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Dissecting the pleiotropic genetic architecture of suicide attempt, suicidal ideation, and thirteen correlated traits

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ABSTRACT

Suicide attempts (SA) and suicidal ideation (SI) are major public health concerns with incompletely understood underlying genetic and molecular mechanisms. We investigated the shared genetic architecture of SA and SI with 13 genetically correlated psychiatric, behavioural, and somatic phenotypes using summary statistics from 15 genome-wide association studies (N=46,350–975,353). Local Analysis of [co]Variant Association (LAVA) quantified locus-specific genetic covariance, while conjunctional false discovery rate (conjFDR) identified pairwise jointly associated genetic variants. Functional annotation and enrichment analyses characterised pathways and tissue-expression patterns. LAVA identified 16 loci with significant local correlations, mapping to 493 unique genes. After conditioning on depression and post-traumatic stress disorder, several locus-trait-pair correlations remained significant, including SI–ADHD, whose mapped genes were differentially expressed in hypothalamus, cortical regions, and peripheral tissues. Correlated loci implicated ion transport and transcriptional regulation. ConjFDR identified shared loci mapping to 798 unique genes, enriched for pathways involving cell adhesion, neurogenesis, signal transduction, chromatin regulation, immune processes, and protein secretion. Stratified analyses showed that SA pairs were enriched for gene sets related to brain morphology, cognition, and sleep regulation, whereas SI pairs for gene sets related to neuroticism, body mass index, and gastrointestinal traits. Shared loci displayed mixed effect directions. Both SA and SI were enriched for gene sets involving glycine, serine, and threonine metabolism, systemic lupus erythematosus, and DNA damage- and telomere stress–induced

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senescence. Recurrently mapped genes exhibited region- and developmental stage–specific brain expression. These findings refine the genetic architecture of suicide and implicate neurodevelopmental, immune, metabolic, and chromatin-related mechanisms in suicidal thoughts and behaviours.

1. Introduction

Suicide-related phenotypes, including suicidal ideation (SI) and suicide attempt (SA), here jointly referred to as suicidal thoughts and behaviours (STBs), represent a major public health challenge and contribute substantially to global morbidity and mortality (Suominen et al., 2004; World Health Organization, 2025). More than 720,000 individuals die by suicide annually, and for every suicide death there are an estimated 20 SAs; long-term follow-up studies suggest that approximately 10–15% of individuals who attempt suicide eventually die by suicide (Suominen et al., 2004; World Health Organization, 2025). In the United States alone, 13.2 million individuals reported SI in 2022, with 1.9 million attempts and 49,000 resulting deaths (CDC, 2025). Together with major depressive disorder (MDD), SA is the strongest known predictor of subsequent death by suicide (Cavanagh et al., 2003; Franklin et al., 2017), but the biological mechanisms underlying both SI and SA remain insufficiently characterised.

Although SI and SA are often conceptualised as points along a severity continuum (DiBlasi et al., 2021), emerging evidence indicates that they exhibit only partial overlap in clinical correlates and genetic liability (Klonsky et al., 2021). Twin studies report heritability estimates for SI ranging from 36% to 47%, even after accounting for psychiatric comorbidities, indicating residual genetic contributions independent of co-occurring disorders (Fu et al., 2002). For SA, family- and twin-based heritability estimates range from 30% to 50% (Voracek and Loibl, 2007), with single-nucleotide polymorphism (SNP)-based heritability from genome-wide association studies (GWASs) ranging between 3.5% and 4.6% depending on phenotype definition and analytical strategy applied (Ruderfer et al., 2020). For SI, recent GWAS estimated SNP-based heritability at 4.6% – unadjusted – and 2.3% when conditioned on post-traumatic stress disorder (PTSD) (Ashley-Koch et al., 2023), with intermediate values when adjusting for MDD, bipolar disorder (BD), or schizophrenia (SCZ). While psychiatric diagnoses - particularly MDD - remain major risk factors for suicidality (Ruderfer et al., 2020; Strawbridge et al., 2019), these estimates indicate that genetic risk for SI and SA is not fully explained by comorbid psychopathology, supporting the hypothesis of both shared and distinct biological mechanisms.

Epidemiological data indicate that approximately 80% of individuals who attempt suicide meet criteria for at least one psychiatric disorder at the time of the attempt (Davis et al., 2020; Nock et al., 2010). Yet, suicidal thoughts and behaviours are not confined to any single diagnosis and can be observed across nearly all major nosographic categories. The strongest associations are reported for MDD, but elevated risk is also reported in SCZ, autism spectrum disorder (ASD), BD, and attention-deficit/hyperactivity disorder (ADHD) (Docherty et al., 2023; McCall and Black, 2013; Oquendo et al., 2024; Sanchez-Carro et al., 2023). These associations are mirrored at the genomic level: genetic correlation analyses have consistently shown shared polygenic contributions between suicide risk and a wide array of psychiatric traits (Bertolote and Fleischmann, 2002; Li et al., 2023). Importantly, suicidal phenotypes have also been linked to several non-psychiatric traits, including physical health, behavioural, and socio-demographic factors. Traits such as smoking behaviour, body mass index (BMI), chronic pain, and educational attainment (EA) have all been associated with suicide at both the phenotypic and genomic levels (Docherty et al., 2023; McCall and Black, 2013; Mullins et al., 2022; Sariaslan et al., 2022; Sher, 2024; Zinchuk et al., 2024). These findings suggest that suicide vulnerability extends beyond psychiatric nosology and may involve biological, behavioural, and socio-environmental pathways.

Despite the growing recognition of these associations, most prior research has focused on global genetic correlations, which provide genome-wide averages of polygenic overlap but do not account for regional specificity or the direction of effects at individual loci (Ruderfer et al., 2020). A limitation of these analyses is that they do not identify the specific genomic regions contributing most to the shared genetic architecture of suicide and its associated traits (Ciochetti et al., 2023). Local patterns of genetic sharing may reveal loci or regions where the direction of effect for suicide risk is concordant or divergent from that of psychiatric and non-psychiatric traits (Fanelli et al., 2025; Kontou and Bagos, 2024), providing novel insights into the biological mechanisms underlying these relationships.

To address these limitations, local genetic correlation methods, such as those implemented in Local Analysis of [co]Variant Association (LAVA), estimate regional genetic covariance across semi-independent loci based on linkage disequilibrium (LD) patterns, allowing for the identification of trait-specific overlap and heterogeneity in directionality (Werme et al., 2022). Complementary pleiotropy-informed approaches, including the conjunctional false discovery rate (conjFDR), increase power to detect shared loci by leveraging cross-trait enrichment patterns and enable the identification of specific SNPs jointly associated with multiple traits (Andreassen et al., 2013; Smeland et al., 2020). These methods are well suited to investigate phenotypes like SI and SA, where genetic architecture is likely to involve both overlapping and distinct pleiotropic components with other traits.

In this study, we systematically assess local patterns of convergent or divergent genetic sharing between suicide phenotypes and other traits by integrating local genetic correlation and conjFDR methods (Figure 1). We focus on SI and SA and examine their locus-specific overlap with a curated set of psychiatric and non-psychiatric traits previously shown to be genetically correlated at the global level (Ashley-Koch et al., 2023; Docherty et al., 2023; Mullins et al., 2022). Specifically, our objectives are to: (1) identify specific genomic regions contributing to the shared genetic liability between SI, SA and other psychiatric/non-psychiatric traits; (2) determine whether these loci or regions show concordant or discordant directions of effect; and (3) refine our understanding of shared biological mechanisms. By increasing the resolution at which genetic sharing is examined, our findings aim to inform suicide risk stratification and support future biomarker discovery and therapeutic development.

2. Experimental procedures

2.1. Input summary statistics of GWASs

We used GWAS summary statistics for SA and SI from the largest available meta-analyses (Ashley-Koch et al., 2023; Docherty et al., 2023). In the original studies, SA was defined as deliberate self-injurious behaviour with intent to die (Docherty et al., 2023), whereas SI referred to thoughts about suicide in the absence of a SA (Ashley-Koch et al., 2023).

We included in the analyses thirteen traits based on prior evidence of global genetic correlation with SA or SI (Ashley-Koch et al., 2023; Docherty et al., 2023; Mullins et al., 2022). The selected traits include: ADHD, ASD, BD, BMI, cigarettes per day (CPD), behavioural disinhibition (DSN), EA, ever smoked (ESMK), insomnia (INS), multi-site chronic pain (MSCP), neuroticism (NEU), risk tolerance (RSKT), and SCZ. Traits were selected based on three criteria: (i) robust prior evidence of global genetic correlation with SA or SI; (ii) availability of well-powered and publicly accessible GWAS summary statistics; and (iii) representation of

distinct liability domains, including neurodevelopmental disorders, psychotic disorders, behavioural disinhibition, substance use, somatic/metabolic traits, and educational/cognitive phenotypes.

MDD and PTSD were included for sensitivity analyses because they are highly associated with suicidality at the genome-wide level: the largest meta-analyses report rg's ~0.8 for SA/SI with either MDD or PTSD (Ashley-Koch et al., 2023; Docherty et al., 2023). Genetic correlations of this magnitude indicate substantial shared polygenic liability. However, an rg of ~0.8 corresponds to an rg^2 of ~0.64, indicating strong but incomplete concordance between the genetic effects contributing to the covariance between the two traits. Thus, despite considerable overlap, disorder-specific genetic liability is still expected. This level of shared liability justified sensitivity analyses to determine whether locus-specific associations persisted beyond broad affective genetic overlap.

For each phenotype, including SA and SI, we obtained summary statistics from the most recent and comprehensive GWAS available for reproducible secondary analyses at the time the analysis plan was locked and the analyses were finalised (October 2025); datasets without externally accessible summary statistics (e.g., under embargo) were not eligible for inclusion. Quality control steps excluded strand-ambiguous variants, duplicated, rare (MAF < 0.01), and with poor imputation quality (INFO < 0.8). Details of the GWAS sources and sample sizes for each phenotype are provided in Table 1.

All GWAS summary statistics included in the present analyses were derived from individuals of European ancestry, as reported in the original publications. This restriction was required to ensure consistency in LD structure across datasets and reflects the limited availability of adequately powered GWASs in other major ancestry groups.

Table 1
Summary statistics and phenotypes.

Trait/disorder	Authors, year	PMID	Total N (N cases)
ADHD	Demontis et al., 2023	36702997	225 534 (38 691)
ASD	Grove et al., 2019	30804558	46 350 (18 381)
BD	Mullins et al., 2021	34002096	413 466 (41 917)
BMI	Yengo et al., 2018	30124842	456 426
CPD	Saunders et al., 2022	30643251	618,489
DSN	Karlsson Linnér et al., 2019	30643258	315 894
EA	Okbay et al., 2022	35361970	765 283
ESMK	Karlsson Linnér et al., 2019	30643258	518 633
INS	Watanabe et al., 2022	35835914	386 988 (109 548)
MSCP	Johnston et al., 2019	31194737	412 985
NEU	Nagel et al., 2018	29942085	390 278
RSKT	Karlsson Linnér et al., 2019	30643258	975 353
SA	Docherty et al., 2023	37777856	815 178 (35 786)
SCZ	Trubetskoy et al., 2022	35396580	100 468 (39 910)
SI	Ashley-Koch et al., 2023	36940203	612 381 (99 814)

ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; BMI, Body Mass Index; CPD, Cigarettes per Day; DSN, Disinhibition; EA, Educational Attainment; ESMK, Ever Smoked; INS, Insomnia; MSCP, Multi-Site Chronic Pain; NEU, Neuroticism; RSKT, Risk Tolerance; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation.

2.2. Local genetic correlation analyses - LAVA

We applied the LAVA (Local Analysis of [co]Variant Association) framework to estimate local genetic correlations (ρ) between suicide-related phenotypes and a range of psychiatric and non-psychiatric traits. LAVA partitions the genome into semi-independent loci based on LD patterns, thereby enabling the identification of specific genomic regions that contribute to global genetic correlations. Each locus contains at least 1,000 SNPs with MAF > 0.01 across all summary statistics, resulting in 2,495 distinct loci. The partitioning script is publicly available at: https://github.com/cadeleeuw/lava-partitioning (Werme et al., 2022).

To identify loci with evidence of local genetic signal, we first conducted univariate heritability tests for each phenotype within each locus. Only loci that showed significant local SNP-based heritability in both phenotypes ($P < 2 \times 10^{-5}$, Bonferroni-corrected for 2,495 loci; 0.05/2,495) were included in the subsequent bivariate local genetic correlation analyses. Bivariate results were then adjusted for multiple testing using a second Bonferroni correction that accounted for the total number of loci tested across all phenotype pairs within each suicide

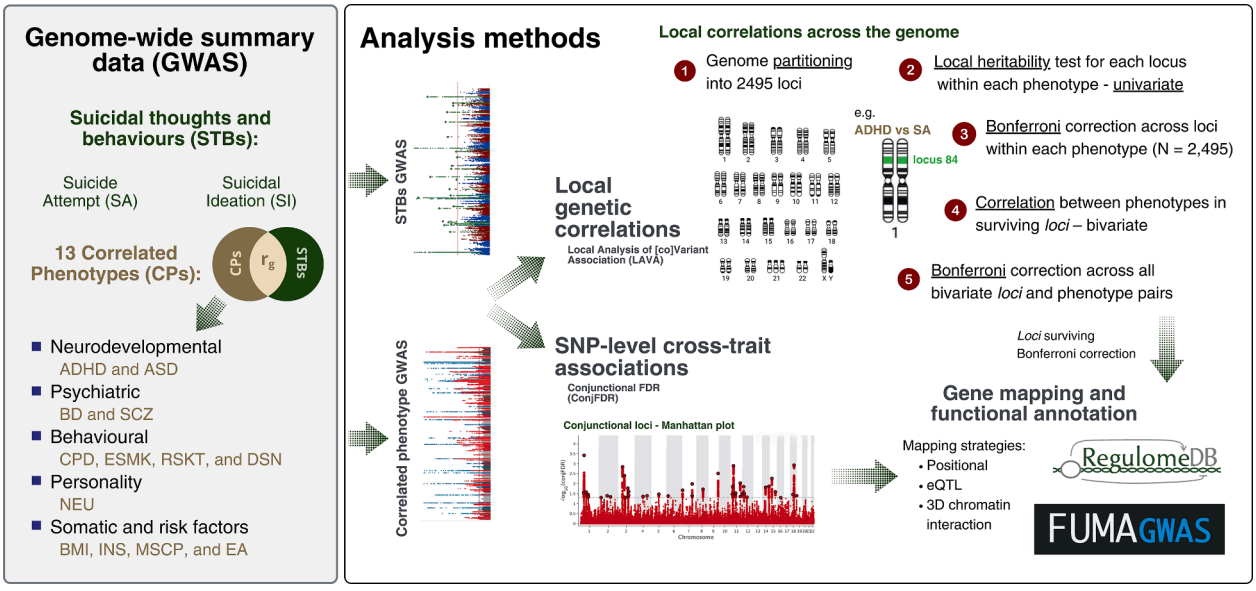

Figure 1. Graphical overview of the analytical workflow used to investigate the shared genetic architecture between suicidal thoughts and behaviours (STBs) and genetically correlated traits. Genome-wide association study (GWAS) summary statistics were obtained for STBs, including suicide attempt (SA) and suicidal ideation (SI), and for thirteen correlated phenotypes (CPs). Local genetic correlations (r_g) were estimated using Local Analysis of [co]Variant Association (LAVA) after partitioning the genome into 2,495 loci. SNP-level cross-trait associations were identified using conjunctional false discovery rate (conjFDR). Significant loci were subsequently subjected to gene mapping and functional annotation using FUMA. ADHD, Attention Deficit and Hyperactivity Disorder; ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; CPD, Cigarettes per Day; DSN, Disinhibition; EA, Educational Attainment; ESMK, Ever Smoked; INS, Insomnia; MSCP, Multi-Site Chronic Pain; NEU, Neuroticism; RSKT, Risk Tolerance; SCZ, Schizophrenia.

phenotype. To control for sample overlap, bivariate LD score regression intercepts were estimated and incorporated into the LAVA model (Bulik-Sullivan et al., 2015).

Next, we performed partial correlation analyses ($|z|$) within the LAVA framework to isolate independent local effects. We first selected loci showing significant local correlations with more than one phenotype pair. For each of these loci, we conducted pairwise conditional analyses, where the correlation between two phenotypes was conditioned on a third correlated phenotype to distinguish shared from independent effects. For example, if locus 32 showed significant correlations for both SA–ADHD and SA–BMI, we performed two conditional tests: (a) SA–ADHD conditioned on BMI, and (b) SA–BMI conditioned on ADHD.

We next focused on loci showing evidence of shared local genetic signals between STBs and either MDD or PTSD. Given the strong genome-wide correlations between these disorders and STBs, we performed LAVA partial genetic correlations to test whether locus-level associations between SI or SA and each target trait persisted after conditioning on MDD, PTSD, or both simultaneously. We restricted these analyses to loci in which SI or SA, MDD or PTSD, and at least one additional target trait showed nominal evidence of local association ($P < 0.05$) in the corresponding bivariate tests. This strategy enabled us to assess whether the associations with suicidal phenotypes persisted after accounting for potential confounding effects of MDD and PTSD. Only loci that remained significant after all conditioning scenarios were carried forward to downstream enrichment analyses.

2.3. Conjunctional false discovery rate (conjFDR) analyses

To identify SNPs jointly associated with SA or SI and each of the thirteen selected traits, we applied the conjFDR approach (Andreassen et al., 2013; Smeland et al., 2020). This method builds upon the condFDR framework, which boosts GWAS discovery by applying an empirical Bayesian statistical framework, conditioning SNPs-associated p-values of a primary phenotype on SNPs' nominal p-values from a secondary trait (Andreassen et al., 2013; Smeland et al., 2020). For a pair of phenotypes, two condFDR values can be computed for each SNP, conditioning the first trait on the second one and vice versa. The highest of these two condFDR values is then defined as the SNP's conjFDR (Andreassen et al., 2013). For phenotypes with overlapping samples, such as SA, sample overlap correction was applied following the protocol reported by the developers (https://github.com/precimed/pleiofdr). The MHC region (chr6:26000000-34000000) was excluded from all conjFDR analyses, as recommended for this analytical framework due to its complex LD structure and potential to inflate pleiotropy estimates (Andreassen et al., 2013; Schwartzman and Lin, 2011). Quantile–quantile (Q–Q) plots were generated to evaluate polygenic enrichment across trait pairs.

Statistically significant associations (i.e., candidate SNPs) were identified with a maximum FDR of 5%. Independent significant SNPs were defined as candidate SNPs with an LD $r^2 < 0.6$ with each other, whereas an LD $r^2 < 0.1$ defined lead SNPs (Watanabe et al., 2017). Genomic loci were defined by grouping candidate SNPs in LD ($r^2 \geq 0.6$) with a given lead SNP and merging loci within 250 kb. Novel loci resulting from conjFDR analyses were defined as loci not identified in parent, single-trait GWASs. To evaluate the effect direction of each lead SNP identified with conjFDR, the corresponding Z-scores from the individual trait GWASs were extracted and the signs compared to determine whether effects were discordant (opposite sign) or concordant (same sign). Finally, the shared genetic loci identified through the conjFDR approach were also compared to LAVA's results by checking overlaps in genomic ranges using the GenomicRanges R package (Lawrence et al., 2013).

2.4. Functional annotation, gene mapping, and gene set analysis

Functional annotation for the shared genetic loci identified in the previous steps was conducted with FUMA (Watanabe et al., 2017), incorporating annotations from the RegulomeDB (Boyle et al., 2012) and 15-core chromatin states (Kundaje et al., 2015), representing expression Quantitative Trait Loci (eQTL) and genomic regions' accessibility, respectively. The MHC region (chr6:26000000-34000000) was excluded. To prioritise the most deleterious variants, a Combined Annotation Dependent Depletion (CADD) Score ≥ 12.37 was used.

To retrieve the list of genes located within each locus identified in the LAVA analysis that survived all partial analysis, we utilised the NCBI Genome Data Viewer (GDV). Subsequently, the GENE2FUNC module from FUMA was employed to assess tissue-specific expression patterns and to explore potential enrichment in biological pathways and gene sets for the genes mapped to each locus.

Three different SNP-to-gene mapping strategies were used for conjFDR significant results, including (1) positional mapping (with a 10 kb window size), (2) 3D chromatin interaction mapping, and (3) eQTL mapping. Gene set enrichment and tissue-specific expression analyses were performed using Multi-marker Analysis of Genomic Association (MAGMA), as implemented in FUMA. Four reference datasets were used to assess spatial and temporal patterns of gene activity. These included 54 distinct tissue types and 30 aggregated tissue categories from GTEx v8, and 29 developmental stages alongside 11 broader developmental windows from BrainSpan. The prenatal stages represented in BrainSpan span from 8 to 37 post-conception weeks, allowing detailed mapping of gene expression trajectories from early neurodevelopment through late gestation.

3. Results

3.1. Local genetic correlations between suicidal and other psychiatric and non-psychiatric phenotypes

3.1.1. Global genetic correlations and locus-level selection

We reexamined the genetic correlations with LD Score Regression (LDSC) among STBs and target phenotypes using the latest GWAS summary statistics. Our findings were consistent with previous published findings (Ashley-Koch et al., 2023; Docherty et al., 2023), as summarised in Supplementary Figure 1 and Table S1. In the univariate LAVA analysis, 1,073 loci exhibited significant local SNP-based heritability for SA and at least one other tested phenotype, while 3,528 loci met this criterion for SI. Only these loci were retained for subsequent bivariate analyses and considered in Bonferroni correction ($P < 0.05/1,073 = 4.6 \times 10^{-5}$ for SA; $P < 0.05/3,528 = 1.4 \times 10^{-5}$ for SI) (Tables S2–S27).

3.1.2. Significant local genetic correlations for SA and SI

Among loci retained for SA bivariate testing, 15 demonstrated significant local genetic correlations with other traits (Table S28). These included three loci with ADHD, also three with BD, two each with DSN, EA and SCZ, and one locus each with BMI, ESMK and NEU. The strongest correlations were observed between SA and DSN at locus chr11:28577719-29530460 (ρ=0.99, P=1.3e-4), followed by ESMK at locus chr6:25684630-26396200 (ρ=0.89, P=2.8e-2), and EA at locus chr1:151146408-152535630 (ρ= -0.89, P=1.5e-3), respectively.

For SI, 13 of 3,528 tested loci exhibited significant local genetic correlations with other phenotypes (Table S28). For SI-EA, five loci were significant: chr2:103305258-105120578 (ρ= -0.47, P=1.7e-2), chr5:166863414-168342743 (ρ= -0.72, P=4.6e-2), chr9:128785783-129617771 (ρ= -0.57, P=3.1e-2), chr12:120567741-121817509 (ρ= -0.71, P=4.9e-3) and chr17:45883902-47516224 (ρ= -0.74, P=1.1e-3). With SCZ, there are three correlations, on loci chr4:113916003-115306149 (ρ=0.73, P=1.9e-2), chr6:25684630-26396200 (ρ=0.71, P=9.2e-4) and loci chr11:112755447-113889019 (ρ=0.42, P=3.0e-2). Two loci were associated between SI and ADHD, on loci chr10:133818037-134856054 (ρ=0.83, P=1.3e-2) and chr11:28577719-29530460 (ρ=0.72, P=4e-3), as well as with NEU on loci

chr11:112755447-113889019 (ρ=0.51, P=1.7e-4), chr18:52512524-53762996 (ρ=0.72, P=2.5e-2). Lastly, there was only one locus for SI and ESMK (ρ=0.86, P=3.2e-4).

Three loci demonstrated local pleiotropy across multiple traits. At locus chr1:43512670–45167235, SA was associated with both ADHD and EA in opposite directions (ρ=0.71, P=1.8e-3 and ρ= -0.56, P=1.8e-3; respectively). In contrast, for SI, locus chr11:28577719–29530460 showed correlations with both ADHD and ESMK in the same direction (ρ=0.72, P=4e-3 and ρ=0.86, P=3.2e-4), as did locus chr11:112755447-113889019 for SI with NEU and SCZ (ρ=0.51, P=1.7e-4 and ρ=0.42, P=3e-2) (Table S28).

3.1.3. Conditional analyses and robustness to MDD/PTSD

Conditional analyses were then performed to assess trait-specific effects at these loci. Most correlations lost significance after conditioning (Table S29). For instance, the correlation between SA and ADHD at locus chr1:43512670-45167235 became non-significant when conditioned on EA (ρ=0.54, P=0.12), as well as the correlation between SA and EA when conditioned on ADHD (ρ=0.13, P=0.74). These findings suggest that other factors may be driving the observed correlations between these phenotypes within this region. Only one remained significant, on locus chr11:112755447-113889019 (ρ=0.7, P=1.8e-3), indicating that the correlation between SI and NEU is independent of SCZ.

Given the high genetic correlation between STBs and both MDD and PTSD, we identified loci showing nominally significant local correlations with these traits ($P < 0.05$; Tables S30–S33) and conditioned the overlapping loci from the main analysis on MDD and PTSD to account for potential confounding. In this step, five loci lost significance, which indicates that MDD and/or PTSD might better explain the correlation between STBs and these traits on specific loci (Table S29). In loci chr6:30070718-30715006 for SA and BD, loci chr7:113339387-115321301 for SA and DSN and loci chr18:52512524-53762996 for SI and NEU, both PTSD and MDD influenced the correlation. The correlation was influenced only by PTSD in locus chr2:103305258-105120578 for SI and EA, and in locus chr11:112755447-113889019 for SI and NEU, while MDD influenced locus chr11:28577719-29530460 correlation between SA and DSN.

In total, 17 correlations persisted significantly even after controlling for all potential confounding effects (Table 2 and Figure 2). The full list of genes within each locus is provided in Table S34 and was used for the enrichment analysis of LAVA results.

3.1.4. Functional annotation of LAVA loci

Using the GENE2FUNC module on the FUMA platform, we identified differential gene expression in at least 10 different tissues for the genes located within loci associated with specific phenotype pairs (Supplementary Figures S2–S5). As expected, several genes involved in the connection between phenotypes were differentially expressed in brain tissues. Genes located within loci mediating the SI–ADHD association (e.g., *JAKMIP3, DPYSL4, INPP5A, CFAP46*) were up-regulated in four brain regions: hypothalamus, frontal cortex, cortex, and anterior cingulate cortex (Supplementary Figure 4B). Additionally, some genes were differentially expressed in non-neural tissues: genes located within SI–ADHD loci were down-regulated in blood vessels, esophagus, and aorta (Supplementary Figure 4A–B). Furthermore, SA–EA genes were up-regulated in the skin, including suprapubic (non–sun-exposed) and lower leg (sun-exposed) regions (Supplementary Figure 2A–B). SA–ESMK genes showed increased expression in liver, small intestine, and colon (Supplementary Figure 3), while SI–EA genes were up-regulated in the transverse and sigmoid colon, small intestine, stomach, and kidney cortex (Supplementary Figure 3A–B).

In addition, several gene sets were identified across phenotype pairs (Supplementary Figures S6–S9). Notably, genes located within SI–EA loci were enriched for gene sets associated with embryonic development (e.g., embryonic organ development, rhombomere development), morphogenesis (e.g., cranial nerve morphogenesis, embryonic organ morphogenesis), regulation of biological processes (e.g., negative regulation of lamellipodium assembly, positive regulation of cytosolic calcium ion transport), cellular components (e.g., chromatin, chromosome, ribonucleoprotein complex), and molecular functions, including DNA-binding transcription factor activity, transcription regulator activity, and sequence-specific DNA binding (Supplementary Figure 8). Additionally, genes within SA–ESMK and SI–SCZ loci were enriched for transport-related processes, such as urate and phosphate ion transport, as well as transmembrane transport activity, including sodium, metal, monoatomic ion, salt, and inorganic molecular entity transport (Supplementary Figures 7 and 9).

Table 2
Results from local correlation analysis after controlling for confounding effects.

Trait 1	Trait 2	Locus	Chr	Start	Stop	N SNPs	Local rg (ρ)	P	P-corr*	Z	Partial rg (ρ_p)	P
SA	ADHD	84	1	96147577	97721186	2815	0.75	1.4e-5	0.013	MDD	0.73	0.001
		2408	20	44072211	45673603	3248	0.66	4.3e-5	0.040	PTSD	0.51	0.005
	BD	1735	11	130500784	131424361	1905	0.68	3.9e-5	0.036	MDD	0.64	0.002
		2109	16	7051430	7704354	2610	0.73	4.5e-5	0.041	MDD	0.78	5.3e-4
	BMI	943	6	19449153	20418020	830	0.72	6.4e-6	0.006	-	-	-
	EA	110	1	151146408	152535630	1844	-0.89	1.4e-6	0.001	-	-	-
	ESMK	950	6	25684630	26396200	1737	0.89	2.6e-5	0.024	MDD	0.89	0.018
	NEU	1544	10	62626466	64069687	2712	0.78	1.4e-5	0.004	-	-	-
	SCZ	652	4	55681702	57103100	3214	0.78	4.0e-5	0.037	-	-	-
		2026	14	99474534	100786189	2514	0.66	3.0e-5	0.028	-	-	-
SI	ADHD	1608	10	133818037	134856054	2341	0.83	3.2e-6	0.011	MDD	1	1.4e-05
	EA	915	5	166863414	168342743	3137	-0.72	1.1e-5	0.039	MDD	-0.70	0.002
		1472	9	128785783	129617771	2038	-0.57	7.6e-6	0.027	PTSD	-0.48	0.008
										MDD	-0.45	0.015
		1849	12	120567741	121817509	3124	-0.71	1.2e-6	0.004	PTSD	-0.58	7.1e-05
										MDD	-0.56	0.004
		2209	17	45883902	47516224	3414	-0.74	3.1e-7	0.001	MDD	-0.72	1.3e-05
	SCZ	701	4	113916003	115306149	2826	0.73	4.6e-6	0.019	-	-	-
		950	6	25684630	26396200	1803	0.71	2.2e-7	0.001	-	-	-

* Bonferroni correction for all bivariate tests (NSA = 1,073; NSI = 3,528). ADHD, Attention Deficit and Hyperactivity Disorder; BD, Bipolar Disorder; BMI, Body Mass Index; Chr, Chromosome; EA, Educational Attainment; ESMK, Ever Smoked; N SNPs, Number of SNPs located within locus region; NEU, Neuroticism; P, p-value; P-corr, p-value corrected using Bonferroni correction for multiple testing; rg, genetic correlation, SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation; SNP, Single-Nucleotide Polymorphism; z, confounding variable controlled; -, not tested.

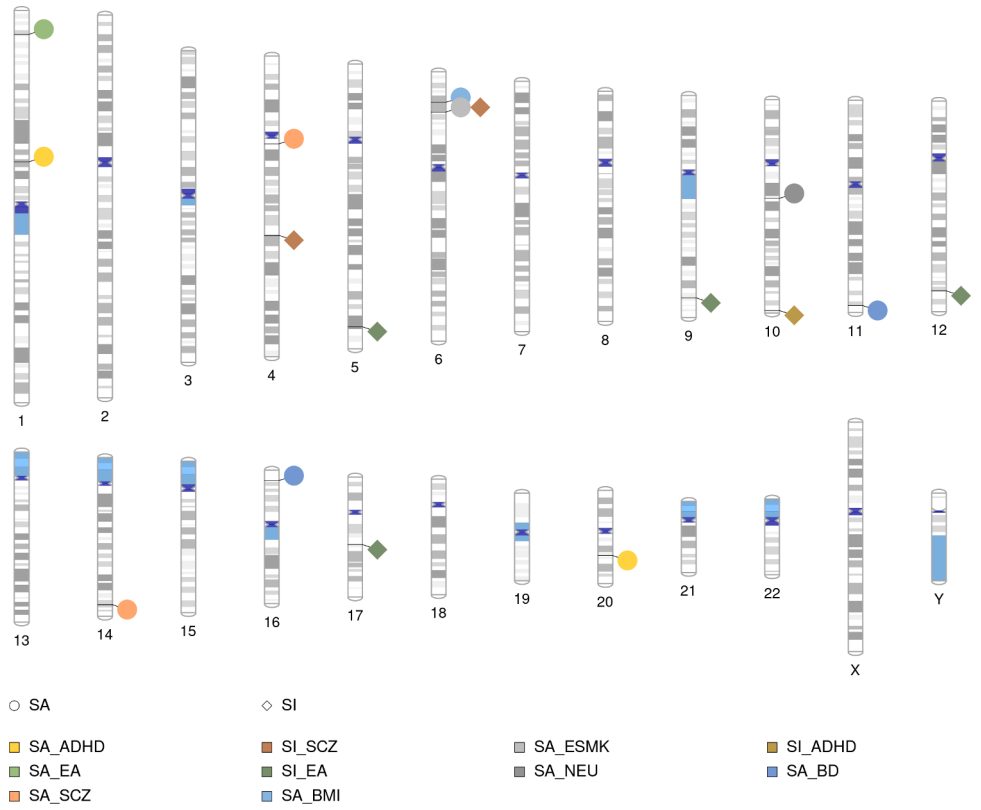

Figure 2. Chromosome view of local, pairwise genetic correlations between suicide attempt/ideation vs the other 13 correlated traits. ADHD, Attention Deficit and Hyperactivity Disorder; BD, Bipolar Disorder; BMI, Body Mass Index; EA, Educational Attainment; ESMK, Ever Smoked; NEU, Neuroticism; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation.

Table 3
Overview of ConjFDR results.

Trait 1	Trait 2	Candidate SNPs	Independent SNPs	Lead SNPs		Loci reported in the original GWAS	Novel reported loci	Percentage of loci with discordant effect direction
				All	With concordant effect direction			
SA	ADHD	3682	69	43	41	40	28	4.7%
	ASD	311	2	1	1	1	1	0%
	BD	1942	46	27	27	25	21	0%
	BMI	2736	39	30	20	29	4	33.3%
	CPD	387	13	6	6	6	5	0%
	DSN	4377	88	51	47	48	33	7.8%
	EA	559	7	7	6	7	0	14.3%
	ESMK	5831	118	61	58	56	31	4.9%
	INS	418	7	6	6	5	5	0%
	MSCP	1717	28	15	14	14	11	6.7%
	NEU	3652	89	55	54	50	37	1.8%
	RSKT	1363	30	15	14	15	9	6.7%
	SCZ	5114	115	60	57	57	23	5%
SI	ADHD	3192	47	34	34	34	29	0%
	ASD	422	5	5	4	5	4	20%
	BD	1223	25	19	18	19	15	5.3%
	BMI	1679	25	19	14	19	4	26.3%
	CPD	910	19	13	11	12	7	15.4%
	DSN	1642	30	23	20	23	13	13.0%
	EA	356	3	2	0	2	0	100%
	ESMK	2499	46	28	27	26	16	3.6%
	INS	215	3	3	2	3	3	33.3%
	MSCP	1580	25	20	20	20	16	0%
	NEU	4972	86	54	53	48	31	1.9%
	RSKT	1213	25	21	19	20	15	9.5%
	SCZ	3621	65	48	39	45	25	18.8%

ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; BMI, Body Mass Index; CPD, Cigarettes per Day; DSN, Disinhibition; EA, Educational Attainment; ESMK, Ever Smoked; INS, Insomnia; MSCP, Multi-Site Chronic Pain; NEU, Neuroticism; RSKT, Risk Tolerance; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation; SNP, Single-Nucleotide Polymorphism.

3.2. Cross-trait genetic associations identified via conjunctional FDR analyses

3.2.1. Polygenic enrichment and jointly associated loci

Results from the conjFDR analysis are summarised in Table 3 and Supplementary Table S35, with top loci for each phenotype pair shown in Table 4. Polygenic enrichment was observed for most SA phenotype pairs, with the exception of SA–EA and SA–INS. This was evident from Q–Q plots, which showed some degree of upward and leftward deviation when conditioned for progressively smaller p-value thresholds (Supplementary Figures S10-S35). Q–Q plots for SI–based pairs exhibited similar features but with smaller deviations. Notably, SI–EA, as SA–EA and SA–INS above, displayed no relevant deviation from the expected distribution, indicating that no polygenic enrichment was found for these pairs. These results are consistent with the findings in terms of novel loci identified (Table 3) where none was found for SA–EA and SI–EA. Among the other trait combinations, the number of jointly associated new loci ranged from 1 (SA–ASD) to 33 (SA–DSN) for SA–based pairs, and from 3 (SI–INS) to 29 (SI–ADHD) for SI–based pairs.

Cross-trait associations - defined by jointly associated loci (conjFDR < 0.05), independent significant SNPs, and lead SNPs - were identified for SA–ESMK, SA–SCZ, SI–NEU, SA–DSN, SA–ADHD, SA–NEU, and SI–SCZ. Among all trait pairs, SI–INS yielded the fewest significant loci (Table 3, Figure 3). Overall, SI–based analyses yielded fewer jointly associated loci than SA–based comparisons, with the exception of the CPD and NEU pairs, where SI results surpassed those for SA.

3.2.2. Effect directions, overlap with LAVA, and functional characterisation

Across phenotype pairs, the majority of lead SNPs exhibited a positive effect direction based on their individual trait z-scores (Table 4). When assessing cross-trait concordance, however, all pairs included a subset of discordant SNPs - defined as those with opposite effect directions between the two traits - ranging from 1.8% to 33.3% (Table 3, Figure 3). Complete concordance was observed for SA–ASD, SA–BD, SA–CPD, SA–INS, SI–ADHD, and SI–MSCP (all with positive effects in both traits), and for SI–EA (all with negative effects).

Of the 484 unique lead SNPs, only two (rs6593600, rs12888948) overlapped with genomic regions showing significant local genetic correlations in the same phenotype pairs after correcting for MDD and PTSD, corresponding to the loci chr1:96147577-97721186 for SA-ADHD and chr14:99474534-100786189 for SA-SCZ, respectively (Table 5).

A substantial proportion of SNPs identified through conjFDR analysis exhibited functional relevance, with 47% of mapped variants having a CADD score $\geq$ 12.37, indicating a deleterious potential. To further characterise the shared genetic architecture between suicidal and the other selected phenotypes, we mapped genes to the identified loci and examined their functional and biological relevance.

A total of 798 unique genes were mapped to SNPs identified through conjFDR analysis, 65.4% of which were protein-coding, 12.1% pseudogenes, 7.8% antisense RNA, and 7.2% long non-coding RNAs (lncRNAs) (Figure 4). Of these, 482 genes were mapped to loci identified in the analyses including SA and 421 to the loci identified in the analyses with SI.

In the SA subset, the most gene-rich trait pairs were SA–SCZ (217 genes, 154 protein-coding), SA–NEU (155, 109 protein-coding), and SA–DSN (135, 89 protein-coding). Fewer genes were mapped for SA–ASD (11, 3 protein-coding), SA–INS (10, 3 protein-coding), and SA–CPD (3, 2 protein-coding). Recurrently implicated genes in at least 5 phenotype pairs included those involved in cell adhesion, cell migration, and neurite growth (e.g. *NCAM1, LSAMP*), signal transduction (e.g. *FES, FAM212A/INKA1*), preprotein activation and secretion (e.g. *FURIN*),

Table 4
ConjFDR top loci (FDR < 0.001) per trait-pairs and relative mapped genes.

SNP	Trait pair (ED trait 1 / ED trait 2)	Mapped gene(s)
rs3791129	SA–ADHD (+ / +)	*ARTN, ST3GAL3, B4GALT2, CCDC24, SLC6A9, ATP6V0B,* RP11-7O11.3, *IPO13*
rs2503185	SA–BMI (- / -)	-
rs35869525	SA–BD (- / -)	Several genes of different families, like *BTN* (MHC-like genes), *HIST, ZSCAN*
rs8039305	SA–BD (- / -)	*FES, FURIN*
rs9641538	SA–BD (+ / +)	-
rs4630328	SA–CPD (- / -)	*DRD2*
rs62474713	SA–DSN (+ / +)	-
rs2503185	SA–DSN (- / -)	-
rs17514846	SA–DSN (- / -)	-
rs2582897	SA–DSN (- / -)	-
rs2503185	SA–ESMK (- / -)	-
rs12798900	SA–NEU (+ / +)	-
rs35526527	SA–NEU (- / -)	Several BTN*, OR*, ZSCAN*, and HIST* genes
rs4275159	SA–RSKT (+ / +)	-
rs6224	SA–SCZ (- / -)	FES, FURIN
rs4245150	SA–SCZ (- / -)	DRD2
rs35869525	SA–SCZ (- / -)	Several genes of different families, like *BTN* (MHC-like genes), *HIST, ZSCAN*
rs10835363	SI–ADHD (- / -)	-
rs1823673	SI–BMI (- / -)	-
rs7200879	SI–BMI (- / +)	*FBXL19, STX1B, HSD3B7, SETD1A, STX4, KAT8, RNF40, ZNF646, VKORC1, ORAI3, RIM72, PRSS36*, C16orf93, RP11-196G11.2, AC135048.13, RP11-388M20.9, *INO80E*
rs1836798	SI–DSN (+ / +)	-
rs10767730	SI–DSN (- / -)	-
rs264921	SI–ESMK (- / -)	-
rs1836798	SI–ESMK (+ / +)	-
rs10835363	SI–ESMK (+ / +)	-
rs62098014	SI–MSCP (+ / +)	-
rs56403421	SI–NEU (+ / +)	*CTD-2171N6.1*
rs17503448	SI–NEU (+ / +)	-
rs1116313	SI–NEU (+ / +)	-
rs56403421	SI–SCZ (+ / +)	*CTD-2171N6.1*

ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; BMI, Body Mass Index; CPD, Cigarettes per Day; DSN, Disinhibition; EA, Educational Attainment; ED, Effect Direction; ESMK, Ever Smoked; INS, Insomnia; MSCP, Multi-Site Chronic Pain; NEU, Neuroticism; RSKT, Risk Tolerance; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation; SNP, Single-Nucleotide Polymorphism.

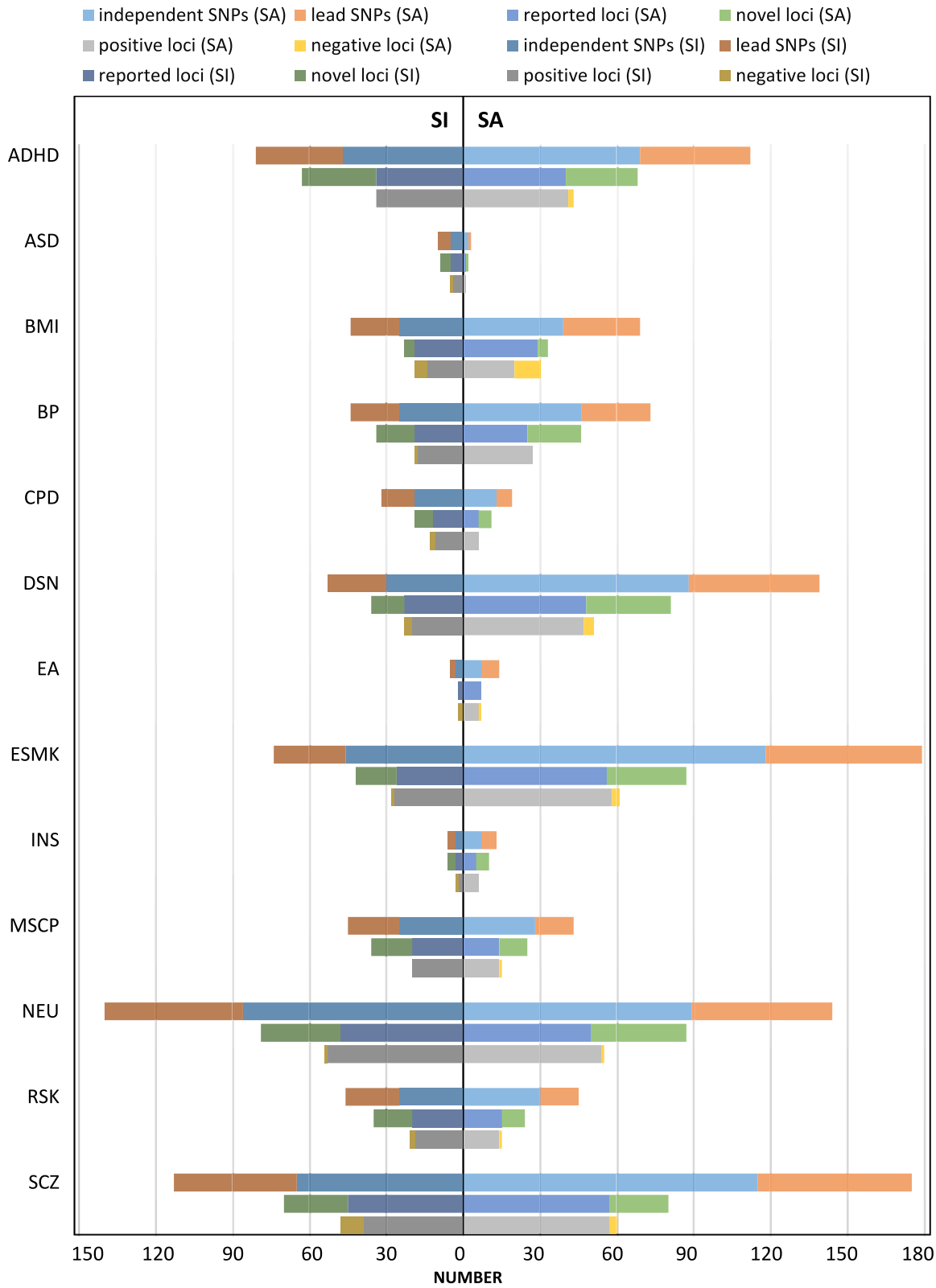

Figure 3. Overview of ConjFDR results. Independent SNPs: number of independent SNPs significantly associated with both traits; lead SNPs: number of lead SNPs; negative loci: number of loci with opposite effect directions in the two traits; novel loci: number of loci significantly associated with both traits that were not significant in the original GWAS; positive loci: number of loci with the same effect directions in the two traits; reported loci: number of loci significantly associated with both traits. ADHD, Attention Deficit and Hyperactivity Disorder; ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; CPD, Cigarettes per Day; DSN, Disinhibition; EA, Educational Attainment; ESMK, Ever Smoked; INS, Insomnia; MSCP, Multi-Site Chronic Pain; NEU, Neuroticism; RSKT, Risk Tolerance; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation.

Table 5
Overlapping results between conjFDR and LAVA.

Trait pair	Chr	Start[a]	Stop[a]	Lead SNP[b]	Genes mapped (from SNPs)	Genes mapped (from locus)
SA–ADHD	1	96147577	97721186	rs6593600	*RP5-898J17.1* (ncRNA-intronic) *RP4-736I12.1* (intergenic), EEF1A1P11 (intergenic)	*DPYD, DPYD-AS1, EEF1A1P11, LINC01787, LINC02790, LOC101060164, NDUFS5P2, PTBP2, RN7SKP270, RN7SL831P, RNU1-130P, RPL7P9, UBE2WP1*
SA–SCZ	14	99474534	100786189	rs12888948	*AL109767.1* (antisense), *BCL11B, VRK1*	*BCL11B, CCDC85C, CCNK, CYP46A1, DEGS2, EML1, EVL, HHIPL1, MIR151B, MIR342, MIR345, MIR6764, RN7SL523P, RNU1-47P, RNU6-91P, RPS2P3, SETD3, SLC25A29, VDAC3P1, YY1, YY1-DT*

Chr, Chromosome; SA, Suicide Attempt; SCZ, Schizophrenia; SI, Suicidal Ideation; SNP, Single-Nucleotide Polymorphism. a Derived from LAVA analyses; b Derived from conjFDR analyses.

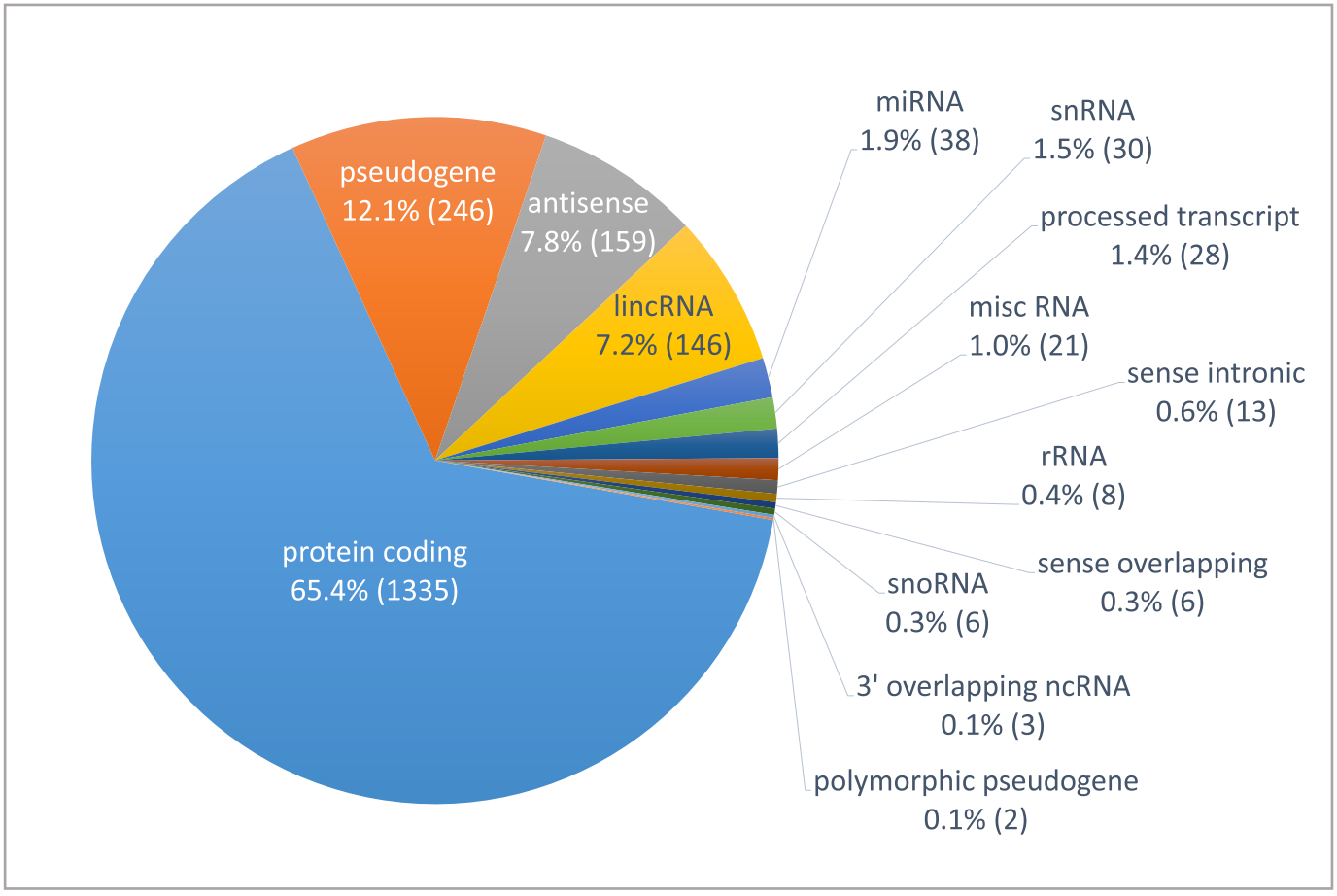

Figure 4. Gene type. Overall gene types mapped from ConjFDR results expressed as percentages (absolute values in parentheses). lincRNA, long non-coding RNA; miRNA, micro RNA; misc RNA, miscellaneous RNA; ncRNA, non-coding RNA; rRNA, ribosomal RNA; snoRNA, small nucleolar RNA.

and transcriptional regulation (e.g. *MED27*) (Table S36). Other recurrent genes across SA-based pairs included *AMT*, encoding a glycine cleavage system component, and *ARTN*, encoding a ligand of the glial cell line-derived neurotrophic factor (GDNF) family (Table S36). With regard to SI, the phenotypes that shared the greatest number of genes with SI were NEU (198 genes, 124 protein-coding), SCZ (157, 97 protein-coding), and ADHD (114, 84 protein-coding), while INS showed the lowest number of jointly associated genes (14 overlapping genes, 8 protein-coding). No gene was mapped to the SI–ESMK trait pair. Notably, some of the most recurrent genes across SI pairs are in common with those mapped for phenotype pairs including SA; these include *NCAM1, FURIN* and *FES*. Other recurrent genes encode for zinc-finger proteins, as well as for proteins involved in transcription (*MAFK*), mitosis (*MAD1L1*), and cell cycle control and DNA repair (*FTSJ2*, also known as *MRM2*).

Gene set enrichment analysis identified 640 unique gene sets - 525 for SA-based analyses and 276 for SI-based analyses. Enrichment was observed for genes implicated in brain morphology, subcortical volumes, cortical surface area, and psychiatric phenotypes including ASD, SCZ, anorexia nervosa, mood instability, risk-taking behaviour, age at first intercourse, and NEU. Additional enrichment was seen for gene sets involved in transcription factor targets, immune response, and other cellular processes (Table S37). Extending the gene set enrichment results, eight SA trait pairs (i.e., SA–ADHD, SA–BMI, SA–DSN, SA–EA, SA–ESMK, SA–MSCP, SA–NEU, and SA–SCZ) showed enrichment in genes located in chr3p21, whereas six SI trait pairs (i.e., SI–ADHD, SI–ASD, SI–DSN, SI–NEU, SI–RSKT, and SI–SCZ) exhibited enrichment for genes located in chr17q21. Notable differences emerged among the two subgroups of SA vs SI trait pairs; SA– trait pairs were predominantly enriched for genes related to brain morphology, psychiatric traits,

cognitive function, and sleep regulation, whereas SI– trait pairs showed greater enrichment in gene sets linked to NEU, BMI, and gastrointestinal diseases (Table S37). Despite these distinctions, both SA– and SI–trait pairs exhibited enrichment in gene sets involved in glycine, serine, and threonine metabolism (SI–ADHD, SA–DSN, and SA–NEU) and systemic lupus erythematosus (SA/SI–BD, SA/SI–NEU, SI–RSKT, and SA/SI–SCZ). Further enrichments were more broadly observed in pathways associated with DNA packaging, DNA/nucleosome binding, and chromatin remodelling (Table S37).

MAGMA gene-property analysis was used to examine tissue-specific expression profiles of genes mapped through conjFDR analyses. Significant enrichment was observed for SA–NEU-associated genes in tibial nerve tissue, as well as in brain tissue at 26 weeks post-conception. Significant enrichment was also found for SA–DSN associated genes at 2 years of age, whilst no tissue enrichment was found for SI pairs. Full results, including non-significant findings, can be found in Table S38.

4. Discussion

4.1. Main findings

This study provides a detailed characterisation of the shared genetic architecture between SI, SA, and a broad set of psychiatric, behavioural, and somatic phenotypes by integrating two complementary analytic frameworks: LAVA and conjFDR. The combination of these methods allows evaluation of regional covariance and SNP-level joint association within the same analytical flow. Whereas LAVA identifies the genomic regions where polygenic covariance arises, conjFDR detects the specific variants driving cross-trait enrichment. Together, these analyses yield a more granular understanding of the pleiotropy underlying vulnerability to suicidal thoughts and behaviour.

Across traits, SA and SI differed substantially in both the number and distribution of jointly associated loci, reinforcing accumulating evidence that they reflect partially distinct etiological processes rather than points along a simple severity continuum. SA demonstrated greater genetic sharing with traits characterised by behavioural disinhibition, substance use, psychosis liability, and metabolic dysregulation, whereas SI mapped more consistently onto internalizing features, cognitive–affective traits (e.g., neuroticism), and sleep- and pain-related phenotypes. These diverging patterns are consistent with epidemiological findings showing the limited predictive value of SI for subsequent SA and suggest that these phenotypes may arise from separable liability pathways with only partial overlap (Klonsky et al., 2021b). This is relevant for risk-stratification frameworks that historically treat SI and SA as gradations of a common process. It is noteworthy that neurodevelopmental disorders such as ADHD and ASD were associated with both SA and SI, and that this pattern was consistent across LAVA and conjFDR analyses. Moreover, the patterns observed for SA and SI were highly similar when considering ADHD and MSCP, reflecting the strong genetic correlation specifically between ADHD and pain traits (Ciochetti et al., 2025).

A small number of loci emerged across both methods despite stringent conditioning on MDD and PTSD in the LAVA analysis. These convergent signals - one for SA–ADHD and one for SA–SCZ - likely represent higher-confidence pleiotropic regions whose effects are robust across statistical frameworks and not simply reflections of global correlation or collinearity with common psychiatric comorbidities. Genes mapped to these SNPs and regions participate in neuronal and immune cell proliferation, differentiation, and survival. Their cross-trait presence suggests that immune and early neurodevelopmental processes may constitute core mechanisms linking suicidality with external phenotypes.

Enrichment analyses further demonstrated that the biological pathways shared with SA and SI extend beyond classical neurobiological processes. Many phenotype pairs showed enrichment for gene sets related to brain morphology, cortical and subcortical structure, chromatin dynamics, transcriptional regulation, and glycine–serine–threonine metabolism - implicating neurotransmission, neuronal growth, and excitatory–inhibitory balance. Notably, glycine transporter genes (e.g., *SLC6A9*), repeatedly implicated in SA- and SI-based pairs, modulate NMDA receptor tone and astrocytic regulation of glutamatergic signalling (Cummings and Popescu, 2015; Mizzi and Blundell, 2025). This aligns with growing evidence that NMDA modulation can acutely reduce suicidal thoughts and supports the hypothesis that glycine–NMDA pathways may be mechanistically relevant to suicidal vulnerability (Canuso et al., 2021; Fu et al., 2023; Pompili, 2020).

An important and often overlooked finding of this study is the reproducible tissue enrichment in non-brain tissues, including liver, intestine, colon, skin, vasculature, and kidney cortex. Rather than representing peripheral noise, these results align with a substantial body of literature documenting bidirectional interactions between psychiatric phenotypes and systemic processes such as inflammation, metabolic regulation, epithelial integrity, microbiome–immune crosstalk, and vascular function. The presence of suicide-associated pleiotropic genes in these tissues suggests that suicidality may not be exclusively neurocentric but may arise from integrated brain–body mechanisms. This perspective is consistent with epidemiological links of suicidality with autoimmune (Brundin et al., 2015; Isung et al., 2020; Yang et al., 2025) and cardiometabolic diseases (Chen et al., 2023), as well as gastrointestinal dysregulation (Costanza et al., 2025), pointing to multisystemic biological signatures worthy of further investigation.

Across multiple trait combinations, we also identified shared loci enriched for gene sets associated with neuroticism, behavioural control, and age at first sexual intercourse (AFSI). Previous Mendelian randomisation studies indicate that AFSI may index underlying neurobiological vulnerability to self-harm, potentially via mediating effects of MDD and SCZ polygenic risk (Dong et al., 2024). This supports the hypothesis that early-life behaviours and developmental trajectories may reflect or contribute to latent liabilities shared with suicidal phenotypes.

Taken together, the patterns observed here - methodological convergence at a small number of high-confidence loci; trait-specific and phenotype-specific enrichment signatures; and the presence of both neural and peripheral tissue signals - support a model in which suicidal thoughts and behaviours arise from a heterogeneous architecture composed of partly independent but interacting neurodevelopmental, neurochemical, behavioural, and somatic pathways. These findings reinforce the need for phenotypic precision when studying suicidal outcomes and indicate the usefulness of integrating multilayered genomic information to uncover biologically meaningful pleiotropy.

4.2. Strengths and limitations

A major strength of this study is the integration of two complementary analytic frameworks that capture distinct dimensions of pleiotropy. LAVA provides spatially localised estimates of genetic covariance, whereas conjFDR detects cross-trait enrichment even when individual GWAS lack genome-wide significant loci. Used together, these approaches allow both validation and refinement of shared genetic signals, increasing robustness and interpretability. Systematic conditioning on MDD and PTSD within the LAVA framework further strengthens inference by differentiating locus-specific sharing from broader affective comorbidity.

Because suicidality is included as a diagnostic criterion for MDD, conditioning may partially attenuate suicidality-related genetic signals due to phenotypic and genetic overlap. Thus, conditioned results should be interpreted as reflecting residual locus-specific sharing beyond general affective liability, rather than entirely independent biological mechanisms. This distinction is particularly relevant when interpreting divergence between SA and SI following conditioning procedures. Additional strengths include the use of large, contemporary GWAS datasets and the inclusion of a broad spectrum of psychiatric and non-psychiatric traits, enabling examination of shared liability beyond traditional diagnostic boundaries.

Several limitations warrant consideration. Some phenotypes, such as ASD, remain relatively underpowered, which may reduce sensitivity to detect pleiotropy. Moreover, LAVA and conjFDR estimate genetic covariance and joint association, but do not establish causal relationships. Functional validation will require integration with transcriptomic, proteomic, and cellular model systems.

The predominance of European-ancestry samples limits generalisability and highlights the urgent need for cross-ancestry genomic resources (Bruxel et al., 2025; Cabrera-Mendoza et al., 2026; da Silva et al., 2026). Although original GWASs adjusted for sex as a covariate, sex-stratified summary statistics were not uniformly available. Consequently, the present analyses characterise shared genetic architecture at the population level and cannot detect sex-specific genetic effects. Given well-established sex differences in suicidal behaviours, future large-scale sex-stratified analyses will be critical to refine and contextualize these findings. In addition, analyses were restricted to autosomal chromosomes. Most large-scale psychiatric GWAS exclude sex chromosomes due to analytical complexities - such as dosage compensation modelling, imputation challenges, and inconsistent reporting standards - but incorporation of sex chromosome variation in future suicidality studies may yield additional biological insight. Enrichment signals observed in peripheral tissues should be interpreted cautiously, given tissue specificity and regulatory architecture. Replication and triangulation in independent multi-omic datasets will be needed to clarify functional relevance.

Finally, these results should be interpreted in light of the rapidly evolving suicidality GWAS literature. Larger datasets generated through coordinated Psychiatric Genomics Consortium efforts have recently become available (Colbert et al., 2025, preprint). When the present analyses were designed and finalised, harmonised summary statistics suitable for systematic cross-trait analyses had not yet been formally released. Future work can build on our findings by leveraging larger suicidality GWAS resources to (i) replicate the locus-specific covariance and cross-trait enrichment signals reported here and (ii) extend inference through analyses that are not feasible in smaller datasets, including sex-stratified models, cross-ancestry evaluation, and functional follow-up (e.g., colocalisation with eQTL/pQTL, TWAS/PWAS, and cell-type regulatory annotation) to further refine candidate mechanisms underlying biologically meaningful pleiotropy.

4.3. Conclusions

This study refines current understanding of the genetic architecture linking SA and SI to a broad spectrum of psychiatric, somatic, and behavioural traits. By integrating region-level genetic covariance with SNP-level cross-trait association mapping, we enhanced the resolution for detecting pleiotropic loci and implicated pathways - particularly those related to neurodevelopment, immune dysregulation, and glycine–NMDA signalling. The distinct and partially overlapping association profiles observed for SA and SI underscore the importance of precise and differentiated phenotypic definitions when interrogating suicidal thoughts and behaviours. Collectively, these findings may inform future efforts in stratified risk prediction and guide the development of mechanistically grounded interventions.

Author disclosure

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Contributors

Diego L. Rovaris and Giuseppe Fanelli conceptualised, supervised and coordinated the study. Isabella Folego-Temoteo and Alfonso Martone performed the statistical analysis, curated the data and wrote the initial draft of the manuscript. Alessandro Serretti, Chiara Fabbri, Eugenio H. Grevet, Claiton H.D. Bau, Cibele E. Bandeira, Gabriel R. Fries, Janita Bralten, Anna R. Docherty, and Allison E. Ashley-Koch, Iria Grande and Xenia Gonda reviewed the manuscript and provided critical insights. Giuseppe Fanelli, Diego L. Rovaris, Alfonso Martone and Isabella Folego-Temoteo finalised the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

To improve the clarity and fluency of the manuscript, we used ChatGPT (OpenAI) for assistance with English grammar, punctuation, and style. The content was entirely generated by the authors, and ChatGPT was not used for data analysis, interpretation, or writing of scientific content.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work described in the manuscript.

Supplementary materials

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