

Joint spatial and gene fine-mapping reveals convergent neuroanatomical niches but limited overlap among associated genes in psychiatric disorders

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Title

Joint spatial and gene fine-mapping reveals convergent neuroanatomical niches but limited overlap among associated genes in psychiatric disorders

Abstract

Translating genetic risk for complex traits into mechanistic insight requires locating risk signals within native tissue architectures. Although spatial transcriptomics (ST) provides high-resolution anatomical context, its integration with genome-wide association studies (GWAS) can be confounded by linkage disequilibrium (LD) and spatial autocorrelation. These factors can generate spurious associations and spread localized genetic signals across non-specific tissue regions. Here we establish a genotype-aware spatial simulation benchmark and develop SDESE (Spatially refined Driver Estimation by Selective Expression), a framework for joint spatial and gene fine-mapping of complex phenotypes. SDESE couples spatial localization with gene prioritization through iterative conditional association analysis, thereby reducing signals attributable to LD proxies and co-expression. We also provide a multi-organ spatial resource and analysis platform for downstream applications. In spatial simulations, SDESE retained high sensitivity while reducing non-specific spatial spread, particularly for localized signals. We then applied SDESE to adult human dorsolateral prefrontal cortex (DLPFC) ST data from five common psychiatric disorders and validated the results using multiple independent GWAS datasets. Genetic risk across these disorders converged on shared neuroanatomical niches, particularly mid-to-deep cortical layers and excitatory neuronal microenvironments. However, the corresponding associated-gene sets showed limited overlap, while functional enrichment implicated neurodevelopmental, synaptic and ion-transport processes across disorders. These findings reveal a layered spatial-genetic architecture in which shared neuroanatomical vulnerability coexists with partially distinct but functionally convergent sets of associated genes.

Main

Genome-wide association studies (GWAS) have identified thousands of loci associated with complex human traits¹. Yet how the predominantly non-coding variants at these loci exert regulatory effects within tissue-specific cellular architectures remains poorly understood. Because variant effects depend strongly on the local cellular and gene-regulatory context², tissue-specific expression patterns of susceptibility genes have been widely used to infer tissue susceptibility to complex diseases^{3–6}. Post-GWAS interpretation must therefore resolve both where genetic risk is concentrated within intact tissues and which genes mediate these spatially localized signals.

Spatial transcriptomics (ST) enables such mapping by preserving the native anatomical coordinates of cellular transcriptional activity^{7,8}. Several approaches have recently been developed to integrate GWAS summary statistics with ST profiles. Methods such as scDRS map polygenic risk at single-cell resolution⁹. The recently introduced gsMap¹⁰ framework combines location-specific gene specificity scores with stratified LD score regression (SLDSC¹¹) to map complex traits spatially. Despite these advances, existing approaches face a statistical trade-off that limits precise spatial localization. Spot-wise testing methods face a substantial multiple-testing burden, reducing sensitivity when trait-associated signals are confined to a small number of focal locations. Conversely, heritability-partitioning frameworks efficiently detect broader trait enrichment spots but can have limited spatial specificity.

Spatial gene expression exhibits structured spatial variation¹². This limitation may arise from the combined effects of linkage disequilibrium (LD), expression sparsity, and spatial autocorrelation. Through LD, association evidence may be distributed across multiple neighbouring genes, including genes that act as proxies for the underlying functional association^{13,14}. In sparse ST datasets, technical dropout may weaken the spatial representation of associated genes, allowing more consistently detected LD-linked proxies to exert disproportionate influence. If these proxy genes are broadly expressed in adjacent or biologically unrelated regions, spatial autocorrelation can further diffuse the inferred signal beyond trait-relevant spatial niches. Current approaches also typically use unidirectional analyses based on either spot-specific expression profiles or trait-associated gene sets. In both settings, trait-irrelevant genes can dilute localized spatial enrichment, reducing sensitivity and spatial precision. Because real tissues lack spatial ground truth, systematic evaluation of sensitivity and non-specific spatial localization remains difficult.

To address these limitations, we developed an integrated framework for spatial genetic mapping. First, we established a genotype-aware spatial simulation benchmark SMECT (Spatial Mapping Evaluation of Complex Traits) that explicitly

models genome-wide LD, expression sparsity, spatial autocorrelation and ST-specific noise. Building on this benchmark, we developed SDESE (Spatially refined Driver Estimation by Selective Expression), a framework for joint spatial and gene fine-mapping. SDESE integrates a continuous gene-level weighted rank-sum test with conditional effective chi-square analysis to perform bidirectional refinement between genes and tissue space. This procedure conditions gene-level association evidence within LD blocks, enabling the identification of focal trait-associated spatial niches and the prioritization of associated genes while limiting non-specific spatial spread. To facilitate broader application, we deployed an accompanying cell-type-resolved spatial resource and analysis platform PSC (estimating Phenotype-associated Spatially specific Cell types; <https://pmglab.top/psc/>). Finally, we applied SDESE to adult human dorsolateral prefrontal cortex (DLPFC) ST data from five psychiatric disorders and validated the results using multiple independent GWAS datasets. Genetic risk across these disorders consistently converged on shared neuroanatomical niches, particularly the mid-to-deep cortical layers. However, the corresponding sets of prioritized associated genes showed limited overlap and high disease specificity. This spatial-genetic architecture suggests that shared spatial vulnerability need not imply highly overlapping associated genes and provides a spatially resolved framework for interpreting pleiotropy in the human brain.

Results

SDESE enables joint spatial and gene fine-mapping through bidirectional iterative refinement

To jointly determine where genetic risk is enriched and which associated genes are involved, we developed SDESE, an iterative framework that jointly refines spatial locations and associated genes (Fig. 1). SDESE integrates two complementary sources of information. On the genetic side, ECS¹⁵ and GATES¹⁶ aggregate GWAS summary statistics into gene-level association evidence, which is used to select an initial set of significant genes for conditional gene-based test (Fig. 1a). On the spatial side, we used gsMap to calculate gene specificity scores (GSS) from spatial transcriptomic data and rank all genes across spatial regions (Fig. 1b).

At its core, SDESE operates as a bidirectional iterative refinement loop (Fig. 1c). In the gene-to-space direction, genes with stronger conditional association evidence receive higher continuous weights, which are used to update the spatial association score of each spot through a non-parametric weighted rank-sum test (Methods; step 1). In the space-to-gene direction, the updated spot-level association scores are used to aggregate gene spatial specificity and calculate gene association scores, thereby updating the priorities of genes for next conditional test (step 2). Following this updated priority, candidate genes undergo a robust conditional test by an absolute-correlation-recalibrated ECS (aECS) (step 3). Notably, our conditional aECS framework provides statistical power comparable to widely used Z-score-based conditional tests¹⁷. Still, it exhibits substantially greater robustness to LD noise (Supplementary Note 3). The conditional aECS penalizes the statistical weights of non-causal LD proxies or indirectly associated genes while isolating the independent marginal effects of conditionally independent association signals (step 3). The resulting conditional *P* values update the gene weights for the next iteration. This bidirectional feedback loop ensures that spatial niche mapping and gene prioritization continuously constrain and refine one another until the spatial association scores of all spots achieve global convergence.

Unlike existing unidirectional workflows^{9,10} and our previous iterative framework⁶, SDESE leverages continuous genetic association weights generated by aECS, a more robust conditional gene-based test, throughout its bidirectional refinement process. By avoiding arbitrary hard-thresholding, SDESE incorporates both strong and moderate polygenic signals into the spatial enrichment test, improving sensitivity to spatially localized polygenic signals. Furthermore, the deployment of a non-parametric rank-sum statistic ensures robust statistical inference despite ST-inherent technical challenges, including severe expression sparsity, dropout events, and highly skewed

non-normal expression distributions. To rigorously control the family-wise error rate (FWER) across high-dimensional spatial spots, we implemented a gene-label permutation coupled with a global min-P strategy. Importantly, this permutation explicitly preserves the native spatial autocorrelation structure of the transcriptome while correcting for iterative selection bias and multiple testing burdens. Ultimately, SDESE yields two refined, mutually calibrated outputs: strictly defined trait-associated spatial niches (calibrated via global min-P permutations) and their prioritized associated genes, defined by aECS P values that remain significant after multiple-testing correction (Fig. 1d).

To evaluate the spatial detection performance of SDESE and support its application to disease studies, we developed a spatial simulation benchmark, SMECT, and a spatial resource and analysis platform, PSC (Fig. 1e). SMECT uses a hierarchical model incorporating real genotype effects to jointly generate GWAS summary statistics and synthetic spatial transcriptomic data. It explicitly models LD, spatial autocorrelation, expression sparsity and count variation, enabling separate evaluation of error control under the null and sensitivity and non-specific signal spread under the alternative. Through PSC, we integrated SDESE with curated organ spatial transcriptomic datasets and scRNA-seq reference data, supporting the complete SDESE workflow using existing tissue datasets.

The conditional aECS test improves robustness to noise in reference LD

Conventional conditional Z-score tests are sensitive to errors in reference LD estimation^{18,19}, which can distort null calibration. Because the conditional aECS test is used in SDESE to limit the influence of LD proxy genes, we evaluated its operating characteristics in Monte Carlo simulations. We generated true LD matrices using first-order autoregressive structures with $\rho = 0.40, 0.80, 0.90, 0.95$ and considered conditioning sets of 50 or 200 SNPs, with 100,000 replicates per configuration. We compared the two tests when the reference LD matrix matched the true LD matrix and after introducing either allele-orientation mismatches or continuous noise into the reference LD matrix. Numerical type I error and power estimates under matched LD are summarized in Table 1, and Q-Q plots under matched and perturbed reference LD are shown in Fig. 2. Details of the conditional aECS test and Monte Carlo simulation design are provided in the Methods.

Under matched LD, both tests were broadly calibrated when the LD matrix was not near-singular (Fig. 2a). Neither test produced a false-positive event at $\alpha = 5 \times 10^{-8}$ in any configuration (Table 1). At $\alpha = 0.01$ and $\rho \leq 0.90$, the type I error ranged from 0.0097 to 0.0102 for the conditional Z-score test and from 0.0078 to 0.0102 for the conditional aECS test. Power was also generally similar at moderate LD ($\rho =$

0.40 or 0.80), consistent with the largely overlapping alternative-hypothesis Q-Q profiles (Table 1 and Fig. 2b). At $\alpha = 0.01$ and $\rho = 0.95$, the type I error of the conditional aECS test reached 0.0126 when $n\text{SnpA} = 200$. At the same significance threshold and LD strength, but with $n\text{SnpA} = 50$, its power was 0.6312, compared with 0.8441 for the conditional Z-score test (Table 1). The corresponding Q-Q plots showed stronger tail deviation under the null hypothesis and greater separation between the two tests under the alternative hypothesis (Fig. 2a,b). For practical SDESE analyses, we therefore recommend LD pruning before conditional aECS testing, for example using $\rho \leq 0.90$.

Under reference-LD noise, the conditional aECS test showed a clear robustness advantage over the conditional Z-score test. Reversing the signs of 5% of the off-diagonal LD elements had little effect at $\rho = 0.40$, but increasingly inflated the conditional Z-score statistics as LD strengthened, whereas the conditional aECS statistics remained closer to the theoretical null distribution (Fig. 2c). Adding Gaussian noise ($\sigma = 0.05$) produced pronounced deviations for the conditional Z-score test across LD settings, with some curves reaching the computational truncation limit. By contrast, the conditional aECS statistics remained substantially closer to the theoretical null distribution (Fig. 2d). Together, these results demonstrate that the conditional aECS test is more robust than the conditional Z-score test to reference-LD noise.

Statistical performance of SDESE in resolving focal and regional genetic signals

To evaluate the ability of SDESE to resolve genetic signals across spatial scales under known spatial ground truth, we developed SMECT, a genotype-aware spatial simulation framework (Fig. 3a). SMECT incorporated 4,206,964 common variants (minor allele frequency > 0.05) from 490,541 UK Biobank participants²⁰ to preserve realistic genome-wide linkage disequilibrium and polygenic backgrounds and generated matched GWAS summary statistics and synthetic spatial transcriptomic data through a hierarchical eQTL-regulatory model. Each simulated section comprised a 100×100 grid of spots and 20,000 genes, with a dropout rate of 0.4. We considered four spatial architectures—one hotspot, two hotspots, one contiguous region and three regions—and driver ratios of 25%, 50% and 75%, defined as the proportion of associated genes among spatially specific genes. For each parameter combination, we generated 100 independent sections and applied SDESE and SLDSC^{10,11} to identical inputs. Detailed simulation settings are provided in the Methods.

Neither method identified a significant spot in any of the 100 null replicates. Under the alternative hypothesis, SDESE detected at least one significant spot in 0.98-1.00

of simulated sections across all spatial architectures and driver ratios (Fig. 3b). SLDSC showed substantially lower detection rates in the focal architectures: 0.10-0.24 for one hotspot and 0.03-0.40 for two hotspots. Its detection rate increased for regional signals but remained dependent on architecture and driver ratio, ranging from 0.58 to 0.73 for one region and from 0.43 to 1.00 for three regions, with complete detection achieved only for the three-region architecture at a 75% driver ratio. Thus, the detection advantage of SDESE was most pronounced for focal signals and at lower driver ratios.

Because sensitivity was defined relative to the ground-truth geometry, we evaluated focal and regional architectures using the corresponding definitions described in the Methods: successful replicate-level detection within the true signal-support domain for focal signals and the proportion of true-region spots detected for regional signals. SDESE maintained a sensitivity of 0.93-1.00 across all architectures and driver ratios (Fig. 3c). By contrast, SLDSC sensitivity ranged from 0.06 to 0.20 for one hotspot and from 0.01 to 0.17 for two hotspots. For regional signals, SLDSC sensitivity ranged from 0.26 to 0.41 for one region and from 0.05 to 0.84 for three regions; the maximum was reached only in the three-region, 75% driver-ratio setting. These results show that SDESE retained stable sensitivity to both focal and regional signals, whereas SLDSC was most effective when the signal was spatially extensive and the driver ratio was high.

To separate detection from localization accuracy, we next evaluated the non-specific rate (NSR), for which lower values indicate that significant spots are concentrated within or near the true signal-support domain (Fig. 3d). SDESE detections were predominantly associated with low NSR values across all four architectures. In focal settings, SLDSC frequently produced no significant spots, shown as grey cells, and its detected sections exhibited more variable NSR values, including occasional high values indicative of non-specific spatial spread. In regional settings, detected spots from both methods generally showed low NSR values, although missing detections remained more frequent for SLDSC at lower driver ratios. SDESE therefore combined high detection sensitivity with spatially specific localization rather than achieving greater sensitivity by broadly expanding the significant area.

Finally, we examined whether the bidirectional spatial-gene refinement implemented in SDESE improved the prioritization of true associated genes (Fig. 3e). Compared with the *P*-value determined conditioning order, the Spatial condition improved prioritization precision by approximately 6%-17% across all four spatial architectures and all three driver ratios. Thus, the benefit of SDESE extended beyond spatial detection: spatial feedback during bidirectional refinement also increased the proportion of true associated genes among all genes reaching significance in the conditional association analysis.

SDESE produces more anatomically concentrated spatial signals in analyses of real phenotypes

Having established sensitivity and the non-specific rate under known spatial ground truth, we next compared the spatial distributions produced by SDESE and SLDSC in real tissue. We analysed high-resolution Stereo-seq data from an embryonic day 16.5 (E16.5) mouse embryo²¹, with spots annotated into 25 anatomical regions (Fig. 4a), and integrated them with GWAS summary statistics for ten human complex phenotypes. Both methods received identical spatial inputs, and regional enrichment was summarized using odds ratios (ORs).

For bipolar disorder (BD), major depressive disorder (MDD) and intelligence quotient (IQ), both methods detected spatial associations but differed markedly in their spatial coverage (Fig. 4b). SDESE identified 15,785, 16,214 and 16,111 significant spots, respectively, which were concentrated primarily in the brain, spinal cord and adjacent neural structures. SLDSC identified 32,988, 27,681 and 52,798 significant spots, respectively—1.7-3.3-fold the corresponding numbers detected by SDESE—and these signals extended more broadly into craniofacial, abdominal and other peripheral tissues.

The regional enrichment profiles supported this distinction (Fig. 4c). With SDESE, profiles for attention-deficit/hyperactivity disorder (ADHD), schizophrenia (SCZ), BD, MDD, anxiety disorder (ANX) and IQ were dominated by brain enrichment, with substantial spinal cord enrichment also present. MDD and ANX additionally showed strong enrichment in the dorsal root ganglia. SLDSC yielded broader profiles for the same phenotypes, extending beyond the brain and spinal cord to the inner ear, sympathetic nerves and multiple non-neural regions. Among the non-neural phenotypes, SDESE produced sparse and distinguishable profiles, including connective-tissue enrichment for leukocyte count and total protein, cartilage-primordium and kidney enrichment for diastolic blood pressure, and connective-tissue and lung enrichment for coronary artery disease. By contrast, SLDSC enrichment extended across multiple skeletal, muscular, connective and visceral tissues.

Overall, SDESE produced more anatomically concentrated and phenotype-differentiated enrichment profiles, whereas SLDSC generated larger sets of significant spots with broader cross-tissue spread. This pattern was consistent with the higher NSR observed for SLDSC in the simulations, indicating that SDESE reduced non-specific spread in spatial disease localization.

Multiple psychiatric disorders share spatial and neuronal enrichment in the DLPFC

To characterize the spatial organization of psychiatric-disorder genetic risk in the human cortex, we applied SDESE to GWAS data for five disorders: ADHD^{22,23}, ANX^{24,25}, BD^{26,27}, MDD^{28,29} and SCZ^{30–33}. The spatial transcriptomic data comprised 12 dorsolateral prefrontal cortex (DLPFC) sections from three neurologically healthy adult donors³⁴, spanning cortical layers L1-L6 and the underlying white matter (Fig. 5a). PSC identified seven spatial regions (SRs). Layer-marker expression mapped SR7 to L1, SR5 to L2/L3, SR6 to L3, SR1 to L3/L4, SR4 to L4-L6 with the strongest L5 programme, SR2 predominantly to L6 and SR3 to white matter (Fig. 5b). These assignments represent continuous cortical-layer transcriptional programmes rather than discrete histological boundaries.

The spatial enrichment profiles revealed a shared middle-to-deep cortical axis across the five disorders (Fig. 5c). Significant SDESE spots were consistently enriched in SR4 and SR2, corresponding predominantly to L5 and L6, respectively, and also showed enrichment in SR1, corresponding to L3/L4. Enrichment in the more superficial SR5 region was evident for BD, MDD and SCZ but was weak or absent for ADHD and ANX. By contrast, SR7 and SR3, corresponding to L1 and white matter, respectively, were depleted across all five disorders.

Cell-type enrichment further localized this shared spatial pattern to neuronal environments (Fig. 5d). All five disorders showed enrichment across multiple excitatory neuron annotations, including L4, L2/3, PLCH1 L4/5, L5/6 and L6 excitatory neurons. Inhibitory-neuron enrichment was more heterogeneous, with MDD showing the broadest enrichment across CXCL14, SST and SV2C inhibitory subtypes, whereas most non-neuronal cell types were depleted. After combining the spatial-region and cell-type enrichment profiles, pairwise Spearman correlations among the five disorders ranged from 0.82 to 0.96 (Fig. 5e), indicating that their enrichment profiles were highly correlated.

We next evaluated the reproducibility of these profiles across GWAS cohorts by repeating the analysis with alternative GWAS summary datasets for each disorder (Fig. 5f). Correlations between profiles generated from the alternative and corresponding primary GWAS datasets ranged from approximately 0.87 to 1.00 across both spatial-region and cell-type analyses. Thus, the shared enrichment of middle-to-deep cortical layers and excitatory neurons was stable across GWAS cohorts.

Shared spatial-cellular enrichment is accompanied by limited overlap in associated-gene composition

We next used SDESE to identify associated genes for the five psychiatric disorders in the human DLPFC. Genes were required to reach significance after BH correction for multiple testing at an FDR of 0.05 in the conditional aECS analysis of all 12 sections. This criterion identified 183 genes for ADHD, 160 for ANX, 122 for BD, 152 for MDD and 131 for SCZ. Based on the median conditional aECS P values across the 12 sections, the strongest associations among the displayed genes were ROBO2 for ADHD ($P = 1.95 \times 10^{-12}$), SOX5 for ANX ($P = 9.95 \times 10^{-15}$), SHANK2 for BD ($P = 1.87 \times 10^{-14}$), RAB27B for MDD ($P = 4.98 \times 10^{-24}$) and TCF4 for SCZ ($P = 1.54 \times 10^{-21}$; Fig. 6a).

Beyond these leading associations, SDESE identified genes with functions relevant to neuronal biology. Using the same median conditional aECS P -value summary, ESRRG was associated with ANX ($P = 9.05 \times 10^{-5}$); ESRRG regulates neuronal mitochondrial metabolism and supports synaptic plasticity³⁵, linking this association to neuronal energy metabolism. GPR155, also known as LYCHOS, was associated with MDD ($P = 1.32 \times 10^{-10}$) and encodes a lysosomal cholesterol sensor that activates mTORC1³⁶, linking the MDD signal to lysosomal lipid sensing and growth-related signalling. UBN2 was associated with SCZ ($P = 1.27 \times 10^{-8}$); UBN1/2-containing HIRA complexes promote histone H3.3 deposition and the activation of neural differentiation genes³⁷, connecting this association to chromatin regulation during neural differentiation.

We next examined whether the apparent overlap among disorders was retained after conditional analysis. Before conditional filtering, ANX-MDD showed the highest pairwise Jaccard index among the five primary GWAS datasets (0.249), followed by BD-SCZ (0.168). Conditional aECS filtering reduced the Jaccard index for every disease pair and decreased the mean from 0.120 to 0.058. ANX-MDD retained the highest overlap after filtering (0.171), whereas BD-SCZ decreased to 0.050 and no longer ranked second (Fig. 6b). These results indicate that local LD and correlated expression among neighbouring genes contributed substantially to the apparent cross-disorder overlap before conditioning.

Despite the reduction in cross-disorder overlap, associated-gene sets remained reproducible across GWAS datasets for the same disorder. Under the all-12-section criterion, overlapping genes showed 3.80-7.21-fold enrichment across 12 same-disorder comparisons, with all overlap tests remaining significant after BH correction (maximum FDR = 9.5×10^{-16} ; Fig. 6c).

Gene Ontology Biological Process enrichment further revealed functional convergence among the conditionally associated genes (Fig. 6d). Across ANX, BD,

MDD and SCZ, enriched terms included generation of neurons, system development, cell communication, synapse organization and monoatomic ion transmembrane transport. MDD-associated genes additionally showed enrichment in neurotransmitter transport and vesicle-mediated transport in synapse. Genes shared by at least two disorders were enriched in neuronal generation, system development, cell communication, synapse organization and ion transport. Thus, cross-disorder genetic convergence was expressed primarily through shared spatial regions, cell types and neuronal processes rather than through extensive overlap among conditionally associated genes.

Discussion

This study establishes an integrated spatial-genetics framework comprising SMECT, SDESE and PSC, linking method evaluation, spatial localization and associated-gene identification. Rather than maximizing the number of significant spots, SDESE aims to localize genetic associations more specifically by iteratively coupling spatial enrichment with conditional gene analysis. Across simulations, mouse embryo data and the human DLPFC, our findings show that detection sensitivity must be considered together with spatial specificity, because more significant spots do not necessarily indicate more accurate localization.

SMECT simulations with known spatial ground truth showed that SDESE maintained high sensitivity while limiting non-specific spatial spread, particularly for focal signals. Conditional aECS was robust to moderate reference-LD noise and allele-orientation mismatches but remained susceptible to near-singular LD structures. Differences in calibration should also be considered when comparing methods: SDESE reruns the complete iterative procedure within global min-P permutations that preserve spatial dependence^{38,39}, whereas SLDSC applies BH-FDR correction without full-pipeline spatial permutation^{10,11}. These safeguards reduce signal propagation arising from LD proxies, correlated expression and multiple testing, but do not replace ancestry-matched LD references, allele harmonization or LD pruning.

In the E16.5 mouse embryo, SDESE identified smaller significant sets that were more concentrated in neural structures, whereas SLDSC signals extended across a broader range of tissues. This pattern is consistent with the reduced non-specific spread observed in simulations. However, because the embryo data lack phenotype-relevant spatial ground truth and differ from adult human tissues in species and developmental stage⁴⁰, the additional spots identified by SLDSC cannot be classified as false positives.

Consistent with previous evidence of shared genetic risk across psychiatric disorders^{41–43} and cortical molecular convergence⁴⁴, all five disorders examined here converged on middle-to-deep cortical programmes and predominantly excitatory neuronal environments. This neuronal enrichment is also consistent with previous genetic evidence implicating specific neuronal populations in schizophrenia⁴⁵. In contrast, conditional aECS substantially reduced associated-gene overlap across disorders, suggesting that local LD and neighbouring-gene co-expression contribute to apparent gene-level sharing. These findings support a hierarchical architecture in which different disorders involve partly distinct associated genes within shared spatial-cellular niches while converging functionally on neurodevelopmental, synaptic and ion-transport processes.

Several boundaries should be considered. The DLPFC analysis included only 12 sections from three neurologically healthy donors and therefore cannot capture

variation associated with disease state, developmental stage, ancestry or environmental exposure. PSC-derived spatial regions and cell types are computational annotations rather than strict histological boundaries. Moreover, SDESE identifies genes jointly supported by GWAS associations, reference LD and spatial expression but does not establish causal variants, regulatory direction or true target genes. Validation using disease-relevant tissues, diverse cohorts, brain eQTL⁴⁶ and pQTL data⁴⁷, spatial multi-omics and perturbation experiments will therefore be required. Within these boundaries, SDESE provides a robust framework for resolving complex-trait associations into spatial, cellular and gene-level hypotheses.

Methods

Non-parametric weighted rank-sum test

To accommodate sparse, dropout-prone and non-normal spatial expression profiles, SDESE evaluates each spot using a non-parametric weighted rank-sum test. At each iteration, genes passing the unconditional association screen are assigned continuous weights derived from their conditional aECS P values. The weights are transformed on the $-\log_{10}(P)$ scale, with baseline truncation to suppress weak signals and an upper cap to prevent a small number of genes from dominating the statistic. Within each spot, the global expression ranks of candidate genes are combined using these weights. The resulting statistic is standardized using its analytical null mean and variance and evaluated with a one-sided normal approximation. Complete definitions, null derivations and computational details are provided in Supplementary Note 1.

Gene association score and prioritization

At each iteration, spot-level enrichment P values are converted into spatial association weights. The within-spot expression ranks of candidate genes are inverse-normal transformed and aggregated across spots using these weights to obtain gene association scores. Candidate genes are then ranked by their scores to determine the order in which they enter conditional aECS testing in the next iteration, allowing spatial evidence to guide gene prioritization. Full definitions are provided in Supplementary Note 2.

Conditional tests by an absolute correlation recalibrated Effective Chi-square Statistics (aECS)

To reduce sensitivity to reference LD noise, SDESE performs conditional association testing in squared Z -score space. For a conditioning set A and target set B , structural weights are estimated by non-negative least squares from the absolute reference LD matrices:

$$W_{full} = NNLS(|R_{A \cup B}|, \mathbf{1}_{|A \cup B|}), \quad W_A = NNLS(|R_A|, \mathbf{1}_{|A|})$$

Here, $\mathbf{1}_{|A \cup B|}$ and $\mathbf{1}_{|A|}$ denote all-ones vectors of lengths equal to the numbers of variants in $A \cup B$ and A , respectively. The $|R_{A \cup B}|$ and $|R_A|$ are the absolute value of their reference LD. The conditional difference weights and residual association statistic are

$$W_{diff} = W_{full} - [W_A^T, 0_B^T]^T, \quad S_{B|A} = W_{diff}^T Z^2$$

where 0_B is a zero vector with length equal to the number of variants in B , and Z^2 denotes the vector of element-wise squared Z -scores. Because W_{diff} can contain

both positive and negative entries, $S_{B|A}$ is an indefinite quadratic form. SDESE therefore approximates its null distribution using a three-moment shifted-Gamma distribution⁴⁸. The kernel matrix and its first three cumulant-generating components are

$$\Omega_{diff} = \text{diag}(W_{diff}), \quad M = \Omega_{diff}|R|, \quad c_r = \text{tr}(M^r), \quad r = 1, 2, 3$$

The corresponding shape, scale and location-shift parameters are

$$\alpha = \frac{c_2^3}{2c_3^2}, \quad \beta = \frac{2|c_3|}{c_2}, \quad \delta = c_1 - \text{sgn}(c_3)\alpha$$

The conditional P value is evaluated from the upper tail when $c_3 > 0$, from the lower tail after reflection when $c_3 < 0$, and using the Gaussian limit when c_3 approaches zero. Structural weight estimation and moment calculation both use the absolute reference LD matrix and require neither matrix inversion nor positive semidefinite projection. Full derivations and sign-specific P -value expressions are provided in Supplementary Note 3, and null-distribution calibration is shown in Supplementary Fig. 1.

Monte Carlo simulations of conditional gene-association tests

Monte Carlo simulations were used to compare the null calibration, statistical power and robustness of conditional aECS and the conditional Z-score test. True LD followed a first-order autoregressive structure with $\rho = 0.40, 0.80, 0.90, 0.95$. The conditioning set contained 50 or 200 SNPs, and the target set contained 30 SNPs. Correlated Z-scores were generated with or without an independent target-set effect under the alternative and null hypotheses, respectively, using 100,000 replicates per parameter setting. Type I error and power were evaluated at significance thresholds of 5×10^{-8} , 5×10^{-5} and 0.01. Reference-LD mismatch was introduced by reversing the signs of 5% of the off-diagonal elements or adding Gaussian noise with a standard deviation of 0.05. The conditional Z-score test used a positive semidefinite projection of the perturbed matrix, whereas conditional aECS used the perturbed matrix directly. Full simulation and implementation details are provided in Supplementary Note 4.

Global min-P permutation and multiple-testing calibration

To account for iterative selection and multiple testing across spatial spots, SDESE uses a global min-P permutation procedure³⁸. In each permutation, gene labels are randomly shuffled while the spatial coordinates and expression matrix remain fixed, after which the complete iterative pipeline is rerun and the minimum null P value

across all spots is recorded. For an observed spot j , the permutation-adjusted empirical P value is calculated as³⁹

$$P_{\text{empirical},j} = \frac{1 + \sum_{b=1}^{N_{\text{perm}}} I(P_{\text{null},\min}^{(b)} \leq P_{\text{observed},j})}{N_{\text{perm}} + 1}$$

where N_{perm} is the number of permutations and $I(\cdot)$ is the indicator function. This procedure preserves the spatial dependence structure while accounting for iterative selection and multiple testing. Spots with permutation-adjusted $P < 0.05$ are considered significant, corresponding to family-wise error rate control at 0.05.

Genotype-aware spatial simulation framework

SMECT was used to generate paired GWAS summary statistics and synthetic spatial transcriptomic data under controlled spatial ground truth. Realistic linkage disequilibrium and polygenic backgrounds were retained using 4,206,964 whole-genome common variants with minor allele frequency greater than 0.05 from 490,541 UK Biobank participants²⁰. GWAS phenotypes were generated using a hierarchical eQTL-regulatory model, whereas spatial expression was simulated on 100×100 grids containing 20,000 genes with a dropout rate of 0.4. Null and alternative settings were generated by excluding or introducing enrichment of susceptibility genes within predefined focal or regional spatial domains, respectively. For each parameter setting, 100 independent spatial sections were simulated. The complete generative model, genetic and spatial parameters, and GWAS sampling procedure are provided in Supplementary Note 5.

SMECT performance metrics and comparator method

SDESE was compared with SLDSC using identical simulated inputs. Significant spots were defined using global min-P permutation-adjusted $P < 0.05$ for SDESE and BH-adjusted $P < 0.05$ for SLDSC. Let R denote the number of simulation replicates and S_r the set of significant spots in replicate r :

$$S_r = \{i: P_{r,i}^{\text{adj}} < 0.05\}$$

For focal architectures, sensitivity was defined as the proportion of replicates containing at least one significant spot within the true signal-support domain T . For regional architectures, sensitivity was defined as the mean proportion of the true region D identified as significant:

$$Sensitivity_{focal} = \frac{1}{R} \sum_{r=1}^R I(S_r \cap T \neq \emptyset), \quad Sensitivity_{region} = \frac{1}{R} \sum_{r=1}^R \frac{|S_r \cap D|}{|D|}$$

Spatial specificity was evaluated using the non-specific rate (NSR). For each significant spot i , spatial membership m_i decreased with its distance δ_i from the true signal-support domain:

$$\delta_i = dist(x_i, T), \quad m_i = \exp\left(-\frac{\delta_i^2}{2\sigma^2}\right), \quad NSR_r = \frac{1}{|S_r|} \sum_{i \in S_r} (1 - m_i)^2$$

Lower NSR values indicate that significant spots are more concentrated within or near the true spatial signal. Gene-prioritization precision was calculated as the proportion of simulated true associated genes among all significant genes. Complete metric definitions, empty-detection handling and SLDSC implementation details are provided in Supplementary Note 6.

E16.5 mouse embryo spatial transcriptomic data and regional enrichment

High-resolution Stereo-seq data from an embryonic day 16.5 mouse embryo (CNP0001543²¹) were used to compare the anatomical distributions identified by SDESE and SLDSC. The expression matrix, spatial coordinates and original annotations for 25 anatomical regions were retained, and gsMap¹⁰ was used to calculate spot-level gene-specificity scores. Identical spatial inputs were analysed using GWAS summary statistics for ten human complex phenotypes. Significant spots were defined using global min-P permutation-adjusted $P < 0.05$ for SDESE (FWER = 0.05) and BH-FDR < 0.05 for SLDSC. Regional enrichment was quantified using a 2×2 contingency-table odds ratio:

$$OR = \frac{(n_{11} + 0.5)(n_{00} + 0.5)}{(n_{10} + 0.5)(n_{01} + 0.5)}$$

where n_{11} and n_{10} are the numbers of significant and non-significant spots within the target region, respectively, and n_{01} and n_{00} are the corresponding counts outside that region. $OR > 1$ indicates enrichment of phenotype-associated spots in the target region.

Construction of the PSC spatial resource and analysis platform

PSC (estimating Phenotype-associated Spatially specific Cell types) was developed as a companion spatial resource and web platform for SDESE. Curated human and

mouse 10x Genomics Visium datasets from STOmicsDB⁴⁹ were integrated with tissue-matched scRNA-seq references. After quality control, the resource comprised 279,974 spatial spots from 114 tissue sections and 641,097 annotated single cells across 16 major organs. Spot-level gene-specificity scores were generated using gsMap¹⁰, spatial domains were identified using BASS⁵⁰, and reference cells were projected onto spatial coordinates using CellTrek⁵¹. The PSC web server (<https://pmglab.top/psc/>) enables users to upload GWAS summary statistics, select curated spatial references, run SDESE, and interactively explore and download phenotype-associated spatial regions, cell types and associated genes. Detailed data curation, preprocessing, spatial mapping and server implementation are provided in Supplementary Note 7.

Human DLPFC data and SDESE initialization

Human dorsolateral prefrontal cortex (DLPFC) spatial transcriptomic data were obtained from the 10x Genomics Visium study by Maynard et al³⁴. The dataset comprised 12 sections from three neurologically healthy adult donors and covered cortical layers L1-L6 and the underlying white matter. Processed h5ad files provided expression matrices, spatial coordinates, PSC spatial-region annotations and PSC cell-type annotations. Gene-specificity scores were calculated separately for each section using gsMap¹⁰ and were used as input to SDESE; detailed gsMap parameters are provided in Supplementary Note 8.

GWAS datasets for attention-deficit/hyperactivity disorder (ADHD^{22,23}), anxiety disorder (ANX^{24,25}), bipolar disorder (BD^{26,27}), major depressive disorder (MDD^{28,29}) and schizophrenia (SCZ^{30–33}) were analysed independently in each section. The predefined primary GWAS datasets were used for the main analyses, whereas the remaining datasets were used for cross-GWAS validation. Association analyses used the European reference panel from the 1000 Genomes Project Phase 3⁵², and the major histocompatibility complex region was excluded.

DLPFC spatial-region and cell-type enrichment

For each disorder, GWAS dataset and DLPFC section, SDESE generated spot-level enrichment scores and global min-P permutation-adjusted *P* values. When multiple records corresponded to the same spot barcode, the record with the smallest adjusted *P* value was retained. Significant spots were defined by global min-P permutation-adjusted $P < 0.05$.

Enrichment was evaluated for all seven PSC spatial regions and all PSC cell types. The 12 sections were organized into six adjacent-section pairs, which were used as strata when calculating the OR for each disorder-region or disorder-cell-type

combination. All spatial regions and cell types were retained without additional selection.

To compare enrichment profiles among disorders, the mean SDESE enrichment score was calculated for each spatial region and cell type. The spatial-region and cell-type scores were concatenated, and pairwise similarity between disorders was quantified using Spearman correlation. Cross-GWAS consistency was evaluated separately for spatial-region and cell-type profiles by calculating Spearman correlations between each alternative GWAS dataset and the primary GWAS dataset for the same disorder.

Cortical-layer annotation of DLPFC spatial regions

PSC spatial regions were interpreted using the layer-enriched marker genes reported in Supplementary Table S4B of the Maynard DLPFC study³⁴. For each of L1-L6 and white matter, the 100 genes with the strongest evidence of layer enrichment were selected. Expression counts were normalized to a library size of 10,000 and log-transformed. Marker expression was averaged within each spatial region, standardized across regions within each section and then averaged across the 12 sections. The resulting assignments were interpreted as layer-related transcriptional programmes rather than discrete histological boundaries.

Associated-gene identification and cross-GWAS validation

Conditional aECS significance was determined separately for each DLPFC section using section-specific Benjamini-Hochberg thresholds at $FDR < 0.05$. Associated genes were defined as all genes passing the corresponding threshold in all 12 sections. Gene-set similarity across disorders and GWAS datasets was quantified using the Jaccard index; pre-filtering sets comprised candidate genes present in all sections, whereas post-filtering sets comprised associated genes meeting the conditional significance criterion in all sections. For same-disorder comparisons across GWAS datasets, enrichment of overlapping associated genes was evaluated using a one-sided hypergeometric test, with genes having finite conditional aECS P values in every section of both datasets used as the background. Fold enrichment was calculated as the observed overlap divided by the expected overlap, and P values across the 12 GWAS-pair comparisons were adjusted using the Benjamini-Hochberg procedure.

Functional enrichment of associated genes

Gene Ontology Biological Process enrichment was performed using g:Profiler⁵³ for genes passing the conditional aECS significance criterion in all 12 sections. Genes

associated with at least two disorders constituted the cross-disorder shared set. All genes tested in the corresponding analysis were used as the background.

Significant terms were defined by $FDR < 0.05$. Terms displayed in Fig. 6d were additionally required to contain at least five overlapping genes and have fold enrichment greater than 1. Semantically redundant terms were grouped using rrvgo⁵⁴ at a similarity threshold of 0.70, and one representative term was selected from each group. ADHD had no terms satisfying the display criteria and was therefore omitted from Fig. 6d.

Data availability

The GWAS data were obtained in part from the Psychiatric Genomics Consortium (PGC; <https://pgc.unc.edu/for-researchers/download-results/>). Additional details are provided in the Supplementary *gwas_meta.xlsx* file. The mouse embryonic brain spatial transcriptomics (ST) data generated using Stereo-seq are available at <https://db.cngb.org/search/project/CNP0001543>. The human dorsolateral prefrontal cortex (DLPFC) ST data are available at <https://research.libd.org/globus/>. The simulated datasets used in this study were generated using KGGSNV (<https://pmglab.top/kggsnv/>).

Code availability

SDESE has been integrated into the PSC platform (<https://pmglab.top/psc/>). It is also available through KGGSUM (V2.0.0, <https://pmglab.top/kggsum/>) for SDESE analysis and KGGSNV (<https://pmglab.top/kggsnv/>) for simulated data generation. The relevant analysis code and scripts are available at <https://github.com/pmglab/SDESE>.

References

1. Visscher, P. M. *et al.* 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am. J. Hum. Genet.* **101**, 5–22 (2017).
2. The GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, 1318–1330 (2020).
3. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
4. Slowikowski, K., Hu, X. & Raychaudhuri, S. SNPsea: an algorithm to identify cell types, tissues and pathways affected by risk loci. *Bioinformatics* **30**, 2496–2497 (2014).
5. Finucane, H. K. *et al.* Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).
6. Jiang, L. *et al.* DESE: estimating driver tissues by selective expression of genes associated with complex diseases or traits. *Genome Biol.* **20**, 233 (2019).
7. Ståhl, P. L. *et al.* Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. *Science* **353**, 78–82 (2016).
8. Longo, S. K., Guo, M. G., Ji, A. L. & Khavari, P. A. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. *Nat. Rev. Genet.* **22**, 627–644 (2021).
9. Zhang, M. J. *et al.* Polygenic enrichment distinguishes disease associations of individual cells in single-cell RNA-seq data. *Nat. Genet.* **54**, 1572–1580 (2022).
10. Song, L., Chen, W., Hou, J., Guo, M. & Yang, J. Spatially resolved mapping of cells associated with human complex traits. *Nature* **641**, 932–941 (2025).
11. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
12. Svensson, V., Teichmann, S. A. & Stegle, O. SpatialDE: identification of spatially variable genes. *Nat. Methods* **15**, 343–346 (2018).
13. Schaid, D. J., Chen, W. & Larson, N. B. From genome-wide associations to candidate causal variants by statistical fine-mapping. *Nat. Rev. Genet.* **19**, 491–504 (2018).
14. Li, X., Jiang, L., Xue, C., Li, M. J. & Li, M. A conditional gene-based association framework integrating isoform-level eQTL data reveals new susceptibility genes for schizophrenia. *eLife* **11**, e70779 (2022).
15. Li, M. *et al.* A powerful conditional gene-based association approach implicated functionally important genes for schizophrenia. *Bioinformatics* **35**, 628–635 (2019).
16. Li, M.-X., Gui, H.-S., Kwan, J. S. H. & Sham, P. C. GATES: A Rapid and Powerful Gene-Based Association Test Using Extended Simes Procedure. *Am. J. Hum. Genet.* **88**, 283–293 (2011).

17. Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369–375 (2012).
18. Deng, Y. & Pan, W. Improved Use of Small Reference Panels for Conditional and Joint Analysis with GWAS Summary Statistics. *Genetics* **209**, 401–408 (2018).
19. Chen, W. *et al.* Improved analyses of GWAS summary statistics by reducing data heterogeneity and errors. *Nat. Commun.* **12**, 7117 (2021).
20. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
21. Chen, A. *et al.* Spatiotemporal transcriptomic atlas of mouse organogenesis using DNA nanoball-patterned arrays. *Cell* **185**, 1777–1792.e21 (2022).
22. Demontis, D. *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat. Genet.* **55**, 198–208 (2023).
23. van der Laan, C. M. *et al.* Genome-wide association meta-analysis of childhood ADHD symptoms and diagnosis identifies new loci and potential effector genes. *Nat. Genet.* **57**, 2427–2435 (2025).
24. Strom, N. I. *et al.* Genome-wide association study of major anxiety disorders in 122,341 European-ancestry cases identifies 58 loci and highlights GABAergic signaling. *Nat. Genet.* **58**, 275–288 (2026).
25. Skelton, M. *et al.* Genome-wide meta-analysis of quantitatively measured generalized anxiety symptoms in individuals of European ancestry. *Nat. Hum. Behav.* **10**, 1594–1608 (2026).
26. O’Connell, K. S. *et al.* Genomics yields biological and phenotypic insights into bipolar disorder. *Nature* **639**, 968–975 (2025).
27. Mullins, N. *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat. Genet.* **53**, 817–829 (2021).
28. Adams, M. J. *et al.* Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. *Cell* **188**, 640–652.e9 (2025).
29. Howard, D. M. *et al.* Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* **22**, 343–352 (2019).
30. Trubetskoy, V. *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502–508 (2022).
31. Lam, M. *et al.* Comparative genetic architectures of schizophrenia in East Asian and European populations. *Nat. Genet.* **51**, 1670–1678 (2019).
32. Pardiñas, A. F. *et al.* Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* **50**, 381–389 (2018).

33. Ripke, S. *et al.* Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
34. Maynard, K. R. *et al.* Transcriptome-scale spatial gene expression in the human dorsolateral prefrontal cortex. *Nat. Neurosci.* **24**, 425–436 (2021).
35. Pei, L. *et al.* Dependence of Hippocampal Function on ERR γ -Regulated Mitochondrial Metabolism. *Cell Metab.* **21**, 628–636 (2015).
36. Shin, H. R. *et al.* Lysosomal GPCR-like protein LYCHOS signals cholesterol sufficiency to mTORC1. *Science* **377**, 1290–1298 (2022).
37. Xiong, C. *et al.* UBN1/2 of HIRA complex is responsible for recognition and deposition of H3.3 at cis-regulatory elements of genes in mouse ES cells. *BMC Biol.* **16**, 110 (2018).
38. Ge, Y., Dudoit, S. & Speed, T. P. Resampling-based multiple testing for microarray data analysis. *Test* **12**, 1–77 (2003).
39. Phipson, B. & Smyth, G. K. Permutation P-values Should Never Be Zero: Calculating Exact P-values When Permutations Are Randomly Drawn. *Stat. Appl. Genet. Mol. Biol.* **9**, (2010).
40. Hodge, R. D. *et al.* Conserved cell types with divergent features in human versus mouse cortex. *Nature* **573**, 61–68 (2019).
41. Lee, P. H. *et al.* Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* **179**, 1469–1482.e11 (2019).
42. The Brainstorm Consortium *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360**, eaap8757 (2018).
43. Grotzinger, A. D. *et al.* Mapping the genetic landscape across 14 psychiatric disorders. *Nature* **649**, 406–415 (2026).
44. Gandal, M. J. *et al.* Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science* **359**, 693–697 (2018).
45. Skene, N. G. *et al.* Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50**, 825–833 (2018).
46. de Klein, N. *et al.* Brain expression quantitative trait locus and network analyses reveal downstream effects and putative drivers for brain-related diseases. *Nat. Genet.* **55**, 377–388 (2023).
47. Wingo, T. S. *et al.* Brain proteome-wide association study implicates novel proteins in depression pathogenesis. *Nat. Neurosci.* **24**, 810–817 (2021).
48. Liu, H., Tang, Y. & Zhang, H. H. A new chi-square approximation to the distribution of non-negative definite quadratic forms in non-central normal variables. *Comput. Stat. Data Anal.* **53**, 853–856 (2009).
49. Xu, Z. *et al.* STOmicsDB: a comprehensive database for spatial transcriptomics data sharing, analysis and visualization. *Nucleic Acids Res.* **52**, D1053–D1061 (2024).

50. Li, Z. & Zhou, X. BASS: multi-scale and multi-sample analysis enables accurate cell type clustering and spatial domain detection in spatial transcriptomic studies. *Genome Biol.* **23**, 168 (2022).
51. Wei, R. *et al.* Spatial charting of single-cell transcriptomes in tissues. *Nat. Biotechnol.* **40**, 1190–1199 (2022).
52. Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
53. Kolberg, L. *et al.* g:Profiler—interoperable web service for functional enrichment analysis and gene identifier mapping (2023 update). *Nucleic Acids Res.* **51**, W207–W212 (2023).
54. Sayols, S. rrvgo: a Bioconductor package for interpreting lists of Gene Ontology terms. *MicroPublication Biol.*
<https://doi.org/10.17912/micropub.biology.000811> (2023).

Figures and tables

Fig. 1 | SDESE enables joint spatial and gene fine-mapping through bidirectional iterative refinement. **a**, Gene-level association P values are calculated from GWAS summary statistics and transformed into initial gene weights through soft thresholding. **b**, Gene specificity scores (GSS) are calculated from spatial transcriptomic data using gsMap, and all genes are subsequently ranked across spatial regions. **c**, Gene weights update spatial association scores through a weighted rank-sum test. The updated spatial association scores are then used to calculate gene association scores and update the priorities of genes to be tested, after which conditional aECS updates gene-level association evidence while accounting for LD. This loop is repeated until convergence. **d**, SDESE outputs significant spots calibrated by global min- P permutations and associated genes whose conditional aECS P values remain significant after multiple-testing correction. **e**, The overall study framework comprises the SMECT simulation benchmark, the SDESE iterative refinement algorithm and the PSC organ-level spatial resource and analysis platform.

Fig. 2 | Statistical calibration, power and robustness of the conditional aECS and conditional Z-score tests across matched and perturbed reference LD. **a**, Q-Q plots of conditional P values under the null hypothesis when the true and reference LD matrices are matched. **b**, Q-Q plots under the alternative hypothesis when the true and reference LD matrices are matched. **c**, Null-hypothesis Q-Q plots after the signs of 5% of the off-diagonal elements in the reference LD matrix were reversed to simulate allele-orientation mismatches. **d**, Null-hypothesis Q-Q plots after Gaussian noise with a standard deviation of 0.05 was added to the reference LD matrix. In all panels, the four columns correspond to LD strengths of $\rho = 0.40, 0.80, 0.90, 0.95$. Circles denote the conditional aECS test and triangles denote the conditional Z-score test. Red and blue indicate conditioning SNP-set sizes of $n_{\text{SnP}} = 50$ and 200, respectively, and dashed lines indicate the theoretical null distribution. Each parameter setting was evaluated using 100,000 Monte Carlo replicates. Observed $-\log_{10}(P)$ values were capped at 30 for visualization.

Fig. 3 | Statistical performance of SDESE in resolving focal and regional genetic signals. **a**, Genotype-aware SMECT workflow using real genotype data to generate matched GWAS summary statistics and synthetic spatial transcriptomic data under four architectures: one hotspot, two hotspots, one region and three regions. **b**, Proportion of simulated sections containing at least one significant spot at driver ratios of 25%, 50% and 75%. **c**, Sensitivity of SDESE and SLDSC. For focal architectures, sensitivity denotes the proportion of replicates with at least one significant spot within the true signal-support domain; for regional architectures, it denotes the proportion of spots within the true region that were significant, averaged across replicates. **d**, NSR for each simulated section, ranging from 0 (blue; significant spots concentrated within or near the true signal-support domain) to 1 (red; greater non-specific spatial spread); grey indicates sections without significant spots. **e**, Precision for prioritizing simulated true associated genes under the P -value condition (conditional testing based only on association P values) and the Spatial condition (SDESE bidirectional spatial-gene refinement). Precision was defined as the proportion of true associated genes among all significant genes. Lighter points represent individual simulations, large points indicate medians and vertical bars denote the interquartile range. In b-d, significant

spots were defined using global min-P permutation-adjusted $P < 0.05$ for SDESE and Benjamini-Hochberg false discovery rate < 0.05 for SLDSC.

Fig. 4 | SDESE produces more anatomically concentrated tissue-enrichment profiles in analyses of real phenotypes. **a**, Spatial annotation of 25 anatomical regions in an E16.5 mouse embryo. **b**, Significant spots identified by SDESE and SLDSC for BD, MDD and IQ. Colours indicate $-\log_{10}$ -transformed adjusted P values; separate colour scales are shown for the two methods, and the total number of significant spots is indicated in each panel. Significant spots were defined using global min-P permutation-adjusted $P < 0.05$ for SDESE and Benjamini-Hochberg FDR < 0.05 for SLDSC. **c**, Enrichment ORs for ten human phenotypes across 25 embryonic anatomical regions. An OR greater than 1 indicates enrichment; values above 10 were truncated for visualization. ADHD, attention-deficit/hyperactivity disorder; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ANX, anxiety disorder; IQ, intelligence quotient; LC, leukocyte count; TP, total protein; DBP, diastolic blood pressure; CAD, coronary artery disease.

Fig. 5 | Psychiatric disorders share middle-to-deep cortical and neuronal enrichment in the human DLPFC. **a**, Twelve DLPFC Visium sections from three adult donors, showing cortical layers, white matter and PSC spatial regions. **b**, Mean expression Z-scores of cortical-layer and white-matter marker genes across the seven PSC spatial regions; outlined cells indicate the predominant layer programmes. **c,d**, Enrichment of significant SDESE spots across spatial regions (c) and cell-type annotations (d). Colours indicate $\log_2$ -transformed Mantel-Haenszel ORs stratified by six pairs of adjacent sections. Significant spots were defined using global min-P permutation-adjusted $P < 0.05$, controlling the FWER at 0.05. The $\log_2(\text{OR})$ scale was capped at -3 to 3 for visualization. **e**, Pairwise Spearman correlations among the five disorders after combining their spatial-region and cell-type enrichment profiles. **f**, Spearman correlations between spatial-region and cell-type enrichment profiles generated using primary and alternative GWAS datasets. Diamonds indicate the primary GWAS datasets and circles indicate alternative GWAS datasets.

Fig. 6 | Conditional aECS analysis reveals limited associated-gene overlap and functional convergence in the DLPFC. Associated genes passed BH correction for multiple testing at FDR < 0.05 in all 12 DLPFC sections. **a**, For each disorder, 20 associated genes with the lowest mean within-section ranks of conditional aECS P values are shown. Associated genes were required to pass the section-specific BH threshold at FDR < 0.05 in all 12 DLPFC sections; provisional LOC genes were excluded from display. The x axis represents $-\log_{10}$ of the median conditional aECS P values across sections. Circles denote disease-specific genes, diamonds denote genes shared by at least two disorders, and point size represents the median gene association score. **b**, Pairwise Jaccard indices among the five primary GWAS datasets before (blue) and after (red) conditional filtering. **c**, Fold enrichment of associated-gene overlap between GWAS datasets for the same disorder; values on the right are BH-adjusted one-sided hypergeometric-test P values. **d**, Gene Ontology Biological Process enrichment for individual disorders and genes shared by at least two disorders. Point size indicates the gene ratio and colour indicates $-\log_{10}(\text{FDR})$.

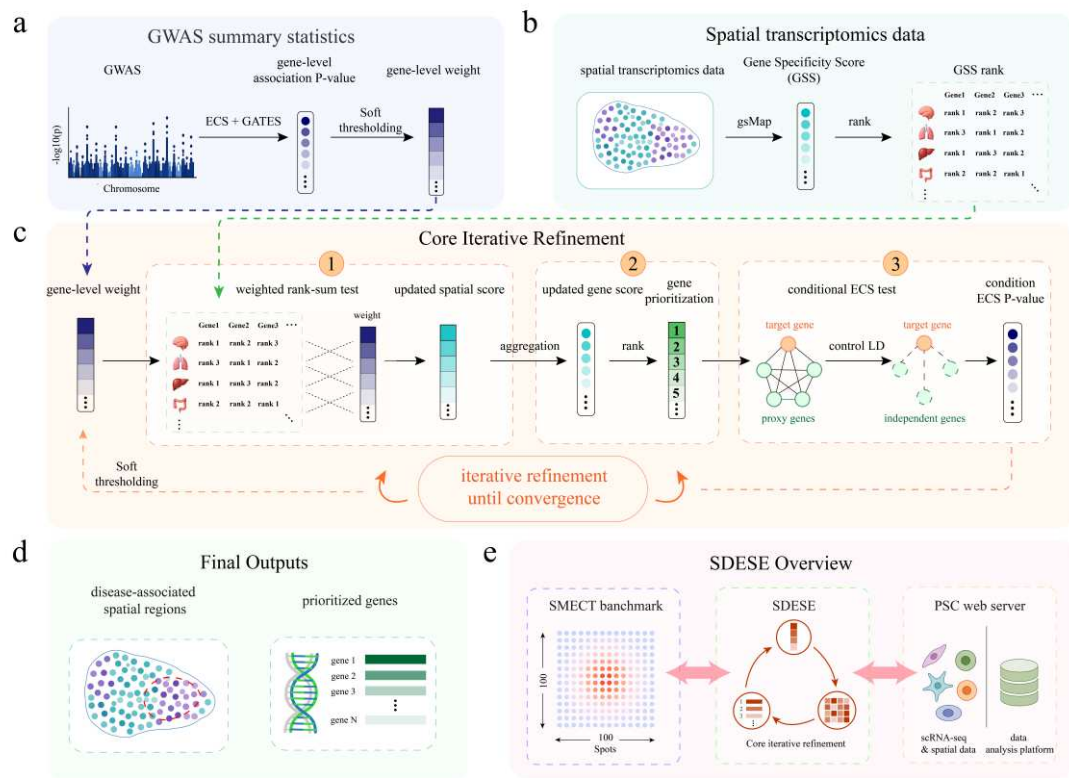


Fig. 1 | SDESE enables joint spatial and gene fine-mapping through bidirectional iterative refinement

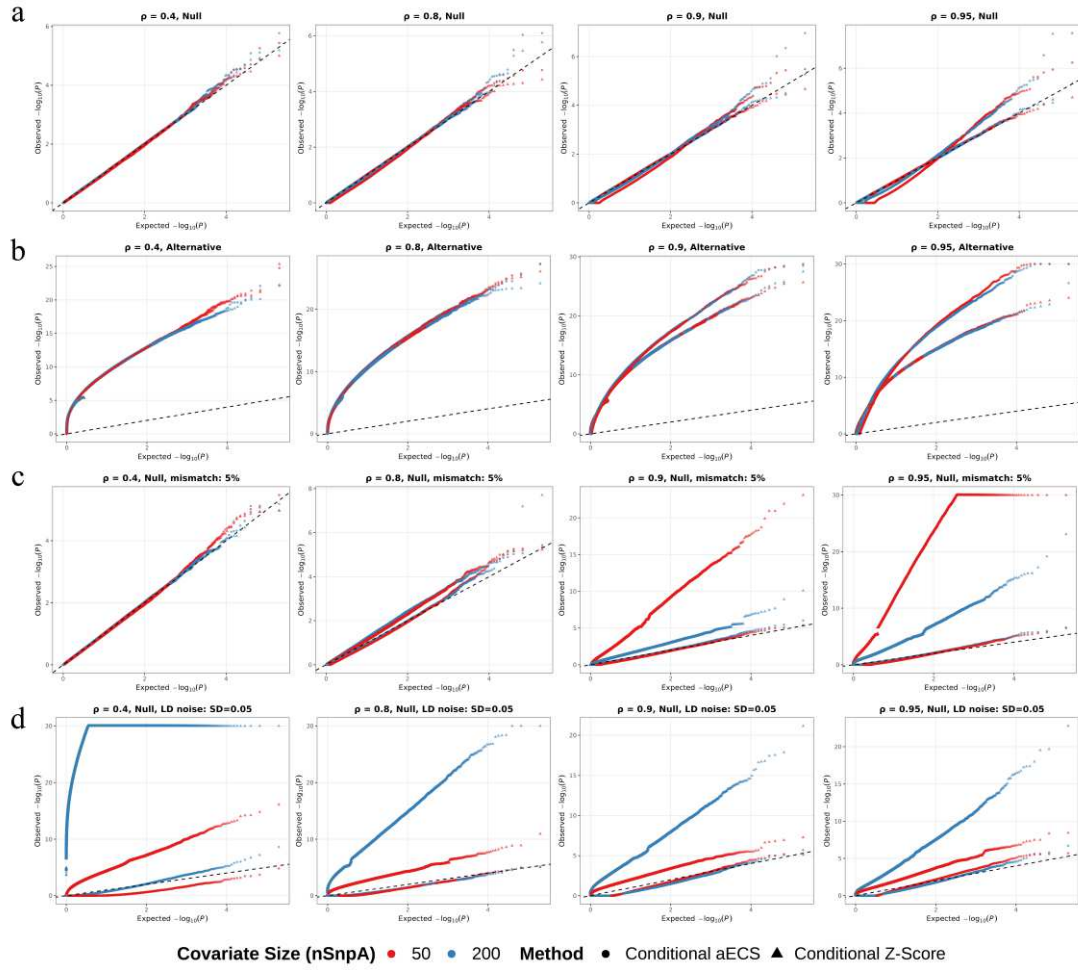


Fig. 2 | Statistical calibration, power and robustness of the conditional aECS and conditional Z-score tests across matched and perturbed reference LD

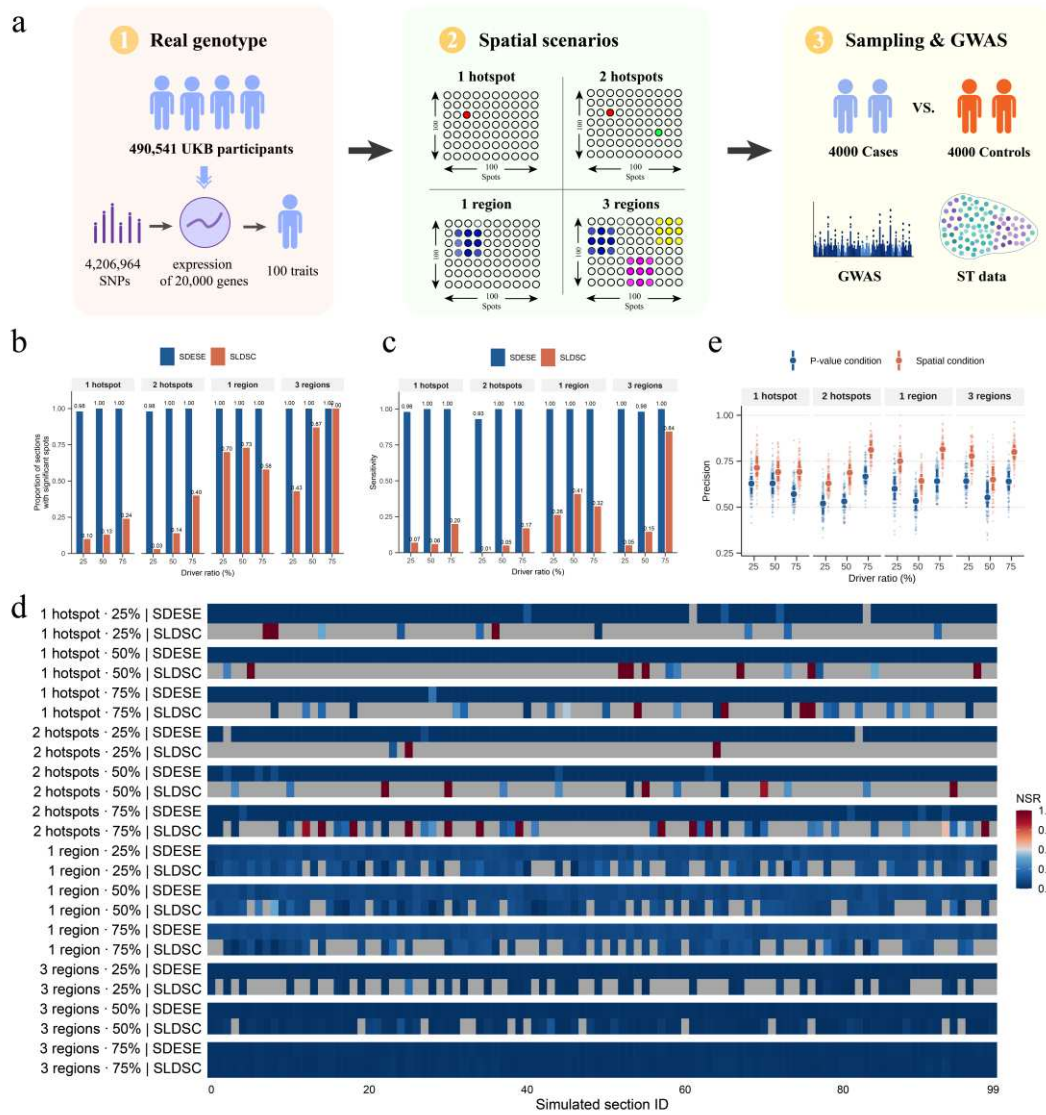


Fig. 3 | Statistical performance of SDESE in resolving focal and regional genetic signals

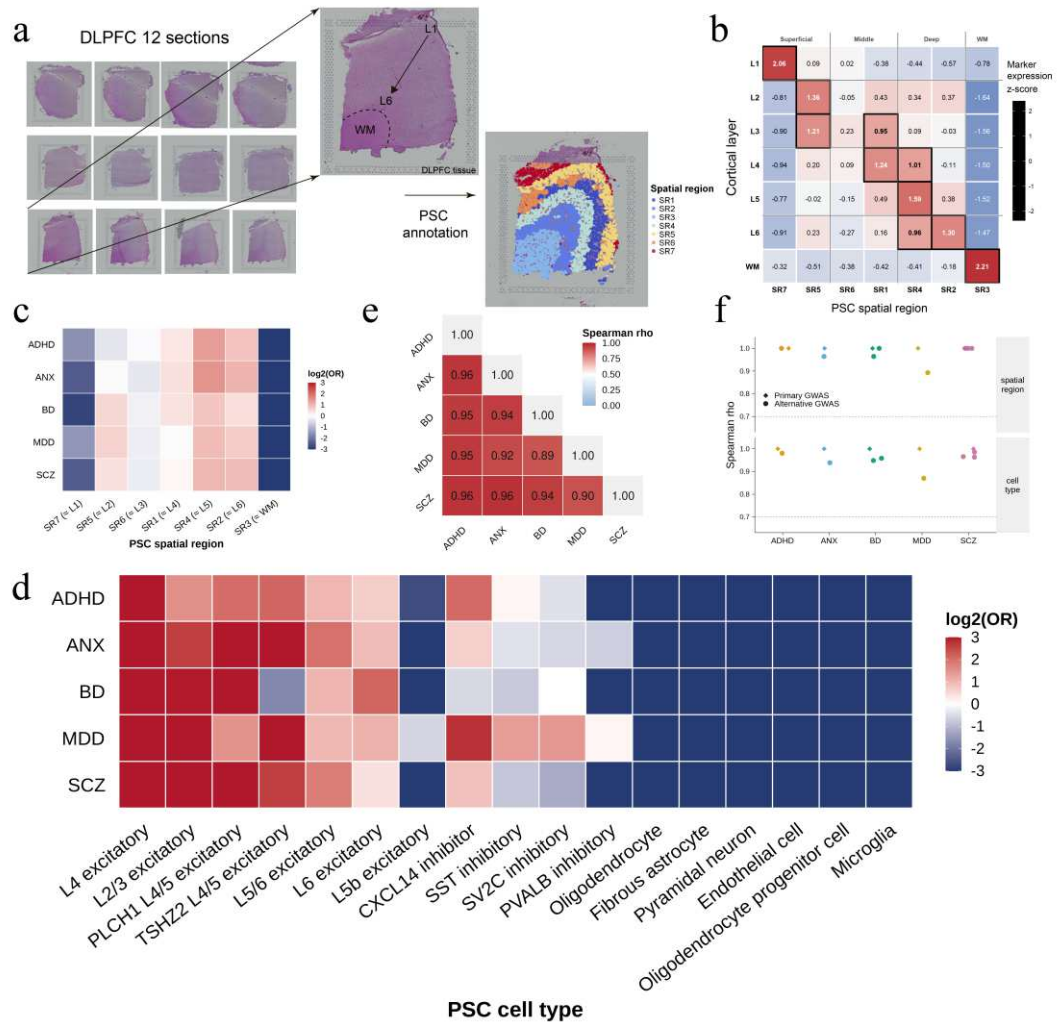


Fig. 4 | SDESE produces more anatomically concentrated tissue-enrichment profiles in analyses of real phenotypes.

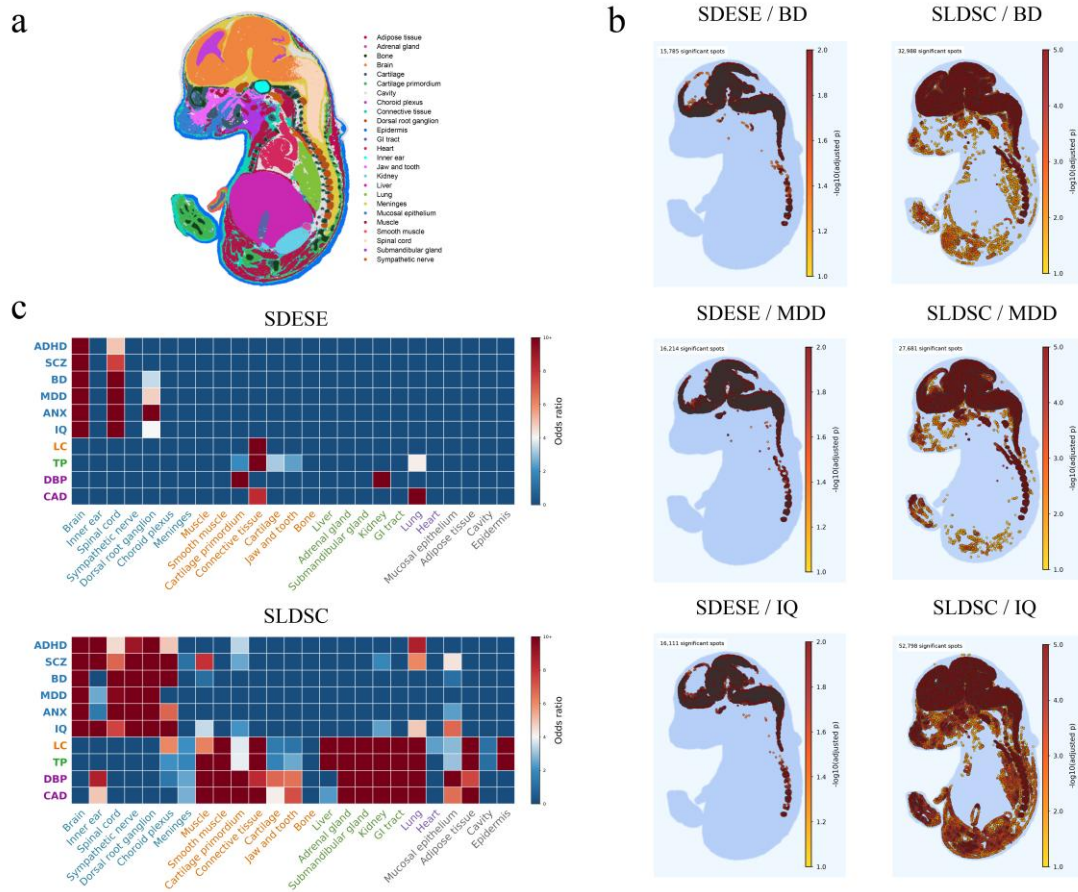


Fig. 5 | Psychiatric disorders share middle-to-deep cortical and neuronal enrichment in the human DLPFC

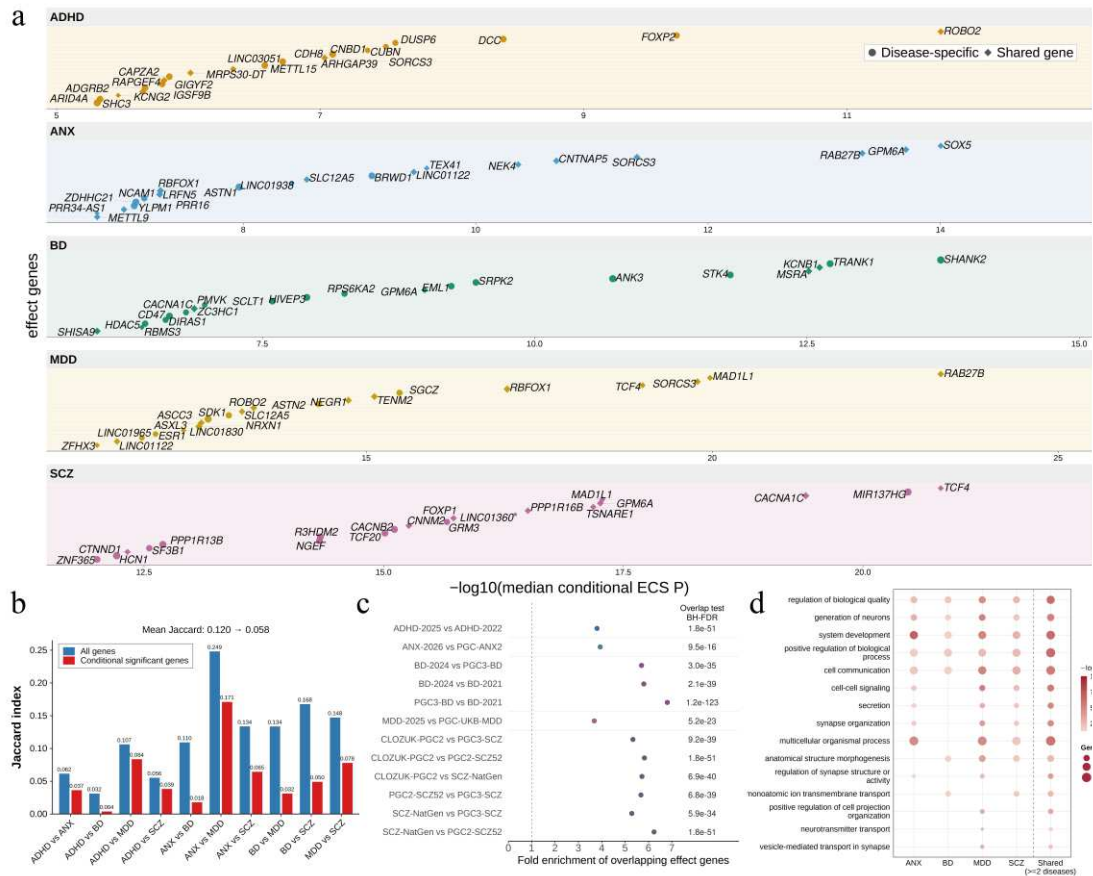


Fig. 6 | Conditional aECS analysis reveals limited associated-gene overlap and functional convergence in the DLPFC

Table 1 | Type I error and statistical power of the conditional aECS and conditional Z-score tests under matched LD. Results are based on 100,000 Monte Carlo replicates for each combination of significance threshold, LD strength and conditioning SNP-set size. Type I error was evaluated under the null hypothesis, and power was evaluated under the alternative hypothesis. The conditioning set contained 50 or 200 SNPs, and the target set contained 30 SNPs.

Threshold	ρ	nSnpA	Type I Error (Z-score)	Type I Error (aECS)	Power (Z-score)	Power (aECS)
5.00E-08	0.4	50	0	0	0.2581	0.2488
5.00E-08	0.4	200	0	0	0.2541	0.2534
5.00E-08	0.8	50	0	0	0.3276	0.3249
5.00E-08	0.8	200	0	0	0.3262	0.346
5.00E-08	0.9	50	0	0	0.3194	0.3054
5.00E-08	0.9	200	0	0	0.3218	0.3427
5.00E-08	0.95	50	0	0	0.2965	0.277
5.00E-08	0.95	200	0	0	0.2994	0.3322
5.00E-05	0.4	50	0.0001	0.0001	0.6878	0.6994
5.00E-05	0.4	200	0.0001	0.0001	0.6856	0.7097
5.00E-05	0.8	50	0	0.0001	0.6667	0.6675
5.00E-05	0.8	200	0.0001	0.0001	0.6624	0.7013
5.00E-05	0.9	50	0	0.0001	0.6076	0.568
5.00E-05	0.9	200	0	0.0002	0.6063	0.6235
5.00E-05	0.95	50	0	0.0003	0.5661	0.4543
5.00E-05	0.95	200	0.0001	0.0003	0.5665	0.5388
0.01	0.4	50	0.0097	0.009	0.973	0.9652
0.01	0.4	200	0.0101	0.0102	0.9723	0.9709
0.01	0.8	50	0.0102	0.0087	0.9476	0.9054
0.01	0.8	200	0.0102	0.01	0.9466	0.9338
0.01	0.9	50	0.01	0.0078	0.9052	0.7982
0.01	0.9	200	0.0099	0.0101	0.9039	0.8547
0.01	0.95	50	0.0102	0.0097	0.8441	0.6312
0.01	0.95	200	0.01	0.0126	0.8438	0.7234

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