNPs). For each trait and type of PGS (original PGS, pleioPGS), we performed 200 iterations randomly
658 sampling 2/3 of controls and 2/3 of corresponding disorder cases with replacement and applying
659 PRSice2 to estimate R^2. Obtained distributions of R^2 values were used to assess confidence intervals.

Data availability

Genome-wide summary statistics will be made publicly available via https://ctg.cncr.nl/software/summary_statistics/ and GWAS Catalog upon acceptance. The individual-level data that support the discovery findings of this study are available from UK Biobank but restrictions apply to the availability of these data, which were used under license no. 27412 for the current study. Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development^{SM} (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). ABCD data used for replication in this study is registered under the NDA study register at https://doi.org/10.15154/1527969. Data from the Norwegian Mother, Father and Child Cohort Study and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway (Norwegian Institute of public health) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owners.

Code availability

Code to obtain the multimodal results presented in this manuscript are available via https://github.com/EPTissink/MOSTest-multimodal. Code from previously published studies based on different modalities from which we used phenotypic data are available at https://github.com/cmig-research-group/RSIGWAS (dMRI), https://github.com/precimed/mostest (sMRI) and https://www.github.com/norment/open-science (fMRI).

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Conflicts of interest

E.P.T., A.A.S., D.v.d.M, N.P., G.H., D.R., O.F., C.C.F., M.N., T.N., M.B., S.D., L.T.W., M.P.v.d.H., D.P. and T.K. declare no conflicts of interest. Dr. Andreassen has received speaker's honorarium from Lundbeck and Janssen, and is a consultant to coretechs.ai. Dr. Dale is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies.

Author contributions

E.P.T., A.A.S., O.F., D.v.d.M. and O.A.A. conceived of the study. E.P.T. performed the analyses with A.A.S. and D.v.d.M. Neuroimaging data were processed by D.R., T.K., C.C.F., A.M.D, D.v.d.M and E.P.T. Genotype data were processed by E.P.T. and D.v.d.M. All authors contributed with conceptual input on methods and/or interpretation of results. E.P.T. wrote the manuscript and all authors contributed to the final manuscript.

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