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Research Article

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

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Abstract

Background: Pain often occurs in parallel with many neuropsychiatric disorders. However, the underlying mechanisms and potential causality have not been well studied.

Methods: 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.

Results: Among the 169 pairwise pain and neuropsychiatric disorders, 55 pairs showed significant ($P < 1.54 \times 10^{-4}$) positive correlations (median $r_g = 0.43$) and 9 pairs showed negative correlations (median $r_g = -0.31$). MR analyses identified 26 significant ($P < 1.48 \times 10^{-4}$) likely causal associations, for instance, neuroticism and insomnia were risk

factors for most of short-term pain, 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 integrating the gene expression information of CNS. The shared genes included *AMT*, *NCOA6* and *UNC45A* which involved in glycine degradation, insulin secretion and cell proliferation, respectively, suggesting pain and neuropsychiatric disorders might share neuronal signaling-related, metabolism-related and proliferation-related pathogenic mechanisms.

Conclusion: 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.

Keywords: pain, neuropsychiatric disorder, genetic correlation, causality, genetic architecture

Introduction

The pain disorders are very common with prevalence of headache 42%, unspecified chronic pain 34%, musculoskeletal pain 25% and back pain 21%, which have imposed a significant socioeconomic burden and contributed to excess mortality[1, 2]. Pain can be caused by diseases stimulating the nociceptors or abnormal function of the nervous system. The duration of pain varies a lot. 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[3]. Pain disorders showed moderate heritability ranging from 0.08~0.31 and many genetic susceptibility loci have been identified by genome-wide association studies (GWASs)[4-8].

Pain is often present in clinical manifestations of many neuropsychiatric disorders[9] in which genetic factors play significant roles[10, 11]. Besides, both immune and nervous systems play vital roles in development and maintenance of pain and neuropsychiatric disorders[12, 13]. Neuropsychiatric disorders include both neurological disorders and psychiatric disorders, such as the well-known Alzheimer's disease (AD), Parkinson's disease (PD), schizophrenia (SCZ) and major depression disorder (MDD), et al. Previous studies have found that neuropsychiatric disorders exhibited similar symptoms, epidemiological comorbidities and shared genetic structures[10, 14, 15]. 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[15]. In common with the pain disorders, neuropsychiatric disorders also have the characteristics of high prevalence and heavy burden in epidemiology[16-18]. Although pain is often present with neuropsychiatric disorders, the underlying shared 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 developed, which can be used to estimate global genetic correlation[19] and partitioned heritability[20] for pain and neuropsychiatric disorders.

Genetic instrumental variable analysis, like Mendelian randomization (MR)[21, 22], 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, like transcriptome-wide association study (TWAS)[23], 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 relationship between a variety of neuropsychiatric disorders and short-term and long-term pain in a variety of 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 $h^2 > 0$), the GWAS summary statistics of 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 were collected (Table 1). The short-term pain disorder was defined as pain that experienced in the last month and has influenced usual activities, and the long-term pain disorder, also known as chronic pain disorder, was defined as pain that has lasted 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[24]. The neuropsychiatric disorders included subjective well-being (SWB, N=298,420)[25], Parkinson's disease (PD, N=482,730)[26], Alzheimer's disease (AD, N=455,258)[27], neuroticism (N=329,821)[28], insomnia (N=237,627)[29], bipolar disorder (BIP, N=413,466)[30], schizophrenia (SCZ, N=105,318)[31], anorexia nervosa (AN, N=72,517)[32], autism spectrum disorder (ASD, N=46,350)[33], anxiety (N=17,310)[34], major depressive disorder (MDD, N=173,005)[35], posttraumatic

stress disorder (PTSD, N=174,659)[36] and attention deficit/hyperactivity disorder (ADHD, N=53,293)[37]. For all pain and neuropsychiatric disorders used in this study (Table 1), the GWAS were conducted in population of European ancestry and the genomic coordinates were built with hg19.

Estimate the genetic correlation with cross-trait LDSC

The cross-trait linkage disequilibrium (LD) score regression (LDSC)[38] 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)[39] 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 by 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 the genome-wide significant ($P < 5\times10^{-8}$) and independent SNPs as the candidate IVs by using the PLINK [40] clumping procedure with thresholds of LD r^2 0.01 and physical distance 10Mb[41, 42]. For any exposure-outcome pairs with no candidate IVs selected, we employed a relatively loose P-value threshold of 1×10^{-5} to choose the candidate IVs as done in previous studies [43, 44]. Generalized summary-data-based MR (GSMR)[22] was used in our main MR analysis. Heterogeneity in dependent instruments (HEIDI) test[22] 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[45]. The $F > 10$ indicated no potential weak instrumental bias[45]. Each LD matrix used in the GSMR model was calculated by PLINK v1.9 based on the genotypes of European in 1KGP3[39]. In order to test whether the GSMR results were robust, we additionally employed the inverse variance weighted (IVW) [46] and robust adjusted profile score (RAPS)[47] methods to perform two-sample MR as sensitivity analysis for the significant results. The MR analyses were performed with GSMR[22] and TwoSampleMR[48] 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[20]. By taking a union of the cell type-specific annotations within each group, a binary annotation was created for each cell-type groups, indicating whether a 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.*[20] 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, *et al.*) in the stratified LD score regression model as suggested to control the potential misspecification[20]. 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[23]. The GWAS summary statistics and

expression quantitative trail loci (eQTL) summary statistics were integrated in TWAS model to test the association between the gene expression and traits. The LD information used in the TWAS model was based on reference genotype of European in 1KGP3[39]. The gene expression datasets of trait-relevant tissues from the Genotype-Tissue Expression project (GTEx) v.7 were used as the reference gene expression panel[49]. The number of available genes from the 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[23] 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 tissues were tested. 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/)[50].

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 ($P<1.54×10^{-4}$, adjust for 325 tests). Specially, 64 of 169 (13×13) pairs of pain and neuropsychiatric disorder were genetically correlated (Figure 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), 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. From another 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), AN and short-term knee pain (r_g = −0.15, P = 3.49×10^{-5}) showed significant negative correlations.

When focusing on the genetic correlations between any two of neuropsychiatric disorders (Figure 1B), PD and AD were not correlated with any neuropsychiatric disorders, while others were correlated with at least 5 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 (Figure 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 3 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 minimum 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 < 1.48×10^{-4}, adjust for 338 tests), including 8 associations that pain lead to neuropsychiatric disorders, and 18 associations that neuropsychiatric disorder result in pain (Figure 2, Supplementary Figure 1).

Specifically, when the pain disorders were set as exposure (Figure 2A, Supplementary Figure 1A), we found that short-term neck/shoulder pain was a risk factor for SCZ (OR = 2.61, P = 3.20×10^{-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 8 causal pairs, multisite chronic pain was not genetically correlated with AD, neither was short-term knee pain with BIP (Figure 1A).

When the neuropsychiatric disorders were set as exposure (Figure 2B, Supplementary Figure 1B), we found that neuroticism was a risk factor for multisite chronic pain and all the 6 short-term pain., and insomnia was a risk factor for multisite chronic pain and 5 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, $P = 2.90 \times 10^{-9}$) 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 the similar effect size and same direction (Supplementary Figure 2), except for short-term neck/shoulder pain-SCZ pair with the IVW method (OR = 2.61, $P = 0.18$).

Although we found 64 pairs of pain and neuropsychiatric disorder were genetically correlated (Figure 1), only 26 pairs showed significant causal associations (Figure 2, Supplementary Figure 1). 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 10 cell-type group specific annotations. The CNS was identified to be relevant to 8 neuropsychiatric disorders and 5 pain disorders after Bonferroni correction ($P<1.92\times10^{-4}$, adjust for 260 tests, Table 2, Supplementary Figure 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. The adrenal or pancreas was identified to be relevant to insomnia.

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 ($P < 1.25\times10^{-6}$, adjust for 39,892 gene-trait associations, Figure 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. It encodes DEAD-Box Helicase 27, a putative RNA helicase. Previous study founded *DDX27* correlated with self-harm behaviors[51], intelligence[52] and schizophrenia[53]. As the only TWAS significant gene for long-term head pain, as well as short-term head pain, *UFL1* encodes *UFM1* (ubiquitin-fold modifier 1) ligase 1 that was reported to be correlated with headache[6, 54] and inflammation[55]. Two zinc-finger protein family members, *ZNF184* and *ZSCAN31*, were TWAS significant for neuroticism, SCZ, BIP and MDD. Both of them were correlated with neuropsychiatric disorders in previous studies[56-59].

Eighty-one genes showed associations with at least one pain disorder. Among them, 19 genes also showed associations with at least one neuropsychiatric disorder (Figure

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 2 traits, *AMT*, *GPX1*, *RBM6*, *RNF123*, and *ZNF646* were shared by 3 traits and *SDCCAG8* was shared by 4 traits (SCZ, short-term head pain, short-term knee pain and multisite chronic pain) (Figure 3B). *AMT* encodes aminomethyltransferase which effects the degradation of glycine, a neurotransmitter that plays an important role in maintaining normal brain development. *UNC45A* encodes UNC-45 myosin chaperone A which is essential for normal cell proliferation and the accumulation of myosin during development of muscle cells. *SDCCAG8* encodes SHH signaling and ciliogenesis regulator, contributing to schizophrenia and cognitive function[60, 61]. *RNF123*, also known as *KPC1*, encodes Kip1 ubiquitination-promoting complex protein 1 which involves in dendritic cell development, apoptosis[62] and pain[63].

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.

Neuroticism, SWB, insomnia, BIP, SCZ, AN, ASD, anxiety, MDD, PTSD and ADHD were genetically correlated with at least one kind of pain, while PD and AD were not. In addition, PD and AD were not genetically correlated with any other neuropsychiatric disorders, which was in keeping with a prior study[15]. Although both PD and AD were reported to be associated with pain in previous observational studies[64, 65], 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. As we all know, SWB was a subjective feeling that was negatively related to pain and disorders[66], which was concordant with our finding that all the significant correlation 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[67]. And patients with anorexia nervosa showed a significantly higher thermal pain threshold[68, 69]. But our subsequent MR analyses showed that there was no causality between them. Therefore, we considered that the genetic correlations we observed between them might be mainly 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[68, 69].

Among 26 significant causalities between pain and neuropsychiatric disorders, 1 of them did not pass the sensitivity analyses (short-term neck/shoulder pain disorder-SCZ). The remaining 25 pairs were more likely to be causal associated. For instance, insomnia was risk factor for multisite chronic pain and 5 short-term pain, and multisite chronic pain was also the risk factor for insomnia. A prospective population-based cohort study found that insomnia was associated with an increased risk of headache 11 years later, and vice versa[70, 71]. On the one hand, pain could be accompanied by higher levels of cognitive and somatic arousal at bedtime and result in insomnia[72].On the other hand, insomnia might affect brain function and result in a decreased pain threshold[73], 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.

In our cell-type specific analyses, the GWAS signals of neuroticism, insomnia, BIP, SCZ, short-term back pain and multisite chronic pain were enriched in the functional regions of CNS cell type groups, which were concordant with previous studies[74-76]. 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[77, 78]. Meanwhile, neuropsychiatric disorders were closely related to brain development[79] and usually involve the neurological changes in brain[80]. In addition, previous studies found that sleep suppressed the hypothalamic-pituitary- adrenal (HPA) axis and activation of the HPA axis could lead to insomnia[81]. And insomnia was associated with less insulin secretion and higher insulin sensitivity[82]. These findings could help explain our results that insomnia was enrichment correlated with the adrenal or pancreas, indicating that insomnia was associated with metabolism.

By integrating the gene expression information from the brain, TWAS identified a total of 19 independent genes, including 12 protein-coding genes that were significant for at least one pain disorder and at least one neuropsychiatric disorder. Among these 12 protein-coding genes, *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[83] and glycine encephalopathy[84]. Enhancing glycinergic neurotransmission showed the potential to treat chronic pain[85, 86]. Glycine transporters were identified as novel therapeutic targets in schizophrenia and pain[86]. Given *AMT* and glycine transporters have similar effects on glycine, thus *AMT* might be a novel therapeutic targets in schizophrenia and pain, too.

UNC45A, *RNF123* and *SDCCAG8* all affected the structure and function of neurons[60, 62]. For instance, *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 dysgnosia[87]. Yoshie Iizuka *et al.* reported that UNC45A was required for neurite extension[88] which could affect neuropsychopathy and pain transmission.

NCOA6 (nuclear receptor coactivator 6) was reported to be associated with insulin secretion and glucose metabolism[89], 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, five of the 12 genes, including *ARHGAP27*, *HEXIM1*, *NCOA6*, *NMT1* and *RBM6*, were correlated with several types of cancer[90-94] (see details in Supplementary Table 2), which was in concordance with the fact that the cancer patients had a high incidence of neuropsychiatric disorders[95] and cancer pain[96]. 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[97-99]. The final manifestations would be pain and neuropsychiatric disorders. We further built a PPI network for the 12 proteins (Supplementary Figure 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 3 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. And we used MR to determine whether the previously observed associations were causal, 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, the sample size issue created some limitations. First, we only

included 13 common neuropsychiatric disorders. Some other neuropsychiatric disorders were not included due to limited sample size or few studies (*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 as possible, the sample sizes of some GWAS data involved in our study were still relatively small. For example, the sample sizes of long-term pain of 6 body sites, ADHD, AN, anxiety and ASD were all less than 100,000. That might lead to some important genetic signals not being observed. Second, the problem accompanied with the limited sample size was few significant genetic signals of some traits, leading to insufficient instrumental variables for some trait pairs to estimate causal association when performing MR. To solve this problem, we employed a relatively loose *P*-value threshold of 1×10^{-5} to choose the candidate IVs as done in previous studies for these trait pairs. Third, our study was 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.

Abbreviations

GWAS, genome-wide association studies; LD, linkage disequilibrium; LDSC, linkage disequilibrium score regression; TWAS, transcriptome-wide association study; CNS, central nervous system; SNP, single nucleotide polymorphisms; 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 trail 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.

Supplementary Information

Supplementary Tables 1-3 and Supplementary Figures 1-4.

Authors' contributions

Study design: M.C. and X.H.; data collection, analysis and interpretation: M.C., S.L., Z.ZH., C.D. and X.H.; manuscript writing: M.C. and X.H.; final approval of manuscript: All authors; accountable for aspects of the work: All authors.

Data Availability Statement

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Reference

1. Jackson T, Thomas S, Stabile V, Shotwell M, Han X, McQueen K: **A Systematic Review and Meta-Analysis of the Global Burden of Chronic Pain Without Clear Etiology in Low- and Middle-Income Countries: Trends in Heterogeneous Data and a Proposal for New Assessment Methods.** *Anesth Analg* 2016, **123:**739-748.

2. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, et al: **Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.** *The Lancet* 2018, **392:**1789-1858.

3. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al: **UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age.** *PLoS medicine* 2015, **12:**e1001779-e1001779.

4. Meng W, Adams MJ, Reel P, Rajendrakumar A, Huang Y, Deary IJ, Palmer CNA, McIntosh AM, Smith BH: **Genetic correlations between pain phenotypes and depression and neuroticism.** *European Journal of Human Genetics* 2020, **28:**358-366.

5. Johnston KJA, Adams MJ, Nicholl BI, Ward J, Strawbridge RJ, Ferguson A, McIntosh AM, Bailey MES, Smith DJ: **Genome-wide association study of multisite chronic pain in UK Biobank.** *PLoS genetics* 2019, **15:**e1008164-e1008164.

6. Meng W, Adams MJ, Hebert HL, Deary IJ, McIntosh AM, Smith BH: **A Genome-Wide Association Study Finds Genetic Associations with Broadly-Defined Headache in UK Biobank (N=223,773).** *EBioMedicine* 2018, **28:**180-186.

7. Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, Evans DS, Gelemanovic A, Bartz TM, Nethander M, et al: **Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain.** *PLoS genetics* 2018, **14:**e1007601-e1007601.

8. Meng W, Adams MJ, Palmer CNA, andMe Research T, Shi J, Auton A, Ryan KA, Jordan JM, Mitchell BD, Jackson RD, et al: **Genome-wide association study of knee pain identifies associations with GDF5 and COL27A1 in UK Biobank.** *Communications biology* 2019, **2:**321-321.

9. Goesling J, Lin LA, Clauw DJ: **Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health.** *Curr Psychiatry Rep* 2018, **20:**12.

10. Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS: **Psychiatric genetics and the structure of psychopathology.** *Mol Psychiatry* 2019, **24:**409-420.

11. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, Posthuma D: **Meta-analysis of the heritability of human traits based on fifty years of twin studies.** *Nat Genet* 2015, **47:**702-709.

12. Pinho-Ribeiro FA, Verri WA, Jr., Chiu IM: **Nociceptor Sensory Neuron-Immune Interactions in Pain and Inflammation.** *Trends Immunol* 2017, **38:**5-19.

13. Hao X, Zeng P, Zhang S, Zhou X: **Identifying and exploiting trait-relevant tissues with multiple functional annotations in genome-wide association studies.** *PLOS Genetics* 2018, **14:**e1007186.

14. **Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders.** *Cell* 2019, **179:**1469-1482.e1411.

15. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, Escott-Price V, Falcone GJ, Gormley P, Malik R, et al: **Analysis of shared heritability in common disorders of the brain.** *Science* 2018, **360**.

16. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, Rahman A: **No health without mental health.** *Lancet* 2007, **370:**859-877.

17. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, et al: **Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010.** *Lancet* 2013, **382:**1575-1586.

18. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D: **The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013.** *Int J Epidemiol* 2014, **43:**476-493.

19. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, Daly MJ, Price AL, Neale BM: **LD Score regression distinguishes confounding from polygenicity in genome-wide association studies.** *Nat Genet* 2015, **47:**291-295.

20. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, Anttila V, Xu H, Zang C, Farh K, et al: **Partitioning heritability by functional annotation using genome-wide association summary statistics.** *Nat Genet* 2015, **47:**1228-1235.

21. Pierce BL, Burgess S: **Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators.** *Am J Epidemiol* 2013, **178:**1177-1184.

22. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, Robinson MR, McGrath JJ, Visscher PM, Wray NR, Yang J: **Causal associations between risk factors and common diseases inferred from GWAS summary data.** *Nat Commun* 2018, **9:**224.

23. Gusev A, Ko A, Shi H, Bhatia G, Chung W, Penninx BW, Jansen R, de Geus EJ, Boomsma DI, Wright FA, et al: **Integrative approaches for large-scale transcriptome-wide association studies.** *Nat Genet* 2016, **48:**245-252.

24. Johnston KJA, Adams MJ, Nicholl BI, Ward J, Strawbridge RJ, Ferguson A, McIntosh AM, Bailey MES, Smith DJ: **Genome-wide association study of multisite chronic pain in UK Biobank.** *PLoS Genet* 2019, **15:**e1008164.

25. Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, Meddens SF, Linnér RK, Rietveld CA, Derringer J, et al: **Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses.** *Nat Genet* 2016, **48:**624-633.

26. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, et al: **Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies.** *Lancet Neurol* 2019, **18:**1091-1102.

27. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, Sealock J, Karlsson IK, Hägg S, Athanasiu L, et al: **Author Correction: Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk.** *Nat Genet* 2020, **52:**354.

28. Luciano M, Hagenaars SP, Davies G, Hill WD, Clarke TK, Shirali M, Harris SE, Marioni RE,

Liewald DC, Fawns-Ritchie C, et al: **Author Correction: Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism.** *Nat Genet* 2019, **51:**577.

29. Dashti HS, Daghlas I, Lane JM, Huang Y, Udler MS, Wang H, Ollila HM, Jones SE, Kim J, Wood AR, et al: **Genetic determinants of daytime napping and effects on cardiometabolic health.** *Nat Commun* 2021, **12:**900.

30. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, Als TD, Bigdeli TB, Børte S, Bryois J, et al: **Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology.** *Nat Genet* 2021, **53:**817-829.

31. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, Legge SE, Bishop S, Cameron D, Hamshere ML, et al: **Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection.** *Nat Genet* 2018, **50:**381-389.

32. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, Bryois J, Hinney A, Leppä VM, Mattheisen M, et al: **Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa.** *Nat Genet* 2019, **51:**1207-1214.

33. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, Pallesen J, Agerbo E, Andreassen OA, Anney R, et al: **Identification of common genetic risk variants for autism spectrum disorder.** *Nat Genet* 2019, **51:**431-444.

34. Otowa T, Hek K, Lee M, Byrne EM, Mirza SS, Nivard MG, Bigdeli T, Aggen SH, Adkins D, Wolen A, et al: **Meta-analysis of genome-wide association studies of anxiety disorders.** *Mol Psychiatry* 2016, **21:**1391-1399.

35. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, et al: **Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression.** *Nat Genet* 2018, **50:**668-681.

36. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen CY, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, et al: **International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci.** *Nat Commun* 2019, **10:**4558.

37. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Baldursson G, Belliveau R, Bybjerg-Grauholm J, Bækvad-Hansen M, et al: **Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder.** *Nat Genet* 2019, **51:**63-75.

38. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh P-R, Duncan L, Perry JR, Patterson N, Robinson EB: **An atlas of genetic correlations across human diseases and traits.** *Nature genetics* 2015.

39. The 1000 Genomes Project Consortium: **A global reference for human genetic variation.** *Nature* 2015, **526:**68-74.

40. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC: **PLINK: a tool set for whole-genome association and population-based linkage analyses.** *Am J Hum Genet* 2007, **81:**559-575.

41. Nazarzadeh M, Pinho-Gomes A-C, Bidel Z, Canoy D, Dehghan A, Smith Byrne K, Bennett DA, Smith GD, Rahimi K: **Genetic susceptibility, elevated blood pressure, and risk of atrial fibrillation: a Mendelian randomization study.** *Genome medicine* 2021, **13**:38-38.

42. Geng T, Smith CE, Li C, Huang T: **Childhood BMI and Adult Type 2 Diabetes, Coronary Artery Diseases, Chronic Kidney Disease, and Cardiometabolic Traits: A Mendelian Randomization Analysis.** *Diabetes Care* 2018, **41**:1089-1096.

43. Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, Abdellaoui A, Nivard MG, Baselmans BML, Ong J-S, et al: **GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia.** *Nature neuroscience* 2018, **21**:1161-1170.

44. Lu H, Qiao J, Shao Z, Wang T, Huang S, Zeng P: **A comprehensive gene-centric pleiotropic association analysis for 14 psychiatric disorders with GWAS summary statistics.** *BMC medicine* 2021, **19**:314-314.

45. Staiger D, Stock JH: **Instrumental Variables Regression with Weak Instruments.** *National Bureau of Economic Research Technical Working Paper Series* 1994, **No. 151**.

46. Burgess S, Butterworth A, Thompson SG: **Mendelian Randomization Analysis With Multiple Genetic Variants Using Summarized Data.** *Genetic Epidemiology* 2013, **37**:658-665.

47. Zhao Q, Wang J, Hemani G, Bowden J, Small DSJae-p: **Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score.** pp. arXiv:1801.09652; 2018:arXiv:1801.09652.

48. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, et al: **The MR-Base platform supports systematic causal inference across the human phenome.** *Elife* 2018, **7**.

49. Battle A, Brown CD, Engelhardt BE, Montgomery SB: **Genetic effects on gene expression across human tissues.** *Nature* 2017, **550**:204-213.

50. von Mering C, Huynen M, Jaeggi D, Schmidt S, Bork P, Snel B: **STRING: a database of predicted functional associations between proteins.** *Nucleic Acids Res* 2003, **31**:258-261.

51. Campos AI, Verweij KJH, Statham DJ, Madden PAF, Maciejewski DF, Davis KAS, John A, Hotopf M, Heath AC, Martin NG, Rentería ME: **Genetic aetiology of self-harm ideation and behaviour.** *Sci Rep* 2020, **10**:9713.

52. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, Nagel M, Awasthi S, Barr PB, Coleman JRI, et al: **Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence.** *Nat Genet* 2018, **50**:912-919.

53. Zhang Y, You X, Li S, Long Q, Zhu Y, Teng Z, Zeng Y: **Peripheral Blood Leukocyte RNA-Seq Identifies a Set of Genes Related to Abnormal Psychomotor Behavior Characteristics in Patients with Schizophrenia.** *Med Sci Monit* 2020, **26**:e922426.

54. Eising E, Huisman SMH, Mahfouz A, Vijfhuizen LS, Anttila V, Winsvold BS, Kurth T, Ikram MA, Freilinger T, Kaprio J, et al: **Gene co-expression analysis identifies brain regions and cell types involved in migraine pathophysiology: a GWAS-based study using the Allen Human Brain Atlas.** *Hum Genet* 2016, **135**:425-439.

55. Yang G, Wang Y, Chen Y, Huang R: **UFL1 attenuates IL-1β-induced inflammatory**

response in human osteoarthritis chondrocytes. *Int Immunopharmacol* 2020, **81:**106278.

56. Keo A, Mahfouz A, Ingrassia AMT, Meneboo JP, Villenet C, Mutez E, Comptdaer T, Lelieveldt BPF, Figeac M, Chartier-Harlin MC, et al: **Transcriptomic signatures of brain regional vulnerability to Parkinson's disease.** *Commun Biol* 2020, **3:**101.

57. Wu W, Howard D, Sibille E, French L: **Differential and spatial expression meta-analysis of genes identified in genome-wide association studies of depression.** *Transl Psychiatry* 2021, **11:**8.

58. Li S, Li X, Liu J, Huo Y, Li L, Wang J, Luo XJ: **Functional variants fine-mapping and gene function characterization provide insights into the role of ZNF323 in schizophrenia pathogenesis.** *Am J Med Genet B Neuropsychiatr Genet* 2021, **186:**28-39.

59. Bhalala OG, Nath AP, Inouye M, Sibley CR: **Identification of expression quantitative trait loci associated with schizophrenia and affective disorders in normal brain tissue.** *PLoS Genet* 2018, **14:**e1007607.

60. Flynn M, Whitton L, Donohoe G, Morrison CG, Morris DW: **Altered gene regulation as a candidate mechanism by which ciliopathy gene SDCCAG8 contributes to schizophrenia and cognitive function.** *Hum Mol Genet* 2020, **29:**407-417.

61. Hamshere ML, Walters JT, Smith R, Richards AL, Green E, Grozeva D, Jones I, Forty L, Jones L, Gordon-Smith K, et al: **Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC.** *Mol Psychiatry* 2013, **18:**708-712.

62. Lu C, Huang X, Zhang X, Roensch K, Cao Q, Nakayama KI, Blazar BR, Zeng Y, Zhou X: **miR-221 and miR-155 regulate human dendritic cell development, apoptosis, and IL-12 production through targeting of p27kip1, KPC1, and SOCS-1.** *Blood* 2011, **117:**4293-4303.

63. Rahman MS, Winsvold BS, Chavez Chavez SO, Børte S, Tsepilov YA, Sharapov SZ, Aulchenko YS, Hagen K, Fors EA, Hveem K, et al: **Genome-wide association study identifies RNF123 locus as associated with chronic widespread musculoskeletal pain.** *Ann Rheum Dis* 2021, **80:**1227-1235.

64. Cao S, Fisher DW, Yu T, Dong H: **The link between chronic pain and Alzheimer's disease.** *J Neuroinflammation* 2019, **16:**204.

65. Ford B: **Pain in Parkinson's disease.** *Mov Disord* 2010, **25 Suppl 1:**S98-103.

66. McNamee P, Mendolia S: **The effect of chronic pain on life satisfaction: evidence from Australian data.** *Soc Sci Med* 2014, **121:**65-73.

67. Dunne JP, Shindul-Rothschild J, White L, Lee CS, Wolfe BE: **Mindfulness in persons with anorexia nervosa and the relationships between eating disorder symptomology, anxiety and pain.** *Eat Disord* 2021, **29:**497-508.

68. Bär KJ, de la Cruz F, Berger S, Schultz CC, Wagner G: **Structural and functional differences in the cingulate cortex relate to disease severity in anorexia nervosa.** *J Psychiatry Neurosci* 2015, **40:**269-279.

69. Bär KJ, Berger S, Schwier C, Wutzler U, Beissner F: **Insular dysfunction and descending pain inhibition in anorexia nervosa.** *Acta Psychiatr Scand* 2013, **127:**269-278.

70. Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K: **The long-term effect of insomnia on primary headaches: a prospective population-based cohort study**

(HUNT-2 and HUNT-3). *Headache* 2011, **51:**570-580.

71.   Ødegård SS, Sand T, Engstrøm M, Zwart JA, Hagen K: **The impact of headache and chronic musculoskeletal complaints on the risk of insomnia: longitudinal data from the Nord-Trøndelag health study.** *J Headache Pain* 2013, **14:**24.

72.   Palermo TM, Wilson AC, Lewandowski AS, Toliver-Sokol M, Murray CB: **Behavioral and psychosocial factors associated with insomnia in adolescents with chronic pain.** *Pain* 2011, **152:**89-94.

73.   Haack M, Scott-Sutherland J, Santangelo G, Simpson NS, Sethna N, Mullington JM: **Pain sensitivity and modulation in primary insomnia.** *Eur J Pain* 2012, **16:**522-533.

74.   Hall LS, Pain O, O'Brien HE, Anney R, Walters JTR, Owen MJ, O'Donovan MC, Bray NJ: **Cis-effects on gene expression in the human prenatal brain associated with genetic risk for neuropsychiatric disorders.** *Mol Psychiatry* 2021, **26:**2082-2088.

75.   Li X, Xu LS, Xu YF, Yang Q, Fang ZX, Yao M, Chen WY: **The gene regulatory network in different brain regions of neuropathic pain mouse models.** *Eur Rev Med Pharmacol Sci* 2020, **24:**5053-5061.

76.   O'Brien HE, Hannon E, Hill MJ, Toste CC, Robertson MJ, Morgan JE, McLaughlin G, Lewis CM, Schalkwyk LC, Hall LS, et al: **Expression quantitative trait loci in the developing human brain and their enrichment in neuropsychiatric disorders.** *Genome Biol* 2018, **19:**194.

77.   Kucyi A, Davis KD: **The dynamic pain connectome.** *Trends Neurosci* 2015, **38:**86-95.

78.   Thompson JM, Neugebauer V: **Cortico-limbic pain mechanisms.** *Neurosci Lett* 2019, **702:**15-23.

79.   Gilmore JH, Knickmeyer RC, Gao W: **Imaging structural and functional brain development in early childhood.** *Nat Rev Neurosci* 2018, **19:**123-137.

80.   Nayak D, Roth TL, McGavern DB: **Microglia development and function.** *Annu Rev Immunol* 2014, **32:**367-402.

81.   Nicolaides NC, Vgontzas AN, Kritikou I, Chrousos G: **HPA Axis and Sleep.** In *Endotext.* Edited by Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S*, et al.* South Dartmouth (MA): MDText.com, Inc.

82.   Vasisht KP, Kessler LE, Booth JN, 3rd, Imperial JG, Penev PD: **Differences in insulin secretion and sensitivity in short-sleep insomnia.** *Sleep* 2013, **36:**955-957.

83.   Narisawa A, Komatsuzaki S, Kikuchi A, Niihori T, Aoki Y, Fujiwara K, Tanemura M, Hata A, Suzuki Y, Relton CL, et al: **Mutations in genes encoding the glycine cleavage system predispose to neural tube defects in mice and humans.** *Hum Mol Genet* 2012, **21:**1496-1503.

84.   Coughlin CR, 2nd, Swanson MA, Kronquist K, Acquaviva C, Hutchin T, Rodríguez-Pombo P, Väisänen ML, Spector E, Creadon-Swindell G, Brás-Goldberg AM, et al: **The genetic basis of classic nonketotic hyperglycinemia due to mutations in GLDC and AMT.** *Genet Med* 2017, **19:**104-111.

85.   Zeilhofer HU, Acuña MA, Gingras J, Yévenes GE: **Glycine receptors and glycine transporters: targets for novel analgesics?** *Cell Mol Life Sci* 2018, **75:**447-465.

86.   Harvey RJ, Yee BK: **Glycine transporters as novel therapeutic targets in schizophrenia,**

alcohol dependence and pain. *Nat Rev Drug Discov* 2013, **12:**866-885.

87.   Esteve C, Francescatto L, Tan PL, Bourchany A, De Leusse C, Marinier E, Blanchard A, Bourgeois P, Brochier-Armanet C, Bruel AL, et al: **Loss-of-Function Mutations in UNC45A Cause a Syndrome Associating Cholestasis, Diarrhea, Impaired Hearing, and Bone Fragility.** *Am J Hum Genet* 2018, **102:**364-374.

88.   Iizuka Y, Mooneyham A, Sieben A, Chen K, Maile M, Hellweg R, Schütz F, Teckle K, Starr T, Thayanithy V, et al: **UNC-45A is required for neurite extension via controlling NMII activation.** *Mol Biol Cell* 2017, **28:**1337-1346.

89.   Yeom SY, Kim GH, Kim CH, Jung HD, Kim SY, Park JY, Pak YK, Rhee DK, Kuang SQ, Xu J, et al: **Regulation of insulin secretion and beta-cell mass by activating signal cointegrator 2.** *Mol Cell Biol* 2006, **26:**4553-4563.

90.   Katoh Y, Katoh M: **Identification and characterization of ARHGAP27 gene in silico.** *Int J Mol Med* 2004, **14:**943-947.

91.   Lew QJ, Chu KL, Chia YL, Cheong N, Chao SH: **HEXIM1, a New Player in the p53 Pathway.** *Cancers (Basel)* 2013, **5:**838-856.

92.   Lee SK, Anzick SL, Choi JE, Bubendorf L, Guan XY, Jung YK, Kallioniemi OP, Kononen J, Trent JM, Azorsa D, et al: **A nuclear factor, ASC-2, as a cancer-amplified transcriptional coactivator essential for ligand-dependent transactivation by nuclear receptors in vivo.** *J Biol Chem* 1999, **274:**34283-34293.

93.   Chen YC, Navarrete MS, Wang Y, McClintock NC, Sakurai R, Wang F, Chen KT, Chou TF, Rehan VK, Lee DJ, Diaz B: **N-myristoyltransferase-1 is necessary for lysosomal degradation and mTORC1 activation in cancer cells.** *Sci Rep* 2020, **10:**11952.

94.   Wang Q, Wang F, Zhong W, Ling H, Wang J, Cui J, Xie T, Wen S, Chen J: **RNA-binding protein RBM6 as a tumor suppressor gene represses the growth and progression in laryngocarcinoma.** *Gene* 2019, **697:**26-34.

95.   Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N: **Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies.** *Lancet Oncol* 2011, **12:**160-174.

96.   Copenhaver DJ, Huang M, Singh J, Fishman SM: **History and Epidemiology of Cancer Pain.** *Cancer Treat Res* 2021, **182:**3-15.

97.   Karaca E, Weitzer S, Pehlivan D, Shiraishi H, Gogakos T, Hanada T, Jhangiani SN, Wiszniewski W, Withers M, Campbell IM, et al: **Human CLP1 mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function.** *Cell* 2014, **157:**636-650.

98.   Antoniou A, Khudayberdiev S, Idziak A, Bicker S, Jacob R, Schratt G: **The dynamic recruitment of TRBP to neuronal membranes mediates dendritogenesis during development.** *EMBO Rep* 2018, **19.**

99.   Ding N, Tomomori-Sato C, Sato S, Conaway RC, Conaway JW, Boyer TG: **MED19 and MED26 are synergistic functional targets of the RE1 silencing transcription factor in epigenetic silencing of neuronal gene expression.** *J Biol Chem* 2009, **284:**2648-2656.
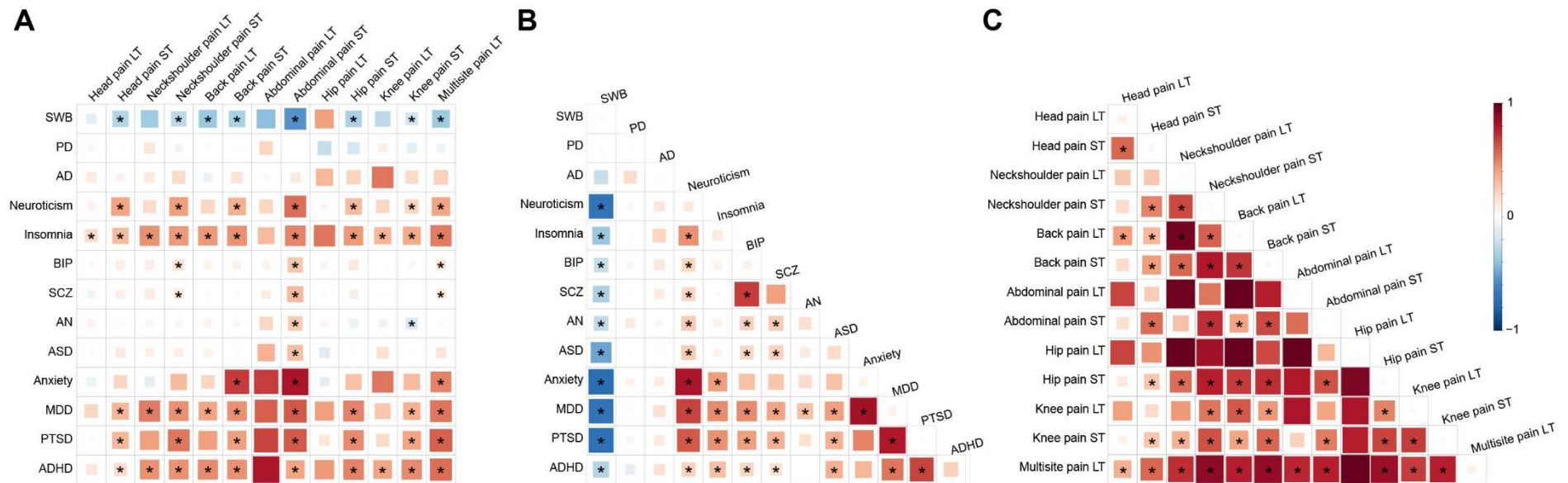
Figure 1 (A) Genetic correlations between pairwise pain and neuropsychiatric disorders. (B) Genetic correlations between 13 neuropsychiatric disorders. (C) Genetic correlations between 13 pain disorders. The colors represent the genetic correlation between the corresponding two disorders using LD score regression, red for positive genetic correlation and blue for negative genetic correlation. The significant genetic correlations after Bonferroni correction ($P < 1.54 \times 10^{-4}$) are labeled with asterisks.

Exposure	Outcome	No. IVs	F		OR (95% CI)	P
Neckshoulder pain ST	SCZ	3	37.3		2.61 (1.86, 3.67)	3.20×10^{-8}
Knee pain ST	BIP	7	42.9		0.65 (0.53, 0.79)	1.21×10^{-5}
Multisite pain LT	AD	33	36.5		1.12 (1.06, 1.19)	1.10×10^{-4}
	Neuroticism	21	36.5		1.52 (1.34, 1.72)	6.50×10^{-11}
	Insomnia	26	36.1		1.27 (1.22, 1.32)	1.76×10^{-33}
	MDD	32	36.2		1.95 (1.59, 2.39)	1.30×10^{-10}
	PTSD	32	36.2		2.63 (1.83, 3.76)	1.35×10^{-7}
	ADHD	32	36.2		5.06 (3.58, 7.14)	3.09×10^{-20}

OR: 1 3 5 7

B

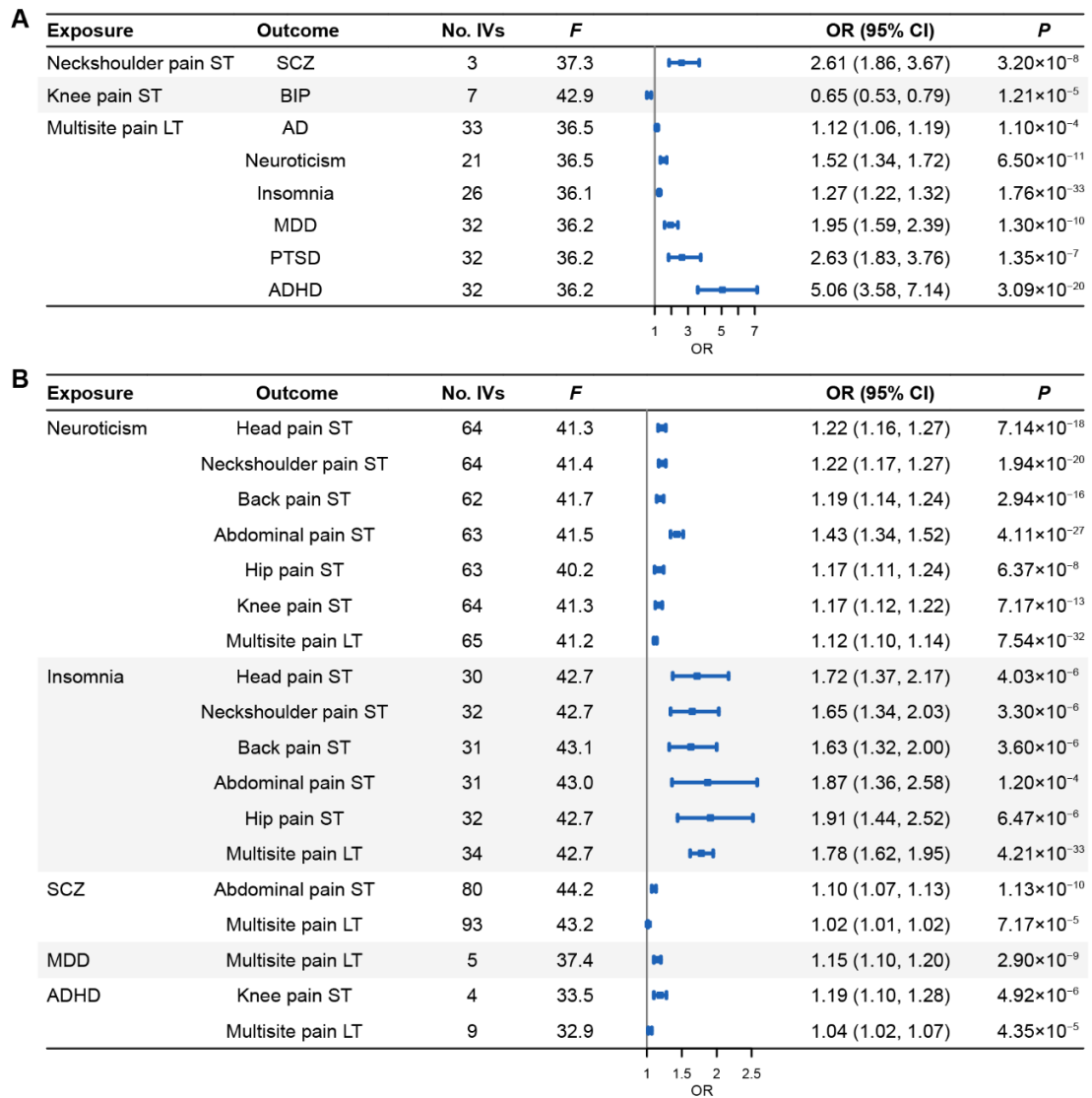| Exposure	Outcome	No. IVs	F		OR (95% CI)	P
Neuroticism	Head pain ST	64	41.3		1.22 (1.16, 1.27)	7.14×10^{-18}
	Neckshoulder pain ST	64	41.4		1.22 (1.17, 1.27)	1.94×10^{-20}
	Back pain ST	62	41.7		1.19 (1.14, 1.24)	2.94×10^{-16}
	Abdominal pain ST	63	41.5		1.43 (1.34, 1.52)	4.11×10^{-27}
	Hip pain ST	63	40.2		1.17 (1.11, 1.24)	6.37×10^{-8}
	Knee pain ST	64	41.3		1.17 (1.12, 1.22)	7.17×10^{-13}
	Multisite pain LT	65	41.2		1.12 (1.10, 1.14)	7.54×10^{-32}
Insomnia	Head pain ST	30	42.7		1.72 (1.37, 2.17)	4.03×10^{-6}
	Neckshoulder pain ST	32	42.7		1.65 (1.34, 2.03)	3.30×10^{-6}
	Back pain ST	31	43.1		1.63 (1.32, 2.00)	3.60×10^{-6}
	Abdominal pain ST	31	43.0		1.87 (1.36, 2.58)	1.20×10^{-4}
	Hip pain ST	32	42.7		1.91 (1.44, 2.52)	6.47×10^{-6}
	Multisite pain LT	34	42.7		1.78 (1.62, 1.95)	4.21×10^{-33}
SCZ	Abdominal pain ST	80	44.2		1.10 (1.07, 1.13)	1.13×10^{-10}
	Multisite pain LT	93	43.2		1.02 (1.01, 1.02)	7.17×10^{-5}
MDD	Multisite pain LT	5	37.4		1.15 (1.10, 1.20)	2.90×10^{-9}
ADHD	Knee pain ST	4	33.5		1.19 (1.10, 1.28)	4.92×10^{-6}
	Multisite pain LT	9	32.9		1.04 (1.02, 1.07)	4.35×10^{-5}

OR: 1 1.5 2 2.5

Figure 2 The significant causal associations between pain and neuropsychiatric traits using bi-directional GSMR. (A) When pain disorders are set as exposure, neuropsychiatric traits as outcome. **(B)** When neuropsychiatric disorders are set as exposure, pain disorders as outcome. No. IVs column shows the number of IVs, and *F* column shows the conditional *F* statistic for each exposure-outcome pair. Significant exposure-outcome pairs are showed in the figure ($P < 1.48 \times 10^{-4}$).
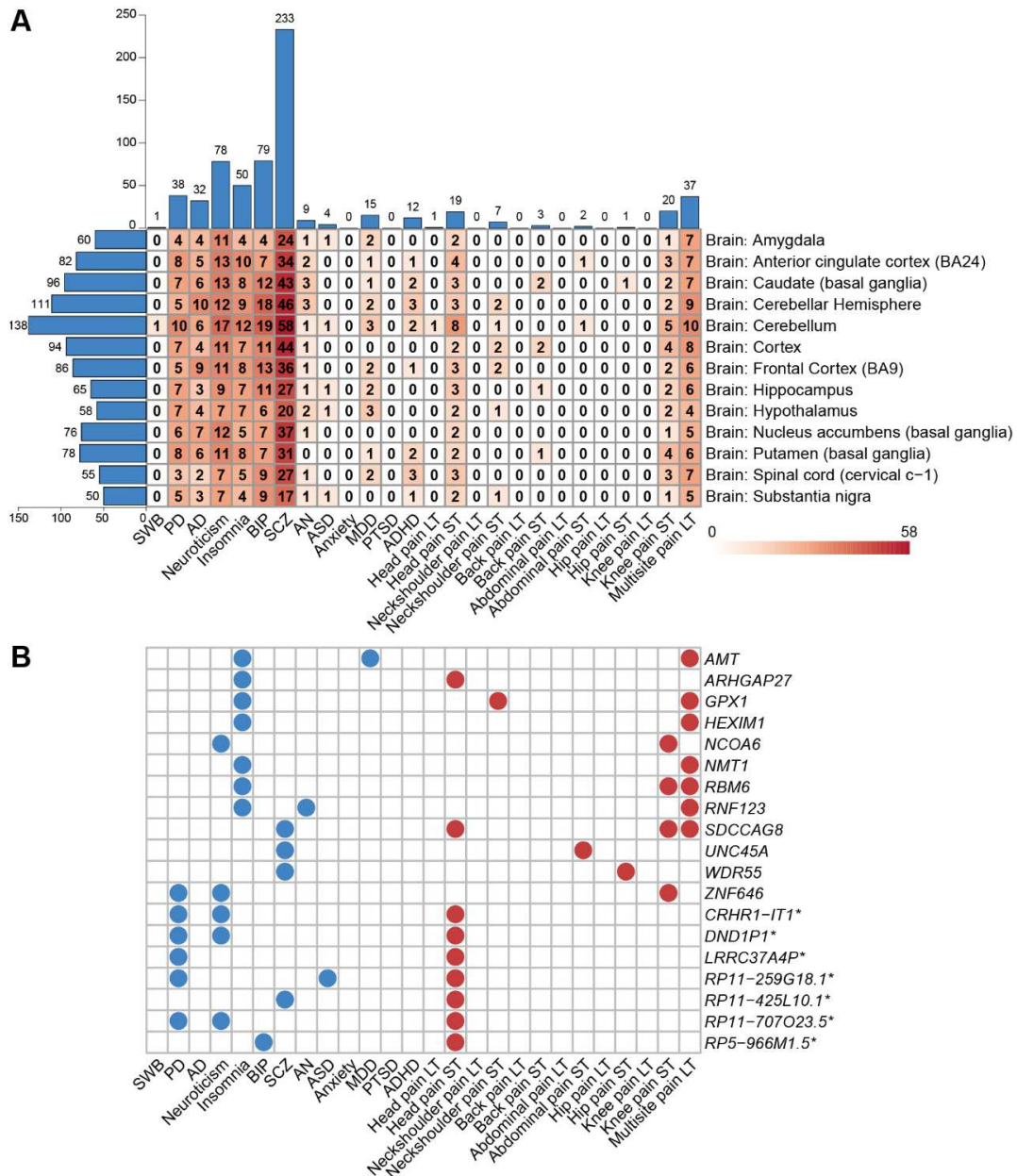
Figure 3 The results of TWAS for 26 pain and neuropsychiatric disorders across 13 brain tissues from GTEx. (A) Number of the significant genes for 26 pain and neuropsychiatric disorders. The bar chart on the top/left reflects the number of TWAS significant unique genes identified for each disorder/tissue from TWAS using gene expression panel of 13 tissues. The color and number of the heat map represent the count of TWAS significant genes identified for each disorder. The significance threshold was corrected for the total number of TWAS gene-tissue pairs ($P < 1.25 \times 10^{-6}$). **(B)** 19 genes associated with at least one pain traits and at least one neuropsychiatric disorder, 7 of them were pseudogenes. Pseudogenes are labeled with asterisks. All of the associations were positive. The dots represent the corresponding trait and gene TWAS significant correlated and the color of red and blue represent pain and neuropsychiatric disorders, respectively.

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 K, et al., Nat Genet, 2019
Head pain ST	77,568/308,130	0.0406 (0.0023)	0.0990 (0.0057)	Watanabe K, et al., Nat Genet, 2019
Neck/shoulder pain LT	60,226/27,147	0.0250 (0.0054)	0.0381 (0.0082)	Watanabe K, et al., Nat Genet, 2019
Neck/shoulder pain ST	88,299/297,399	0.0315 (0.0018)	0.0688 (0.0040)	Watanabe K, et al., Nat Genet, 2019
Back pain LT	66,773/30,751	0.0352 (0.0049)	0.0298 (0.0041)	Watanabe K, et al., Nat Genet, 2019
Back pain ST	98,389/287,309	0.0349 (0.0019)	0.0671 (0.0037)	Watanabe K, et al., Nat Genet, 2019
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 K, et al., Nat Genet, 2019
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 K, et al., Nat Genet, 2019
Knee pain LT	63,679/17,463	0.0250 (0.0055)	0.0376 (0.0083)	Watanabe K, et al., Nat Genet, 2019
Knee pain ST	81,814/303,884	0.0370 (0.0021)	0.0809 (0.0046)	Watanabe K, et al., Nat Genet, 2019
Multisite pain LT	387,649	0.0731 (0.0028)		Johnston KJA, et al., PLoS Genet, 2019
Neuropsychiatric disorders				
SWB	298,420	0.0250 (0.0020)		Okbay A, et al., Nat Genet, 2016
PD	33,674/449,056	0.0183 (0.0017)	0.0274 (0.0025)	Nalls MA, et al., Lancet Neurol, 2019
AD	71,880/383,378	0.0144 (0.0020)	0.0230 (0.0032)	Jansen IE, et al., Nat Genet, 2019
Neuroticism	329,821	0.1073 (0.0045)		Luciano M, et al., Nat Genet, 2019
Insomnia	129,270/108,357	0.1145 (0.0043)	0.1214 (0.0046)	Dashti HS, et al., Nat Commun, 2021
BIP	41,917/371,549	0.0703 (0.0026)	0.1012 (0.0038)	Mullins N, et al., Nat Genet, 2021
SCZ	40,675/64,643	0.4088 (0.0139)	0.1950 (0.0066)	Pardiñas AF, et al., Nat Genet, 2018
AN	16,992/55,525	0.1771 (0.0118)	0.0979 (0.0065)	Watson HJ, et al., Nat Genet, 2019
ASD	18,381/27,969	0.1947 (0.0170)	0.0963 (0.0084)	Grove J, et al., Nat Genet, 2019
Anxiety	7,016/14,745	0.0779 (0.0296)	0.0607 (0.0231)	Otowa T, et al., Mol Psychiatry, 2016
MDD	59,851/113,154	0.0783 (0.0047)	0.0602 (0.0036)	Wray NR, et al., Nat Genet, 2018
PTSD	23,212/151,447	0.0169 (0.0029)	0.0292 (0.0051)	Nievergelt CM, et al., Nat Commun, 2019
ADHD	19,099/34194	0.2339 (0.0151)	0.2158 (0.0139)	Demontis D, et al., Nat Genet, 2019

Note: 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.

Table 2 Enrichment of individual tissue types.

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
AN	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

Note: We report the cell type with the lowest coefficient *P* value for each disorder analyzed.

Supplementary Files

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

- 02SuppFigures.pdf
- 03SuppTables.xlsx