

Original Article

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Integrating HiTOP and RDoC frameworks part II: shared and distinct biological mechanisms of externalizing and internalizing psychopathology

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Abstract

Background. The Hierarchical Taxonomy of Psychopathology (HiTOP) and Research Domain Criteria (RDoC) frameworks emphasize transdiagnostic and mechanistic aspects of psychopathology. We used a multi-omics approach to examine how HiTOP's psychopathology spectra (externalizing [EXT], internalizing [INT], and shared EXT + INT) map onto RDoC's units of analysis.

Methods. We conducted analyses across five RDoC units of analysis: genes, molecules, cells, circuits, and physiology. Using genome-wide association studies from the companion Part I article, we identified genes and tissue-specific expression patterns. We used drug repurposing analyses that integrate gene annotations to identify potential therapeutic targets and single-cell RNA sequencing data to implicate brain cell types. We then used magnetic resonance imaging data to examine brain regions and circuits associated with psychopathology. Finally, we tested causal relationships between each spectrum and physical health conditions.

Results. Using five gene identification methods, EXT was associated with 1,759 genes, INT with 454 genes, and EXT + INT with 1,138 genes. Drug repurposing analyses identified potential therapeutic targets, including those that affect dopamine and serotonin pathways. Expression of EXT genes was enriched in GABAergic, cortical, and hippocampal neurons, while INT genes were more narrowly linked to GABAergic neurons. EXT + INT liability was associated with reduced gray matter volume in the amygdala and subcallosal cortex. INT genetic liability showed stronger causal effects on physical health – including chronic pain and cardiovascular diseases – than EXT.

Conclusions. Our findings revealed shared and distinct pathways underlying psychopathology. Integrating genomic insights with the RDoC and HiTOP frameworks advanced our understanding of mechanisms that underlie EXT and INT psychopathology.

Introduction

The history of psychiatric nosology reflects an ongoing tension between the search for discrete categories of mental illness and the reality of complex, overlapping symptomatology. Although categorical classification systems like the Diagnostic and Statistical Manual of Mental Disorders (e.g. DSM-5) (American Psychiatric Association, 2013) provide a common language for diagnosis, they have faced criticism for their unreliability (Gordon & Heimberg, 2011) and the high degree of heterogeneity and comorbidity they yield (Borgogna, Owen, & Aita, 2024). At an aggregate level, there are more than 10 million unique symptom combinations that can result in a diagnosed mental illness and almost two million ways to present with symptoms without meeting the criteria for *any* diagnosis (Borgogna et al., 2024). This imprecision and variability hinder progress in psychiatric research, including efforts to develop targeted interventions.

Compounding these issues is the problem of multiple realizability, where a given psychiatric disorder can emerge from many biological, psychological, and environmental pathways (Kendler, 2022b). Thus, two individuals with depression may present with the same symptoms but differ in the mechanisms that underlie the disorder. This complexity makes it difficult to map psychiatric disorders onto biological etiologies, a challenge amplified by the 'curse of polygenicity' (Kendler, 2022a, 2022b). Psychiatric disorders, among the most complex human traits, are influenced by thousands of genetic variants, each exerting only a small effect (Holland et al.,

2020). The highly polygenic nature of these conditions increases the likelihood that many different combinations of genetic and environmental factors produce similar clinical presentations. Findings from recent genome-wide association studies (GWAS) highlight this complexity. Although GWAS have identified hundreds of loci associated with psychiatric disorders (Als *et al.*, 2023; Trubetskoy *et al.*, 2022), translating these findings into meaningful biological insights has been elusive.

Recent shifts toward dimensional and transdiagnostic frameworks, such as the Hierarchical Taxonomy of Psychopathology (HiTOP) and the Research Domain Criteria (RDoC), aim to address these limitations. HiTOP organizes psychopathology along hierarchical dimensions, from narrow symptoms to broad spectra, culminating in an overarching general psychopathology factor (*p*-factor) (Kotov *et al.*, 2017). By contrast, RDoC focuses on identifying transdiagnostic mechanisms acting across multiple units of analysis, including genes, cells, circuits, and behaviors (Insel *et al.*, 2010). These frameworks offer alternative approaches to conceptualizing and studying mental health, with both emphasizing shared and specific liabilities rather than rigid diagnostic categories.

The connection between mental and physical health further underscores the complexity and clinical relevance of these frameworks. Psychiatric disorders frequently co-occur with physical health conditions like chronic pain, cardiovascular disease, and other chronic illnesses, reflecting shared genetic etiologies (Davis *et al.*, 2024; Lawrence *et al.*, 2024). Furthermore, these conditions are clinically significant outcomes that conceptually align with externalizing (EXT) and internalizing (INT) psychopathology. For example, individuals who score higher on measures of negative valence report greater pain severity (Sambuco *et al.*, 2022), while cardiovascular disease and other chronic illnesses are influenced by stress-related pathways and behavioral risk factors (e.g. smoking) tied to EXT and INT liability (Burke, Genuardi, Shappell, D'Agostino, & Magnani, 2017; Tully, Harrison, Cheung, & Cosh, 2016). Recently, it has been proposed that sensory processing be added to RDoC (Harrison, Kats, Williams, & Aziz-Zadeh, 2019), which has particular relevance for understanding pain as both a physical and psychological phenomenon. The considerable overlap between physical and mental health raises questions about how physical health conditions fit within psychopathology models like HiTOP, which tentatively incorporates a somatoform spectrum, and whether mechanisms identified in RDoC extend across both health domains.

Despite the potential that integration of HiTOP and RDoC has to advance psychiatric nosology, significant gaps in that effort remain. HiTOP's emphasis on shared psychopathology spectra provides insight into the co-occurrence of EXT and INT problems and facilitates research on mechanistic underpinnings through its descriptive classification framework (DeYoung *et al.*, 2024; Waszczuk *et al.*, 2020). RDoC, in turn, emphasizes mechanisms but lacks the hierarchical structure needed to reconcile overlapping yet distinct components of psychopathology. Bridging these frameworks could accelerate etiological research and facilitate the development of novel treatments for psychiatric disorders (Michelin, Palumbo, DeYoung, Latzman, & Kotov, 2021).

This study builds upon Part I (Davis *et al.*, 2025), which leveraged HiTOP's dimensional framework to examine the genetic architecture of EXT and INT psychopathology using genomic structural equation modeling (gSEM). The most parsimonious and best-fitting structure was that of a two-factor correlated model, with EXT and INT having correlated but distinct genetic liabilities. To model the genetic variance shared by EXT and INT, we derived a

higher-order EXT + INT factor. We performed GWAS on the factors and identified hundreds of genetic loci associated with EXT, INT, and their shared liability. Consistent with the HiTOP model, our findings supported both shared and spectrum-specific liabilities.

While Part I evaluated the genetic architecture of EXT and INT within a HiTOP-informed framework, the biological mechanisms that underlie these spectra remain unclear, including the extent to which mechanisms are shared or distinct. To address this, Part II takes an exploratory approach, integrating HiTOP's structural framework with RDoC's units of analysis to investigate how genetic risk for EXT and INT manifests across multiple biological domains. Specifically, we examine mechanisms across genes, molecules, cells, circuits, physiology, and behavior to determine whether associations are unique to each spectrum or reflect common mechanisms of both. Building on insights into the genetic architecture of these spectra provided in the Part I companion article, this study offers a novel integration aimed at deepening our understanding of the genetic architecture of EXT and INT psychopathology and informing more precise approaches to diagnosis, classification, and treatment.

Methods

Genome-wide association studies

This study uses summary statistics from GWAS conducted in the companion Part I article for EXT, INT, and their shared liability (EXT + INT). The GWAS was derived from genomic structural equation models (gSEM) of 16 clinical and subclinical EXT (e.g. substance use disorders and risky behaviors) and INT (e.g. mood, anxiety, and wellbeing) traits. The GWAS results serve as the foundation for all downstream analyses in this article, and details on the GWAS methods employed can be found in Part I.

Unit of analysis: Genes

Gene expression and enrichment

We identified genes associated with EXT, INT, and their shared liability (EXT + INT) using multiple approaches. First, we performed gene-based tests using MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015), which aggregates association signals from genetic variants to genes based on their position. Second, we mapped additional genes based on functional effects, including expression quantitative trait loci (eQTLs), which link genetic variation to gene activity, and chromatin interaction data, which identify physical connections between genomic regions. We then examined the expression of associated genes across developmental stages and within specific brain regions using data from BrainSpan (Li *et al.*, 2018) and GTEx v8 (The GTEx Consortium *et al.*, 2020).

Transcriptome-wide association studies

To prioritize potential causal genes, we conducted transcriptome-wide association studies (TWAS) using two complementary methods. TWAS identifies genes whose predicted expression levels are associated with a trait by integrating GWAS data with gene expression profiles to help pinpoint genes that may play a causal role in the biological pathways underlying the GWAS trait. First, we used S-MultiXcan (Barbeira *et al.*, 2019) to simultaneously integrate gene expression data across 13 brain tissues. Next, we used S-PrediXcan (Barbeira *et al.*, 2018) to focus specifically on data from the frontal and temporal cortices of psychiatric cases and

controls (Gandal et al., 2018; Jourdon, Scuderi, Caputo, Abyzov, & Vaccarino, 2021). We applied a Bonferroni correction to account for multiple tests.

Unit of analysis: Molecules

To identify druggable targets – genes that encode proteins that can be modulated by existing drugs or are predicted to be viable candidates for therapeutic development – we mapped genes associated with EXT, INT, and EXT + INT to databases of known gene-drug interactions using the Drug-Gene-Interaction Database (Freshour et al., 2021). We included genes that interact with currently approved medications and investigational compounds, prioritizing targets supported by multiple lines of genetic evidence, such as chromatin interactions (which identify physical connections between genetic regions) and eQTL analyses (which link genetic variation to gene activity). For EXT and INT, we focused on genes associated with one spectrum but not the other, aiming to identify drugs that could provide targeted therapeutic options based on biological mechanisms specific to EXT or INT.

Unit of analysis: Cells

We examined genetic effects on brain cell types using single-cell RNA sequencing (scRNA-seq) datasets from 15 human brain cell expression profiles (Darmanis et al., 2015; Habib et al., 2017; La Manno et al., 2016; Watanabe, Umičević Mirkov, de Leeuw, van den Heuvel, & Posthuma, 2019). Independently associated cell types were identified using three-step conditional analyses. First, we identified significant cell types within each dataset. Next, we performed within-dataset conditional analyses to identify independent associations among correlated cell types. Finally, we conducted cross-dataset conditional analyses to assess whether associations reflected shared genetic signals across the datasets.

Unit of analysis: Circuits

To examine how EXT, INT, and EXT + INT relate to brain structures and connectivity, we used BrainXcan (Liang et al., 2022), which links genetic data to 327 imaging-derived phenotypes (IDPs) from structural and diffusion magnetic resonance imaging (MRI) scans. Effect sizes and *p*-values were adjusted using linkage disequilibrium (LD) block-based permutation to account for inflation in test statistics that can arise from the correlations among nearby genetic variants. We also applied a Bonferroni correction to account for multiple tests.

Unit of analysis: Physiology

To evaluate potentially causal impacts on 15 physical health traits, we conducted Generalized Summary-data-based Mendelian Randomization (GSMR) analyses (Zhu et al., 2018). GSMR estimates the potential causal effects of exposures (i.e. EXT, INT, or EXT + INT) on outcomes (i.e. physical health traits) by leveraging GWAS summary statistics and treating genetic variants as instrumental variables. We based instrument selection on a genome-wide significance threshold of $p < 5 \times 10^{-8}$ to ensure robust genetic associations. To address horizontal pleiotropy, which violates a major assumption of Mendelian randomization analyses requiring that instruments influence the outcome solely through the exposure, we applied the heterogeneity in dependent instruments (HEIDI)-outlier method (Zhu et al., 2018). This excludes genetic

variants with evidence of such pleiotropic effects to reduce bias in causal estimates. We applied a Bonferroni correction to account for multiple tests.

Physical health traits were chosen from four domains with strong empirical and theoretical links to psychopathology: (1) pain, (2) general health, (3) cardiovascular disease, and (4) other chronic illnesses (Isvoranu et al., 2021; Lawrence et al., 2024; Waszczuk et al., 2023; Zhang et al., 2021). The pain domain comprised GWAS of pain intensity (Toikumo et al., 2024), multisite chronic pain (Johnston et al., 2019), and back pain (Freidin et al., 2019). General health indices included summary statistics from GWAS of long-standing illness, disability, or infirmity; hospitalization; and age at death conducted in the UK Biobank (<http://www.nealelab.is/uk-biobank/>). Cardiovascular disease GWAS comprised five traits: (1) heart failure (Zhou et al., 2022), (2) stroke (Zhou et al., 2022), (3) myocardial infarction (Hartiala et al., 2021), (4) hypertension (<http://www.nealelab.is/uk-biobank/>), and (5) abdominal aortic aneurysm (Zhou et al., 2022). Finally, we selected four GWAS of other chronic illnesses: (1) type 2 diabetes (Mahajan et al., 2022), (2) inflammatory bowel disease (IBD) (Liu et al., 2023), (3) chronic obstructive pulmonary disease (Zhou et al., 2022), and (4) asthma (Zhou et al., 2022).

Results

Unit of analysis: Genes

Gene expression and enrichment

Using MAGMA's genome-wide gene-based test, we identified 326 genes associated with EXT but not INT (Supplementary Table 1; e.g. *CADM2* and *FTO*). Although not differentially expressed during any developmental period, EXT-specific genes were differentially expressed in four brain tissues: the hippocampus, amygdala, putamen, and caudate (Supplementary Figure 1). A gene set related to mRNA binding was the only significant association (Supplementary Table 2). There were 31 genes associated with INT but not EXT (Supplementary Table 3; e.g. *CCDC68*). The INT-specific genes were not differentially expressed in any developmental stages or tissue types, and no gene sets were significant. Of the genes associated with EXT + INT (Supplementary Table 4), 29 were also identified by both first-order factors (e.g. *DRD2*, *NCAM1*, and *DCC*). Gene expression for EXT + INT was significantly upregulated during early and early mid-prenatal periods and downregulated during early childhood. EXT + INT genes were upregulated in 10 brain regions, including the frontal cortex, amygdala, anterior cingulate cortex, and hippocampus (Supplementary Figure 2), but no gene sets were significant.

Transcriptome-wide association studies

Using S-MultiXcan to predict effects on gene expression across 13 brain tissues revealed 352 significant genes for EXT, 141 for INT, and 238 for EXT+INT (Figure 1, Supplementary Figure 3, and Supplementary Tables 5–7). TWAS using PsychENCODE data identified 207 genes for EXT, 52 for INT, and 124 for EXT+INT (Supplementary Tables 8–10 and Supplementary Figure 4). Forty-five genes were identified in both TWAS for EXT, 21 for INT, and 36 for EXT+INT (Supplementary Figures 5–7).

Integration across gene identification methods

Collectively, across all five gene identification methods (MAGMA, chromatin interactions, eQTLs, S-MultiXcan, and S-PrediXcan), we identified 1,759 genes associated with EXT, 454 with INT, and

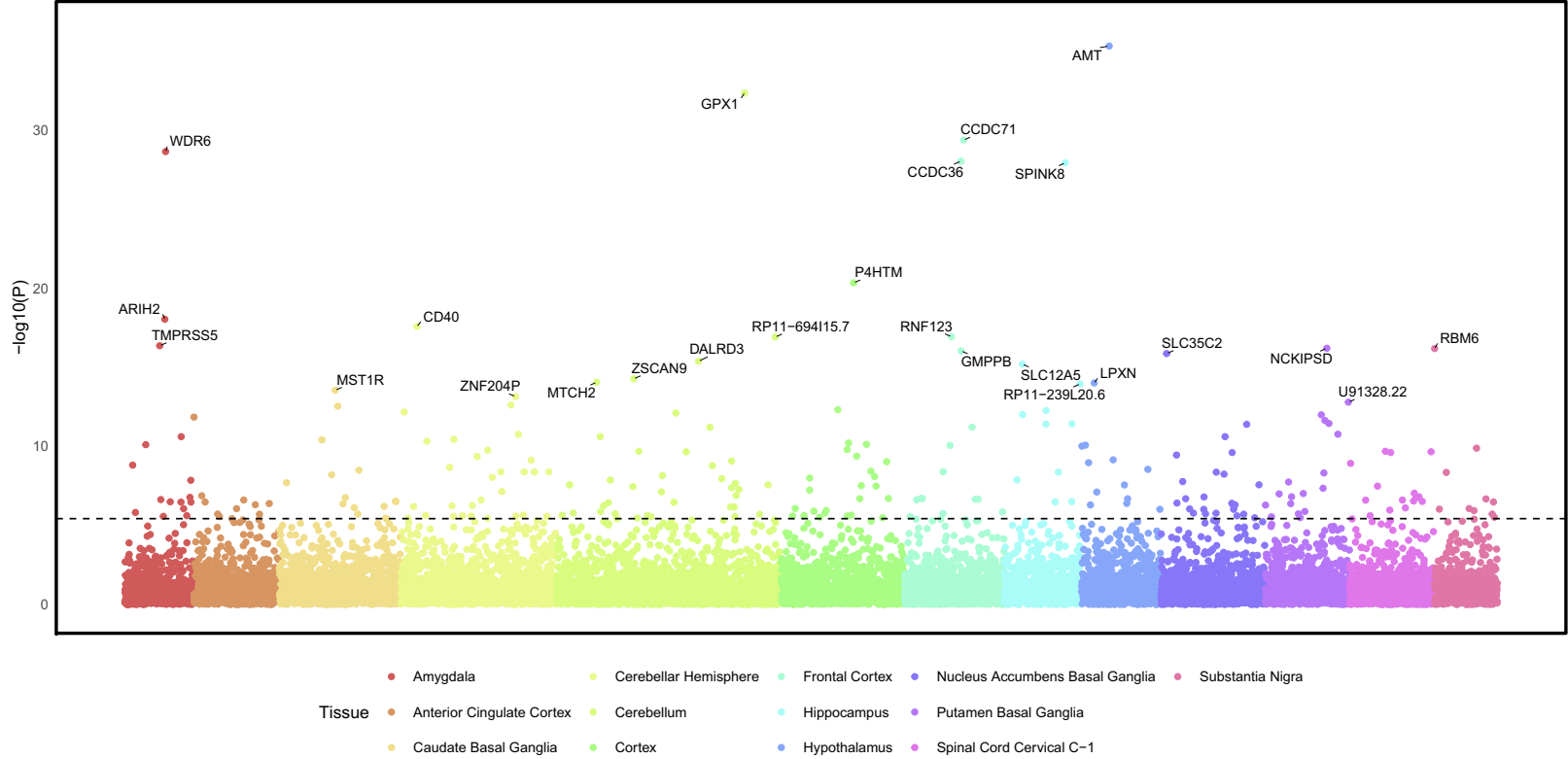


Figure 1. Transcriptome-wide association study (TWAS) for the externalizing and internalizing (EXT + INT) factor across 13 brain tissues. Gene names for the top 25 significant associations are annotated. Significance was determined using a Bonferroni-adjusted p -value of 3.73×10^{-6} ($0.05/13,406$ tests). The dashed line at 5.43 indicates the significance level ($-\log_{10}(3.73 \times 10^{-6})$). A total of 236 associations were significant after multiple testing corrections. Full TWAS results for all the factors can be found in [Supplementary Tables 5–10](#).

1,138 with EXT+INT (Supplementary Figure 8). For EXT, 20.41% of associated genes were identified using more than one method, including seven genes – *AS3MT*, *BTN3A2*, *KHK*, *NOB1*, *RPGRIP1L*, *SMIM19*, *ZKSCAN3* – identified by all five methods. For INT, 20.04% of genes were identified by more than one method, and *QRICH1* was identified by all five methods. For EXT + INT, 23.20% of genes were identified by more than one method, and three genes – *ZKSCAN8*, *TMA7*, and *TREX1* – were identified by all five methods (Figure 2).

Unit of analysis: Molecules

Among the genes identified for EXT, 52 druggable targets specific to EXT were identified by at least two methods. The 52 genes yielded 492 drug-gene interactions (Supplementary Table 11), including dextroamphetamine, phenobarbital, baclofen, naltrexone, naloxone, and methadone. Interactions with medications from anti-migraine, anti-inflammatory, and anticonvulsant therapeutic classes (e.g. topiramate and lamotrigine) were also identified. Most identified drugs (64.84%) have regulatory approval from the U.S. Food and Drug Administration (FDA).

Of the genes associated with INT, seven druggable targets specific to INT were identified by at least two methods, yielding 292 drug-gene interactions (Supplementary Table 12). Drug targets included antidepressants and antipsychotics. Unlike for EXT, most drugs identified for INT (82.33%) are not currently approved by the FDA. For EXT+INT, 47 of the identified genes were druggable targets implicated by more than one method. Of the 460 drug-gene interactions identified (Supplementary Table 13), many were also present in the INT or EXT results. Most of these drugs (75.52%) are not currently approved by the FDA.

Unit of analysis: Cells

EXT was significantly associated with dopaminergic and GABAergic neurons and neuroblasts from embryonic brain samples, human cortical neurons and hybrid cells, and pyramidal neurons from the cornu ammonis (CA1) region of the hippocampus. After conditional analyses, there were independent significant associations for GABAergic, cortical, and hippocampal neurons (Supplementary Figure 9). The only significant cell-type association for INT was with GABAergic neurons, though it was not independently significant after conditional analyses. EXT + INT showed significant associations with dopaminergic, GABAergic, and cortical neurons, though these associations were also not independently significant.

Unit of analysis: Circuits

Twenty brain IDPs were associated with EXT (Supplementary Figures 10 and 11 and Supplementary Table 14), including greater gray matter volumes in the thalamus, caudate nuclei, and occipital pole, and lower volumes in the ventral striatum and amygdala. There were also significant associations with intra-cellular volume fraction or orientation dispersion indices (ODI) in the medial lemniscus, cerebral peduncle, and middle cerebellar peduncle. INT was significantly associated with lower gray matter volume in the subcallosal cortex (Supplementary Figures 12 and 13 and Supplementary Table 15). EXT + INT showed negative associations with gray matter volume in the amygdala and subcallosal cortex (Figure 3), positive associations with ODI in the medial lemniscus and cerebellar peduncle, and negative associations with ODI in the

external capsule (Supplementary Table 16 and Supplementary Figures 14 and 15).

Unit of analysis: Physiology

EXT had significant positive causal effects on all physical health traits, except age at death and IBD. INT was causally associated with all traits except age at death and abdominal aortic aneurysm. INT had protective effects on IBD ($b_{xy} = -0.32$, $SE = 0.09$, $p = 0.0004$), but stronger positive associations than EXT with all pain phenotypes, all cardiovascular diseases, and three of four other chronic illnesses (Figure 4). Like EXT, EXT + INT had positive causal effects on all physical health traits except age at death and IBD (Supplementary Table 17).

Discussion

Our findings demonstrate the value of integrating the HiTOP and RDoC frameworks to advance our understanding of the biological underpinnings of EXT and INT psychopathology. HiTOP's hierarchical structure contextualizes both the co-occurrence and specificity of psychopathology spectra, facilitating research on their mechanisms while serving as a descriptive classification framework (DeYoung et al., 2024; Waszczuk et al., 2020). In contrast, RDoC organizes research around mechanisms but lacks a structured model of psychopathology. Integrating these frameworks provides a more comprehensive approach. For example, although HiTOP conceptualizes overarching patterns of comorbidity and supports mechanistic research, it does not inherently specify mechanisms. Conversely, RDoC's mechanistic approach provides a lens through which to examine basic, underlying biological processes but does not offer a structured model of psychopathology, which is ultimately needed to guide mechanistic research. Genetics provides a promising avenue for bridging these models, offering a lens to identify shared and unique biological mechanisms across EXT and INT and to connect dimensions of psychopathology to their underlying etiology.

In line with HiTOP's hierarchical model, which posits that higher-order psychopathology factors emerge from shared features between lower-level spectra, we identified etiologic factors that contribute to the overlap between EXT and INT psychopathology. Genes like *DRD2*, *NCAM1*, and *DCC* were mapped to both spectra. *DRD2* encodes the dopamine D2 receptor and is implicated in traits related to reward processing and impulse control, including substance use and mood disorders (Friligkou et al., 2024; Levey et al., 2023; Meng et al., 2024). *NCAM1* is involved in neural cell adhesion and synaptic plasticity, processes critical for cognitive and emotional regulation (Conboy, Bisaz, Markram, & Sandi, 2010), while *DCC* encodes a receptor involved in nervous system development and has been linked to psychiatric disorders (Friligkou et al., 2024) and cognitive performance (Williams, Labouret, Wolfram, Peyre, & Ramus, 2023). These genes have been shown to have pleiotropic effects across multiple forms of psychopathology (Lam et al., 2022).

The EXT + INT liability also implicated neural structural differences, such as lower gray matter volume in the amygdala and subcallosal cortex. Lower left amygdala volume has been shown to mediate the relation between childhood threat exposure and the development of EXT and INT symptoms (Picci et al., 2022). Similarly, lower left subcallosal cortical volume is a potential mediator of associations between personality, emotional states, and psychiatric disorders (Wendt et al., 2021). EXT+INT

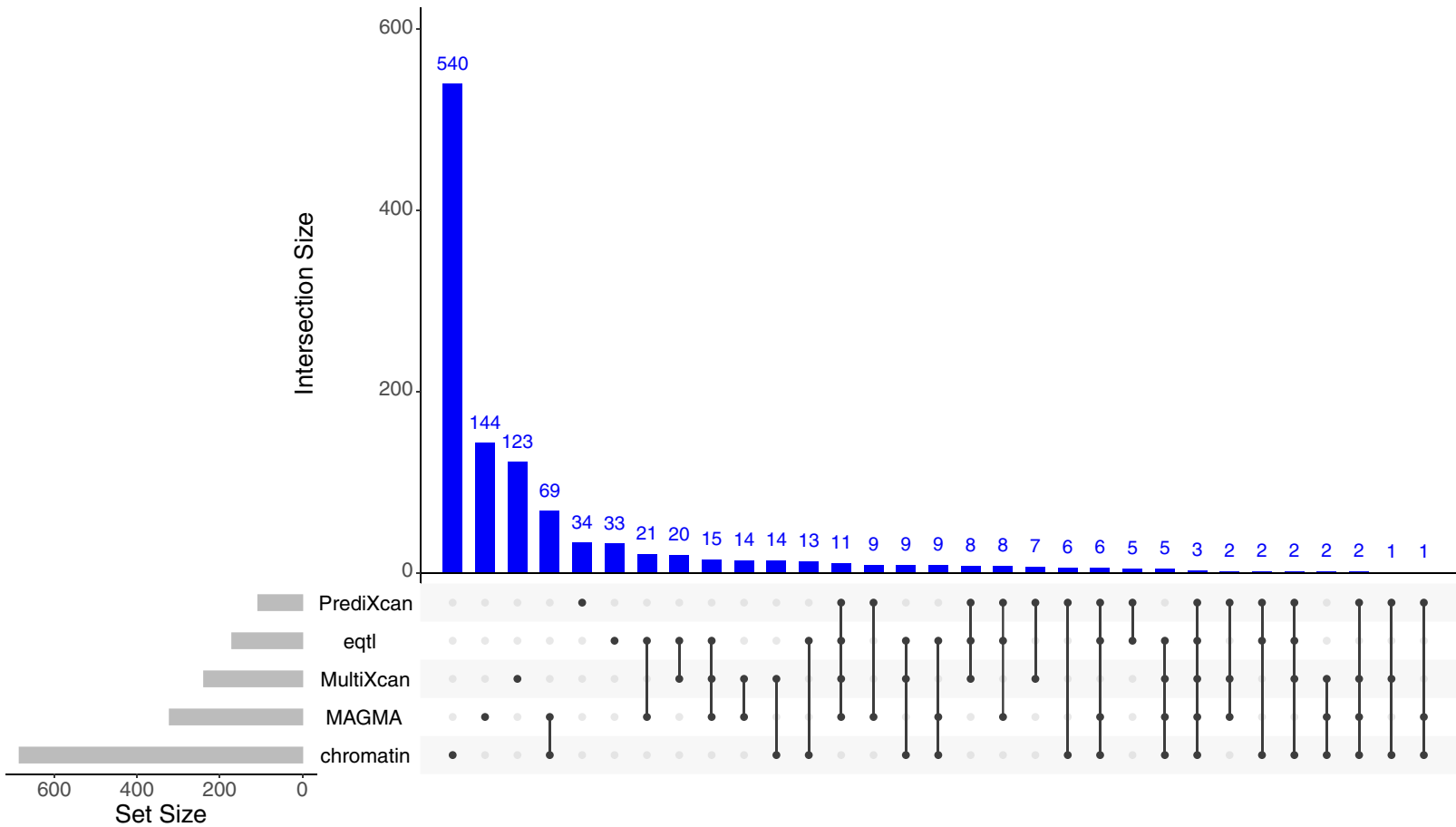


Figure 2. UpSet plot of genes identified for the shared liability to externalizing and internalizing (EXT + INT).

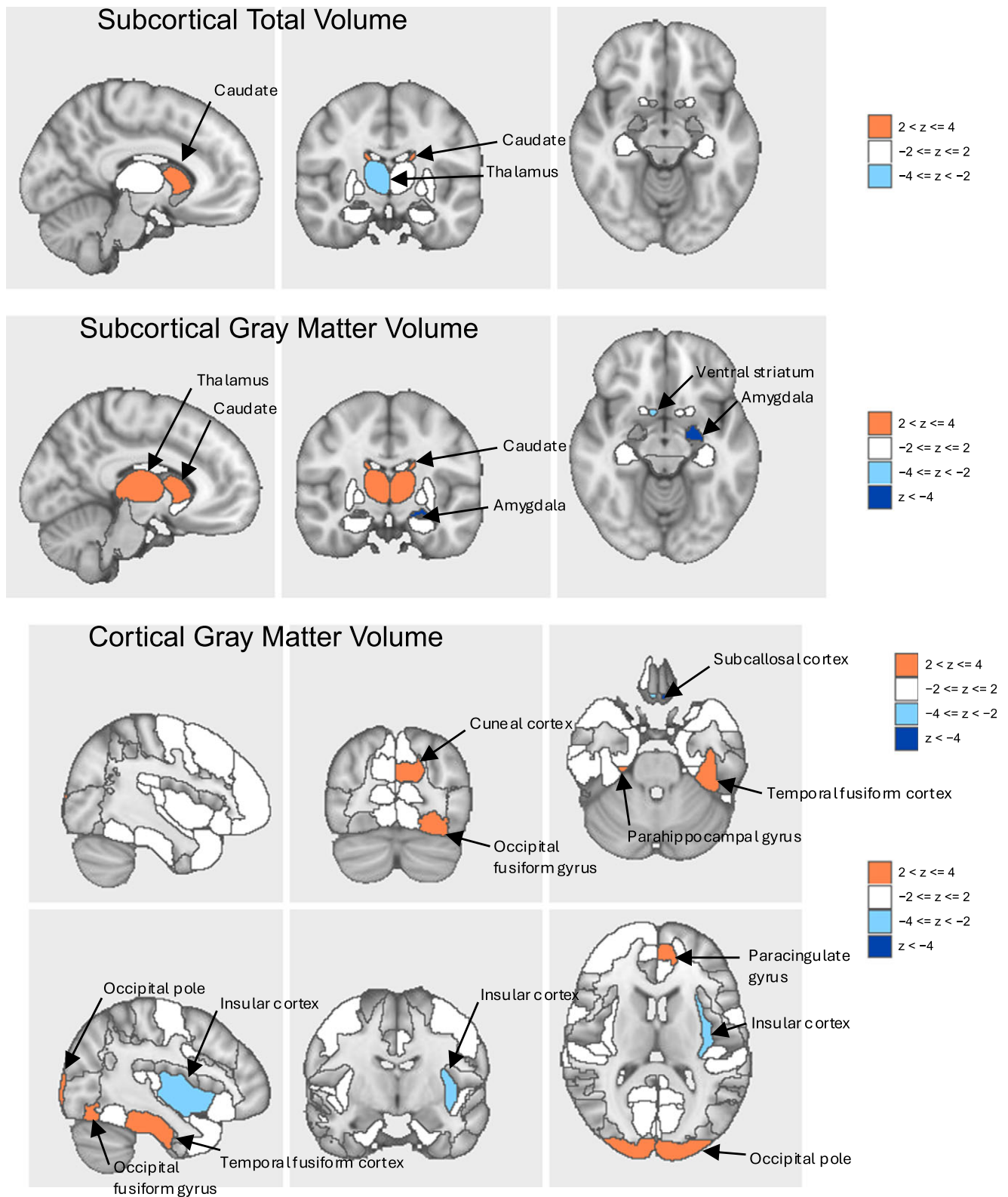


Figure 3. Brain region associations for the externalizing and internalizing (EXT + INT) factor. Associations shown are for image-derived phenotypes from structural magnetic resonance imaging. Full results are in [Supplementary Figures 10–15](#) and [Supplementary Tables 14–16](#). Blue colors represent reduced volume, and orange represents increased volume.

liability was also associated with white matter fiber differences, potentially reflecting disruptions in neural communication pathways that contribute to psychopathology (Kraguljac, Guerreri, Strickland, & Zhang, 2023).

Alongside shared etiologic factors, we identified genes with specific associations to each spectrum: *CADM2* and *FTO* were uniquely associated with EXT traits, suggesting the involvement of pathways related to impulsivity, risk-taking, and reward

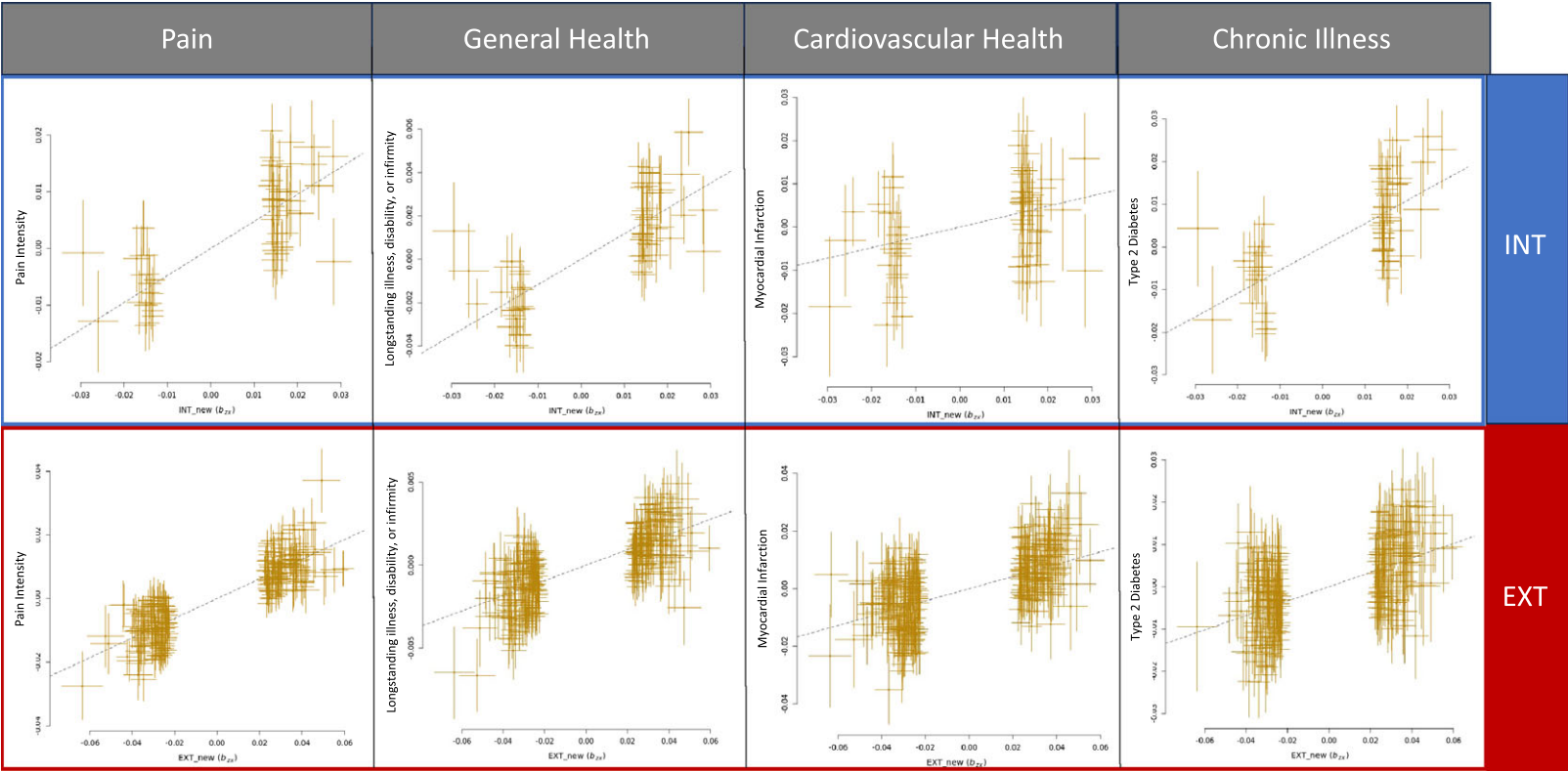


Figure 4. Representative results of generalized summary-data-based Mendelian Randomization (GSMR) across four domains of physical health. Pain intensity results: INT: $b_{xy} = 0.48$, $SE = 0.04$, $p = 1.11E-28$; EXT: $b_{xy} = 0.31$, $SE = 0.01$, $p = 1.44E-155$. Longstanding illness, disability, or infirmity results: INT: $OR = 1.12$, $SE = 0.01$, $p = 9.83E-33$; EXT: $OR = 1.05$, $SE = 0.002$, $p = 2.27E-75$. Myocardial infarction results: INT: $OR = 1.27$, $SE = 0.07$, $p = 0.0003$; EXT: $OR = 1.24$, $SE = 0.02$, $p = 6.32E-38$. Type 2 diabetes results: INT: $OR = 1.72$, $SE = 0.06$, $p = 7.28E-20$; EXT: $OR = 1.19$, $SE = 0.02$, $p = 6.94E-28$. All results depicted are significant at a Bonferroni corrected p -value of 0.001. In all analyses, INT/EXT is the exposure, and the physical health trait is the outcome. INT, internalizing; EXT, externalizing; OR, odds ratio. Full results can be found in [Supplementary Table 17](#).

sensitivity – key components of RDoC's cognitive and positive valence systems. *CADM2* encodes a cell adhesion molecule and has been associated with impulsivity and risky behaviors (e.g. substance use; Sanchez-Roige et al., 2023), while the *FTO* gene has been implicated in obesity (Huang, Chen, & Wang, 2023) and substance use (Hatoum et al., 2023; Kember et al., 2023). For INT, *CCDC68*, involved in cellular structure (Huang et al., 2017), exhibited specificity. This gene has been associated with several INT traits, including depression (Meng et al., 2024) and neuroticism (Baselmans et al., 2019).

Building on the gene associations, drug repurposing analyses identified potential druggable targets specific to each spectrum, including several novel compounds for INT, highlighting opportunities for precision treatment. Genes associated with each spectrum also showed specific expression patterns in brain cell types. EXT genes showed enriched expression in GABAergic, cortical, and pyramidal hippocampal neurons, cell types that align with RDoC constructs related to cognitive control and acute threat. In contrast, INT genes were more narrowly associated with GABAergic neurons involved in inhibitory signaling, consistent with RDoC's negative valence systems, particularly the acute threat construct.

Genetic liability for both the EXT and INT spectra had downstream effects on physical health outcomes. INT liability was causally associated with chronic pain, cardiovascular disease, and other chronic illnesses, consistent with previous research supporting causal links between INT, localized pain (Williams et al., 2022; Yao et al., 2023), and disease outcomes (Mulugeta, Zhou, King, & Hyppönen, 2020). These findings suggest that the negative valence systems implicated in INT psychopathology may extend to somatic outcomes, highlighting shared biological pathways between psychiatric and physical health (Lawrence et al., 2024). Similarly, HiTOP's incorporation of somatoform symptoms into the INT spectrum supports the relevance of dimensional models for understanding the intersection of mental and physical health. EXT liability also exhibited associations, albeit generally weaker, with adverse health outcomes, indicating that liability for both spectra contributes to physical health risk. An exception to this was age at death, which was not associated with EXT or INT liability. This may reflect attenuation due to selection bias in the UK Biobank, whose participants tend to be healthier than the general population.

The combination of shared and distinct mechanisms reinforces the need for an integrated HiTOP-RDoC framework where shared liabilities are contextualized alongside spectrum-specific biological underpinnings. Traditional diagnostic systems have been criticized for their categorical approach, which fails to account for substantial disorder-level heterogeneity and comorbidity. HiTOP's structural approach, which directly addresses these limitations, also facilitates an improved mechanistic understanding of psychopathology. By integrating HiTOP and RDoC, we propose a dimensional-mechanistic framework that identifies shared pathways and distinguishes spectrum-specific mechanisms. This approach offers a cohesive framework for aligning transdiagnostic dimensions with biological mechanisms, paving the way for a more precise and biologically informed psychiatric nosology.

Limitations

The use of summary statistics from large GWAS, comprehensive analyses across multiple RDoC units, and innovative integration of HiTOP and RDoC frameworks using genomics are among the

study's strengths. However, findings should be interpreted in the context of several limitations. First, Mendelian randomization makes several key assumptions that influence the validity of causal inferences: (1) instrumental variables must be robustly associated with the exposure, (2) there must be no direct pathway from the instruments to the outcome other than through the exposure (i.e. no horizontal pleiotropy), and (3) instruments must not be associated with confounders of the exposure-outcome relationship. We implemented methods to address the first two assumptions. First, we selected instruments associated at $p < 5 \times 10^{-8}$ to ensure statistical rigor, addressing the first assumption. To address assumption two, we used the HEIDI-outlier method to detect and exclude genetic instruments with evidence of pleiotropic effects. However, because assumption three is particularly challenging to address, we cannot rule out the possibility of confounding, and the results should be interpreted cautiously. Additionally, the cross-sectional nature of the GWAS data limits our ability to make developmental inferences, as data are not available to identify temporal patterns of genetic and environmental mechanisms. Finally, our analyses were limited to individuals genetically similar to Europeans. Expanding future studies to additional populations is crucial both to ensure the replicability of these results and to extend their generalizability.

Conclusions

Psychiatry has long grappled with the complexity of psychiatric symptomatology and the considerable challenge of linking clinical presentations to their underlying biological mechanisms. By integrating HiTOP's dimensional approach with RDoC's units of analysis, we demonstrate how research that bridges these frameworks can address the limitations of our traditional diagnostic system. This integrative approach moves beyond rigid diagnostic categories to provide a model that can account for both shared and spectrum-specific pathways of psychopathology. A combined HiTOP-RDoC framework has the potential to address enduring challenges in psychiatry, such as the heterogeneity of psychiatric disorders and the numerous biological and environmental pathways that yield similar symptoms. This integration provided unified insights across genetic, neural, and clinical domains, which can ultimately refine psychiatric nosology, guide therapeutic development, and advance precision psychiatry.

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Competing interests. Dr. Kranzler is a member of advisory boards for Altimmune, Clearmind Medicine, Dicerna Pharmaceuticals, Enthion Pharmaceuticals, Lilly Pharmaceuticals, and Sophrosyne Pharmaceuticals; a consultant to Altimmune and Sobrera Pharmaceuticals; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; and a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, Otsuka, and Pear Therapeutics. Drs. Kranzler and Gelernter hold U.S. patent 10,900,082 titled: 'Genotype-

guided dosing of opioid agonists,' issued January 26, 2021. The remaining authors have no disclosures to make.

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