Investigating the shared genetic architecture and causal relationship between pain and neuropsychiatric disorders

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Abstract
Pain often occurs in parallel with neuropsychiatric disorders. However, the underlying mechanisms and potential causality have not been well studied. We collected the genome-wide association study (GWAS) summary statistics of 26 common pain and neuropsychiatric disorders with sample size ranging from 17,310 to 482,730 in European population. The genetic correlation between pair of pain and neuropsychiatric disorders, as well as the relevant cell types were investigated by linkage disequilibrium (LD) score regression analyses. Then, transcriptome-wide association study (TWAS) was applied to identify the potential shared genes by integrating the gene expression information and GWAS. In addition, Mendelian randomization (MR) analyses were conducted to infer the potential causality between pain and neuropsychiatric disorders. Among the 169 pairwise pain and neuropsychiatric disorders, 55 pairs showed positive correlations (median \( r_g = 0.43 \)) and 9 pairs showed negative correlations (median \( r_g = -0.31 \)). Using MR analyses, 26 likely causal associations were identified, including that neuroticism and insomnia were risk factors for most of short-term pain, and multisite chronic pain was risk factor for neuroticism, insomnia, major depressive disorder and attention deficit/hyperactivity disorder, and vice versa. The signals of pain and neuropsychiatric disorders tended to be enriched in the functional regions of cell types from central nervous system (CNS). A total of 19 genes shared in at least one pain and neuropsychiatric disorder pair were identified by TWAS, including \( AMT \), \( NCOA6 \), and \( UNC45A \), which involved in glycine degradation, insulin secretion, and cell proliferation, respectively. Our findings provided the evidence of shared genetic structure, causality and potential shared pathogenic mechanisms between pain and neuropsychiatric disorders, and enhanced our understanding of the comorbidities of pain and neuropsychiatric disorders.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| GWAS         | Genome-wide association study |
| LD           | Linkage disequilibrium |
| LDSC         | Linkage disequilibrium score regression |
| TWAS         | Transcriptome-wide association study |
| CNS          | Central nervous system |
| SNP          | Single-nucleotide polymorphism |
| 1KGP3        | The 1,000 Genomes project phase 3 |
| MR           | Mendelian randomization |
| GSMR         | Generalized summary-data-based Mendelian randomization |
| HEIDI        | Heterogeneity in dependent instruments |
| IV           | Instrumental variable |
| IVW          | Inverse variance weighted |
| RAPS         | Robust adjusted profile score |
| eQTL         | Expression quantitative trait loci |
| GTEx         | Genotype-tissue expression project |
| PPI          | Protein–protein interaction |
| LT           | Long term |
| ST           | Short term |
| OR           | Odds ratio |
| CI           | Confidence interval |
| SWB          | Subjective well-being |
| PD           | Parkinson’s disease |
| AD           | Alzheimer’s disease |
| BIP          | Bipolar disorder |
| SCZ          | Schizophrenia |
| AN           | Anorexia nervosa |
| ASD          | Autism spectrum disorder |
| MDD          | Major depressive disorder |
| PTSD         | Posttraumatic stress disorder |
| ADHD         | Attention deficit/hyperactivity disorder |

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Introduction

The pain disorders are very common with prevalence of headache 42%, unspecified chronic pain 34%, musculoskeletal pain 25%, and back pain 21%, which imposed a significant socioeconomic burden and contributed to excess mortality (Jackson et al. 2016; James et al. 2018). Pain can be caused by diseases stimulating the nociceptors or abnormal function of the nervous system, the duration of which varies a lot. For example, the chronic pain, also known as long-term pain, is conventionally defined as pain lasting longer than 3 months. Alternatively, the short-term pain has been defined as pain experienced in the last month that interfered with individual usual activities in the UK biobank (Sudlow et al. 2015). Pain disorders showed moderate heritability which ranged from 0.08–0.31 and many susceptibility loci have been identified by genome-wide association studies (GWASs) (Meng et al. 2020, 2018; Johnston et al. 2019; Suri et al. 2018; Meng W, Adams MJ, Palmer CNA, andMe Research T, Shi J, Auton A, Ryan KA, Jordan JM, Mitchell BD, Jackson RD, et al. 2019).

Pain is often present in clinical manifestations of neuropsychiatric disorders (Goesling et al. 2018) in which genetic factors play significant roles (Smoller et al. 2019; Polderman et al. 2015). Neuropsychiatric disorders include both neurological disorders and psychiatric disorders, such as the well-known Alzheimer’s disease (AD), Parkinson’s disease (PD), schizophrenia (SCZ), major depression disorder (MDD), etc. Previous studies have found that neuropsychiatric disorders exhibited similar symptoms, epidemiological comorbidities, and shared genetic structures (Smoller et al. 2019; Cross-Disorder Group of the Psychiatric Genomics Consortium 2019; Anttila et al. 2018). Moreover, psychiatric disorders tended to share common risk of genetic variation, while neurological disorders shared less genetic architecture with each other and with psychiatric disorders (Anttila et al. 2018). In common with the pain disorders, neuropsychiatric disorders also have the characteristics of high prevalence and heavy burden in epidemiology (Prince et al. 2007; Whiteford et al. 2013; Steel et al. 2014). Although pain is often present with neuropsychiatric disorders, the underlying mechanisms and causality between pain and neuropsychiatric disorders have yet to be well elucidated.

Recently, genetic methods leveraging GWAS summary statistics and integrating functional annotations have been developed, which can be used to estimate global genetic correlation (Bulik-Sullivan et al. 2015a) between pain and neuropsychiatric disorders, as well as identify the relevant cell types (Finucane et al. 2015) for pain and neuropsychiatric disorders. Genetic instrumental variable analysis, like Mendelian randomization (MR) (Pierce and Burgess 2013; Zhu et al. 2018), can aid the inference of causality of pain on neuropsychiatric disorders, and vice versa. In addition, methods combining GWAS summary data and gene expression data in different tissues, such as transcrip-tome-wide association study (TWAS) (Gusev et al. 2016), can be used to identify trait-relevant genes underlying the shared pathophysiology between pain and neuropsychiatric disorders. Here, we proposed to investigate the shared genetic architecture and causal relationships between a variety of neuropsychiatric disorders and short-term and long-term pain in different body sites. By exploring the possible shared biological mechanisms between pain and neuropsychiatric disorders, our understanding of pain and neuropsychiatric disorders would be enhanced.

Materials and methods

GWAS summary statistics for pain and neuropsychiatric disorders

We collected GWAS summary statistics of pain disorders and neuropsychiatric disorders. To ensure the large sample size (N > 15,000) and trait being heritable (observed h² > 0), the GWAS summary statistics were collected, including 13 pain disorders (N ranges from 46,879 to 387,649 in the UK biobank) including short-term pain disorders (ST) and long-term pain disorders (LT) in different body sites (i.e., head, neck/shoulder, back, abdomen, hip, and knee), as well as multisite chronic pain (Table 1). The short-term pain disorder was defined as pain that experienced in the last month and influenced usual activities, whereas the long-term pain disorder, also known as chronic pain disorder, was defined as pain lasting for more than 3 months. In addition, the multisite chronic pain disorder was defined as the number of body sites suffering long-term pain, including face, head, neck/shoulder, back, abdomen, hip, and knee (Johnston et al. 2019). The neuropsychiatric disorders included subjective well-being (SWB, N = 298,420) (Okbay et al. 2016), Parkinson’s disease (PD, N = 482,730) (Nalls et al. 2019), Alzheimer’s disease (AD, N = 455,258) (Jansen et al. 2020), neuroticism (N = 329,821) (Luciano et al. 2019), insomnia (N = 237,627) (Dashti et al. 2021), bipolar disorder (BIP, N = 413,466) (Mullins et al. 2021), schizophrenia (SCZ, N = 105,318) (Pardiñas et al. 2018), anorexia nervosa (AN, N = 72,517) (Watson et al. 2016), major depressive disorder (MDD, N = 173,005) (Dashti et al. 2021), autism spectrum disorder (ASD, N = 46,350) (Grove et al. 2019), anxiety (N = 17,310) (Otowa et al. 2016), attention deficit/hyperactivity disorder (ADHD, N = 53,293) (Demontis et al. 2019). For all pain and neuropsychiatric
disorders used in this study (Table 1), the GWASs were conducted in population of European ancestry and the genomic coordinates were built on hg19.

### Estimate the genetic correlation with cross-trait LDSC

The cross-trait linkage disequilibrium (LD) score regression (LDSC) (Bulik-Sullivan et al. 2015b) was applied to assess the genetic correlations between each pair of disorders. The LD score for each single-nucleotide polymorphism (SNP) estimated based on the genotypes of European in the 1,000 Genomes Project Phase 3 (1KGP3) (The 1000 Genomes Project Consortium 2015) was downloaded from LDSC website (https://alkesgroup.broadinstitute.org/LDSCORE/). Then, LDSC applied a weighted linear model by regressing the product of Z-statistics of pairwise disorders on the LD scores of SNPs across the whole genome. The regression slope provided an unbiased genetic correlation estimate for pairwise disorders even when sample overlaps in the two GWASs. For the genetic correlation and the following cell-type specific analyses, we only used the GWAS summary statistics of HapMap3 SNPs and further removed the SNPs in the major histocompatibility complex region (chr6:25–35 Mb) as suggested by LDSC.

### Mendelian randomization analysis

MR is a commonly used approach to infer the causality between the exposure and outcome using the genetic instrumental variables (IVs). To systematically investigate the potential causal relationships between pain and neuropsychiatric disorders, we conducted bi-directional MR analyses for pairwise pain and neuropsychiatric disorder. We selected

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**Table 1** Disorders analyzed in this study

| Disorder        | Sample size (case/control, if applicable) | Observed h² (se) | Liability h² (se) | Data source                  |
|-----------------|-------------------------------------------|------------------|-------------------|------------------------------|
| **Pain disorders** |                                           |                  |                   |                              |
| Head pain LT    | 34,810/41,088                             | 0.0619 (0.0074)  | 0.0476 (0.0057)  | Watanabe et al. (2019) Nat Genet |
| Head pain ST    | 77,568/308,130                            | 0.0406 (0.0023)  | 0.0990 (0.0057)  | Watanabe et al. (2019) Nat Genet |
| Neck/shoulder pain LT | 60,226/27,147                       | 0.0250 (0.0054)  | 0.0381 (0.0082)  | Watanabe et al. (2019) Nat Genet |
| Neck/shoulder pain ST | 88,299/297,399                      | 0.0315 (0.0018)  | 0.0688 (0.0040)  | Watanabe et al. (2019) Nat Genet |
| Back pain LT    | 66,773/30,751                             | 0.0352 (0.0049)  | 0.0298 (0.0041)  | Watanabe et al. (2019) Nat Genet |
| Back pain ST    | 98,389/287,309                            | 0.0349 (0.0019)  | 0.0671 (0.0037)  | Watanabe et al. (2019) Nat Genet |
| Abdominal pain LT | 16,580/13,167                           | 0.0185 (0.0093)  | 0.0204 (0.0102)  | Ben Neale UKBB GWAS Round 2  |
| Abdominal pain ST | 32,823/352,875                         | 0.0175 (0.0015)  | 0.0735 (0.0064)  | Watanabe et al. (2019) Nat Genet |
| Hip pain LT     | 31,303/8,758                              | 0.0051 (0.0068)  | 0.0064 (0.0084)  | Ben Neale UKBB GWAS Round 2  |
| Hip pain ST     | 42,944/342,754                            | 0.0223 (0.0016)  | 0.0736 (0.0053)  | Watanabe et al. (2019) Nat Genet |
| Knee pain LT    | 63,679/17,463                            | 0.0250 (0.0055)  | 0.0376 (0.0083)  | Watanabe et al. (2019) Nat Genet |
| Knee pain ST    | 81,814/303,884                            | 0.0370 (0.0021)  | 0.0809 (0.0046)  | Watanabe et al. (2019) Nat Genet |
| Multisite pain LT | 387,649                                  | 0.0731 (0.0028)  |                   | Johnston et al. (2019) PLoS Genet |
| **Neuropsychiatric disorders** |                                           |                  |                   |                              |
| SWB             | 298,420                                   | 0.0250 (0.0020)  |                   | Okbay et al. (2016) Nat Genet |
| PD              | 33,674/449,056                            | 0.0183 (0.0017)  | 0.0274 (0.0025)  | Nalls et al. (2019) Lancet Neurol  |
| AD              | 71,880/383,378                            | 0.0144 (0.0020)  | 0.0230 (0.0032)  | Jansen et al. (2020) Nat Genet |
| Neuroticism     | 329,821                                   | 0.1073 (0.0045)  |                   | Luciano et al. (2019) Nat Genet |
| Insomnia        | 129,270/108,357                           | 0.1145 (0.0043)  | 0.1214 (0.0046)  | Dushi et al. (2021) Nat Commun |
| BIP             | 41,917/371,549                            | 0.0703 (0.0026)  | 0.1012 (0.0038)  | Mullins et al. (2021) Nat Genet |
| SCZ             | 40,675/64,643                             | 0.4088 (0.0139)  | 0.1950 (0.0066)  | Pardiñas et al. (2018) Nat Genet |
| AN              | 16,992/55,525                             | 0.1771 (0.0118)  | 0.0979 (0.0065)  | Watson et al. (2019) Nat Genet |
| ASD             | 18,381/27,969                             | 0.1947 (0.0170)  | 0.0963 (0.0084)  | Grove et al. (2019) Nat Genet |
| Anxiety         | 7,016/14,745                              | 0.0779 (0.0296)  | 0.0607 (0.0231)  | Otowa et al. (2016) Mol Psychiatry |
| MDD             | 59,851/113,154                            | 0.0783 (0.0047)  | 0.0602 (0.0036)  | Wray et al. (2018) Nat Genet |
| PTSD            | 23,212/151,447                            | 0.0169 (0.0029)  | 0.0292 (0.0051)  | Nievergelt et al. (2019) Nat Commun |
| ADHD            | 19,099/34194                              | 0.2339 (0.0151)  | 0.2158 (0.0139)  | Demontis et al. (2019) Nat Genet |

UKBB UK biobank, LT long term, ST short term, SWB subjective well-being, PD Parkinson’s disease, AD Alzheimer’s disease, BIP bipolar disorder, SCZ schizophrenia, AN anorexia nervosa, ASD autism spectrum disorder, MDD major depressive disorder, PTSD posttraumatic stress disorder, ADHD attention deficit/hyperactivity disorder
the genome-wide significant \( P < 5 \times 10^{-8} \) and independent SNPs as the candidate IVs by using the PLINK (Purcell et al. 2007) clumping procedure with thresholds of LD \( r^2 \) 0.01 and physical distance 10 Mb (Nazarzadeh et al. 2021; Geng et al. 2018). For any exposure–outcome pairs with no candidate IVs selected, we employed a relatively loose \( P \) value threshold of \( 1 \times 10^{-5} \) to choose the candidate IVs as done in previous studies (Pasman et al. 2018; Lu et al. 2021). Generalized summary-data-based MR (GSMR) (Zhu et al. 2018) was used in our main MR analysis. Heterogeneity in dependent instruments (HEIDI) test (Zhu et al. 2018) was performed to remove the likely horizontal pleiotropic SNPs \( (P_{\text{HEIDI}} < 0.01) \) from the candidate IVs. We calculated the \( F \) statistics to confirm that there was no potential weak instrumental bias of our MR analyses (Staiger and Stock 1994). The \( F \) > 10 indicated no potential weak instrumental bias (Staiger and Stock 1994). Each LD matrix used in the GSMR model was calculated by PLINK v1.9 based on the genotypes of European in 1KGP3 (The 1000 Genomes Project Consortium 2015). To test whether the GSMR results were robust, we additionally employed the inverse variance weighted (IVW) (Burgess et al. 2013) and robust adjusted profile score (RAPS) (Zhao et al. 2020) methods to perform two-sample MR as sensitivity analysis for the significant results in the main MR analysis. MR analyses were performed with GSMR (Zhu et al. 2018) and TwoSampleMR (Hemani et al. 2018) packages in R version 4.0.4.

**Cell-type specific analysis with stratified LDSC**

To identify the trait-relevant cell types, the stratified LDSC was used to test if the GWAS signals were enriched in the functional annotation regions of cell-type groups (Finucane et al. 2015). By taking a union of the cell-type specific annotations within each group, a binary annotation was created for each cell-type group, indicating whether an SNP resided in the cell-type group specific functional annotation regions. The 10 cell-type groups included adrenal and pancreas, central nervous system (CNS), cardiovascular, connective and bone, gastrointestinal, immune and hematopoietic, kidney, liver, skeletal muscle, and other. The annotations and partitioned LD scores of cell-type groups were created by Finucane et al. (Finucane et al. 2015) and downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/. The stratified LD score regression model tested one cell-type group each time. We also included 53 non-cell-type specific baseline annotations (including coding, promoter, enhancer, etc.) in the stratified LD score regression model as suggested to control the potential misspecification (Finucane et al. 2015). The \( P \) value of the regression coefficient of stratified LDSC was set as a measure of the association of the cell-type group with the traits.

**Transcriptome-wide association studies**

To identify genes whose expression pattern implicates etiology or biological mechanisms, we conducted transcriptome-wide association studies (TWAS) implemented in the FUSION software (Gusev et al. 2016). The GWAS summary statistics and expression quantitative trait loci (eQTL) summary statistics were integrated in TWAS model to test the association between the gene expression and traits. The LD information used in TWAS model was based on the reference genotype of European in 1KGP3 (The 1000 Genomes Project Consortium 2015). The gene expression datasets of trait-relevant tissues from Genotype-Tissue Expression project (GTEx) v.7 were used as the reference gene expression panel (Battle et al. 2017). The number of available genes from GTEx ranged from 1,603 in brain substantia nigra to 5,854 in brain cerebellum. We performed the TWAS for one tissue–trait pair at a time. The permutation test (Gusev et al. 2016) for each gene with 1,000 resampling iterations was carried out to control false positives due to accidental co-localization of eQTL and SNP. For each trait, a total of 39,892 gene–trait associations in different CNS-related tissues were tested. Specifically, adrenal and pancreas tissues were relevant to insomnia, and we additionally performed TWAS by integrating the gene expression information from adrenal and pancreas related tissues in GTEx. A total of 49,505 gene–trait associations were tested for insomnia. For the shared genes between pain and neuropsychiatric disorders, we conducted a gene–gene interaction analysis in the context of STRING-based protein–protein interaction (PPI) networks (https://string-db.org/) (Mering et al. 2003).

**Results**

**Genetic correlations between pain and neuropsychiatric disorders**

Genetic correlations were calculated to explore the genetic overlap between 13 pain and 13 neuropsychiatric disorders. A total of 150 out of 325 (26 × 25/2) pairwise disorders showed significant genetic correlation after Bonferroni correction \( (P < 1.54 \times 10^{-4}, \) adjust for 325 tests). Specially, 64 of 169 (13 × 13) pairs of pain and neuropsychiatric disorder were genetically correlated (Fig. 1A). 11 of 13 neuropsychiatric disorders were genetically correlated with at least one pain disorder, among which neuroticism, SWB, insomnia, MDD, PTSD, and ADHD were genetically correlated with most of pain disorders (52/78), and BIP, SCZ, AN, ASD, and anxiety were only genetically correlated with a few pain disorders (12/65), while PD and AD were not genetically correlated with any pain disorders. Although both PD and AD were reported to
be associated with pain in previous observational studies (Cao et al. 2019; Ford 2010), PD and AD are age-related neurodegenerative diseases, in which the causes and mechanisms of pain might be different from that of other psychiatric disorders or behavioral cognitive phenotypes. From another point of view, short-term pain and multisite chronic pain were more likely to be genetically correlated with neuropsychiatric disorders than long-term pain. Specifically, short-term pain disorders were genetically correlated with 6–11 neuropsychiatric disorders, while long-term pain disorders were only 0–4. In addition, long-term abdominal pain and long-term hip pain were not genetically correlated with any neuropsychiatric disorders, and long-term head pain showed unique genetic correlation with insomnia. Among the 64 significant genetic correlations between pain and neuropsychiatric disorders, 55 of them were positive genetically correlated with a median genetic correlation ($r_g$) of 0.43. In contrast, SWB and 8 pain disorders (median $r_g = -0.31$), and AN and short-term knee pain ($r_g = -0.15$, $P = 3.49 \times 10^{-5}$) showed significant negative correlations.

When focusing on the genetic correlations between any two of neuropsychiatric disorders (Fig. 1B), PD and AD were not correlated with any neuropsychiatric disorders, which was consistent with a prior study (Anttila et al. 2018), while others were correlated with at least five other neuropsychiatric disorders. For the 42 significant correlated pairs, except that SWB was negative correlated with 10 neuropsychiatric disorders, the other 32 significant correlations were all positive with median $r_g = 0.37$. Additionally, when focusing on any two of pain disorders (Fig. 1C), long-term hip pain was not genetically correlated with any pain disorders and long-term abdominal pain was only genetically correlated with multisite chronic pain, while others were correlated with at least three other pain disorders. There were a total of 44 significant genetic correlations between the pain disorders, which were all positive with median $r_g = 0.62$.

### Causal inference between pain and neuropsychiatric disorders

We conducted bi-directional GSMR analyses to identify the causality between pain and neuropsychiatric disorders. The $F$ statistic was above 20.61 (from 20.61 to 159.71, Supplementary Table 1), indicating that weak instrumental bias was not a concern. Among all the 338 examined exposure–outcome pairs (13 × 13 × 2), we found 26 significant causal associations after Bonferroni correction ($P < 1.48 \times 10^{-4}$, adjust for 338 tests), including 8 associations that pain lead to neuropsychiatric disorders, and 18 associations that neuropsychiatric disorder result in pain (Fig. 2, Supplementary Fig. 1).

Specifically, when the pain disorders were set as exposure (Fig. 2A, Supplementary Fig. 1A), we found that short-term neck/shoulder pain was a risk factor for SCZ (OR = 2.61, $P = 3.20 \times 10^{-8}$). Multisite chronic pain was a risk factor for AD (OR = 1.12, $P = 1.10 \times 10^{-4}$), neuroticism (OR = 1.52, $P = 6.50 \times 10^{-11}$), insomnia (OR = 1.27, $P = 1.76 \times 10^{-33}$), MDD (OR = 1.95, $P = 1.30 \times 10^{-10}$), PTSD (OR = 2.63, $P = 1.35 \times 10^{-7}$), and ADHD (OR = 5.06, $P = 3.09 \times 10^{-20}$). Short-term knee pain was identified as a protective factor for BIP (OR = 0.65, $P = 1.21 \times 10^{-5}$). Notably, among the eight causal pairs, multisite chronic pain was not genetically correlated with AD, and neither was short-term knee pain correlated with BIP (Fig. 1A).

When the neuropsychiatric disorders were set as exposure (Fig. 2B, Supplementary Fig. 1B), we found that neuroticism was a risk factor for multisite chronic pain and all the six short-term pain, and insomnia was a risk factor for multisite chronic pain and five short-term pain, including short-term...
pain in head, neck/shoulder, back, abdomen, and hip. Neuroticism (OR = 1.12, \( P = 7.54 \times 10^{-32} \)), insomnia (OR = 1.78, \( P = 4.21 \times 10^{-33} \)), SCZ (OR = 1.02, \( P = 7.17 \times 10^{-5} \)), MDD (OR = 1.15, \( P = 2.90 \times 10^{-5} \)), and ADHD (OR = 1.04, \( P = 4.35 \times 10^{-5} \)) were risk factors for multisite chronic pain.

Sensitivity analyses were further conducted for the 26 significant causal-associated pairs using IVW and RAPS methods to check whether the results of GSMR analyses were robust. At the significant threshold of 0.05, 25 of the 26 pairs passed the sensitivity analyses and had similar effect size and the same direction (Supplementary Fig. 2), except for short-term neck/shoulder pain-SCZ pair with the IVW method (OR = 2.61, \( P = 0.18 \)). The remaining 25 pairs were more likely to be causal associated.

Although we found 64 pairs of pain and neuropsychiatric disorders were genetically correlated (Fig. 1), only 24 pairs among them showed significant causal associations (Fig. 2, Supplementary Figs. 1, 2). For example, AN was not causal associated with short-term knee pain and SWB was not causal associated with any pain disorders, while they were in negative genetic correlation with pain disorders as aforementioned. Among those identified causal relationships between pairs of pain neuropsychiatric disorders, we found several bi-directional causalities that neuroticism, insomnia, MDD, and ADHD were risk factors for multisite chronic pain, and vice versa.

**Relevant cell-type groups for pain and neuropsychiatric disorders**

To understand whether the GWAS signals of pain and neuropsychiatric disorders were enriched in the cell-type group specific annotation regions, we performed the stratified LD score regression analyses with ten cell-type group specific annotations. The CNS was identified to be relevant to eight neuropsychiatric disorders and five pain disorders after Bonferroni correction (\( P < 1.92 \times 10^{-4} \), adjust for 260 tests, Table 2, Supplementary Fig. 3), including PD, neuroticism, insomnia, BIP, SCZ, ASD, MDD, ADHD, short-term neck/shoulder pain, short-term back pain, short-term hip pain, short-term knee pain, and multisite chronic pain. These findings were concordant with previous studies (Hall et al. 2021; Li et al. 2020; O’Brien et al. 2018). The associated loci could act in tissue specific fashion, suggesting that pain and...
neuropsychiatric disorders might share common pathogenic mechanisms. The CNS played an important role in pain perception and neuropsychiatric disorders. Pain could involve the structure and function alterations of brain at numerous levels (Kucyi and Davis 2015; Thompson and Neugebauer 2019). Meanwhile, neuropsychiatric disorders were closely related to brain development (Gilmore et al. 2018) and usually involve the neurological changes in brain (Nayak et al. 2014).

The adrenal or pancreas was identified to be relevant to insomnia. Previous studies found that sleep suppressed the hypothalamic–pituitary–adrenal (HPA) axis and activation of the HPA axis could lead to insomnia (Nicolaides et al. 2020). In addition, insomnia was associated with less insulin secretion and higher insulin sensitivity (Vasisht et al. 2013), indicating that insomnia was associated with metabolism.

Shared genes between pain and neuropsychiatric disorders from TWAS

We performed TWAS to identify the gene-level overlap between any pair of pain and neuropsychiatric disorders. Since the CNS were relevant to most of pain and neuropsychiatric disorders, the gene expressions of 13 brain tissues in GTEx were used as the reference panel in TWAS. We did not find any significant gene–trait associations ($P < 1.25 \times 10^{-6}$, adjust for 39,892 gene–trait associations, Fig. 3A) for anxiety, PTSD, long-term neck/shoulder pain, long-term back pain, long-term abdominal pain, long-term hip pain, and long-term knee pain.

The number of associated genes ranged from 1 (SWB) to 233 (SCZ) for the other neuropsychiatric disorders and 1 (long-term head pain and short-term hip pain) to 37 (multisite chronic pain) for the other pain disorders.

DDX27 was the only TWAS significant gene for SWB, correlated with self-harm behaviors (Campos et al. 2020), intelligence (Savage et al. 2018), and schizophrenia (Zhang et al. 2020). As the only TWAS significant gene for long-term head pain, as well as short-term head pain, UFL1 was correlated with headache (Meng et al. 2018; Eising et al. 2016) and inflammation (Yang et al. 2020). Two zinc-finger protein family members, ZNF184 and ZSCAN31, were TWAS significant for neuroticism, SCZ, BIP, and MDD. Both of them were correlated with

| Disorder          | Tissue group     | Enrichment | Coefficient | Coefficient SE | Coefficient $P$ |
|-------------------|------------------|------------|-------------|----------------|----------------|
| BIP               | CNS              | 3.66       | 3.28E-08    | 3.41E-09       | 2.71E-22       |
| SCZ               | CNS              | 3.22       | 1.61E-07    | 1.75E-08       | 1.79E-20       |
| Neuroticism       | CNS              | 2.97       | 3.70E-08    | 5.23E-09       | 7.21E-13       |
| Insomnia          | CNS              | 2.99       | 3.52E-08    | 5.76E-09       | 4.98E-10       |
| MDD               | CNS              | 2.85       | 1.99E-08    | 4.62E-09       | 8.16E-06       |
| ASD               | CNS              | 3.04       | 7.86E-08    | 1.85E-08       | 1.02E-05       |
| ADHD              | CNS              | 2.40       | 6.30E-08    | 1.55E-08       | 2.45E-05       |
| PD                | CNS              | 3.56       | 8.22E-09    | 2.13E-09       | 5.67E-05       |
| AD                | CNS              | 2.85       | 4.21E-08    | 1.48E-08       | 2.19E-03       |
| SWB               | CNS              | 3.32       | 6.43E-09    | 2.88E-09       | 1.25E-02       |
| PTSD              | CNS              | 3.17       | 7.56E-09    | 4.05E-09       | 3.07E-02       |
| AD                | Immune/hematopoietic | 4.38    | 8.02E-09    | 4.61E-09       | 4.09E-02       |
| Anxiety           | Connective/bone  | 11.85      | 7.41E-08    | 5.37E-08       | 8.38E-02       |
| Multisite pain LT| CNS              | 2.96       | 2.37E-08    | 3.15E-09       | 2.96E-14       |
| Neck/shoulder pain ST | CNS         | 3.46       | 1.15E-08    | 2.53E-09       | 2.95E-06       |
| Back pain ST      | CNS              | 3.26       | 1.04E-08    | 2.43E-09       | 8.93E-06       |
| Knee pain ST      | CNS              | 2.79       | 9.76E-09    | 2.46E-09       | 3.59E-05       |
| Hip pain ST       | CNS              | 3.35       | 7.98E-09    | 2.06E-09       | 5.22E-05       |
| Head pain LT      | Connective/bone  | 4.23       | 4.01E-08    | 1.16E-08       | 2.60E-04       |
| Head pain ST      | Adrenal/pancreas | 3.00       | 1.29E-08    | 3.93E-09       | 5.38E-04       |
| Abdominal pain ST | CNS              | 2.92       | 5.34E-09    | 1.99E-09       | 3.57E-03       |
| Neck/shoulder pain LT | Connective/bone | 5.23   | 1.45E-08    | 8.51E-09       | 4.46E-02       |
| Hip pain LT       | Immune/hematopoietic | 1.40    | 1.79E-08    | 1.14E-08       | 5.71E-02       |
| Abdominal pain LT | Connective/bone  | 6.31       | 2.62E-08    | 1.69E-08       | 6.06E-02       |
| Knee pain LT      | Cardiovascular   | 6.32       | 1.72E-08    | 1.16E-08       | 6.94E-02       |
| Back pain LT      | Connective/bone  | 3.03       | 1.03E-08    | 8.72E-09       | 1.17E-01       |

We report the cell type with the lowest coefficient $P$ value for each disorder analyzed.
neuropsychiatric disorders in previous studies (Keo et al. 2020; Wu et al. 2021; Li et al. 2021; Bhalala et al. 2018).

Eighty-one genes showed associations with at least one pain disorder. Among them, 19 genes also showed associations with at least one neuropsychiatric disorder (Fig. 3B); 12 of them were protein-coding genes (AMT, ARHGAP27, GPX1, HEXIM1, NCOA6, NMT1, RBM6, RNF123, SDCCAG8, UNC45A, WDR55, and ZNF646). Among the 12 protein-coding genes, ARHGAP27, HEXIM1, NCOA6, NMT1, UNC45A, and WDR55 were shared by two traits; AMT, GPX1, RBM6, RNF123, and ZNF646 were shared by three traits; and SDCCAG8 was shared by four traits (SCZ, short-term head pain, short-term knee pain, and multisite chronic pain) (Fig. 3B).

**Discussion**

We investigated the shared genetic architecture and causal relationship between pain and neuropsychiatric disorders in this study. We found that most of neuropsychiatric disorders were genetically correlated with at least one pain disorder, and 23 pairs of them were genetically correlated which might be due to causality. Furthermore, cell-type specific enrichment analysis and TWAS indicated that the neuronal signaling-related, metabolism-related, and proliferation-related pathogenic mechanisms could be shared between pain and neuropsychiatric disorders.
As we all know, SWB was a subjective feeling that was negatively related to pain and disorders (McNamee and Mendolia 2014), which was concordant with our finding that all the significant correlations between SWB and pain disorders were negative. In addition, we found a significant negatively genetic correlation between AN and short-term knee pain. Previous observational studies reported that less eating disorder symptoms were associated with greater pain (Dunne et al. 2021). And patients with anorexia nervosa showed a significantly higher thermal pain threshold (Bär et al. 2015, 2013). However, our subsequent MR analyses showed that there was no causality between them. Therefore, we considered that the genetic correlations we observed might be due to horizontal pleiotropy. Furthermore, our finding also suggested the CNS as the relevant tissue for most of pain and neuropsychiatric disorders; thus, we speculated that the functional changes in the brain might affect both the pain threshold and AN (Bär et al. 2013).

In accordance with our results of causal inference, a prospective population-based cohort study found that insomnia was associated with an increased risk of headache 11 years later, and vice versa (Ödegård et al. 2011; Ödegård et al. 2013). On the one hand, pain could be accompanied by higher levels of cognitive and somatic arousal at bedtime and result in insomnia (Palermo et al. 2011). On the other hand, insomnia might affect brain function and result in a decreased pain threshold (Haack et al. 2012), which was concordant with our result that the signals of pain and neuropsychiatric disorders tended to be enriched in the functional regions of cell types from CNS. Among the 12 TWAS significant protein-coding genes (see details in Fig. 3 and Supplementary Table 2), AMT encodes aminomethyltransferase effecting the degradation of glycine, which is a neurotransmitter, and plays an important role in maintaining normal brain development. Mutations in AMT predispose to neural tube defects (Narisawa et al. 2012) and glycine encephalopathy (Coughlin et al. 2017). Enhancing glycnergic neurotransmission showed the potential to treat chronic pain (Zeilhofer et al. 2018; Harvey and Yee 2013). Glycine transporters were identified as novel therapeutic targets in schizophrenia and pain (Harvey and Yee 2013). Given AMT and glycine transporters have similar effects on glycine; thus, AMT might be a novel therapeutic target in schizophrenia and pain, too.

UNC45A, RNF123, and SDCCAG8 all affected the structure and function of neurons (Lu et al. 2011; Flynn et al. 2020). UNC45A encodes UNC-45 myosin chaperone A, essential for normal cell proliferation and the accumulation of myosin during development of muscle cells. Mutations in UNC45A might cause cholestasis, diarrhea, bone fragility, and even dysgnesia (Esteve et al. 2018). Yoshie Iizuka et al. reported that UNC45A was required for neurite extension (Iizuka et al. 2017) which could affect neuropsychopath and pain transmission. RNF123, also known as KPC1, encodes Kip1 ubiquitination-promoting complex protein 1 which involves in dendritic cell development, apoptosis (Lu et al. 2011), and pain (Rahman et al. 2021). SDCCAG8 encodes SHH signaling and ciliogenesis regulator, contributing to schizophrenia and cognitive function (Flynn et al. 2020; Hamshere et al. 2013).

NCOA6 (nuclear receptor coactivator 6) was reported to be associated with insulin secretion and glucose metabolism (Yeom et al. 2006), and GPX1 (glutathione peroxidase 1) played an important role in insulin signaling. These findings were consistent with ours that the signals of insomnia were enriched in the adrenal or pancreas from cell-type specific analysis, suggesting that pain and neuropsychiatric disorders might share metabolism-related pathogenic mechanisms.

In addition, 5 of the 12 genes, including ARHGAP27, HEXIM1, NCOA6, NMT1, and RBM6, were correlated with several types of cancer (Katoh and Katoh 2004; Lew et al. 2013; Lee et al. 1999; Chen et al. 2020; Wang et al. 2019) (see details in Supplementary Table 3), which was in concordance with the fact that the cancer patients had a high incidence of neuropsychiatric disorders (Mitchell et al. 2011) and cancer pain (Copenhaver et al. 2021). We presumed that the abnormal expression of these cancer-related genes, which affected cell development, proliferation, and function, not only led to tumorigenesis, but also affected the function of nervous system (Karaca et al. 2014; Antoniou et al. 2018; Ding et al. 2009). The final manifestations would be pain and neuropsychiatric disorders. We further built a PPI network for the 12 proteins (Supplementary Fig. 4), showing that 4 of 5 cancer-related proteins we identified were related to each other.

This study comprehensively investigated shared genetic structure, causality, and potential shared pathogenic mechanisms between pain and neuropsychiatric disorders. There were three main strengths of our study. First, we included as many traits as possible from publicly available databases with an assurance of large sample size (N > 15,000). We ultimately included 26 traits of two kinds of disorders to assess the associations between two kinds of disorders, rather than two specific traits. Second, we explored the correlations between the two kinds of disorders from multiple perspectives and levels. Specifically, we explored the genetic associations between the disorders at the genome-wide level and the possible shared pathogenic mechanisms at the cell/tissue level and gene level. In addition, we used MR to determine whether the previously observed associations were causal, which enhanced our understanding of the comorbidities of pain and neuropsychiatric disorders. Third, our finding had certain clinical significance. The potential pathogenic mechanisms we found between pain and neuropsychiatric disorders might suggest novel drug targets for clinical treatment of patients with these
two disorders. However, there were several limitations in our study. First, we only included 13 common neuropsychiatric disorders. Some other neuropsychiatric disorders were not included due to limited sample size (e.g., obsessive–compulsive disorder was not included, because the sample size of GWAS of psychiatric genomics consortium was less than 10,000). Although we have included GWAS data with the largest sample size, the sample sizes of some GWAS data involved in our study were still relatively small. The number of genes identified by TWAS could be influenced by the sample size, as well as the genetic structure of the disorders. Second, the instrumental variables from GWAS with limited sample size were insufficient, which may influence the power of MR analyses. To solve this problem, we employed a relatively loose $P$ value threshold of $1 \times 10^{-5}$ to choose the candidate IVs as done in the previous studies for some disorders. Third, our study focused on European populations. The relationship between pain and neuropsychiatric traits in other populations remained to be studied.

Conclusions

Our findings provided the evidence of shared genetic structure, causality, and potential shared pathogenic mechanisms between pain and neuropsychiatric disorders, and enhanced our understanding of pain and neuropsychiatric disorders.

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Author contributions Study design: MC and XH; data collection, analysis, and interpretation: MC, SL, ZZ, CD, and XH; manuscript writing: MC and XH; final approval of manuscript: all authors; accountable for aspects of the work: all authors.

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Data availability The original contributions presented in the study are included in the article/Supplementary information, and further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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