

A temporal transcriptomic framework resolves age-specific polygenic vulnerability and prioritizes therapeutic targets for brain disorders

Chao Xue

Sun Yat-sen University

Xuegao Yu

Sun Yat-sen University

Lihang Ye

Sun Yat-sen University

Ying Luo

Sun Yat-sen University

Liubin Zhang

Sun Yat-sen University

Bin Tang

Sun Yat-sen University

Hongsheng Gui

Henry Ford Health System

Lin Jiang

Guangdong Provincial People's Hospital

Miaoxin Li

`limiaoxin@mail.sysu.edu.cn`

Sun Yat-sen University

Research Article

Keywords: lifespan gene expression, genome-wide association studies, neuropsychiatric disorders, neurodegenerative disorders, spatiotemporal specificity, age of onset, complex disease genetics

Posted Date: October 9th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10676073/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

A temporal transcriptomic framework resolves age-specific polygenic vulnerability and prioritizes therapeutic targets for brain disorders

Chao Xue^{1,3,#}, Xuegao Yu^{1,4,#}, Lihang Ye¹, Ying Luo¹, Liubin Zhang¹, Bin Tang¹, Hongsheng Gui^{5,6}, Lin Jiang^{2,*}, Miaoxin Li^{1,3,7,*}

¹ Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, 510080, China

² Research Center of Medical Sciences, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China

³ Key Laboratory of Tropical Disease Control (Sun Yat-sen University), Ministry of Education, Guangzhou, 510080, China

⁴ Department of Clinical Laboratory, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, China

⁵ Psychiatry Research and Behavioral Health Services, Henry Ford Health, Detroit, MI, USA.

⁶ Department of Psychiatry, Michigan State University, East Lansing, MI, USA.

⁷ Center for Precision Medicine, Sun Yat-sen University, Guangzhou, 510080, China

The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

* To whom correspondence should be addressed. Email: jianglin@gdph.org.cn (L. J.); limiaoxin@mail.sysu.edu.cn (M. L.).

Abstract

Translating thousands of genome-wide association study (GWAS) hits into actionable clinical targets remains a major bottleneck in precision medicine. This difficulty partly stems from using static functional annotations that ignore the dynamic, age-dependent nature of human brain development. To address this, we developed a temporal-specific statistical framework (tDESE) that maps large-scale psychiatric polygenic signals onto continuous lifespan transcriptomic trajectories from the human prefrontal cortex. Applying this framework across five major brain disorders revealed a precise chronological alignment: polygenic risk loci consistently reach peak cortical expression exactly when typical clinical onset occurs. The underlying genetic architecture dictates a distinct spatial migration in synaptic vulnerability, shifting from pan-synaptic networks in childhood to strict postsynaptic dominance in adult-onset psychiatric conditions. We also identified sex-divergent molecular lags that closely mirror known epidemiological differences in onset rates. Importantly, anchoring post-GWAS functional annotation to these developmental timeframes substantially improves the predictive accuracy for recovering clinically established therapeutic targets. Expanding this approach to pharmacogenomics, we screened age-resolved gene profiles against *in vitro* drug perturbation signatures. The results isolated a concentrated 20-to-40-year therapeutic window where targets of standard psychiatric interventions are most actively expressed. This dynamic is powerfully exemplified by *PDE4D*, a schizophrenia risk gene showing adult-specific expression and profound downregulation by targeted interventions. Ultimately, this time-aware genomic framework provides

a powerful, data-driven engine for unraveling disease etiology and optimizing post-GWAS target discovery pipelines.

Keywords: lifespan gene expression; genome-wide association studies; neuropsychiatric disorders; neurodegenerative disorders; spatiotemporal specificity; age of onset; complex disease genetics.

Introduction

The phenotypic consequences of genetic variants are governed by a fundamental spatiotemporal context, manifesting only when target genes are expressed at the right time and in the right place¹⁻³. While immense progress has been made in mapping the spatial context of disease risk from bulk tissues to single cells⁴⁻⁸, the temporal dimension of genetic vulnerability remains poorly resolved. Since the human brain undergoes profound, stage-specific structural and functional reorganizations across the lifespan, understanding how the pathogenic effects of genetic risk factors unfold over time represents a critical bottleneck not only in human genetics but also in identifying optimal timing for therapeutic interventions.

The clinical relevance of this temporal dimension is particularly striking in neuropsychiatric disorders, which are clinically defined by distinct, age-specific windows of onset⁹. Currently, pharmacological interventions—such as typical antipsychotics and antidepressants—are frequently administered as static, "one-size-fits-all" therapies, largely ignoring the dynamic neurodevelopmental context of the maturing brain. Consequently, psychiatric medicine faces profound challenges, most notably high rates of treatment resistance. Clinical and epidemiological evidence consistently demonstrates that a younger age of onset in schizophrenia and severe mood disorders is one of the strongest predictors of refractoriness to standard psychotropic medications^{10,11}. This disconnect suggests that missing a critical "developmental window" for intervention may irrevocably alter a patient's clinical trajectory. Elucidating the mechanisms driving this age-dependent susceptibility is therefore crucial for understanding pathogenesis and identifying precise developmental epochs where pharmacological target engagement will yield maximum clinical efficacy^{12,13}.

Yet, systematically mapping this temporal landscape has been methodologically challenging. This endeavor has been historically hindered by the scarcity of high-resolution lifespan transcriptomic cohorts and the lack of robust analytical frameworks capable of integrating dynamic expression trajectories with summary-level genome-wide association studies (GWAS) and in vitro drug perturbation signatures. Without integrating these multilayered datasets, prioritizing actionable disease targets tailored to specific life stages remains an intractable task.

Here, we bridge this gap by developing tDESE (temporal-specific Driver-tissue Estimation by Selective Expression), an analytical framework designed to systematically resolve the temporal windows of genetic risk for complex brain disorders. By integrating lifespan gene expression dynamics from the human prefrontal cortex with large-scale GWAS for major neuropsychiatric and neurodegenerative disorders, we define critical developmental epochs of disease vulnerability.

Moreover, we extend this framework to evaluate pharmacological target engagement. Our study demonstrates that classical psychiatric medications preferentially perturb genetic networks that are active during a concentrated 20~40-year therapeutic window. Highly specific, mechanism-based interventions, such as the PDE4 inhibitor rolipram and its cognate target gene PDE4D, exhibit the same pattern. Ultimately, this lifespan-anchored approach establishes a new temporal dimension for prioritizing actionable disease targets, providing a data-driven pharmacological framework to guide age-appropriate precision psychiatry.

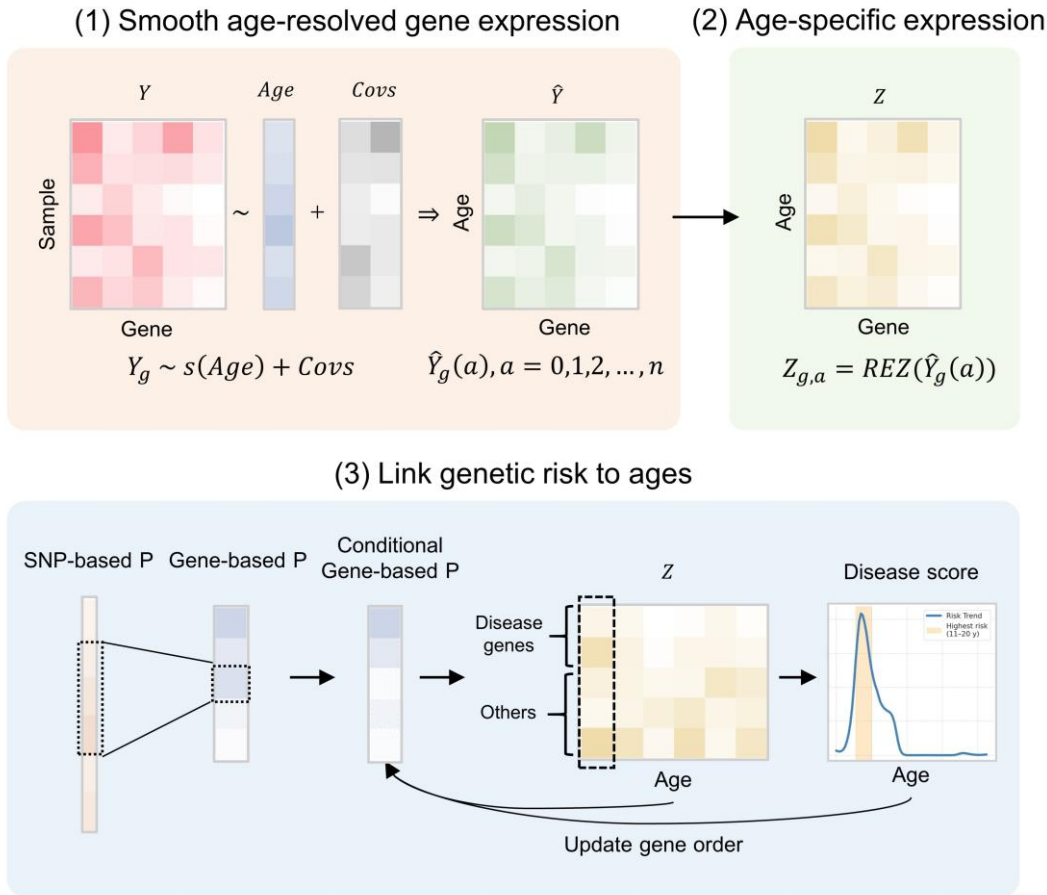
Results

A framework to resolve the temporal dynamics of disease risk

We began by investigating the hypothesis that the distinct clinical ages of onset for neuropsychiatric disorders are fundamentally driven by the temporal dynamics of genetic risk expression. To systematically test this, we developed tDESE, a statistical genetics framework that integrates lifespan transcriptomics with GWAS summary statistics to pinpoint critical developmental windows of disease vulnerability (Fig. 1). A primary methodological challenge in this endeavor is distilling authentic developmental signals from inherently noisy, post-mortem human brain expression datasets.

To overcome this, we constructed high-resolution, lifespan-wide expression trajectories for each gene using two independent prefrontal cortex developmental cohorts. We applied a generalized additive model (GAM) to capture complex, non-linear developmental trends, modeling gene expression as a continuous function of chronological age while stringently controlling for critical technical and biological confounders, including RNA integrity number (RIN) and sex. This yielded robust, smoothed expression profiles representing the continuous dynamic activity of thousands of transcripts.

To quantify temporal specificity, we computed a relative expression Z-score (REZ) at yearly intervals, thereby converting raw expression curves into standardized profiles that mark each gene's peak functional activity over time. The central innovation of tDESE consists in integrating these temporal profiles with GWAS data. Extending our previously validated DESE method⁵, the approach uses an iterative conditional procedure to refine putative disease-associated genes and markedly enhance the signal-to-noise ratio for polygenic traits. Consequently, tDESE calculates a statistical enrichment score for every developmental year, pinpointing the precise age windows of maximal polygenic risk expression and thereby revealing the temporal origins of disease pathology.



108

109 **Figure 1 | Schematic overview of the tDESE analytical framework.** tDESE integrates age-
 110 resolved developmental transcriptomic data and disease GWAS summary statistics to identify
 111 temporally specific enrichment of genetic risk. The output consists of year-by-year enrichment
 112 scores and adjusted P-values for disease association across developmental ages. The framework
 113 comprises three major steps: (1) Temporal modeling of gene expression. For each gene, tDESE fits a
 114 generalized additive model (GAM) to capture the relationship between expression and age, while
 115 adjusting for potential confounders (Covs). Partial dependence analysis is used to estimate the
 116 marginal effect of age on expression after controlling for covariates, generating smoothed, high-
 117 resolution expression trajectories across age. In the diagram, Y denotes the raw expression data, $\hat{Y}$
 118 represents the predicted smoothed expression, $s(\cdot)$ denotes the smooth function from GAM, a
 119 denotes age, and g denotes gene. (2) Quantification of temporal expression specificity. Relative
 120 expression Z-scores are computed to quantify the expression specificity of each gene across
 121 developmental time points, yielding an age-specific expression matrix Z . (3) Enrichment analysis via
 122 DESE framework. The age-specific expression matrix Z and GWAS P-values are jointly analyzed.
 123 SNP-level associations are first aggregated to the gene level. DESE then performs conditional
 124 enrichment analysis to test whether genes associated with disease show significantly higher temporal
 125 specificity than non-associated genes at each age.

126 Simulations confirm the accuracy and specificity of tDESE

127 To rigorously benchmark the statistical validity of tDESE, we conducted extensive simulations using
128 real genotype data from the UK Biobank¹⁴. Under a null model—where the expression of
129 susceptibility genes lacked any temporal dynamic—tDESE demonstrated a strictly controlled type I
130 error rate across all developmental ages for both binary and continuous traits (Fig. 2a and c). The
131 false positive rate remained robustly below 5%, confirming that the framework is highly resistant to
132 stochastic noise.

133 Having established high specificity, we evaluated tDESE's statistical power to recover a defined
134 temporal signal. In a simulated binary disease model driven by causal genes peaking strictly at age
135 20, tDESE resolved the risk window with remarkable precision (Fig. 2b). The resulting enrichment
136 profile formed a sharp, high-amplitude peak that faithfully mirrored the underlying expression
137 trajectory of the driver genes. The signal was highly localized; 96% of simulations yielded
138 significant enrichment tightly confined to the peak and its immediately adjacent years (age 20 ± 3
139 years, adjusted $P < 0.05$).

140 Finally, to assess versatility against a more statistically challenging quantitative trait, we simulated a
141 phenotype driven by an expression peak at age 60. Despite the reduced signal-to-noise ratio typical
142 of quantitative genetics, tDESE generated a highly significant enrichment profile accurately centered
143 on the target age (median enrichment score = 4.72; 84% power at the peak) (Fig. 2d). Collectively,
144 these rigorous simulations establish that tDESE provides a robust statistical foundation for accurately
145 anchoring the polygenic architecture of complex diseases to specific developmental epochs.

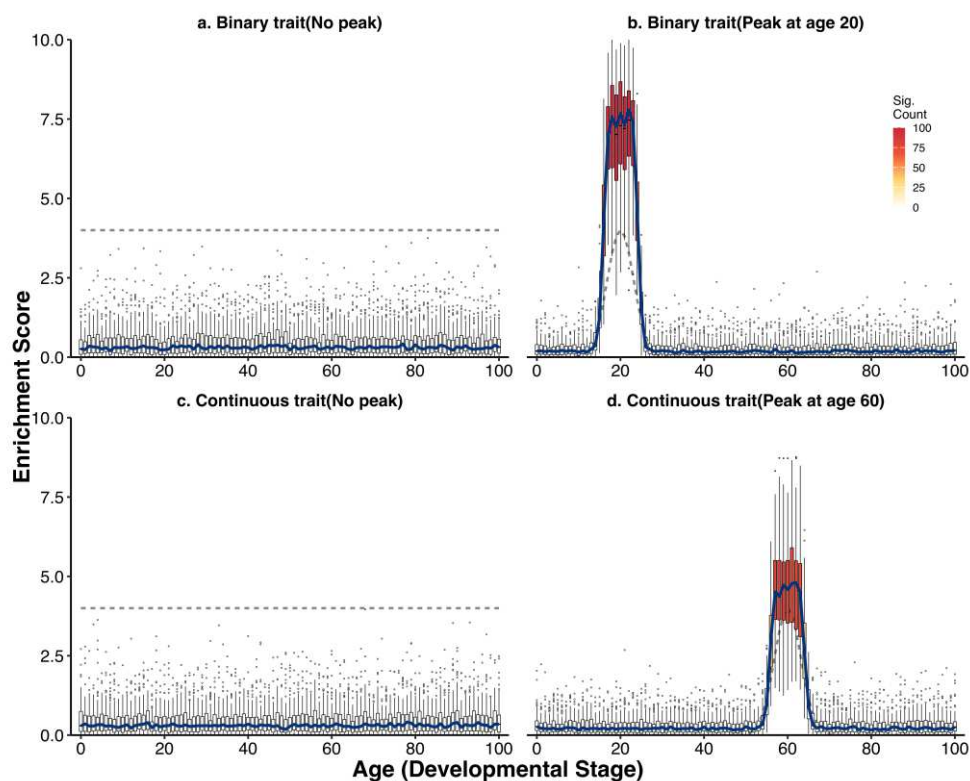


Figure 2 | tDESE accurately identifies temporal risk windows in simulations. (a, c) Under null models with no temporal gene expression patterns, tDESE shows few enrichments of significant ages for either binary (a) or continuous (c) traits with a reasonable type 1 error rate. (b) For a simulated binary trait driven by genes peaking at age 20, tDESE identifies the correct risk window with high power and accuracy. (d) For a simulated continuous trait with risk driven by genes peaking at age 60, the framework again correctly prioritizes the peak age. In all panels, bars represent enrichment scores (red indicates significance at $P < 0.05$), the solid blue line is the mean enrichment score across 100 simulations, and the dashed green line is the simulated mean expression profile of driver genes.

Temporal windows of genetic risk for neuropsychiatric disorders align with clinical onset

Having benchmarked the statistical robustness of tDESE, we applied it to uncover the temporal origins of genetic risk for five major brain disorders with well-characterized clinical onset profiles: attention-deficit/hyperactivity disorder (ADHD)¹⁵, schizophrenia (SCZ)¹⁶, major depressive disorder (MDD)¹⁷, bipolar disorder (BIP)¹⁸, and Alzheimer's disease (AD)¹⁹. These specific conditions were selected due to their pronounced age-specific incidence patterns^{9,20} and the availability of highly powered, large-scale GWAS ($N > 225K$ per trait). The analysis was conducted using two independent developmental transcriptomic cohorts from the dorsolateral prefrontal cortex (DLPFC), referred to as LIBD_szControl and CMC, assembled by the PsychENCODE project²¹ (see Methods). The prefrontal cortex plays a critical role in higher-order cognitive functions and undergoes

166 prolonged maturation during adolescence and adulthood, a period highly relevant to the etiology of
167 various psychiatric conditions²¹. These datasets offered complementary age coverage—with
168 LIBD_szControl spanning birth to age 71 (N=253), and CMC spanning age 17 to 90 (N=283)
169 (Supplementary Fig. 1)—allowing for lifespan-wide assessment and cross-cohort validation.

170 To ensure the biological fidelity of our analysis, it was imperative to resolve true developmental
171 trajectories from the profound inter-individual variability and technical noise inherent in post-
172 mortem tissue. As expected, raw transcriptomic profiles exhibited high inter-sample variability and
173 failed to cluster by chronological age (Fig. 3a,c; Supplementary Fig. 2a,c), confirming that tissue
174 heterogeneity profoundly masks age-dependent temporal trends. In striking contrast, the GAM-
175 smoothed expression trajectories established clear, age-continuous clustering (Fig. 3b,d;
176 Supplementary Fig. 2b,d), demonstrating that our statistical approach effectively isolates true
177 developmental signals from biological noise.

178 Applying this refined data revealed a striking concordance between the developmental windows of
179 peak genetic risk and the established clinical age-of-onset for each respective disorder. For ADHD, a
180 classic childhood-onset disorder, the LIBD_szControl cohort identified a significant genetic risk
181 peak at age 15 (adjusted $P = 0.04$), falling squarely within the diagnostic window of 8–18 years⁹
182 (Fig. 3e). Importantly, the CMC cohort failed to detect an ADHD signal (Fig. 3f); rather than a
183 discrepancy, this serves as an intrinsic negative control, as the CMC dataset lacks samples younger
184 than 17 years, thus inherently missing early developmental signals.

185 Conversely, severe psychiatric disorders emerging in early to mid-adulthood demonstrated highly
186 reproducible risk windows across both independent cohorts. For SCZ, significant temporal
187 enrichment spanned ages 30–35 in LIBD_szControl and 28–35 in CMC, aligning with its established
188 clinical onset of 21–35 years⁹ (Fig. 3e,f). A similar high degree of consistency was observed for
189 MDD, with significant windows at 24–33 years in LIBD_szControl and 28–33 years in CMC, and
190 for BIP, with windows at 26–32 years in LIBD_szControl and 26–31 years in CMC. For both
191 disorders, the peak enrichments were highly significant (adjusted $P < 0.01$) and consistent with their
192 respective clinical onset ages⁹.

193 Finally, we evaluated AD as a canonical late-onset benchmark. The results further corroborated the
194 temporal precision of our framework. As predicted, no signal emerged in the LIBD_szControl
195 cohort, which lacks geriatric samples. However, in the older CMC cohort, tDESE captured a distinct
196 late-life risk window, with enrichment scores escalating sharply after age 80 and peaking at age 89
197 (adjusted $P < 0.01$) (Fig. 3f). This finding directly mirrors epidemiological data, such as a meta-
198 analysis reporting a sharp rise in AD prevalence from ages 65–69 to ages 85–89²².

199 Taken together, these analyses establish a robust, data-driven link between the dynamic expression
200 of polygenic risk and the age-specific clinical manifestation of major brain disorders. These findings
201 shift the paradigm from a static view of genetic susceptibility to a dynamic one, demonstrating that
202 pathogenic genetic networks are activated within specific developmental windows, thereby dictating
203 the precise timing of clinical vulnerability.

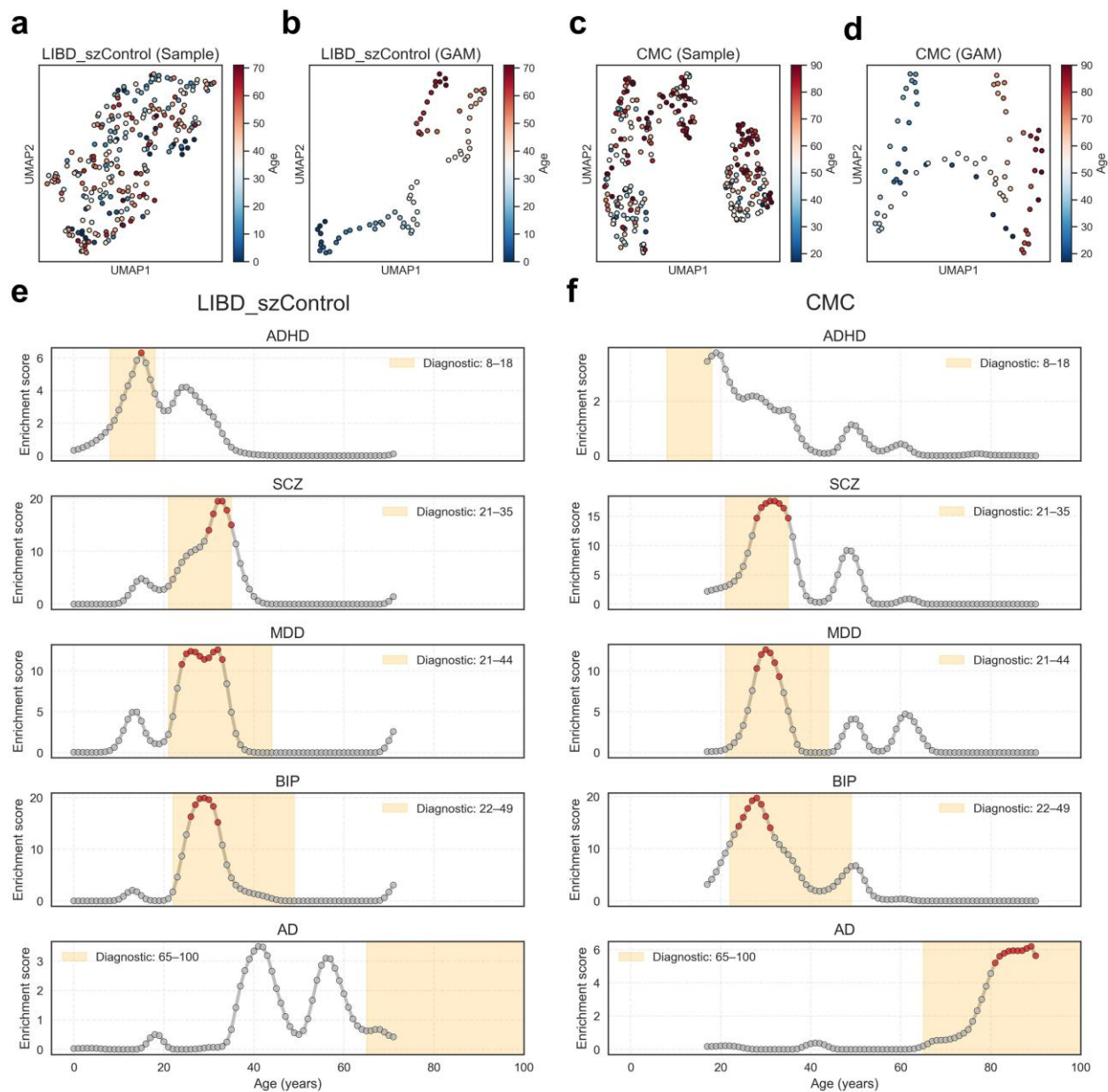


Figure 3 | Estimated age-specific associations for five neuropsychiatric disorders. tDESE was applied to identify temporally enriched genetic risk windows for five neuropsychiatric disorders with known age-of-onset patterns: ADHD, SCZ, BIP, MDD, and AD. The analysis was performed using two independent developmental gene expression datasets from the dorsolateral prefrontal cortex (DLPFC), namely LIBD_szControl and CMC. After quality control, the LIBD_szControl dataset covered ages 0–71 years, and the CMC dataset spanned ages 17–90 years. (a, c) UMAP visualization based on raw sample-level gene expression profiles. Each point represents a sample, colored by chronological age; axes represent reduced dimensions. (b, d) UMAP visualization based on smoothed, year-specific expression profiles generated via GAM. Each point represents a single year of age, colored by age. (e, f) tDESE-inferred enrichment profiles across age for each of the five

disorders. The x-axis indicates age (in years), and the y-axis shows the disease enrichment score. Red dots denote ages with statistically significant enrichment (adjusted $P < 0.05$); grey dots indicate non-significant associations. Yellow shaded regions indicate the reported age-of-onset ranges based on prior literature (see Methods for details).

Disease risk windows reveal distinct biological programs

To translate these macroscopic temporal risk windows into actionable molecular insights, we sought to define the specific biological programs driving them. We utilized a temporal correlation analysis to identify "temporally sensitive genes"—defined as genes whose dynamic expression trajectories are highly correlated with a disorder's tDESE enrichment profile (see Methods). Functional characterization of these genes revealed that each risk window is underpinned by a distinct and pathophysiologically coherent biological program.

Gene Ontology (GO) enrichment analysis of the top 200 temporally sensitive genes for each disorder revealed a fundamental biological dichotomy between the psychiatric and neurodegenerative conditions (Fig. 4a). For the psychiatric phenotypes (ADHD, SCZ, MDD, and BIP), the most significantly enriched Cellular Component was uniformly the synapse, reaffirming synaptic biology as the shared cornerstone of their temporal risk²³⁻²⁵. In contrast, the late-life risk window for AD was decisively dominated by genes governing the inflammatory response (Biological Process, adjusted $P = 2.6 \times 10^{-9}$), consistent with the well-established role of neuroinflammation in its pathogenesis²⁶.

However, within this overarching synaptopathy of psychiatric disorders, the precise temporal dynamics of synaptic sub-processes were markedly distinct. ADHD's early-life window was most significantly enriched for anterograde trans-synaptic signaling (adjusted $P = 6.8 \times 10^{-12}$). The adult-onset disorders also centered on synaptic transmission, but with different mechanistic emphases: trans-synaptic signaling was the top term for both SCZ (adjusted $P = 5.3 \times 10^{-8}$) and BIP (adjusted $P = 1.3 \times 10^{-12}$), while MDD was defined by the modulation of chemical synaptic transmission (adjusted $P = 3.3 \times 10^{-6}$).

To resolve these synaptic signatures with higher spatial precision, we leveraged the expert-curated SynGO database²⁷, revealing a clear developmental shift in the implicated synaptic compartments (Fig. 4b). The early-life ADHD risk window was characterized by genes significantly enriched in both presynaptic (adjusted $P = 1.1 \times 10^{-4}$) and postsynaptic (adjusted $P = 2.3 \times 10^{-4}$) components. In contrast, the adulthood risk windows for SCZ, MDD, and BIP were overwhelmingly dominated by postsynaptic enrichment. For instance, in SCZ, the postsynaptic signal (adjusted $P = 3.2 \times 10^{-10}$) was five orders of magnitude stronger than the presynaptic signal (adjusted $P = 2.2 \times 10^{-5}$). This profound postsynaptic skew was consistently replicated in MDD (adjusted $P = 2.3 \times 10^{-11}$ vs. 9.9×10^{-7}) and BIP (adjusted $P = 1.2 \times 10^{-12}$ vs. 3.9×10^{-10}). This suggests a refined pathogenic model wherein the locus of synaptic vulnerability spatially migrates from a pan-synaptic involvement in childhood to a strictly postsynaptic dominance in early adulthood.

253 These systems-level transcriptomic signatures are mechanistically anchored by the temporal
254 expression dynamics of individual, high-confidence risk genes (Fig. 4c). The ADHD risk window
255 tightly aligns with the adolescent peak expression of *ARHGEF7*, which encodes β -PIX, a key
256 regulator of Rac1/Cdc42 GTPases essential for dendritic spine formation²⁸. For SCZ, the risk
257 window perfectly coincides with the peak expression of *ATP2A2*, encoding the calcium pump
258 SERCA2, a critical regulator of intracellular calcium signaling heavily implicated in the disorder²⁹.
259 Similarly, the MDD and BIP risk windows align with the peak functional activity of genes crucial for
260 synaptic plasticity (*LRFN5*)³⁰ and neuronal excitability (*KCNB1*, encoding the Kv2.1 channel)³¹.
261 Finally, the late-life risk for AD is hallmarked by the peak expression of *VAC14*, part of the PIKfyve
262 complex essential for lysosomal-autophagic function, whose disruption directly drives
263 neurodegeneration³².

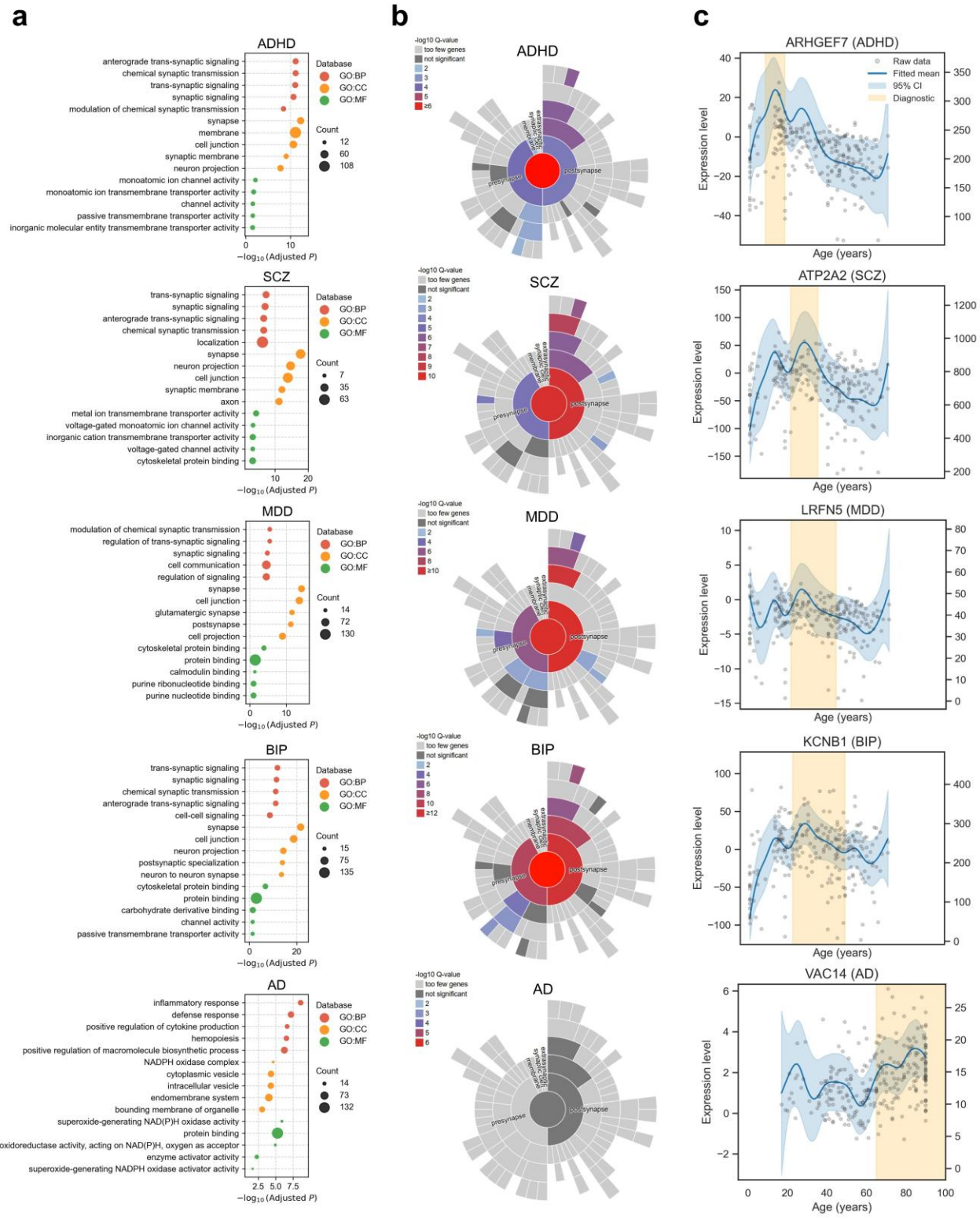


Figure 4 | Functional and molecular signatures of disease-specific risk windows. (a) Gene Ontology (GO) enrichment for the top 200 genes temporally correlated with each disorder's risk profile. Dot size is proportional to the number of genes in a term; color denotes the GO domain (BP, Biological Process; CC, Cellular Component; MF, Molecular Function). (b) Synaptic Gene Ontology (SynGO) analysis reveals compartment-specific enrichment. Color intensity in the circular plot

corresponds to statistical significance ($-\log_{10}$ adjusted P-value). (c) Expression trajectories of representative, high-confidence risk genes whose expression dynamics correlate with disease risk. Grey points are raw expression values from individual samples (scaled to the right y-axis); the blue curve is the GAM-smoothed mean expression trajectory (95% CI shaded; scaled to the left y-axis). The yellow shaded area denotes the clinical onset window. Analyses for ADHD, SCZ, MDD, and BIP used the LIBD_szControl dataset; AD analysis used the CMC dataset due to the absence of post-71-year samples in LIBD_szControl.

Temporal risk profiles are sexually dimorphic

Given the profound sex differences in the prevalence, onset, and treatment trajectories of many psychiatric disorders, we investigated whether our framework could resolve sexually dimorphic temporal risk profiles. By stratifying our analysis for SCZ, MDD, and BIP—the conditions with sufficient sample sizes to maintain statistical robustness—we uncovered a highly consistent, pan-disorder pattern: genetic risk windows systematically emerge earlier in males than in females (Fig. 5a).

For SCZ, females exhibited a significant risk window between ages 31 and 38 (peaking at 35, adjusted $P < 0.01$), whereas males demonstrated an earlier, suggestively significant susceptibility phase at ages 29–30 (adjusted $P = 0.07$). This 3-to-5-year molecular lag in the female risk profile mirrors long-standing epidemiological observations that women typically experience a later onset of SCZ, often with distinct clinical presentations^{33,34}. A parallel temporal shift characterized BIP, where the male risk window (ages 26–30; peak at 28) significantly preceded the female window (ages 28–37; peak at 32). This sequential activation aligns with clinical reports of earlier onset in males, particularly in Bipolar I disorder³⁵. Similarly, MDD risk emerged earlier in males (peak age 26) but manifested as a delayed and markedly more prolonged vulnerability window in females (peak age 34), offering a strong molecular substrate for the complex, sex-biased epidemiology of depression^{9,36}.

Importantly, these macroscopic sexually dimorphic risk profiles are mechanistically driven by the sex-divergent expression dynamics of temporally sensitive gene networks (Fig. 5b). For instance, the expression of *MYO5A* (implicated in SCZ) exhibits a distinctly earlier rise and peak in males, tightly tracking their accelerated risk window. Likewise, the up-regulation of *ATP2A2* in MDD and *KCNBI* in BIP occurs chronologically earlier in the male cortex. While further validation in larger sex-stratified cohorts will refine these timelines, our framework effectively bridges the gap between static genetics and sex-aware precision medicine, highlighting the critical need to consider biological sex and age interactively in future diagnostic and therapeutic strategies.

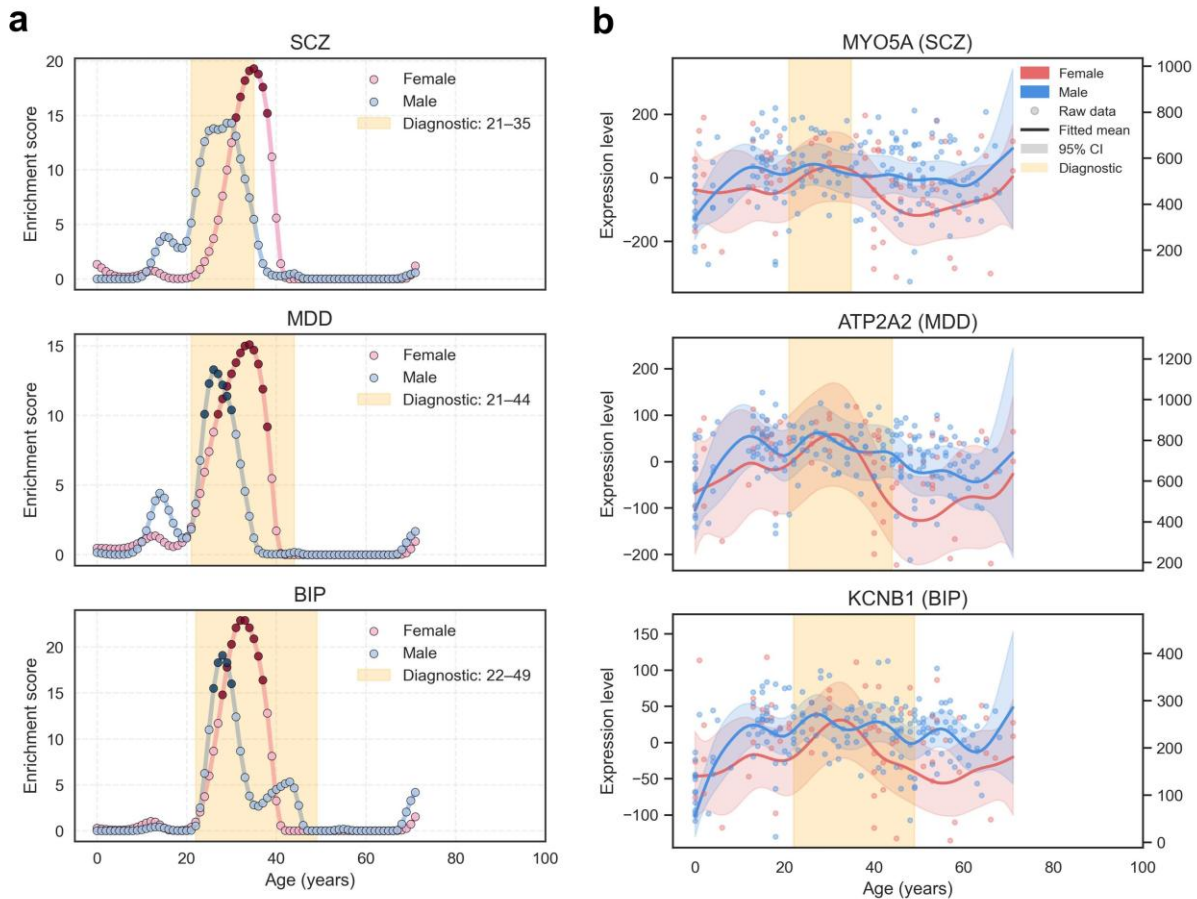


Figure 5 | Sexually dimorphic risk windows and gene expression in psychiatric disorders. (a) Sex-stratified tDESE enrichment profiles for SCZ, MDD, and BIP. Female (pink) and male (blue) profiles are shown. Darker points denote statistically significant enrichment (adjusted $P < 0.05$). The shaded yellow area represents the overall clinical onset window. (b) Sex-specific expression trajectories for representative temporally sensitive genes. Curves show GAM-smoothed mean expression for females (red) and males (blue) (95% CI shaded; scaled to the left y-axis). Raw data points for individuals are shown in the background (scaled to the right y-axis). The temporal architecture of genetic risk extends to cognitive and behavioral traits.

The temporal architecture of genetic risk extends to cognitive and behavioral traits

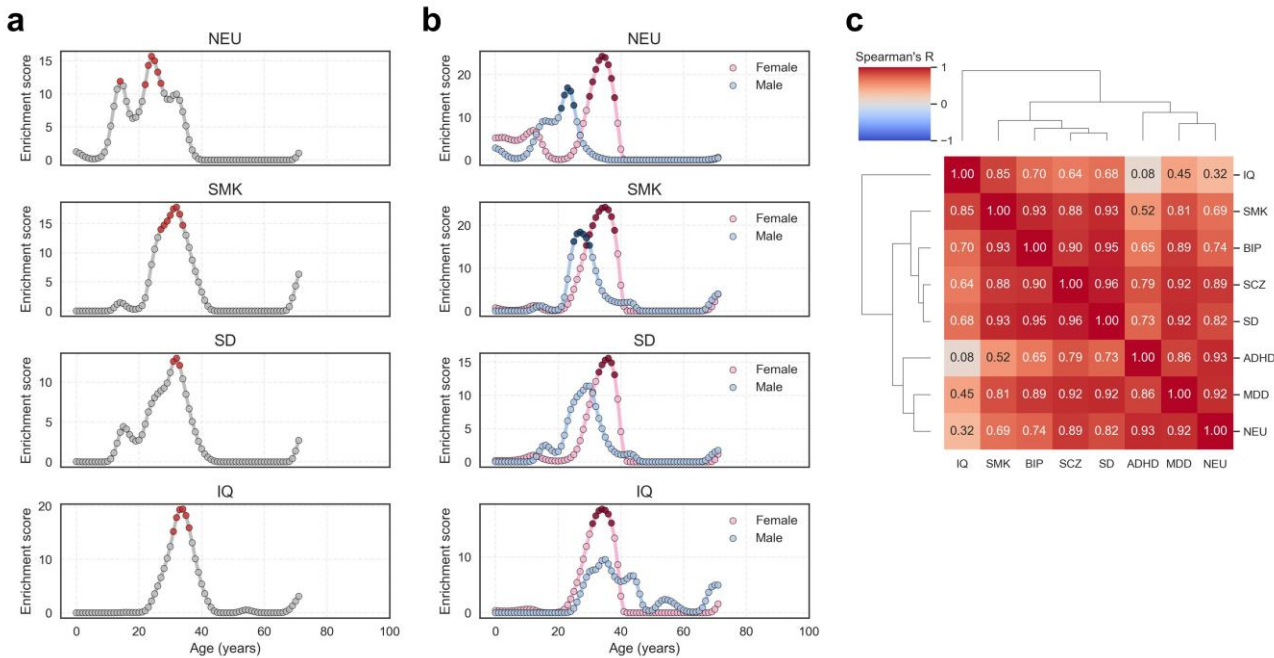
Recognizing that cognitive and behavioral traits frequently serve as prodromal indicators or shared intermediate phenotypes for psychiatric conditions, we expanded our tDESE analysis to four major traits: neuroticism (NEU)³⁷, smoking behavior (SMK)³⁸, sleep duration (SD)³⁹ and general intelligence (IQ)⁴⁰. This analysis revealed that the genetic architecture of these continuous traits is also highly dynamic, punctuated by distinct developmental windows of enrichment primarily concentrated in adolescence and early adulthood (Fig. 6a).

Neuroticism—a prominent developmental risk factor for mood disorders—was unique in displaying a bimodal polygenic risk profile, featuring an initial adolescent peak (age 14) and a subsequent, more

pronounced peak in early adulthood (age 24, adjusted $P < 0.01$). Sex-stratified analysis revealed a complex, sexually divergent temporal topology: the adolescent peak appeared earlier in females, whereas the adult peak emerged significantly earlier in males (age 23 vs. 34 in females, adjusted $P < 0.01$) (Fig. 6b). This developmental "cross-over" suggests that the underlying genetic networks dictating neuroticism are engaged via distinct, sex-specific trajectories across human maturation. In contrast, SMK and SD exhibited singular, early-adulthood enrichment windows (both peaking at age 32). They fully recapitulated the earlier male enrichment pattern characteristic of severe psychiatric clinical cohorts (Fig. 6b). The genetic architecture underlying IQ was similarly localized to early adulthood (ages 31–36), but it lacked observable sex dimorphism.

To investigate potential temporal pleiotropy between these behavioral endophenotypes and clinical disorders, we evaluated the concordance of their genome-wide enrichment profiles across the lifespan (Fig. 6c). Neuroticism displayed strikingly high correlation with ADHD ($r = 0.93$) and MDD ($r = 0.92$), highlighting a deeply synchronized developmental architecture among these conditions^{41–43} SMK most strongly synchronized with BIP ($r = 0.93$), providing a temporal molecular rationale for the frequent clinical co-occurrence of bipolar disorder and addictive behaviors⁴⁴. Remarkably, sleep duration (SD) exhibited nearly perfect temporal concordance with SCZ ($r = 0.96$), BIP ($r = 0.95$), and MDD ($r = 0.92$), implicating sleep-regulating neurocircuitry as a shared developmental vulnerability hub for severe psychopathology. IQ demonstrated comparatively weaker temporal correlations across all clinical disorders (maximum $r = 0.7$), reflecting a more orthogonal and distinct ontogenetic trajectory.

342



343

344 **Figure 6 | Temporal architecture of genetic risk for cognitive and behavioral traits.** (a) Age-
 345 age-specific enrichment profiles for neuroticism (NEU), smoking behavior (SMK), sleep duration (SD),
 346 and intelligence (IQ). Red points indicate significant enrichment (adjusted $P < 0.05$). (b) Sex-

stratified enrichment profiles for the four traits. Female (pink) and male (blue) profiles are shown; darker points denote statistical significance. (c) Heatmap of Spearman's correlation between the temporal enrichment profiles of all eight phenotypes. Dendrograms represent hierarchical clustering based on correlation patterns.

Age-specific gene expression enhances the prioritization of known disease genes

We evaluated the performance of age-specific expression profiles for ranking known disease susceptibility genes. Traditional approaches to gene annotation often rely on gene expression data averaged across the brain or developmental stages, potentially masking dynamic molecular signatures associated with specific windows of disease vulnerability. To address this, we used age-specific gene expression levels at each age point to rank candidate genes and evaluated the ability of each age-specific ranking to recover known disease-gene associations. Benchmark gene sets were compiled from the Open Targets Platform⁴⁵, including genes with drug target evidence or high integrative scores from the platform (see Methods for details). The prioritization performance at each age was quantified using the area under the receiver operating characteristic curve (AUC).

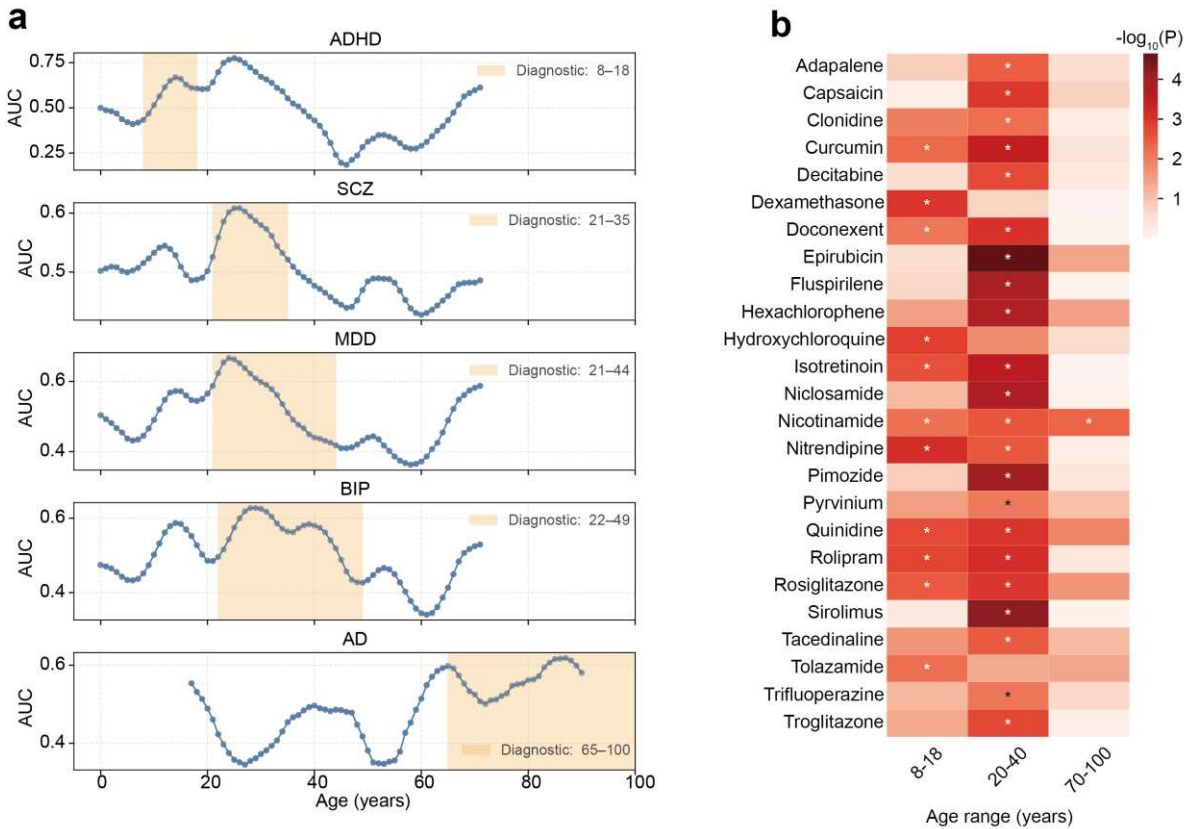
For all five neuropsychiatric disorders examined, the highest prioritization performance occurred near the age range of peak disease vulnerability (Fig. 7a): ADHD showed the best performance at age 25 (AUC = 0.77), SCZ at age 25 (AUC = 0.61), MDD at age 24 (AUC = 0.67), BIP at age 29 (AUC = 0.61), and AD at age 87 (AUC = 0.62). While the optimal age for ADHD slightly deviated from its epidemiological peak onset, the overall trend suggests that gene expression profiles during high-risk developmental windows more effectively capture pathogenic signals. These findings provide direct support for a key principle: genes with elevated expression during a disorder's risk period are more likely to be core contributors to disease pathogenesis. This reinforces the notion of an age-dependent genetic architecture in psychiatric disorders and highlights the value of incorporating developmental timing into functional annotation and disease gene discovery. Integrating age-specific expression profiles into future analyses may enhance biological interpretability and improve the translational relevance of gene prioritization frameworks.

Temporal transcriptomics enhances the discovery and prioritization of actionable therapeutic targets

A major bottleneck in translating GWAS findings into clinical applications is the accurate prioritization of causal, druggable targets. Conventional target discovery pipelines typically rely on static or time-averaged brain expression data, which inevitably dilutes transient, highly pathogenic signals restricted to specific developmental epochs. To overcome this limitation, we utilized our temporal expression profiles to rank candidate genes year-by-year, assessing their ability to recover established therapeutic targets. Benchmark target sets were rigorously curated from the Open Targets

383 Platform, focusing exclusively on high-confidence genes supported by direct pharmacological
384 evidence or high integrative validation scores.

385 For all five brain disorders examined, target identification accuracy (quantified by the area under the
386 ROC curve, AUC) peaked strictly within or immediately adjacent to their clinical vulnerability
387 windows (Fig. 7a). Maximum target recovery was achieved at age 25 for ADHD (AUC = 0.77), age
388 25 for SCZ (AUC = 0.61), age 24 for MDD (AUC = 0.67), age 29 for BIP (AUC = 0.61), and age 87
389 for AD (AUC = 0.62). While the optimal predictive age for ADHD exhibited a slight developmental
390 delay relative to its clinical onset, the overarching trend unequivocally demonstrates that
391 transcriptomic profiles from high-risk developmental epochs most effectively capture actionable
392 pathogenic signals. These findings establish a fundamental translational principle: a genetic risk
393 factor is most therapeutically actionable when its corresponding transcript is peaking during the
394 disease's natural clinical onset window. Consequently, integrating lifespan temporal dynamics into
395 post-GWAS functional annotations substantially enriches the yield of drug target discovery
396 pipelines.



397

398 **Figure 7 | Age-specific gene prioritization and psychiatric drug-target enrichment.**

399 (a) Accuracy of gene prioritization based on age-specific expression profiles for neuropsychiatric
400 disorders. The ability to prioritize benchmark disease genes curated from the Open Targets platform
401 was quantified at each age using the area under the receiver operating characteristic curve (AUC).
402 AUC values are plotted against age, with clinically defined onset windows indicated by shading. For
403 all five disorders, prioritization performance peaked within or adjacent to the corresponding onset
404 window. Analyses of ADHD, SCZ, MDD and BIP used the LIBD_szControl dataset, whereas AD

was analyzed using the CMC dataset. (b) Age-specific enrichment of psychiatric drug targets. Heatmap showing $-\log_{10}(P)$ values from Wilcoxon rank-sum tests comparing age-specific expressed genes with CMap 2 neuronal drug perturbation profiles. Asterisks indicate significant enrichment ($P < 0.01$), and only drugs showing significant enrichment in at least one age group are displayed. Fluspirilene, Pimozide and Trifluoperazine showed enrichment specifically in the 20–40-year age group.

Translational mapping of drug targets highlights the 20–40 years therapeutic window

Having established that temporal anchoring improves theoretical target prioritization, we next asked whether existing psychiatric drugs effectively exploit this temporal alignment in vivo. Translational mapping of our age-specific gene sets against neuronal drug perturbations from the CMap 2⁴⁶ database revealed a highly specific temporal alignment between psychiatric drug targets and the early adulthood developmental window. Genes preferentially expressed during the 20–40-year epoch showed the most profound enrichment for transcriptional signatures induced by classical psychiatric medications. In particular, typical antipsychotics that primarily modulate dopaminergic transmission—namely fluspirilene, pimozide, and trifluoperazine—displayed highly significant target enrichment specifically for the 20–40-year gene set (all $P < 0.001$, Fig. 7b). Clinically, these agents are foundational for the treatment of schizophrenia, with pimozide also indicated for severe tic disorders, and trifluoperazine occasionally utilized for managing acute manic episodes in bipolar disorder.

Furthermore, we observed significant target enrichment within this same age bracket for rolipram (Fig. 7b), a selective phosphodiesterase-4 (PDE4) inhibitor extensively investigated for its robust antidepressant mechanisms and its potential to rescue cognitive deficits relevant to both MDD and schizophrenia. This temporal pharmacodynamic relationship can be exemplified at the single-gene level by PDE4D, a highly significant schizophrenia-associated risk gene (conditional $P = 1.48 \times 10^{-7}$, Supplementary Fig. 3a). Consistent with the macro-level transcriptomic network, PDE4D exhibited pronounced expression specificity exclusively during early adulthood (20–40 years; REZ = 0.336), whereas it lacked specificity in both the adolescent (8–18 years; REZ = -0.423) and elderly (70–100 years; REZ = -0.949) cohorts (Supplementary Fig. 3b). Notably, the in vitro NEU neuronal perturbation data revealed that PDE4D expression is profoundly downregulated by classical antipsychotics, demonstrating an approximate 4.1-fold decrease ($\log_2\text{FC} = -2.02$) in response to trifluoperazine and a 3.2-fold decrease ($\log_2\text{FC} = -1.69$) in response to pimozide (Supplementary Fig. 3c). Importantly, this targeted transcriptional suppression was also evident following treatment with the selective PDE4 inhibitor rolipram, which induced a marked downregulation of *PDE4D* itself (approximately 2.2-fold decrease, $\log_2\text{FC} = -1.13$). This strict age-restricted expression, coupled with specific drug-induced suppression, strongly suggests that PDE4D not only drives age-specific genetic vulnerability but also acts as a critical mechanistic node in the pharmacological response to established schizophrenia treatments.

In contrast, the therapeutic transcriptional signatures of these SCZ, BIP, and MDD interventions were virtually absent in both the adolescent (8–18 years; $P > 0.05$) and elderly (70–100 years; $P >$

0.05) gene sets. Across all compounds examined, the strongest pharmacological correspondence was consistently localized to the 20–40-year window.

Discussion

The distinct chronological onset profiles of complex brain disorders represent a foundational challenge in medicine. Here, we establish a dynamic framework demonstrating that the clinical manifestation of genetic risk is dictated by specific developmental windows of gene expression, which in turn define actionable therapeutic intervals. This work extends the prevailing spatially dominated view of genetic risk, recently advanced by single-cell and spatial transcriptomics^{7,8,47}, to introduce a critical temporal dimension. By integrating human lifespan transcriptomics with large-scale GWAS summary statistics, we demonstrate that the vulnerability of the prefrontal cortex is not a static liability, but a dynamic property defined by chronological age-specific functional states. This principle provides a molecular explanation for the alignment of childhood-onset ADHD with periods of intense synaptic maturation, and late-life AD with epochs of heightened neuroimmune activity.

Our findings provide a novel lens through which to interpret the shared and divergent biology of psychiatric disorders. It refines the broad "synaptopathy" paradigm²⁵ by revealing a distinct developmental shift in synaptic compartments: the balanced presynaptic and postsynaptic vulnerability in childhood-onset ADHD yields to an overwhelmingly postsynaptic dominance in adult-onset disorders like SCZ, BIP, and MDD. This spatial migration of synaptic vulnerability across time provides a mechanistic basis for the distinct clinical trajectories observed in these conditions. By demonstrating that the prefrontal cortex can harbor latent polygenic risks for vastly different disorders at different times, our study establishes that the biological context conferred by age is as critical as that conferred by anatomy.

A fundamental translational implication of our work is that the common practice of using static or time-averaged expression data dilutes transient, highly pathogenic signals. We provide direct, quantitative evidence for this by demonstrating that target identification accuracy is age-dependent, peaking within disease-relevant developmental epochs. Our translational mapping of these age-specific networks against drug perturbation signatures revealed that targets of standard psychiatric interventions are heavily concentrated within a 20~40-year therapeutic window. This discovery is mechanistically anchored by *PDE4D*, a schizophrenia risk gene exhibiting high adult expression specificity and profound downregulation by both typical antipsychotics and selective PDE4 inhibitors like rolipram⁴⁸⁻⁵⁰. These data provide a data-driven framework for precision medicine, emphasizing that therapeutic target engagement is governed by dynamic, age-specific pharmacodynamics.

Despite these insights, several limitations warrant consideration. First, while the lifespan transcriptomic cohorts utilized are among the best currently available, their sample sizes remain modest, meaning that our sex-stratified findings require validation in larger, independent datasets. Second, our analysis was restricted to the prefrontal cortex; extending this framework to other brain regions and peripheral tissues will be a critical future direction. Third, while tDESE identifies robust temporal associations between gene expression and polygenic risk, establishing definitive causality remains a major challenge in human genomics^{7,8}. Integrating longitudinal datasets with causal inference strategies will be essential to fully realize the potential of time-aware approaches in unraveling disease mechanisms and optimizing the timing of clinical interventions.

Material and Methods

Study Design and Computational Framework

This study employed a retrospective computational multi-omics design. We developed the tDESE (temporal-specific Driver-tissue Estimation by Selective Expression) framework to integrate temporal transcriptomic dynamics with GWAS summary statistics, systematically pinpointing critical developmental windows of disease vulnerability. By evaluating the age-specific expression patterns of genes linked to polygenic risk, tDESE pinpoints temporal intervals during which genetic risk exerts its maximal influence. The key methodological challenge was addressing the high inter-sample variability inherent to developmental post-mortem transcriptomics, caused by uneven sampling density and biological confounding. Therefore, we implemented a generalized additive model (GAM)-based smoothing strategy, enabling robust, unbiased estimation of gene expression trajectories across the human lifespan under high-noise conditions.

Data input

The inputs to tDESE include GWAS summary statistics, temporal gene expression data, and genotype data from a reference population. For each sample in the temporal expression dataset, the exact age in years is recorded together with relevant covariates, including sex and RNA integrity number (RIN).

Expression trajectory modelling and prediction

Because our study focuses on age-dependent dynamic changes in gene expression, we first applied the trimmed mean of M-values (TMM) method to normalize raw expression values across samples, ensuring comparability between samples. As gene expression changes with age are not linear, we used a smoothing approach to model the relationship between gene expression and age. To account for non-age-related sources of variation, sex and RIN were included as covariates in the model. Notably, when modelling was performed separately by sex, sex was naturally excluded as a covariate. tDESE fits a GAM model for each gene individually:

$$E_g(t) = \beta_0 + f(t) + \sum_{k=1}^K \gamma_k C_k + \varepsilon$$

Here, $E_g(t)$ denotes the expression level of gene g at age t , $f(t)$ is the smoothing function of age implemented using penalized B-splines (P-splines), C_k represents the k -th covariate including sex and RIN, γ_k is its regression coefficient, and ε is the error term. For categorical covariates, such as sex, values were first converted to dummy variables before linear fitting. The model was implemented using the *pygam* package (version 0.9.1) in Python. The smoothing function parameters followed the default settings in *pygam*, with the number of basis functions (*n_splines*) set to 20 and the penalty strength (*lam*) set to 0.6.

After model fitting, we used partial dependence analysis to extract the marginal effect of age on gene expression while controlling for covariates. We then predicted expression values for each integer age, from the minimum to the maximum sample age, to generate a smoothed expression trajectory at one-year resolution together with the corresponding 95% confidence interval and standard error (SE), which were used to assess the stability and uncertainty of the estimates. This step reduces noise while preserving the authentic signal of temporal dynamic changes as much as possible.

Calculation of age-specific expression

To quantify the expression specificity of genes across different ages, we employed the robust-regression z-score (REZ) method⁵. The core concept of this method is to measure the relative expression level of a gene at a given age, defined as its standardized difference compared with other ages. REZ uses robust regression to reduce the influence of outliers, thereby improving the stability of the estimates. In addition, the standard error of expression is incorporated as an indicator of uncertainty, enabling a more reliable representation of the age specificity of gene expression.

Linking disease risk to age

We next used the tDESE framework to integrate age-specific gene expression profiles with GWAS summary statistics for each disease, to decipher ages of elevated disease risk. In the original DESE framework, tissue-specific expression profiles are used as input; here, they were replaced by age-specific expression profiles. For a given GWAS dataset, DESE first calculates gene-based association P-values using the ECS statistical model⁵¹, based on the GWAS P-values of SNPs located within 1 kb upstream or downstream of each gene. We then selected significant genes (Benjamini–Hochberg adjusted $P < 0.01$; if more than 1,000 genes met this criterion, only the top 1,000 by P value were retained) for conditional gene-based association analysis. Specifically, genes were ranked by their gene-based association P values, and conditional gene-based association analysis was performed to remove redundant associations, yielding a set of independently associated genes.

For each age, we used the Wilcoxon rank-sum test to assess whether the age-specific expression of the independently associated genes was higher than that of other genes. The base-10 negative logarithm of the test P-value was defined as the disease enrichment score, which indicates the gene-

level association significance of age-specific expression and the disease risk. Based on these enrichment scores and the selective expression profiles of genes, disease-associated genes were re-prioritized, assigning higher priority to genes with high specific expression at disease-enriched ages. Conditional association analysis was then repeated to obtain a new set of disease genes and updated enrichment scores. This procedure was iterated until the results converged.

Because the iterative procedure can introduce potential selection bias for the Wilcoxon rank-sum test, DESE employs a permutation-based global test (maxT permutation test) to estimate the null distribution. Specifically, the age labels in the input age-specific expression profiles are randomly permuted B times (100 by default). For each permutation, the analysis is repeated, and the maximum enrichment score (max-ES) across all ages is recorded. These max-ES values form the empirical distribution under the null hypothesis and are used to directly evaluate the significance of the observed statistics. For each age, the permutation P-value is defined as the proportion of values in the null distribution that are greater than or equal to the observed statistic:

$$p_i = \frac{\#\{M^{(b)} \geq ES_i^{\text{obs}}\}}{B}$$

Here, $M^{(b)}$ denotes the maximum enrichment score across all ages in the b -th permutation. Because this approach compares the observed statistic with the global maximum from each permutation, the resulting P-values inherently control the family-wise error rate (FWER) and require no additional multiple-testing correction.

In this study, linkage disequilibrium calculations were performed using Phase 3 genotype data from the 1000 Genomes Project, matched to the ancestry of the GWAS samples.

Simulations

Simulation models of gene expression and disease risk

We first modeled the age-dependent expression of a given gene. Its mean expression level, $f(x)$, as a function of age x , is described by a Gaussian function:

$$f(x) = A \exp\left(-\frac{(x - c)^2}{d}\right)$$

where A is the maximum expression amplitude, c is the age of peak expression, and d is a scale parameter controlling the width of the expression profile. This function approximates biological scenarios where gene activity is highest at a specific developmental stage.

We then assume that part of the genes with age-dependent expression are disease susceptibility genes. Each gene has at most 3 independent ($LD\ r^2 < 0.01$) disease susceptibility loci (sampling without replacement). These loci (m in total) collectively explain h_g^2 liability to a disease. An

individual's liability for a disease, L , is a linear combination of the m loci weighted by w , plus an additional error term ϵ :

$$L = \sum_{t=1}^m w_t g_t + \epsilon$$

where $g_i \in \{0, 1\}$ is the encoded genotype and the term ϵ represents environmental and unmodeled genetic factors, following a normal distribution $\epsilon \sim N(0, \sigma_\epsilon^2)$. Its variance, σ_ϵ^2 , is set to ensure that the total genetic component explains a target heritability of liability (h_g^2), such that $\sigma_\epsilon^2 =$

$\text{Var}(\sum_{t=1}^m w_t g_t) \left(\frac{1}{h_g^2} - 1 \right)$. For simplicity, all the weights w_t were set to 1.

Disease status was determined using the liability-threshold model⁵². Given a population prevalence K , individuals with a standardized liability L_x exceeding the corresponding threshold z (where $z = \Phi^{-1}(1 - K)$ and Φ^{-1} is the inverse normal cumulative distribution function) were classified as cases.

Simulation design and parameterization

Simulations were based on the following parameters:

- Simulated Gene Set: We simulated 20,000 genes. Of these, 500 were modeled with age-dependent expression, while the remaining 19,500 had constant mean expression.
- Disease Susceptibility Genes: A subset of 250 of the 500 age-dependent genes was designated as causal for the simulated phenotype.
- Age-Dependent Expression Parameters: For binary trait simulations, the peak expression age (c) was 20, and the peak width (d) was also 20. For continuous trait simulations, c and d were set to 60 and 20, respectively. Maximum amplitude (A) was 10 in all cases.
- Genotype Data: We utilized real genotypes for common variants ($\text{MAF} > 0.05$) from 490,541 participants in the UK Biobank.
- eQTL Architecture: Each of the 250 susceptibility genes was regulated by 1 to 5 eQTLs, which collectively explained 25% of its expression variance ($h_e^2 = 0.25$).
- Genetic Contribution to Liability: The 250 susceptibility genes explained 25% of the variance in disease liability ($h_g^2 = 0.25$).
- Disease Prevalence: For binary trait simulations, the population prevalence (K) was set to 1%.
- Study Cohorts: We simulated a gene expression reference panel of 1,000 individuals across 100 age points (0-100). For association analysis of binary traits, we drew a separate case-control GWAS cohort of 3,000 cases and 3,000 controls. Association summary statistics were generated

using a logistic regression analysis via the KGGA software (<https://pmglab.top/kgga>). For the association analysis of liability as a continuous trait, we drew a GWAS cohort of 6000 individuals from the simulated population to examine the genetic association by linear regression via KGGA.

Evaluation of Type I Error Rate and Statistical Power

We evaluated the performance of tDESE by generating 100 independent GWAS cohorts for each simulation scenario. To assess the type I error rate, we simulated data under the null hypothesis where susceptibility genes had no age-specific expression (i.e., $f_t(x)$ was set to a constant A_t). The empirical type I error was calculated as the proportion of the 100 simulations that yielded a P-value < 0.05. To assess statistical power, we simulated data under the alternative hypothesis, where the 250 susceptibility genes followed the age-dependent expression patterns described above. Power was calculated as the proportion of the 100 simulations in which tDESE detected a significant association ($P < 0.05$) at the designated peak age.

GWAS summary statistics

We collected GWAS summary statistics from public databases for five well-studied neuropsychiatric disorders with distinct age-of-onset patterns: attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BIP), and Alzheimer's disease (AD). We also included four psychological or behavioral traits: neuroticism (NEU), smoking (SMK), sleep duration (SD), and intelligence (IQ). These disorders and traits have large sample sizes, with an average of 442K individuals, ensuring sufficient statistical power for the analyses (see Supplementary Table 1 for details). In all analyses, the major histocompatibility complex (MHC) region was excluded to avoid confounding from its complex linkage disequilibrium structure.

Developmental dynamic gene expression profiles

RNA-seq datasets from the LIBD_szControl and CommonMind (CMC) cohorts were obtained from the PsychENCODE project²¹. To rigorously control for tissue heterogeneity and post-mortem degradation, inclusion criteria were strictly predefined: only healthy postnatal human samples specifically derived from the dorsolateral prefrontal cortex (DLPFC) with an RNA Integrity Number (RIN) > 6 were retained for temporal modeling. To mitigate boundary bias and statistical instability in the GAM caused by sparse sampling at demographic extremes, we applied a prespecified age-based trimming algorithm prior to analysis. Specifically, samples were sorted by age, and a fixed-width sliding window (width = 5 years) identified the robust sampling boundaries (minimum ≥ 5 samples). This stabilized the local smoothing process, reduced variance in tail estimates, and ensured high reliability of both the developmental trend and its derivative estimates.

In the actual data, the LIBD_szControl dataset originally spanned ages 0–85 years (N=259), which, after quality control, ranged 0–71 years (N=253). The CMC dataset originally spanned ages 17–90 years (N=284), with no change in range or sample size after quality control. For each dataset, genes

were retained for downstream analysis if they had non-zero expression in at least five samples, based on the raw count data.

Age at diagnosis from epidemiological surveys

For four psychiatric disorders, namely attention deficit hyperactivity disorder, schizophrenia, major depressive disorder and bipolar disorder, we referred to a large-scale meta-analysis of epidemiological studies on mental disorders⁹ to obtain the interquartile range (Q1–Q3) of the age-at-onset distribution, which was taken as the peak age range for each disorder. For AD, the clinical risk epoch was anchored to 65–100 years, aligning strictly with established geriatric and epidemiological consensus guidelines²⁰.

Identification of time-sensitive genes at high-risk disease ages and functional enrichment analysis

To identify genes specifically highly expressed during disease high-risk age periods, we calculated the Spearman's rank correlation coefficient between each gene's expression levels across different ages and the disease enrichment scores at corresponding ages. A higher correlation coefficient indicates stronger age-specific expression of the gene during the disease high-risk period. Genes with the highest correlation coefficients were defined as “temporally sensitive genes” at high-risk disease ages. In subsequent analyses, the top 200 temporally sensitive genes ranked by correlation coefficient were selected for functional enrichment analysis, including both the general Gene Ontology (GO) database and the SynGO database focused on synaptic function.

GO enrichment analysis was performed using the API provided by g:Profiler (<https://biit.cs.ut.ee/gprofiler>)⁵³, selecting three GO categories: Biological Process (GO:BP), Cellular Component (GO:CC), and Molecular Function (GO:MF). Enrichment significance was assessed by Fisher's exact test, and multiple testing correction was applied using the default g:SCS algorithm. SynGO enrichment analysis was conducted via the SynGO online platform²⁷ (<https://www.syngoportal.org/>), using Fisher's exact test for significance and false discovery rate (FDR) correction for multiple testing.

Sex-specific analysis of disease-associated ages

We stratified the developmental dynamic expression profiles by biological sex and performed the tDESE analysis independently to resolve sex-specific temporal risk architectures. To maintain robust statistical power and prevent confounding from sparse demographic sampling, cohorts lacking sufficient baseline representation of both sexes across all age bins (e.g., the CMC dataset lacked adequate female samples < 35 years; see Supplementary Fig. 1) were excluded from the sex-stratified analyses *a priori*. In the LIBD_szControl dataset, sex stratification was successfully performed, though the inherently reduced sample size per strata slightly attenuated the statistical significance of some enrichment signals.

683 Similarity analysis of high-risk age patterns across phenotypes

684 To assess the similarity of high-risk age patterns among different phenotypes, we calculated the
685 Spearman's rank correlation coefficient between enrichment scores of each phenotype across
686 different ages. A higher correlation coefficient indicates a stronger concordance between two
687 phenotypes in their high-risk age patterns.

688 Gene prioritization and evaluation based on age-specific expression

689 To evaluate whether prioritizing disease risk genes based on age-specific expression during peak
690 disease ages improves gene prioritization performance, we ranked disease-associated genes
691 according to their specificity of expression at each age. Disease-associated genes were defined as
692 those with Benjamini-Hochberg adjusted P values below 0.01. If more than 1000 genes met this
693 threshold, only the top 1000 genes by P-value were retained.

694 Next, we curated a stringent benchmark therapeutic target set using the Open Targets Platform
695 (release 25.06)⁵³, focusing exclusively on high-confidence actionable genes. For our benchmark, we
696 selected genes exhibiting an overall association score ≥ 0.4 , reflecting moderate to high aggregated
697 genetic and molecular evidence, as well as genes with direct pharmacological drug target evidence
698 recorded in ChEMBL (ChEMBL score > 0). The union of these criteria provided a clinically
699 grounded reference set. Based on this benchmark, we performed receiver operating characteristic
700 (ROC) analysis and calculated the area under the curve (AUC) for gene prioritization at each age.
701 This evaluation assessed the accuracy of gene prioritization at different ages and identified the age at
702 which prioritization performance was optimal.

703

704 Translational mapping of drug targets by genes with age-specific expression

705 Age-specific transcriptional signatures were derived from the CMC cohort to isolate genes with
706 distinct developmental trajectories. Post-mortem samples were stratified into three biologically
707 relevant developmental epochs: adolescence (8–18 years), early-to-mid adulthood (20–40 years), and
708 late life (70–100 years). For each gene within a given age interval, we calculated the mean
709 expression level and standard error (SE) across samples. Age-specific expression scores were
710 subsequently computed using the robust regression Z-score (REZ) framework to quantify the relative
711 specificity of gene expression across these developmental windows. To capture the core functional
712 networks defining each epoch, the top 500 genes exhibiting the highest REZ specificity scores per
713 age interval were designated as the age-specific gene sets.

714 To evaluate whether these developmentally regulated gene sets exhibited preferential susceptibility
715 to pharmacological perturbation, we mapped them against drug-induced expression signatures from
716 the Connectivity Map (CMap 2)⁴⁶. To ensure neurobiological relevance, we utilized drug
717 perturbation profiles specifically derived from the NEU neuronal cell line, curated by Li et al.⁵⁴. In

718 this context, differential expression was quantified as the fold change between drug-treated and
719 vehicle-control samples. For each therapeutic compound, a Wilcoxon rank-sum test was employed to
720 compare the absolute magnitude of expression fold changes of the age-specific genes against the
721 background transcriptome. This approach provided a systematic framework for determining whether
722 genetic networks that define specific human developmental windows are preferentially modulated by
723 existing psychotropic medications.

724

725 **Data availability**

726 GWAS summary statistics for the five neuropsychiatric disorders were obtained from the Psychiatric
727 Genomics Consortium (PGC, <https://pgc.unc.edu/for-researchers/download-results/>), and those for
728 four psychological and behavioral traits were obtained from the GWAS Catalog
729 (<https://www.ebi.ac.uk/gwas/>). Developmental dynamic expression data for the human dorsolateral
730 prefrontal cortex were retrieved from the PsychENCODE project²¹ via NIMH Data Archive (NDA).
731 Genotype data for the European population from Phase 3 of the 1000 Genomes Project were
732 downloaded from <ftp://ftp-trace.ncbi.nih.gov/1000genomes/ftp/release/20130502>. Benchmark
733 disease genes were obtained from the Open Targets Platform⁴⁵ (<https://platform.opentargets.org/>). In
734 the simulation study, the common variants (MAF>0.04) in whole genome sequencing datasets of
735 the UK Biobank¹⁴ (<https://www.ukbiobank.ac.uk>) were accessed through a collaboration under
736 application ID 86920. Genotype data in VCF.GZ format were obtained under Field ID 24310.
737 These data are available to bona fide researchers upon application to the UK Biobank.

738 **Code availability**

739 The functionality of tDESE has been implemented within the Java-based KGGSUM (V.15/Jun/2025)
740 analysis platform (<https://pmglab.top/kggsum>). Source code for the analyses and visualizations
741 presented in this study is available at <https://github.com/chaoxue-gwas/tDESE>.

742

743 **References**

- 744 1. D'Antonio, M. *et al.* Fine mapping spatiotemporal mechanisms of genetic variants underlying
745 cardiac traits and disease. *Nat Commun* **14**, 1132 (2023).
- 746 2. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for
747 schizophrenia. *Nat Neurosci* **19**, 1442–1453 (2016).
- 748 3. Sinnott-Armstrong, N. *et al.* Understanding genetic variants in context. *Elife* **13**(2024).
- 749 4. Finucane, H.K. *et al.* Heritability enrichment of specifically expressed genes identifies
750 disease-relevant tissues and cell types. *Nat Genet* **50**, 621–629 (2018).

5. Jiang, L. *et al.* DESE: estimating driver tissues by selective expression of genes associated with complex diseases or traits. *Genome Biol* **20**, 233 (2019).
6. Xue, C. *et al.* PCGA: a comprehensive web server for phenotype-cell-gene association analysis. *Nucleic Acids Res* **50**, W568–W576 (2022).
7. 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).
8. 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).
9. Solmi, M. *et al.* Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Mol Psychiatry* **27**, 281–295 (2022).
10. Legge, S.E. *et al.* Clinical indicators of treatment-resistant psychosis. *Br J Psychiatry* **216**, 259–266 (2020).
11. Iasevoli, F. *et al.* Relationships between early age at onset of psychotic symptoms and treatment resistant schizophrenia. *Early Interv Psychiatry* **16**, 352–362 (2022).
12. Fusar-Poli, P., McGorry, P.D. & Kane, J.M. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry* **16**, 251–265 (2017).
13. Correll, C.U. *et al.* Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Psychiatry* **75**, 555–565 (2018).
14. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
15. 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).
16. Trubetskoy, V. *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* **604**, 502–508 (2022).
17. 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).
18. 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).
19. Jansen, I.E. *et al.* Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet* **51**, 404–413 (2019).
20. Seath, P., Macedo-Orrego, L.E. & Velayudhan, L. Clinical characteristics of early-onset versus late-onset Alzheimer's disease: a systematic review and meta-analysis. *Int Psychogeriatr* **36**, 1093–1109 (2024).
21. Psych, E.C. *et al.* The PsychENCODE project. *Nat Neurosci* **18**, 1707–12 (2015).
22. Chan, K.Y. *et al.* Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: a systematic review and analysis. *Lancet* **381**, 2016–23 (2013).
23. Lepeta, K. *et al.* Synaptopathies: synaptic dysfunction in neurological disorders - A review from students to students. *J Neurochem* **138**, 785–805 (2016).
24. Howes, O., Marcinkowska, J., Turkheimer, F.E. & Carr, R. Synaptic changes in psychiatric and neurological disorders: state-of-the art of in vivo imaging. *Neuropsychopharmacology* **50**, 164–183 (2024).

25. van Spronsen, M. & Hoogenraad, C.C. Synapse pathology in psychiatric and neurologic disease. *Curr Neurol Neurosci Rep* **10**, 207–14 (2010).
26. Heneka, M.T. *et al.* Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388–405 (2015).
27. Koopmans, F. *et al.* SynGO: An Evidence-Based, Expert-Curated Knowledge Base for the Synapse. *Neuron* **103**, 217–234 e4 (2019).
28. Lopez Tobon, A. *et al.* The guanine nucleotide exchange factor Arhgef7/betaPix promotes axon formation upstream of TC10. *Sci Rep* **8**, 8811 (2018).
29. Nakajima, K. *et al.* Brain-specific heterozygous loss-of-function of ATP2A2, endoplasmic reticulum Ca²⁺ pump responsible for Darier's disease, causes behavioral abnormalities and a hyper-dopaminergic state. *Hum Mol Genet* **30**, 1762–1772 (2021).
30. Luan, D. *et al.* The regulatory variant rs1950834 confers the risk of depressive disorder by reducing LRFN5 expression. *BMC Med* **23**, 316 (2025).
31. Misonou, H., Mohapatra, D.P. & Trimmer, J.S. Kv2.1: a voltage-gated k⁺ channel critical to dynamic control of neuronal excitability. *Neurotoxicology* **26**, 743–52 (2005).
32. Zhang, Y. *et al.* Loss of Vac14, a regulator of the signaling lipid phosphatidylinositol 3,5-bisphosphate, results in neurodegeneration in mice. *Proc Natl Acad Sci U S A* **104**, 17518–23 (2007).
33. Li, R., Ma, X., Wang, G., Yang, J. & Wang, C. Why sex differences in schizophrenia? *J Transl Neurosci (Beijing)* **1**, 37–42 (2016).
34. Jones, P.B. Adult mental health disorders and their age at onset. *Br J Psychiatry Suppl* **54**, s5–10 (2013).
35. Baldessarini, R.J. *et al.* Onset-age of bipolar disorders at six international sites. *J Affect Disord* **121**, 143–6 (2010).
36. Salk, R.H., Hyde, J.S. & Abramson, L.Y. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychol Bull* **143**, 783–822 (2017).
37. Baselmans, B.M.L. *et al.* Multivariate genome-wide analyses of the well-being spectrum. *Nat Genet* **51**, 445–451 (2019).
38. Karlsson Linner, R. *et al.* Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. *Nat Genet* **51**, 245–257 (2019).
39. Dashti, H.S. *et al.* Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun* **10**, 1100 (2019).
40. Savage, J.E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* **50**, 912–919 (2018).
41. Van Dijk, F.E. *et al.* Five factor model personality traits relate to adult attention-deficit/hyperactivity disorder but not to their distinct neurocognitive profiles. *Psychiatry Res* **258**, 255–261 (2017).
42. Park, S.H. *et al.* Neuroticism and the Overlap Between Autistic and ADHD Traits: Findings From a Population Sample of Young Adult Australian Twins. *Twin Res Hum Genet* **20**, 319–329 (2017).

- 837 43. Adams, M.J. *et al.* Genetic stratification of depression by neuroticism: revisiting a diagnostic
838 tradition. *Psychol Med* **50**, 2526–2535 (2020).
- 839 44. Heffner, J.L., Strawn, J.R., DelBello, M.P., Strakowski, S.M. & Anthenelli, R.M. The co-
840 occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment
841 considerations. *Bipolar Disord* **13**, 439–53 (2011).
- 842 45. Buniello, A. *et al.* Open Targets Platform: facilitating therapeutic hypotheses building in drug
843 discovery. *Nucleic Acids Res* **53**, D1467–D1475 (2025).
- 844 46. Subramanian, A. *et al.* A Next Generation Connectivity Map: L1000 Platform and the First
845 1,000,000 Profiles. *Cell* **171**, 1437–1452 e17 (2017).
- 846 47. Jain, S. & Eadon, M.T. Spatial transcriptomics in health and disease. *Nat Rev Nephrol* **20**,
847 659–671 (2024).
- 848 48. Burrack, N. *et al.* Altered Expression of PDE4 Genes in Schizophrenia: Insights from a Brain
849 and Blood Sample Meta-Analysis and iPSC-Derived Neurons. *Genes (Basel)* **15**(2024).
- 850 49. Jiang, M. *et al.* Phosphodiesterase and psychiatric disorders: a two-sample Mendelian
851 randomization study. *J Transl Med* **21**, 560 (2023).
- 852 50. Kanes, S.J. *et al.* Rolipram: a specific phosphodiesterase 4 inhibitor with potential
853 antipsychotic activity. *Neuroscience* **144**, 239–46 (2007).
- 854 51. Li, M. *et al.* A powerful conditional gene-based association approach implicated functionally
855 important genes for schizophrenia. *Bioinformatics* **35**, 628–635 (2019).
- 856 52. Hujoel, M.L.A., Gazal, S., Loh, P.R., Patterson, N. & Price, A.L. Liability threshold
857 modeling of case-control status and family history of disease increases association power.
858 *Nat Genet* **52**, 541–547 (2020).
- 859 53. Kolberg, L. *et al.* g:Profiler-interoperable web service for functional enrichment analysis and
860 gene identifier mapping (2023 update). *Nucleic Acids Res* **51**, W207–W212 (2023).
- 861 54. Li, X. *et al.* Application of GWAS summary data and drug-induced gene expression profiles
862 of neural progenitor cells in psychiatric drug prioritization analysis. *Mol Psychiatry* **30**, 111–
863 121 (2025).
- 864

865 **Clinical trial number**

866 Not applicable.

867 **Funding**

868 This work was supported by the National Natural Science Foundation of China (grant numbers
869 32470683, 32470680, 32300500, and 32170637).

870 **Competing interests**

871 The authors declare no competing interests.

872 **Supplementary information**

873 Supplementary Information: Supplementary Figure 1-3 and Table 1.

874 **Acknowledgement**

875 We thank NDA for approving our data access for PsychENCODE project (DAR ID 23214). NDA is
876 a collaborative informatics system created by the National Institutes of Health to provide a national
877 resource to support and accelerate research in mental health. This manuscript reflects the views of
878 the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting
879 original data to NDA.

880 The authors used ChatGPT (OpenAI) to assist with language editing and improving the clarity of the
881 manuscript. All scientific content, data analysis, and conclusions were developed by the authors.

882 **Author Contribution**

883 C.X., X.Y., and M.L. conceived the study. C.X., X.Y., L.Y., and B.T. developed the statistical
884 methods. L.J. performed the simulation analyses. M.L. and H.G. applied and provided the dataset for
885 analysis. C.X., X.Y. and H.G. conducted data processing, computational analyses, and biological
886 interpretation of the results. C.X., Y.L., L.Z. and M.L. developed the software. C.X., X.Y., L.J., and
887 M.L. wrote the manuscript. C.X. and M.L. secured funding. M.L. provided supervision throughout
888 the study.
889

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [timeDESE.Supp.Info.anonymised.pdf](#)