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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Individual-level genotype data were extracted from blood samples. MRI data from the local community cohort were acquired using a 3.0T GE750 scanner (General Electric, Milwaukee, WI, USA) equipped with an 8-channel receive-only head coil. Chronic pain intensity were obtained from online "Experience of pain" questionnaire These data for the UK Biobank cohort were obtained directly from the UK Biobank resource.
Data analysis	Genome-wide association analysis was performed using PLINK v2.00 (https://www.cog-genomics.org/plink/2.0/); SNP-based heritability was estimated using linkage disequilibrium score regression v1.0.1 (https://github.com/bulik/ldsc) Function annotation, gene mapping, gene-set enrichment and trait related cell mapping were performed using FUMA v1.5.2 (https://fuma.ctglab.nl/) and gsMap v1.73.0 (https://github.com/JianYang-Lab/gsMap); Phenotypic associations were assessed using general linear models in R v4.3.1 (https://www.r-project.org/); Genetic correlation analysis was performed using GNOVA (https://github.com/xtonyjiang/GNOVA) and PRS-CS (vMay 14, 2024) (https://github.com/getian107/PRScs) Mediation analyses were performed using the Lavaan package v0.6-19 in R v4.3.1 (https://github.com/yrosseel/lavaan); Mendelian randomization (MR) analyses were conducted using the TwoSampleMR package v0.6.8 in R v4.3.1 (https://mrcieu.github.io/

TwoSampleMR/).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data Availability

The chronic pain intensity GWAS summary statistics generated in this study have been deposited in the Zenodo database (DOI: 10.5281/zenodo.17122257). All data used in this study are publicly available from the UK Biobank through the standard application procedure (www.ukbiobank.ac.uk), under application number 75556. Researchers can apply for access via the Access Management System (AMS) (www.ukbiobank.ac.uk/enable-your-research/apply-for-access). The 1000 Genomes Project LD reference panels are available at https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html. GWAS summary statistics for UK Biobank imaging-derived phenotypes can be accessed via the BIG40 resource (https://open.win.ox.ac.uk/ukbiobank/big40/). Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was included as covariate in the analyses. Sex information for all participants was determined based on self-reported data (Field ID 31) and genetic-infer data (Field ID 22001) in the UK Biobank.
Reporting on race, ethnicity, or other socially relevant groupings	Participants included in this study were selected based on white British ancestry to minimize population stratification. Ancestry was determined using a combination of self-reported ethnicity and genetic principal component analysis provided by the UK Biobank (Field ID 22006). No analyses were performed on other racial or ethnic groups.
Population characteristics	GWAS: Participants number: 134,627; Age: 66.6±7.6 years; Sex: 58,905 male and 75,722 female. Phenotypic correlation: Participants number: 14,519~18,098; Mean age = 63.1 years; 8020 ~ 9545 female. PRS-based cross-trait prediction: Participants number: 24,503~25,566; Mean age = 64.1 years; 13047 ~ 13551 female. Mediation analyses: Participants number: 16,995~16,996; Mean age = 63.2 years; 8997 female.
Recruitment	The participants of the UK Biobank were recruited through postal invitations, while participants from the local community were recruited via advertisements posted on social media platforms.
Ethics oversight	The UK Biobank has received approval from the North West Multi-Centre Research Ethics Committee to obtain and disseminate data and samples (REC reference: 11/NW/0382on June 17, 2011, http://www.ukbiobank.ac.uk/ethics), and these ethical regulations apply to the work presented in this study.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical method was used to predetermine the sample size. All available UK Biobank participants with complete data (N = 134,627) were included.
Data exclusions	The study applied different participant exclusion criteria across different analyses, as detailed below: Exclusions criteria for GWAS: 1) without chronic pain intensity data; 2) withdrawn from UKBB project until December, 2024; 3) not white British ancestry; 4) sex chromosome aneuploidy; 5) sex mismatch; 6) outliers for heterozygosity or missing rate (field ID: 22027); 7) kinship coefficient > 0.0884; Exclusions criteria for Phenotypic association, PRS-based cross-trait prediction and Mediation analyses: 1) withdrawn from UKBB project until

	December, 2024; 2) brain MRI with notable structural abnormalities, artifacts, or incomplete scans; 3) neurological disorder; 4) not white British ancestry; 5) completed the online "Experience of Pain" questionnaire before or within three months following the collection of imaging data; 6) missing covariates data; 7) with brain IDP values greater than six times the median absolute deviation from the median.
Replication	Replication analyses were conducted using three independent cohorts (FinnGen, MVP, and UK Biobank replication dataset). Among the six lead SNPs identified in the primary GWAS, five were successfully replicated in all three validation cohort.
Randomization	In our statistical analyses, including general linear models (GLMs), PRS-based cross-trait prediction, and mediation analyses, we adjusted for the following covariates: age at data acquisition, sex, age-by-sex interaction, quadratic age-by-sex interaction, the first 10 genetic principal components (PCs), total intracranial volume, follow-up interval, body mass index (BMI), index of multiple deprivation (a measure of socioeconomic status), smoking status, alcohol consumption status, educational attainment, analgesic usage, and history of seeking medical advice for nervousness, anxiety, tension, or depression.
Blinding	Blinding was not applicable to this study as this is observational.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Magnetic resonance imaging

Experimental design

Design type	T1-weighted MRI, Diffution MRI, task functional MRI, resting-state functional MRI.
Design specifications	UK Biobank designed imaging acquisition protocals including 6 modalities. The collection order is T1-weighted structural imaging, resting-state functional MRI, task functional MRI, T2-weighted FLAIR structural imaging, Diffution MRI, and susceptibility-weighted imaging.
Behavioral performance measures	Detailed pipeline can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf).

Acquisition

Imaging type(s): T1-weighted MRI, resting-state functional MRI, task functional MRI, T2-weighted FLAIR MRI, Diffution MRI, and susceptibility-weighted MRI.

Field strength: 3T

Sequence & imaging parameters: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf).

Area of acquisition: Whole brain

Diffusion MRI ☒ Used ☐ Not used

Parameters: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Preprocessing

Preprocessing software: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Normalization: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Normalization template: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Noise and artifact removal: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Volume censoring: Detailed sequence and imaging parameters can be obtained from an open-source document (https:// biobank.ndph.ox.ac.uk/ showcase/showcase/docs/brain_mri.pdf).

Statistical modeling & inference

Model type and settings: Univariate analyses were used to assess the associations of brain IDPs with both chronic pain intensity and polygenic risk scores for chronic pain intensity, implemented by linear regression with multiple covariates.

Effect(s) tested: Beta coefficients from general linear models were used to assess the associations between SNPs and chronic pain intensity, as well as between baseline brain IDPs and both future chronic pain intensity and PRS for chronic pain intensity;

Genetic correlations between brain IDPs and chronic pain intensity were estimated using GNOVA correlation coefficients;

Indirect effects (a × b) from structural equation models were used to evaluate the mediating role of brain IDPs in the relationship between genetic factors and chronic pain intensity;

Causal effects of brain IDPs on chronic pain intensity were assessed using beta coefficients from Mendelian randomization analyses.

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016): FAST atlas; FIRST atlas; aseg atlas; aparc-DKT atlas; aparc-Desikan atlas; BA atlas; aparc-a2009s atlas; aparc-pial atlas.

Correction: Family-wise error correction for effective number of independent tests (Meff)

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity: Functional connectivity measured by Pearson correlation