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ENIGMA-Chronic Pain: a worldwide initiative to identify brain correlates of chronic pain

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Chronic pain has a profound societal burden, affecting 20% to 30% of the world population,^{10,13,14,47} and is associated with high rates of comorbid mental health conditions, especially depression and anxiety.¹⁵ Women and people of increasing age are disproportionately affected by chronic pain,^{14,32} and while there are pharmacological and nonpharmacological treatments available, many individuals still do not benefit from these treatments.^{11,16,19,31,35,45} One significant challenge in providing effective pain-relieving treatments arises from our incomplete understanding of the mechanisms underlying the development and maintenance of chronic pain. Some of these mechanisms include changes in brain morphology and function.^{2,8,12,18,25,28,37} One approach to better understand these mechanisms is to combine neuroimaging studies of diverse populations with the purpose of identifying common phenotypes and neuroimaging correlates. Phenotyping to explore both similarities and heterogeneity across pain conditions is necessary to inform disease prognosis and elucidate common treatment targets. To this endeavor, the Enhancing Neuroimaging and Genetics through Meta-Analysis (ENIGMA)-Chronic Pain working group was formed in November 2022. ENIGMA-Chronic Pain has since welcomed over 70 pain investigators from all over the world, to pool and integrate existing neuroimaging and clinical data from approximately 2000 chronic pain and 4000 pain-free healthy individuals, from over 30 international and independently collected datasets.

1. What is ENIGMA? What are the aims of the ENIGMA-Chronic Pain Working Group?

Founded in 2009, the aim of the ENIGMA Consortium is to address the growing replication problems in neuroimaging

research. ENIGMA is a global collaboration of more than 2000 scientists from over 45 countries studying the human brain, in health and over 30 neurological, mental, and neurogenetic diseases.⁴² ENIGMA coordinates large-scale neuroimaging analyses, pooling existing datasets from around the world,^{6,34,39} actively coordinating the reuse of data, while accommodating data privacy safeguards, bringing rich resources and expertise to answer fundamental questions related to major brain disorders. By integrating available existing datasets and building on the growing infrastructure of the ENIGMA consortium, ENIGMA-Chronic Pain provides a platform and a resource to the chronic pain community allowing for data findability, accessibility, interoperability, and⁴⁴ reusability—all vital aspects of reproducible research. Using a cost-effective and innovative global approach by merging the resources and data of leading chronic pain neuroimaging centers, ENIGMA-Chronic Pain offers a unique opportunity to obtain detailed, reproducible, and reliable data on brain mechanisms associated with chronic pain. ENIGMA-Chronic Pain integrates single studies of specific chronic pain conditions, including precursor data repositories (eg, OpenPain), and larger population-based biobanks with recorded indices of chronic pain (eg, UK Biobank).⁸ Recent advances in machine learning and artificial intelligence technologies also offer new and powerful ways to analyze these existing neuroimaging data. Through a worldwide collaboration of pain researchers and clinicians, ENIGMA-Chronic Pain will aim to (1) determine common and pain condition-specific brain correlates of chronic pain through multimodal neuroimaging (relative to pain-free healthy controls); (2) examine the interactions between chronic pain and comorbid mental health conditions on brain morphology and function; and (3) identify the roles of key sociodemographic factors and medication on brain morphology and function.

2. Determine common and pain condition-specific brain correlates of chronic pain through multimodal neuroimaging

ENIGMA-Chronic Pain combines smaller datasets from heterogeneous chronic pain conditions. This approach maximizes the power of planned analyses and is necessary to identify brain correlates shared across chronic pain conditions. Through planned follow-up analyses on pooled datasets of similar pain types, pain locations across the body, or specific diagnoses, ENIGMA-Chronic Pain will identify correlates specific to the studied conditions at a larger scale than has previously been possible. ENIGMA-Chronic Pain will begin with examining brain topography of chronic pain by using common processing pipelines and software such as FreeSurfer for T1-weighted structural magnetic resonance imaging scans (sMRI)^{17,20,21} or Functional MRI of the Brain Software Library (FSL) for diffusion

MRI (dMRI).^{23,38} Further to brain-wide region-of-interest analyses, investigation of multimodal correlates and brain networks of chronic pain will be conducted using whole-brain analyses, including standardized indices of functional connectivity from resting-state functional MRI (rs-fMRI) processed with ENIGMA's HALPipe,⁴³ voxel-based morphometry, and machine learning approaches to fuse multimodal features from sMRI, dMRI, and rs-fMRI to make diagnostic classification or prediction of a future clinical state.

3. Examine the interactions between chronic pain and comorbid mental health conditions on brain morphology and function

Chronic pain is often accompanied by comorbid mental health conditions that can prevent treatment success.⁴⁶ For example, 5% to 85% of individuals with chronic pain (depending on the

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study populations and settings) experience depression.^{1,9} The ENIGMA Consortium has extensively investigated the detailed brain and genetic markers of most common mental health conditions and reported alterations in brain regions similar to those commonly reported in smaller chronic pain studies.^{4,36} Evidence for shared or specific brain mechanisms between chronic pain and depression and anxiety is now growing,^{33,40,49,50} but no definite conclusion can be drawn from these smaller studies. Using advanced statistical models, our unique sample size, and availability of indices of comorbid mental health conditions, the pooled dataset from ENIGMA-Chronic Pain will aim to disentangle the fine morphological and functional brain alterations across all pain conditions, but also within specific pain types. This approach will contribute to identify plausible targets for more effective treatments for people living with both chronic pain and these comorbid conditions.

4. Examine the roles of key sociodemographic factors and medication on brain morphology and function

Sex and age are key factors that can influence the transition to chronic pain.⁴⁸ Women have greater prevalence rates for chronic pain conditions compared with men and experience more frequent, intense, and longer-lasting pain across the lifespan.^{14,24,30} These sex-specific differences can affect treatment choice, side effect profiles, and therapeutic responses.³ Although incompletely understood, many processes including genetic,²⁹ neuroendocrine/neuroimmune,²⁶ or brain-based differences,²² contribute to sex differences observed in chronic pain. Chronic pain is also highly prevalent in people of increasing age,¹⁴ along with other age-related pathologies, but the relationship between increasing age and chronic pain on brain morphology and function is still to be clearly determined. The inclusion of studies with comorbidity information that may inform causal modeling (eg, traumatic injuries, repetitive stress injuries, osteoporosis, metabolic disorders like diabetes, etc.) will clarify some of the brain–body connections at play. Existing preliminary evidence for the influence of these key sociodemographic factors needs further replication and refinement using large datasets. Another critical factor impacting brain morphology and function in chronic pain is the use of various types of pharmacological treatments,²⁷ including tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, antiepileptics, nonsteroidal anti-inflammatory drugs, and benzodiazepines.^{11,35} Using the available and detailed medication information recorded within ENIGMA-Chronic Pain, the aim of this study is to determine the variations in brain morphology and function associated with specific pharmacological treatment categories or combinations of thereof.

5. ENIGMA-Chronic Pain: expanding to other imaging modalities

ENIGMA-Chronic Pain builds on the experience of the Consortium to host the largest and most comprehensive dataset for neuroimaging studies of chronic pain. In addition to sMRI, dMRI, and rs-fMRI data, ENIGMA-Chronic Pain will leverage the contribution of chronic pain researchers and clinicians with data and expertise in other neuroimaging modalities, including resting-state electroencephalography (EEG), task-based fMRI and EEG, event-related potentials, magnetoencephalography, functional near-infrared spectroscopy, and magnetic resonance spectroscopy. In addition, the aim of ENIGMA-Chronic Pain is to include neuromodulation studies, such as repetitive transcranial

magnetic resonance stimulation, TMS-EEG, transcranial direct current stimulation, or transcranial alternating current stimulation studies, to examine potential causal associations.⁷ Finally, following work from the ENIGMA-Clinical Endpoint working group,⁴¹ a long-term goal includes building a framework of standardized questionnaires and tools for future research, to be applied to most, if not all, chronic pain conditions and to integrate genetics data to better understand the relationship between genetic and environmental risks on brain phenotypes of chronic pain overall and for available subtypes.

6. Conclusions

ENIGMA-Chronic Pain will establish the largest worldwide platform for neuroimaging data dedicated to chronic pain research. This approach enables large-scale collaborative opportunities to identify the common and specific brain correlates of chronic pain conditions, as well as the role of mental health comorbidities, key sociodemographic factors, and pharmacological treatment on these alterations. This initiative will provide invaluable new knowledge based on adequately powered neuroimaging datasets. Future aims of the working group could include extending the scope to the earliest periods of the human lifespan, leveraging neonatal MRI and EEG datasets with pain-relevant paradigms,⁵ to investigate the potential developmental origins of chronic pain susceptibility in later years. Last, we extend the call to additional groups to join, contribute their expertise, and share their neuroimaging, genetic, psychological, and clinical data from healthy controls and individuals with chronic pain (see information and contact details on <https://enigma.ini.usc.edu/ongoing/enigma-chronic-pain/>). Through the inclusion of most, if not all, chronic pain neuroimaging research groups, we hope to grow the working group and thereby fulfill its goals.

Conflict of interest statement

None of the authors declare any conflicts of interest. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government, or those of the NHS, the NIHR, or the Department of Health from the United Kingdom.

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References

- Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433–45.
- Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* 2012;15:1117–9.
- Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth* 2013;111:52–8.
- Bas-Hoogendam JM, Groenewold NA, Aghajani M, Freitag GF, Harrewijn A, Hilbert K, Jahanshad N, Thomopoulos SI, Thompson PM, Veltman DJ, Winkler AM, Lueken U, Pine DS, van der Wee NJA, Stein DJ; ENIGMA-Anxiety Working Group. ENIGMA-anxiety working group: rationale for and organization of large-scale neuroimaging studies of anxiety disorders. *Hum Brain Mapp* 2022;43:83–112.
- Baxter L, Moultrie F, Fitzgibbon S, Aspbury M, Mansfield R, Bastiani M, Rogers R, Jbabdi S, Duff E, Slater R. Functional and diffusion MRI reveal the neurophysiological basis of neonates' noxious-stimulus evoked brain activity. *Nat Commun* 2021;12:2744.
- Bayer JMM, Thompson PM, Ching CRK, Liu M, Chen A, Panzenhagen AC, Jahanshad N, Marquand A, Schmaal L, Samann PG. Site effects how-to and when: an overview of retrospective techniques to accommodate site effects in multi-site neuroimaging analyses. *Front Neurol* 2022;13:923988.
- Bergmann TO, Hartwigsen G. Inferring causality from noninvasive brain stimulation in cognitive neuroscience. *J Cogn Neurosci* 2021;33:195–225.
- Bhatt RR, Haddad E, Zhu AH, Thompson PM, Gupta A, Mayer EA, Jahanshad N. Mapping brain structure variability in chronic pain: the role of widespreadness and pain type and its mediating relationship with suicide attempt. *Biol Psychiatry* 2024;95:473–81.
- Brandl F, Weise B, Mulej Bratec S, Jassim N, Hoffmann Ayala D, Bertram T, Ploner M, Sorg C. Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: a transdiagnostic multimodal meta-analysis of structural and functional MRI studies. *Neuropsychopharmacology* 2022;47:1071–80.
- Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10:287–333.
- Cashin AG, Wand BM, O'Connell NE, Lee H, Rizzo RR, Bagg MK, O'Hagan E, Maher CG, Furlan AD, van Tulder MW, McAuley JH. Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2023;4:CD013815.
- Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, Geminiani G, Torta DM. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. *Neuroimage Clin* 2014;4:676–86.
- Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* 2021;397:2082–97.
- Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:1001–6.
- De La Rosa JS, Brady BR, Ibrahim MM, Herder KE, Wallace JS, Padilla AR, Vanderah TW. Co-occurrence of chronic pain and anxiety/depression symptoms in U.S. adults: prevalence, functional impacts, and opportunities. *PAIN* 2024;165:666–73.
- Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2016;4:CD007400.
- Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006;31:968–80.
- Farrell SF, Campos AI, Kho PF, de Zoete RMJ, Sterling M, Renteria ME, Ngo TT, Cuellar-Partida G. Genetic basis to structural grey matter associations with chronic pain. *Brain* 2021;144:3611–22.
- Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–73.
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002;33:341–55.
- Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cereb Cortex* 2004;14:11–22.
- Gupta A, Mayer EA, Fling C, Labus JS, Naliboff BD, Hong JY, Kilpatrick LA. Sex-based differences in brain alterations across chronic pain conditions. *J Neurosci Res* 2017;95:604–16.
- Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. *Fsl. Neuroimage* 2012;62:782–90.
- Keogh E. Sex and gender differences in pain: past, present, and future. *PAIN* 2022;163(suppl 1):S108–16.
- Kuner R, Flor H. Structural plasticity and reorganization in chronic pain. *Nat Rev Neurosci* 2016;18:20–30.
- Lenert ME, Avona A, Garner KM, Barron LR, Burton MD. Sensory neurons, neuroimmunity, and pain modulation by sex hormones. *Endocrinology* 2021;162:bqab109.
- Martucci KT, Mackey SC. Neuroimaging of pain: human evidence and clinical relevance of central nervous system processes and modulation. *Anesthesiology* 2018;128:1241–54.
- McCarberg B, Peppin J. Pain pathways and nervous system plasticity: learning and memory in pain. *Pain Med* 2019;20:2421–37.
- Mogil JS. Qualitative sex differences in pain processing: emerging evidence of a biased literature. *Nat Rev Neurosci* 2020;21:353–65.
- Mogil JS. Sources of individual differences in pain. *Annu Rev Neurosci* 2021;44:1–25.
- Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, Lanteri-Minet M, Lefaucheur JP, Mick G, Piano V, Pickering G, Piquet E, Regis C, Salvat E, Attal N. Pharmacological and non-pharmacological treatments for neuropathic pain: systematic review and French recommendations. *Rev Neurol (Paris)* 2020;176:325–52.
- Osborne NR, Davis KD. Sex and gender differences in pain. *Int Rev Neurobiol* 2022;164:277–307.
- Quidé Y, Norman-Nott N, Hesam-Shariati N, McAuley JH, Gustin SM. Depressive symptoms moderate functional connectivity within the emotional brain in chronic pain. *BJPsych Open* 2023;9:e80.
- Radua J, Vieta E, Shinohara R, Kochunov P, Quidé Y, Green MJ, Weickert CS, Weickert T, Bruggemann J, Kircher T, Nenadic I, Cairns MJ, Seal M, Schall U, Henskens F, Fullerton JM, Mowry B, Pantelis C, Lenroot R, Croyvel V, Loughland C, Scott R, Wolf D, Satterthwaite TD, Tan Y, Sim K, Piras F, Spalletta G, Banaj N, Pomarol-Clotet E, Solanes A, Albajes-Eizaguirre A, Canales-Rodriguez EJ, Sarro S, Di Giorgio A, Bertolino A, Stablein M, Oertel V, Knochel C, Borgwardt S, du Plessis S, Yun JY, Kwon JS, Dannowski U, Hahn T, Grotegerd D, Alloza C, Arango C, Janssen J, Diaz-Caneja C, Jiang W, Calhoun V, Ehrlich S, Yang K, Cascella NG, Takayanagi Y, Sawa A, Tomyshev A, Lebedeva I, Kaleda V, Kirschner M, Hoschl C, Tomecek D, Skoch A, van Amelsvoort T, Bakker G, James A, Preda A, Weideman A, Stein DJ, Howells F, Uhlmann A, Temmingh H, Lopez-Jaramillo C, Diaz-Zuluaga A, Fortea L, Martinez-Heras E, Solana E, Llufrú S, Jahanshad N, Thompson P, Turner J, van Erp T; ENIGMA Consortium collaborators. Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *Neuroimage* 2020;218:116956.

- [35] Rosner J, de Andrade DC, Davis KD, Gustin SM, Kramer JLK, Seal RP, Finnerup NB. Central neuropathic pain. *Nat Rev Dis Primers* 2023;9:73.
- [36] Schmaal L, Pozzi E, C Ho T, van Velzen LS, Veer IM, Opel N, Van Someren EJW, Han LKM, Aftanas L, Aleman A, Baune BT, Berger K, Blanken TF, Capitao L, Couvy-Duchesne B, K RC, Dannlowski U, Davey C, Erwin-Grabner T, Evans J, Frodl T, Fu CHY, Godlewska B, Gotlib IH, Goya-Maldonado R, Grabe HJ, Groenewold NA, Grotegerd D, Gruber O, Gutman BA, Hall GB, Harrison BJ, Hatton SN, Hermesdorf M, Hickie IB, Hilland E, Irungu B, Jonassen R, Kelly S, Kircher T, Klimes-Dougan B, Krug A, Landro NI, Lagopoulos J, Leerssen J, Li M, Linden DEJ, MacMaster FP, A MM, Mehler DMA, Nenadic I, Penninx B, Portella MJ, Reneman L, Renteria ME, Sacchet MD, P GS, Schranter A, Sim K, Soares JC, Stein DJ, Tozzi L, van Der Wee NJA, van Tol MJ, Vermeiren R, Vives-Gilbert Y, Walter H, Walter M, Whalley HC, Wittfeld K, Whittle S, Wright MJ, Yang TT, Zarate C Jr, Thomopoulos SI, Jahanshad N, Thompson PM, Veltman DJ. ENIGMA mdd: seven years of global neuroimaging studies of major depression through worldwide data sharing. *Transl Psychiatry* 2020;10:172.
- [37] Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. *J Pain* 2013;14:663–75.
- [38] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–505.
- [39] Sun D, Rakesh G, Haswell CC, Logue M, Baird CL, O'Leary EN, Cotton AS, Xie H, Tamburrino M, Chen T, Dennis EL, Jahanshad N, Salminen LE, Thomopoulos SI, Rashid F, Ching CRK, Koch SBJ, Frijling JL, Nawijn L, van Zuiden M, Zhu X, Suarez-Jimenez B, Sierk A, Walter H, Manthey A, Stevens JS, Fani N, van Rooij SJH, Stein M, Bomyea J, Koerte IK, Choi K, van der Werf SJA, Vermeiren R, Herzog J, Lebois LAM, Baker JT, Olson EA, Straube T, Korgaonkar MS, Andrew E, Zhu Y, Li G, Ipser J, Hudson AR, Peverill M, Sambrook K, Gordon E, Baugh L, Forster G, Simons RM, Simons JS, Magnotta V, Maron-Katz A, du Plessis S, Disner SG, Davenport N, Grupe DW, Nitschke JB, deRoon-Cassini TA, Fitzgerald JM, Krystal JH, Levy I, Olf M, Veltman DJ, Wang L, Neria Y, De Bellis MD, Jovanovic T, Daniels JK, Shenton M, van de Wee NJA, Schmahl C, Kaufman ML, Rosso IM, Sponheim SR, Hofmann DB, Bryant RA, Fercho KA, Stein DJ, Mueller SC, Hosseini B, Phan KL, McLaughlin KA, Davidson RJ, Larson CL, May G, Nelson SM, Abdallah CG, Gomaah H, Etkin A, Seedat S, Harpaz-Rotem I, Liberzon I, van Erp TGM, Quidé Y, Wang X, Thompson PM, Morey RA. A comparison of methods to harmonize cortical thickness measurements across scanners and sites. *Neuroimage* 2022;261:119509.
- [40] Tanguay-Sabourin C, Fillingim M, Guglietti GV, Zare A, Parisien M, Norman J, Sweatman H, Da-Ano R, Heikkala E, Perez J, Karppinen J, Villeneuve S, Thompson SJ, Martel MO, Roy M, Diatchenko L, Vachon-Presseau E, PREVENT-AD Research Group. A prognostic risk score for development and spread of chronic pain. *Nat Med* 2023;29:1821–1831.
- [41] Tate DF, Dennis EL, Lindsey HM, Wilde EA. Harmonization of neuropsychological and other clinical endpoints: pitfalls and possibilities. *Neuropsychology* 2023;37:233–6.
- [42] Thompson PM, Jahanshad N, Ching CRK, Salminen LE, Thomopoulos SI, Bright J, Baune BT, Bertolin S, Bralten J, Bruin WB, Bulow R, Chen J, Chye Y, Dannlowski U, de Kovel CGF, Donohoe G, Eyer LT, Faraone SV, Favre P, Filippi CA, Frodl T, Garijo D, Gil Y, Grabe HJ, Grasby KL, Hajek T, Han LKM, Hatton SN, Hilbert K, Ho TC, Holleran L, Homuth G, Hosten N, Houenou J, Ivanov I, Jia T, Kelly S, Klein M, Kwon JS, Laansma MA, Leerssen J, Lueken U, Nunes A, Neill JO, Opel N, Piras F, Piras F, Postema MC, Pozzi E, Shatikhina N, Soriano-Mas C, Spalletta G, Sun D, Teumer A, Tilot AK, Tozzi L, van der Merwe C, Van Someren EJW, van Wingen GA, Volzke H, Walton E, Wang L, Winkler AM, Wittfeld K, Wright MJ, Yun JY, Zhang G, Zhang-James Y, Adhikari BM, Agartz I, Aghajani M, Aleman A, Althoff RR, Altmann A, Andreassen OA, Baron DA, Bartnik-Olson BL, Marie Bas-Hoogendam J, Baskin-Sommers AR, Bearden CE, Berner LA, Boedhoe PSW, Brouwer RM, Buitelaar JK, Caeyenberghs K, Cecil CAM, Cohen RA, Cole JH, Conrod PJ, De Brito SA, de Zwarte SMC, Dennis EL, Desrivieres S, Dima D, Ehrlich S, Esopenko C, Fairchild G, Fisher SE, Fouche JP, Francks C, Frangou S, Franke B, Garavan HP, Glahn DC, Groenewold NA, Gurholt TP, Gutman BA, Hahn T, Harding IH, Hernaus D, Hibar DP, Hillary FG, Hoogman M, Hulshoff Pol HE, Jalbrzikowski M, Karkashadze GA, Klapwijk ET, Knickmeyer RC, Kochunov P, Koerte IK, Kong XZ, Liew SL, Lin AP, Logue MW, Luders E, Macciardi F, Mackey S, Mayer RM, McDonald CR, McMahon AB, Medland SE, Modinos G, Morey RA, Mueller SC, Mukherjee P, Namazova-Baranova L, Nir TM, Olsen A, Paschou P, Pine DS, Pizzagalli F, Renteria ME, Rohrer JD, Samann PG, Schmaal L, Schumann G, Shiroishi MS, Sisodiya SM, Smit DJA, Sonderby IE, Stein DJ, Stein JL, Tahmasian M, Tate DF, Turner JA, van den Heuvel OA, van der Wee NJA, van der Werf YD, van Erp TGM, van Haren NEM, van Rooij D, van Velzen LS, Veer IM, Veltman DJ, Villalon-Reina JE, Walter H, Whelan CD, Wilde EA, Zarei M, Zelman V; ENIGMA Consortium. ENIGMA and global neuroscience: a decade of large-scale studies of the brain in health and disease across more than 40 countries. *Transl Psychiatry* 2020;10:100.
- [43] Waller L, Erk S, Pozzi E, Toenders YJ, Haswell CC, Buttner M, Thompson PM, Schmaal L, Morey RA, Walter H, Veer IM. ENIGMA HALFpipe: interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data. *Hum Brain Mapp* 2022;43:2727–42.
- [44] Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J, Brookes AJ, Clark T, Crosas M, Dillo I, Dumon O, Edmunds S, Evelo CT, Finkers R, Gonzalez-Beltran A, Gray AJ, Groth P, Goble C, Grethe JS, Heringa J, t Hoen PA, Hooft R, Kuhn T, Kok R, Kok J, Lusher SJ, Martone ME, Mons A, Packer AL, Persson B, Rocca-Serra P, Roos M, van Schaik R, Sansone SA, Schultes E, Sengstag T, Slater T, Strawn G, Swertz MA, Thompson M, van der Lei J, van Mulligen J, Velterop J, Waagmeester A, Wittenburg P, Wolstencroft K, Zhao J, Mons B. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:160018.
- [45] Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2020;8:CD007407.
- [46] Woo AK. Depression and anxiety in pain. *Rev Pain* 2010;4:8–12.
- [47] Yongjun Z, Tingjie Z, Xiaoqi Y, Zhiying F, Feng Q, Guangke X, Jinfeng L, Fachuan N, Xiaohong J, Yanqing L. A survey of chronic pain in China. *Libyan J Med* 2020;15:1730550.
- [48] Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic pain and high-impact chronic pain among U.S. Adults. *NCHS Data Brief* 2019; 2020:1–8.
- [49] Zheng CJ, Van Druenen S, Egorova-Brumley N. Neural correlates of co-occurring pain and depression: an activation-likelihood estimation (ALE) meta-analysis and systematic review. *Transl Psychiatry* 2022;12:196.
- [50] Zhou W, Jin Y, Meng Q, Zhu X, Bai T, Tian Y, Mao Y, Wang L, Xie W, Zhong H, Zhang N, Luo MH, Tao W, Wang H, Li J, Li J, Qiu BS, Zhou JN, Li X, Xu H, Wang K, Zhang X, Liu Y, Richter-Levin G, Xu L, Zhang Z. A neural circuit for comorbid depressive symptoms in chronic pain. *Nat Neurosci* 2019;22:1649–58.