Perspectives

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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, and[44] 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 HALFpipe,[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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