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Multimodal covarying brain patterns mediate genetic and psychological contributions to individual differences in pain sensitivity

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Abstract

Individuals vary significantly in their pain sensitivity, with contributions from the brain, genes, and psychological factors. However, a multidimensional model integrating these factors is lacking due to their complex interactions. To address this, we measured pain sensitivity (ie, pain threshold and pain tolerance) using the cold pressor test, collected magnetic resonance imaging (MRI) data and genetic data, and evaluated psychological factors (ie, pain catastrophizing, pain-related fear, and pain-related anxiety) from 450 healthy participants with both sexes (160 male, 290 female). Using multimodal MRI fusion methods, we identified 2 pairs of covarying structural and functional brain patterns associated with pain threshold and tolerance, respectively. These patterns primarily involved regions related to self-awareness, sensory-discriminative, cognitive-evaluative, motion preparation and execution, and emotional aspects of pain. Notably, pain catastrophizing was negatively correlated with pain tolerance, and this relationship was mediated by the multimodal covarying brain patterns in male participants only. Furthermore, we identified an association between the single-nucleotide polymorphism rs4141964 within the fatty acid amide hydrolase gene and pain threshold, mediated by the identified multimodal covarying brain patterns across all participants. In summary, we suggested a model that integrates the brain, genes, and psychological factors to elucidate their role in shaping interindividual variations in pain sensitivity, highlighting the important contribution of the multimodal covarying brain patterns as important biological mediators in the associations between genes/psychological factors and pain sensitivity.

Keywords: Pain sensitivity, Fatty acid amide hydrolase, Pain catastrophizing, Sensory-discriminative component, Cognitive and emotional components, MRI

1. Introduction

Individual differences in pain sensitivity are important in explaining the susceptibility to developing chronic pain conditions and responses to pain management.[26,52] Pain threshold and pain tolerance are common measurements of pain sensitivity, representing the minimum stimulus intensity required to elicit noticeable pain and the maximum intensity an individual can tolerate, separately.[11] To investigate the variations in pain sensitivity, researchers have used structural and functional magnetic resonance imaging (MRI) to study brain patterns associated with pain threshold and tolerance. Studies have demonstrated that differences in brain morphology, such as cortical thickness, gray matter (GM) density, and gray matter volume (GMV), and functional profiles, such as functional activity and connectivity, can explain variations in pain sensitivity across individuals.[15,16,38,54,58,64]

Growing evidence suggests that the variation in pain sensitivity may be influenced by complex interactions between gene–brain and psychological state/trait–brain. Genetic studies have shown that pain sensitivity is moderately heritable, implying that certain genes underlay an individual's pain sensitivity.[34] Variants of certain genes might regulate specific brain patterns within the nociceptive pathway to either alleviate or intensify certain types of pain.[4,13,19,42,79] In addition, pain-related changes in the brain might be linked to psychological factors,[78] such as pain catastrophizing, which is one of the most powerful predictors of heightened experimental pain perception and negative pain outcomes for both acute and chronic pain, indicating that the impact of pain catastrophizing on pain sensitivity may be mediated through brain patterns.[17]

These emerging findings urge us to build a model that integrates the brain, gene, and psychological factors to provide a deeper understanding of individual pain sensitivity because the interactions among these factors are complex and multifaceted.[15,34,54,68] In addition, although pain threshold and tolerance

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are normally correlated, they exhibit substantial differences in their reliance on physiological and psychological components,[21] with pain tolerance likely having a greater psychological component, while pain threshold is more susceptible to physiological conditions.[18] The distinct neuropsychological mechanisms between these 2 measurements remain unclear and warrant further investigation.

To explore the aforementioned issues and build the model, we enrolled 450 healthy participants and measured their pain sensitivity (ie, pain threshold and pain tolerance) using the cold pressor test (CPT). We gathered MRI and genetic data and evaluated psychological factors (ie, pain catastrophizing, pain-related fear, and pain-related anxiety) in this large sample to examine how brain patterns, genetic phenotypes, and psychological factors contribute to interindividual variations in pain sensitivity, in the whole group and each sex group. Our study aimed to investigate the following: (1) the covarying structural and functional brain patterns associated with pain threshold and pain tolerance, separately, using a multimodal fusion method that enables linking brain patterns from multiple neuroimaging modalities (because previous studies have primarily focused on signal MRI modalities and have not adequately explored joint information that could emerge from the nonspatial overlap between different modalities); (2) how the covarying brain patterns mediate the relationship between pain catastrophizing, genotypes, and pain sensitivity; (3) the sex differences in the relationships among these variables.

2. Materials and methods

2.1. Participants

Four hundred fifty healthy participants were recruited for this study. Participants who were either left-handed (n = 12, considering the brain morphology and function differences between left-handed and right-handed individuals)[1,2,49] or had incomplete and/or low signal-to-noise ratio MRI data (n = 17) were removed from further analysis, yielding a final sample of 421 participants (277 female; age: mean ± SD = 20.75 ± 2.04 years, ranging from 18 to 26 years of age). All the participants included in the study had no safety contraindications for MRI and no history of major medical or psychiatric illness, pain-related diseases, or alcohol or drug abuse. The experiment was approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences. All procedures were performed under the Declaration of Helsinki. All participants completed the informed consent form and received monetary compensation after their participation.

2.2. Experimental procedures

Five milliliters of blood were collected from participants' veins of the upper limb between 8:00 and 8:30 AM. Half an hour later, participants were requested to complete 3 pain-related questionnaires, including Chinese versions of the Pain Catastrophizing Scale (PCS),[62] Fear of Pain Questionnaire (FPQ),[37] and Pain Anxiety Symptoms Scale–20 (PASS-20).[36] The PCS is a 13-item questionnaire on a 6-point Likert scale that measures the degree of individuals experiencing catastrophic thinking related to pain.[62] The FPQ is a 30-item questionnaire scored using a 4-point Likert scale, which is used to assess situationally specific fears of painful stimuli as a trait-like phenomenon.[37] The PASS-20 is a short version of the PASS with 20 items on a 6-point Likert scale to measure latent, nonspecific pain-related anxiety under daily pain events.[36] The reliability of the Chinese version of these questionnaires has been well verified.[71,75,81] The total score of each subscale was used in subsequent statistical analyses.

Five minutes after completing the questionnaires, participants were instructed to undertake a CPT to assess their pain sensitivity. Cold pain was induced by placing participants' left hand into cold water at a temperature of 2 ± 0.1°C using a circulating water bath (DX-208 water bath, Beijing Changliu Scientific Instruments Co, China) with water continuously circulating at a flow speed of 15 L/min. Both pain threshold and pain tolerance were evaluated as 2 measurements representing an individual's pain sensitivity. Pain threshold was determined as the duration of immersion from the moment that the left hand was placed in water until the participant began to feel pain, while pain tolerance was defined as the total time from when the left hand was immersed in water to when the participant withdrew it from the water. The unit of the 2 measurements was seconds. Further details of the measurements are presented in supplementary material (available at http://links.lww.com/PAIN/B949).

2.3. Magnetic resonance imaging data acquisition

Magnetic resonance imaging data were collected using a 3.0-Telsa MRI system (Discovery MR 750; General Electric Healthcare, Milwaukee, WI) with an 8-channel head coil at the Brain and Cognitive Neuroscience Research Center, Liaoning Normal University, Dalian, China. High-resolution T1-weighted structural images were acquired using a gradient echo (3D SPGR) sequence with the following parameters: flip angle = 8°; field of view = 256 × 256 mm^2; data matrix = 256 × 256; in-plane resolution = 1 × 1 mm^2; slices = 176; and slice thickness = 1 mm. Ten-minute resting-state functional images were acquired using an echo-planar imaging sequence with the following parameters: repetition time = 2000 milliseconds; echo time = 29 milliseconds; flip angle = 90°; field of view = 192 × 192 mm^2; data matrix = 64 × 64; in-plane resolution = 3 × 3 mm^2; and slice thickness = 3 mm. During the resting-state functional MRI (rs-fMRI) data acquisition, participants were instructed to relax and remain still with their eyes open while looking at the screen presented a white fixation "+" in the center of the black background and not to engage in any specific thoughts.

2.4. Magnetic resonance imaging data preprocessing and feature extraction

Structural MRI (sMRI) data were analyzed using CAT12 (https://neuro-jena.github.io/cat/), which is an extension of SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Gray matter volume, which can provide structural information not only about cortical areas but also about the subcortical regions at the voxel level, has been shown to be associated with pain sensitivity.[38] Therefore, voxel-based morphometry analysis was used to calculate GMV in each voxel. The preprocessing steps included segmentation of the MR images into GM, white matter (WM), and cerebrospinal fluid (CSF), normalization using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)[6]; and smoothing the GM probability values using a Gaussian kernel with 6-mm full-width half-maximum (FWHM). The images were then resliced to a voxel size of 2 × 2 × 2 mm^3.

RS-MRI data were analyzed using Data Processing and Analysis for (Resting-State) Brain Imaging (DPABI) software.[72] The preprocessing steps included discarding the first 10 volumes, correcting for slice timing and spatial realignment, spatial normalization, regressing out nuisance covariates, and spatial smoothing with a 6-mm FWHM Gaussian kernel. More

details on MRI data preprocessing can be found in supplementary material (available at http://links.lww.com/PAIN/B949).

After preprocessing, voxel-wise estimates of GMV for sMRI and the amplitude of low-frequency fluctuation (ALFF) values for rs-fMRI were obtained as the input for multimodal fusion analysis. The voxel-wise GMV was extracted directly after preprocessing. The ALFF values, which reflect the intensity of regional spontaneous brain activity, were calculated to characterize functional features of rs-fMRI.[76] ALFF exhibited both good test–retest reliability and replicability compared with other functional MRI measures and has been widely adopted in the fusion analyses of multimodality MRI data.[23,70] In addition, numerous studies have used ALFF to investigate pain perception and chronic pain conditions.[33,69,77] Specifically, the time series of each voxel was transformed into the frequency domain using the fast Fourier transform to obtain the power spectrum. The square root of the power spectrum was computed at each frequency for each voxel, and the square root was averaged across frequencies ranging from 0.01 to 0.1 Hz to calculate the ALFF value.

2.5. Multimodal canonical correlation analysis–joint independent component analysis

Multimodal fusion methods can examine the covariations of structural–functional brain patterns and uncover the complex interplay of different modalities by jointly analyzing multimodal MRI data.[61] Among the fusion techniques, multimodal canonical correlation analysis–joint independent component analysis (mCCA-jICA) can provide a powerful and robust approach to linking brain patterns in different sources, even if they are not spatially overlapping. It has excellent performance in achieving both flexible modal association and source separation.[60] In addition, this method has been widely used in multimodal fusion analysis to identify the neural mechanisms underlying mental illness.[60,61]

The Fusion ICA Toolbox (FITv2.0d, https://trendscenter.org/software/fit/) was used to perform the mCCA-jICA, as depicted in **Figure 1**. After feature extraction, the 3D image of each modality (GMV and ALFF) for each participant was reshaped into a 1-dimensional vector and stacked into 2D matrices, forming a feature matrix with dimensions of [number of subjects] × [number of voxels] for each modality (ie, X1, X2). Because GMV and ALFF data had different ranges, both feature matrices were normalized to have the same average sum of squares across all participants and all voxels for each modality. Then mCCA was applied to the dimensionally reduced matrices to obtain the canonical variant matrices B1 and B2 and the associated component matrices C1 and C2 for each modality. Next, the jICA algorithm was applied to the associated components matrix [C1, C2] to obtain the maximized joint independent components (ICs) [S1, S2] and the mixing coefficient matrix W. Based on the minimum description length (MDL) criterion,[32] 14 and 21 ICs were estimated for each feature (GMV and ALFF), respectively. To ensure computational feasibility and maintain a balanced representation of both modalities, we chose 14 multimodal components. The infomax algorithm was repeated 20 times in ICASSO toolbox,[22] and the quality index (Iq) was used to assess the reliability of the results, ensuring that all 14 ICs included in the analyses had Iq values above the threshold (Iq = 0.90).

The final mixing coefficient matrices A1 and A2 were computed by multiplying the canonical variant matrix and the mixing coefficient matrix of the jICA (B1, W for GMV; B2, W for ALFF), representing the subject-specific weights for each modality. The spatial maps of the 2 modalities were coupled by the shared loading parameter (W). Thus, the mixing coefficient matrices A1 and A2 (ie, loadings of all participants for each component) and their corresponding sources (ie, spatial map for each component) contained both unique and shared information across the 2 modalities.

2.6. DNA extraction and single-nucleotide polymorphism selection

The QIAamp DNA Mini Kit (Qiagen, Hilden, Germany, Cat No: 51306) was used to extract DNA from the peripheral blood of participants, which was then subjected to quality control. Genotyping was performed using the Capital Biotechnology Precision Medicine Research Array (CBT-PMRA) Kit (Thermo Fisher Scientific, Waltham, MA), resulting in more than 787,400 single-nucleotide polymorphisms (SNPs) available. Additional technical information on DNA extraction can be found in supplementary material (available at http://links.lww.com/PAIN/B949). The PLINK software was used to perform genotype quality control.[51] Specifically, we excluded variants with a minor allele frequency <0.05, a call rate of $<95\%$, and a Hardy–Weinberg equilibrium test $P < 1e-6$. Participants who were missing genotype data for more than 5% of the typed SNPs were also excluded from further genetic analysis.

The included SNPs in this study were identified by searching PubMed using the terms "pain perception" and "cold pressor test" with the following criteria: (1) the SNPs were previously identified as potentially modulating pain perception elicited by a CPT; (2) the SNPs were common variants with a minor allele frequency greater than 5%; and (3) the SNPs were successfully genotyped in our genetic data.

2.7. Statistical analyses

2.7.1. Behavioral data analysis

We conducted independent sample *t* tests to explore the differences between the male and female groups in pain sensitivity and pain-related psychological factors. Then we performed Pearson correlation analyses to examine the association between pain threshold and tolerance, as well as to investigate possible correlations between pain sensitivity measurements and pain-related psychological factors as evaluated by PCS, FPQ, and PASS scores, in the whole group and each sex group, respectively.

2.7.2. Multimodal fusion data analysis

To explore whether the multimodal brain patterns jointly underpin individual variations in different pain sensitivity measurements, we performed Pearson correlations between the pairs of feature loadings (each pair contains 1 IC for GMV and 1 IC for ALFF) and pain sensitivity measurements (ie, pain threshold and pain tolerance). In the whole-group analysis, sex and age were regressed as covariates, while in sex-specific subgroup analyses, age was regressed as a covariate. We reported significant associations when both ICs in a pair showed a significant correlation with pain sensitivity measurements.[9] To visualize the spatial maps of these ICs, the source matrix was converted to Z scores and then reshaped to 3D brain maps. The statistically significant threshold was set at $|Z| \geq 2.5$. We summarized the primary anatomical structures of each spatial map based on the Automated Anatomical Labeling (AAL) atlas.[65]

In addition, we performed correlation analyses between pain-related psychological variables and the loadings of joint components that were significantly associated with pain sensitivity, while controlling for sex and age or age only, in the

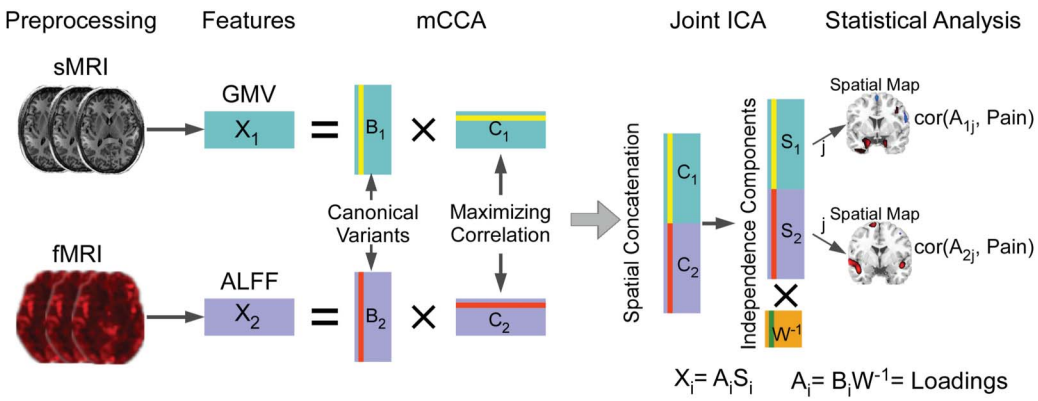

Figure 1. The pipeline of mCCA-jICA for multimodal MRI fusion analysis. First, GMV maps and ALFF maps were extracted from sMRI and rs-fMRI data, respectively. Then mCCA was applied to the dimensionally reduced matrices to obtain the canonical variant matrices B1 and B2, as well as the associated component matrices C1 and C2 for each modality. Subsequently, the jICA algorithm was implemented on the associated components matrix [C1, C2] to obtain the maximized joint independent components [S1, S2] and the mixing coefficient matrix W. The final mixing coefficient matrices A1 and A2 (B1 × W for GMV; B2 × W for ALFF) were calculated, and correlation analyses were conducted to evaluate the associations between the pairs of feature loadings (A_{1j} and A_{2j}) and pain sensitivity measurements. ALFF, the amplitude of low-frequency fluctuation; GMV, grey matter volume; jICA, joint independent component analysis; mCCA, multimodal canonical correlation analysis; MRI, magnetic resonance imaging; rs-fMRI, resting-state functional MRI; sMRI, structural MRI.

whole group and sex-specific subgroup analyses, respectively. Based on the significant results of the abovementioned statistical analyses, we hypothesized a series of mediation models to explore the potential role of those brain patterns in the relationship between pain-related psychological factors and pain sensitivity. Specifically, we used the joint IC loadings (ICs for GMV, ALFF, or both) as mediator variables, the scores of pain-related psychological variables as the independent variable, and pain sensitivity measurement as the dependent variable to examine the role of the joint IC loadings on the relationship between pain-related psychological factors and pain sensitivity.

2.7.3. Genetic data analysis

After quality control, 395 of 421 participants were included in the genetic analysis. Three SNPs rs4646312 (T>C), rs4141964 (T>C), and rs2295633 (A>G),[28,45] met the inclusion criteria and were selected for the genetic analysis (the detailed process is shown in supplementary material, available at http://links.lww.com/PAIN/B949). To investigate the genotypic effects on pain sensitivity measurements, we applied 1-way analysis of covariance (ANCOVA) to 3 groups of individuals determined by the genotype (2 homozygous and 1 heterozygous genotypes) of each SNP, with sex and age or only age as covariates, in the whole group and sex-specific subgroup analyses, respectively. To maximize statistical power, given our sample size, genotypes that did not show significant differences in pain sensitivity, as determined by post hoc test, were combined into a single group for subsequent analysis. Therefore, we obtained 2 distinct genotypic groups characterized by high and low pain sensitivity, respectively. Subsequently, ANCOVA was conducted to assess the statistically significant differences between the 2 genotypic groups in pain sensitivity–related joint IC loadings.

Building on the significant findings from the aforementioned analyses on pain sensitivity–related genotypes, we examined the potential mediation effect of covarying brain structural or functional patterns by using the joint IC loadings (ie, ICs for GMV, ALFF, or both) as mediator variables, genotype as the independent variable, and pain sensitivity measurement as the dependent variable.

To account for multiple comparisons in the analyses, a false discovery rate (FDR) procedure[8] was adopted to adjust the *P* values. All tests were 2 tailed, and the level of significance was $P = 0.05$.

2.7.4. Mediation analysis

The adequacy of the hypothetical mediation models was tested using path analyses or structural equation modeling (SEM) with maximum likelihood estimation. The model fit of SEM was assessed using the following criteria: the significance of χ^2 statistic (*P* value) > 0.05, the ratio of chi-square to degrees of freedom (χ^2/df) < 2,[29] the root mean square error of approximation (RMSEA) ≤ 0.06,[27] both the goodness-of-fit index (GFI) and the adjusted goodness-of-fit index (AGFI) ≥ 0.90, and both the comparative fit index (CFI) and the normed fit index (NFI) ≥ 0.95.[25] In addition, to assess the significance of the indirect and direct effects in the mediation model, bias-corrected 95% confidence intervals (CIs) were calculated using the bootstrapping procedure.[50] The estimate was considered statistically significant when the 95% CI (based on 5000 bootstrap samples) excluded zero. Standardized estimate (b), standard error (SE), 95% CI, and *P* value were reported for both direct and indirect effects. There are 3 types of mediating effects: (1) complementary mediation exhibits both significant indirect and direct effects, which point to the same (positive or negative) direction; (2) competitive mediation exhibits both significant indirect and direct effects, which point to opposite directions; and (3) indirect-only mediation exhibits a significant indirect effect but an insignificant direct effect.[10] These statistical analyses were performed using Amos (Version 24.0, IBM Corp, Armonk, NY).

3. Results

3.1. Behavioral results

Male participants exhibited significantly higher pain threshold (t (419) = 2.97, P_{FDR} = 0.005) and pain tolerance (t (419) = 2.50, P_{FDR} = 0.016), as well as lower FPQ (t (419) = −4.18, $P_{FDR} < 0.001$) and PASS (t (419) = −2.98, P_{FDR} = 0.003) scores than female participants, while there was no significant difference between male and female participants in PCS score (t (419) = −1.34, P_{FDR} = 0.180).

Correlation analyses showed that pain threshold was positively correlated with pain tolerance (whole: $r = 0.49$, $P_{FDR} < 0.001$; male: $r = 0.53$, $P_{FDR} < 0.001$; female: $r = 0.42$, $P_{FDR} < 0.001$, **Fig. 2A**). In addition, pain tolerance showed negative correlations with PCS score in the whole group ($r = -0.11$, $P_{FDR} = 0.019$) and male participants (PCS: $r = -0.17$, $P_{FDR} = 0.037$) but not in female participants (PCS: $r = -0.06$, $P_{FDR} = 0.325$, **Fig. 2B**). By contrast, there was no significant correlation between pain threshold and PCS score (whole: $r = -0.07$, $P_{FDR} = 0.136$; male: $r = -0.11$, $P_{FDR} = 0.185$; female: $r = -0.02$, $P_{FDR} = 0.790$, **Fig. 2C**). We also evaluated the associations between pain sensitivity measurements and FPQ and PASS scores, and these results are shown in the supplementary material (available at http://links.lww.com/PAIN/B949).

3.2. Correlations between the joint independent component loadings and pain sensitivity measurements

In the whole group, the loadings of the first joint IC (IC1) among the 14 paired ICs were identified to be negatively associated with pain threshold for both GMV ($r = -0.13$, $P = 0.009$) and ALFF ($r = -0.13$, $P = 0.007$) (**Fig. 3** and Table 1 in supplementary material, available at http://links.lww.com/PAIN/B949), namely, participants with larger loadings were more sensitive to pain. The contributing GMV regions in IC1 are mainly located in the temporal and parietal lobes (ie, middle temporal gyrus [MTG], inferior parietal lobule [IPL], angular gyrus [AG], and precuneus [PCu]), as well as the visual cortex (ie, middle occipital gyrus [MOG], fusiform gyrus [FG], and calcarine fissure [CF]). For ALFF, in addition to the regions observed in GMV, we found that the medial prefrontal cortex (mPFC) and contralateral postcentral gyrus (ie, right S1) contributed to the interindividual variations of pain threshold.

We further explored the associations between the joint IC loadings and pain threshold in each sex group. We observed significant negative correlations between pain threshold and the loadings of IC1 for both GMV ($r = -0.27$, $P < 0.001$) and ALFF ($r = -0.20$, $P = 0.016$) in male, but not in female participants (all $P > 0.05$, **Fig. 3**).

In addition, the loadings of the second joint ICs (IC2) were negatively correlated with pain tolerance for both GMV ($r = -0.15$, $P = 0.002$) and ALFF ($r = -0.18$, $P < 0.001$) in the whole group (**Fig. 4** and Table 2 in the supplementary material, available at http://links.lww.com/PAIN/B949), indicating that participants with larger loadings were less tolerant to pain (ie, more sensitive to pain). The contributing GMV regions are mainly located in the bilateral dorsolateral prefrontal cortex (DLPFC), parahippocampal gyrus (PHG), supplementary motor area (SMA), PCu, and CF. By contrast, the contributing ALFF regions involved precentral and postcentral gyri (ie, M1 and S1), superior frontal gyrus (SFG), SMA, PCu, superior temporal gyrus (STG), and visual cortex. Note that there were no significant correlations between pain sensitivity measurements and the GMV or ALFF values of the single modality (as shown in the supplementary material, available at http://links.lww.com/PAIN/B949).

Sex-specific subgroup analyses revealed the significant negative correlations between pain tolerance and the loadings of IC2 for both GMV ($r = -0.25$, $P = 0.003$) and ALFF ($r = -0.28$, $P < 0.001$) in male but not in female participants (all $P > 0.05$, **Fig. 4**).

3.3. The mediation effects of the joint independent component loadings on the relationship between psychological factors and pain sensitivity measurements

In the whole group, the PCS score was positively correlated with the loadings of IC2 for ALFF ($r = 0.14$, $P_{FDR} = 0.031$, **Fig. 5A**) but not for

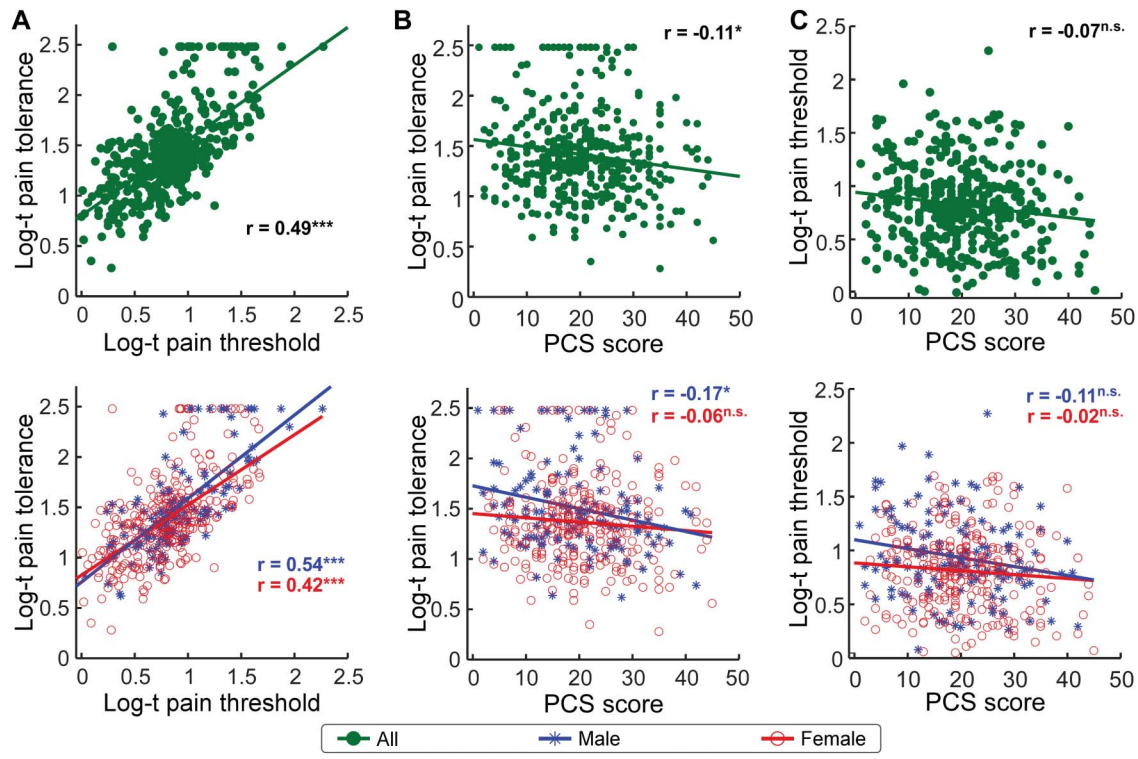

Figure 2. The scatterplots of pain sensitivity measurements and PCS score. (A) Pain threshold was positively correlated with pain tolerance across all groups. (B) Pain tolerance was negatively correlated with PCS score in the whole group and male participants but not in female participants. (C) No significant correlation was observed between pain threshold and PCS score across all groups. For improved visualization, pain threshold and tolerance values were log transformed. Log-t, log-transformed; PCS, pain catastrophizing scale; n.s. not significant; *$P < 0.05$; ***$P < 0.001$.

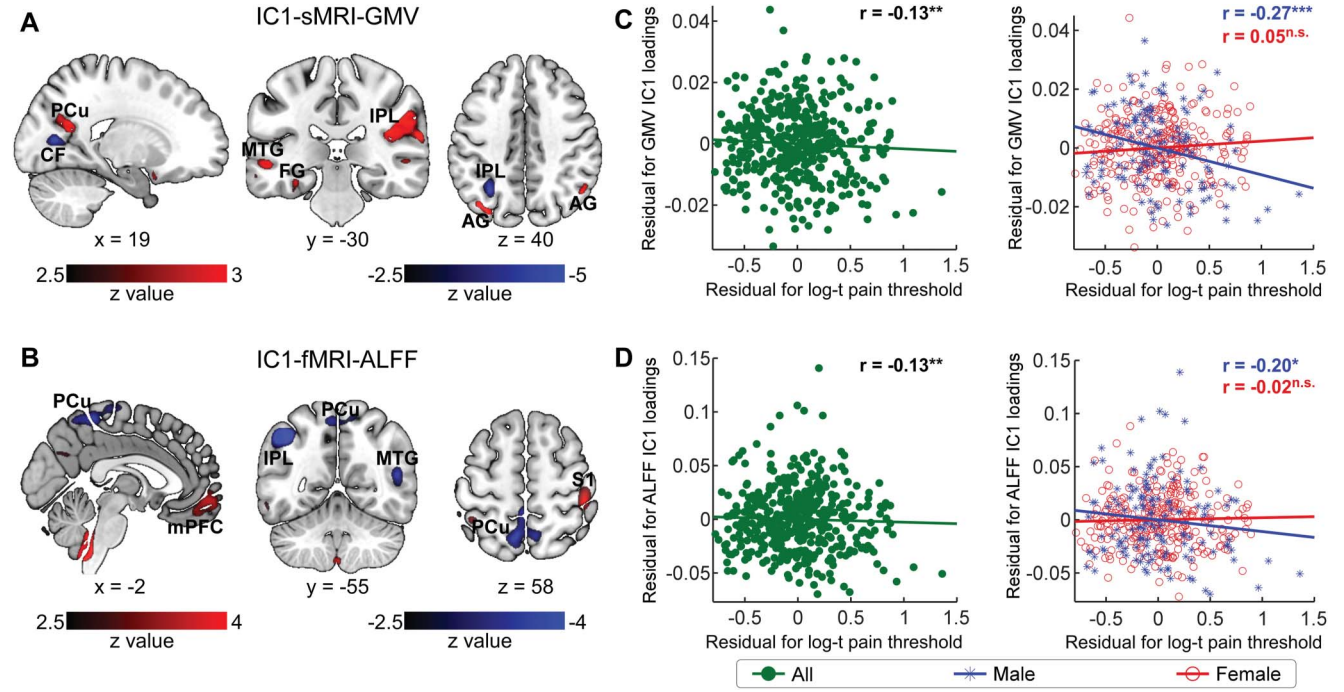

Figure 3. Brain maps of the joint ICs with significant association with pain threshold, as well as scatterplots of the IC loadings and pain threshold in different modalities across all groups. (A) GMV maps of IC1. (B) ALFF maps of IC1. (C and D) Pain threshold was significantly associated with the loadings of IC1 for both GMV and ALFF in the whole group and male participants but not in female participants. The color bar presented the Z scores, and the maps were displayed with a threshold of $|Z| > 2.5$. The values of coordinates in the scatterplots in the whole group and each sex group were the residuals controlling for sex and age or only age, respectively. For improved visualization, pain threshold values were log transformed. AG, angular gyrus; ALFF, the amplitude of low-frequency fluctuation; CF, calcarine fissure; GMV, grey matter volume; IC, independent component; IPL, inferior parietal lobule; Log-t, log transformed; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; PCu, precuneus; S1, postcentral gyrus; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

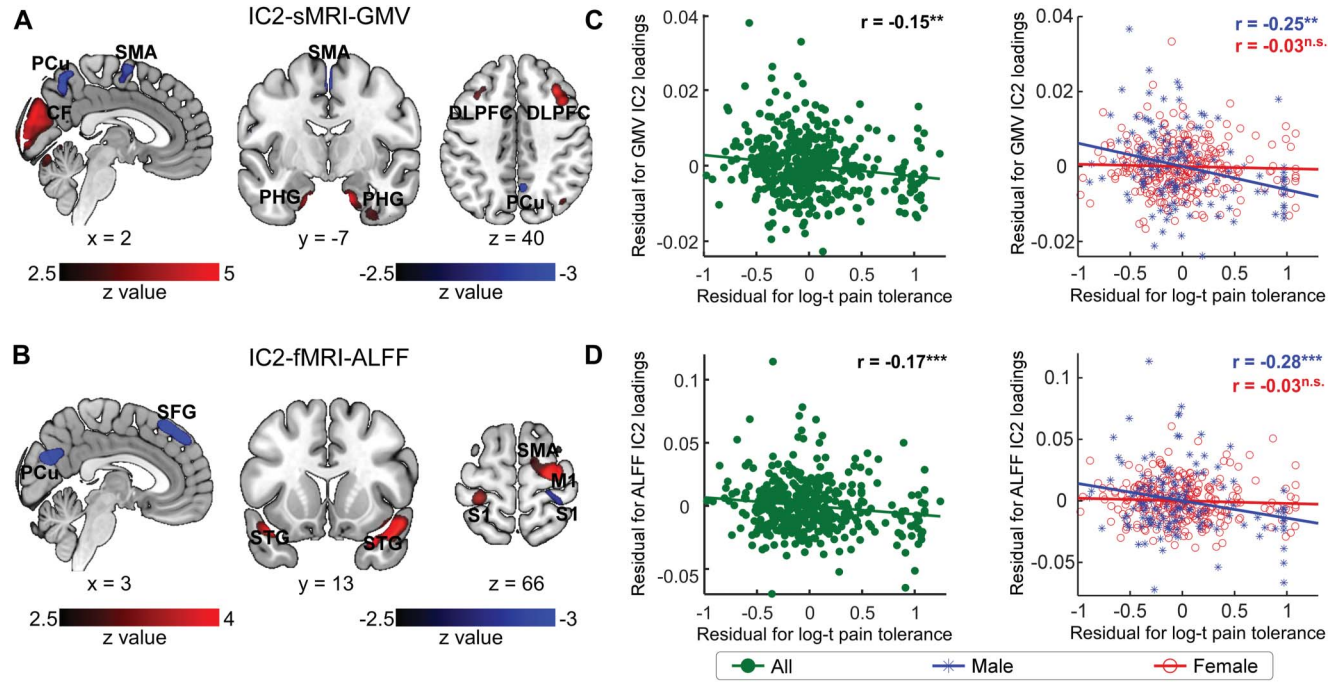

Figure 4. Brain maps of the joint ICs with significant association with pain tolerance and the scatterplots of corresponding loadings and pain tolerance in different modalities. (A) GMV maps of IC2. (B) ALFF maps of IC2. (C and D) Pain tolerance was significantly associated with the loadings of IC2 for both GMV and ALFF in the whole group and male participants but not in female participants. The color bar presented the Z scores, and the maps were displayed with a threshold of $|Z| > 2.5$. The values of coordinates in the scatterplots in the whole group and each sex group were the residuals controlling for sex and age or only age, respectively. For improved visualization, pain threshold values were log transformed. ALFF, the amplitude of low-frequency fluctuation; CF, calcarine fissure; DLPFC, dorsolateral prefrontal cortex; GMV, grey matter volume; IC, independent component; Log-t, log transformed; M1, postcentral gyrus; PCu, precuneus; PHG, parahippocampal gyrus; S1, precentral gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; $^{**}P < 0.01$, $^{***}P < 0.001$.

GMV ($r = 0.07$, $P_{FDR} > 0.05$, **Fig. 5B**). By contrast, there were no significant correlations among FPQ or PASS scores and the joint IC loadings (all $P_{FDR} > 0.05$). We then investigated the relationship between psychological factors and pain sensitivity measurements in each sex group. We found that only the PCS score was positively correlated with the loadings of IC2 for both GMV ($r = 0.17$, $P_{FDR} = 0.036$, **Fig. 5B**) and ALFF ($r = 0.20$, $P_{FDR} = 0.036$, **Fig. 5A**) in male but not in female participants (all $P_{FDR} > 0.05$, **Fig. 5**).

Because FPQ and PASS scores showed no significant correlations with the joint IC loadings associated with pain sensitivity measurements, both variables were not considered in subsequent statistical analyses. Based on the significant associations among pain tolerance, PCS score, and the loadings of IC2, the mediation analysis in the whole group showed that the PCS score had a direct effect ($b = -0.09$, SE = 0.04, CI = [−0.18, −0.004], $P = 0.040$) but not an indirect effect ($b = -0.01$, SE = 0.01, CI = [−0.03, 0.002], $P = 0.098$) on pain tolerance through the loadings of IC2 for GMV (**Fig. 5C**). This indicates that the loadings of IC2 for GMV did not mediate the relationship between pain catastrophizing and pain tolerance. By contrast, the PCS score had an indirect effect ($b = -0.02$, SE = 0.01, CI = [−0.05, −0.01], $P = 0.003$) but not a direct effect ($b = -0.08$, SE = 0.05, CI = [−0.17, 0.01], $P = 0.068$) on pain tolerance through the loadings of IC2 for ALFF (**Fig. 5D**), suggesting that the loadings of IC2 for ALFF were indirect-only mediators of the relationship between pain catastrophizing and pain tolerance. In addition, we also tested a mediation model with both GMV and ALFF loadings as mediators, and all fit indices met the aforementioned criteria. The PCS score had an indirect effect ($b = -0.03$, SE = 0.02, CI = [−0.08, −0.01], $P = 0.009$) but not a direct effect ($b = -0.07$, SE = 0.05, CI = [−0.16, 0.03], $P = 0.145$) on pain tolerance through the loadings of both GMV and ALFF (**Fig. 5E**). This result suggests that the loadings of IC2 for the 2 modalities were indirect-only mediators of the relationship

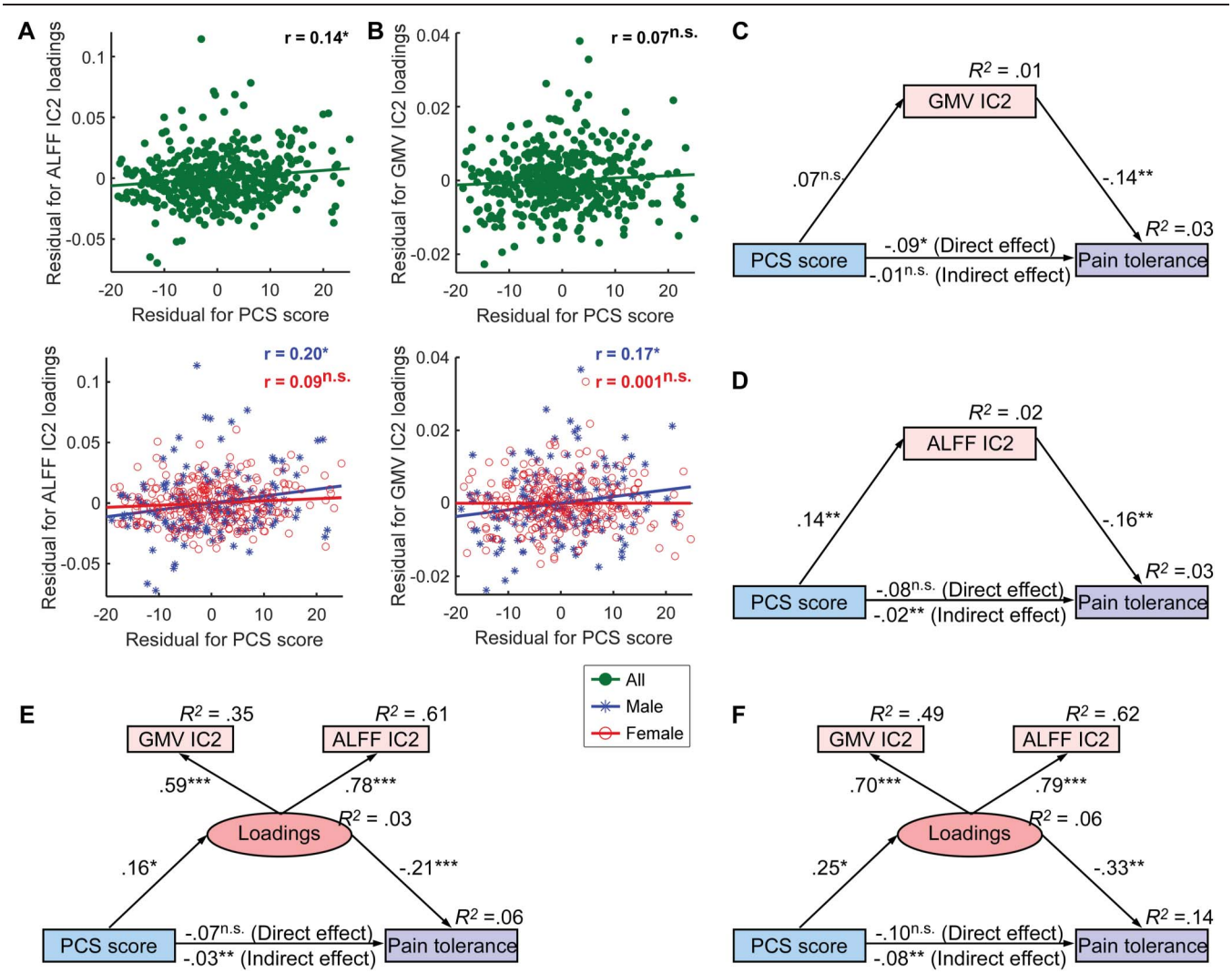

Figure 5. The mediation effects of multimodal covarying brain patterns on the relationship between pain catastrophizing and pain tolerance. (A) The PCS score was positively correlated with the loadings of IC2 for ALFF in the whole group and male group but not in the female group. (B) The correlation between PCS score and the loadings of IC2 for GMV was significant in male participants but not in the whole group and female participants. (C and D) The relationship between pain catastrophizing and pain tolerance was indirect-only mediated by the loadings of IC2 for ALFF but not for GMV in the whole group; (E) the relationship between pain catastrophizing and pain tolerance was indirect-only mediated by the loadings of IC2 loaded by GMV and ALFF in the whole group. (F) The relationship between pain catastrophizing and pain tolerance was indirect-only mediated by the loadings of IC2 loaded by GMV and ALFF in male participants. Standardized regression weights and squared multiple correlation coefficients are shown for each model. The values of coordinates in the scatterplots at the whole group and each sex group were the residuals controlling for sex and age or only age, respectively. ALFF, the amplitude of low-frequency fluctuation; GMV, grey matter volume; IC, independent component; n.s., not significant; PCS, pain catastrophizing scale; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

between pain catastrophizing and pain tolerance. It is worth noting that although the loadings of IC2 for GMV did not independently mediate the relationship, the total indirect effect of the GMV and ALFF loadings was higher than the mediation effect of any single modality.

Similarly, we tested a mediation model with both GMV and ALFF loadings as mediators in the male group; the results showed that the PCS score had an indirect effect ($b = -0.08$, SE = 0.04, CI = [−0.18, −0.02], $P = 0.005$) but not a direct effect ($b = -0.10$, SE = 0.07, CI = [−0.24, 0.05], $P = 0.190$) on pain tolerance through the loadings of both GMV and ALFF (**Fig. 5F**). This result suggests that the loadings of IC2 for the 2 modalities were indirect-only mediators of the relationship between pain catastrophizing and pain tolerance in male participants.

3.4. The mediation effects of the joint independent component loadings on the relationship between genotype and pain sensitivity measurements

In the whole group, the genotypic effect of SNP rs4141964 was significant for pain threshold ($F = 3.10$, $P = 0.046$, $\eta_p^2 = 0.02$, **Fig. 6A**), but not for pain tolerance ($P > 0.05$). Post hoc analysis revealed that CC homozygotes had a higher pain threshold than those carrying 1 or 2 T alleles (TC/TT, $P_{FDR} = 0.044/0.044$, **Fig. 6A**), while there was no significant difference between the TC and TT genotype groups in their pain threshold. Therefore, participants were divided into the genotypic group of CC homozygotes and the genotypic group of T allele carriers (TT + TC). Single-nucleotide polymorphisms rs4646312 and rs2295633 did not have any significant effects on pain sensitivity measurements (all $P > 0.05$) and were not included in the subsequent analyses. Furthermore, for SNP rs4141964 in the fatty acid amide hydrolase (*FAAH*) gene, CC genotypic group exhibited significantly decreased loadings of GMV ($F = 4.29$, $P_{FDR} = 0.039$, $\eta_p^2 = 0.11$, **Fig. 6B**) and ALFF ($F = 4.63$, $P_{FDR} = 0.032$, $\eta_p^2 = 0.12$, **Fig. 6C**) in IC1 compared with TT + TC genotypic group, indicating a significant effect of rs4141964 genotype on pain threshold and its related multimodal covarying component loadings. We also examined the genotypic effect of the included 3 SNPs on pain sensitivity measurements in each sex group. However, no significant genotypic effect of these SNPs on pain threshold or pain tolerance was observed in either male or female participants (all $P > 0.05$).

Based on the significant associations among pain threshold, SNP rs4141964 genotype, and the loadings of IC1 in the whole group, the mediation analysis showed that the SNP rs4141964 had an indirect effect ($b = -0.01$, SE = 0.01, CI = [−0.03, −0.001], $P = 0.038$) but not a direct effect ($b = -0.11$, SE = 0.05, CI = [−0.20, 0.002] $P = 0.054$) on pain threshold through the loadings of IC1 for GMV (**Fig. 6D**) and similarly for the loadings of IC1 for ALFF (indirect effect: $b = -0.01$, SE = 0.01, CI = [−0.03, −0.001], $P = 0.033$; direct effect: $b = -0.11$, SE = 0.05, CI = [−0.20, 0.001], $P = 0.051$) (**Fig. 6E**). The mediation model, where the loadings were the mediators and loaded by the IC1 for both GMV and ALFF, fit the data well with adequate fit indices (**Fig. 6F**). The genotype had an indirect effect ($b = -0.03$, $SE = 0.02$, CI = [−0.07, −0.004], $P = 0.018$) but not a direct effect ($b = -0.10$, SE = 0.05, CI = [−0.18, 0.01], $P = 0.075$) on pain threshold through the loadings of IC1 for both GMV and ALFF, indicating that the loadings of IC1 for 2 modalities indirectly only mediated the effect of the SNP rs4141964 genotype on pain threshold.

4. Discussion

In this study, we investigated the interplay of the brain, gene, and psychological factors in shaping the interindividual variations in pain sensitivity in the whole and each sex group using a large sample size (N = 450). First, we identified 2 distinct covarying structural and functional brain patterns significantly associated with variations in cold pain threshold and tolerance, respectively (**Figs. 3 and 4**). Second, we found that pain catastrophizing was negatively correlated with pain tolerance and this relationship was mediated by the multimodal covarying brain patterns related to pain tolerance in male participants only (**Fig. 5**). Third, we observed that the SNP rs4141964 exhibited an effect on pain threshold differences, possibly through its modulation of the multimodal covarying brain patterns affecting pain threshold across all participants (**Fig. 6**). In summary, we suggested a model integrating the brain, genes, and psychological factors to unravel the intricate interplay among these factors in shaping interindividual variations in pain sensitivity, which may contribute to our understanding of the mechanisms underlying pain sensitivity (**Fig. 7**).

4.1. Multimodal covarying brain patterns related to pain sensitivity measurements

The brain patterns associated with pain sensitivity measurements were not limited to one area but instead involved multiple brain structural and functional regions. The multimodal covarying brain patterns related to pain threshold mainly involved structural regions in the IPL, AG, MTG, and PCu and functional regions in the IPL, MTG, and PCu (**Fig. 3**). These regions are parts of the default mode network (DMN), associated with self-awareness and consciousness,[3] which has been found to be commonly associated with thermal pain sensitivity, as indicated by both GM morphometry[15,80] and functional activity.[30] In addition, ALFF in 2 key regions (ie, S1 and mPFC) was associated with pain threshold. S1 encodes information about the location and intensity of nociceptive stimuli,[43] while the mPFC involves the cognitive evaluation and modulation of pain in the descending pain inhibitory pathway.[44] Thus, the finding that larger loadings of multimodal covarying brain patterns were linked to higher pain sensitivity suggests that intrinsic brain features involving self-awareness, sensory discrimination, and cognitive evaluation components have a greater influence on individuals with higher pain sensitivity.

By contrast, multimodal covarying brain patterns related to pain tolerance mainly comprised the sensorimotor areas (ie, SMA and precentral and postcentral gyri [M1 and S1]), PHG, DLPFC, and SFG (**Fig. 4**). Sensorimotor areas play key roles in the sensory-discriminative component of pain processing[31,43] and contribute to both motion preparation and execution in response to pain, such as the withdrawal reflex, to avoid further tissue damage.[35,56] While the PHG is involved in processing the emotional component of pain.[14,55] Functional activities in the DLPFC and SFG can affect the recruitment of the descending pain modulation networks[73] and modulate top-down attentional processes.[40] Thus, brain patterns associated with pain tolerance not only involved the sensory-discriminative component but also the motivational-affective and attentional aspects of pain processing.

In addition, the brain patterns associated with pain sensitivity included the visual cortex, as previously reported.[30,58,74] However, we did not find areas typically associated with pain processing in multimodal covarying brain patterns, consistent with a recent study showing that typical pain-processing regions did not exhibit significant associations with interindividual pain differences.[24]

By using a multimodality fusion approach, we identified pairs of joint structural and functional patterns associated with pain

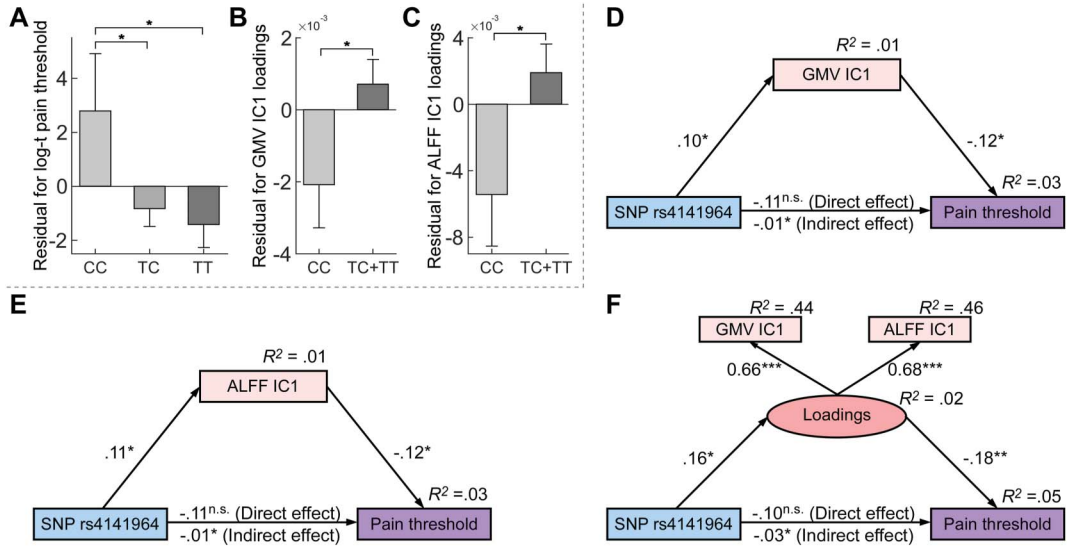

Figure 6. The mediation effects of multimodal covarying brain patterns on the relationship between genotypes and pain threshold. (A) Pain threshold was significantly higher in participants with the CC genotype for SNP rs4141964 compared with those with the TC and TT genotypes. (B) GMV and (C) ALFF loadings in IC1 were significantly lower in the CC genotype group for rs4141964 compared with participants in the TC + TT genotype group. (D) The relationship between genotypes of SNP rs4141964 and pain threshold was indirect-only mediated by the loadings of IC1 for GMV and (E) the loadings of IC1 for ALFF. In addition, (F) the relationship between genotypes of SNP rs4141964 and pain threshold was indirect-only mediated by the loadings of IC1 loaded by both GMV and ALFF. CC, homozygous genotype with two copies of the C allele at the SNP rs4141964; TC, heterozygous genotype with one copy of the C allele and one copy of the T allele at the SNP rs4141964; TT, homozygous genotype with two copies of the T allele at the SNP rs4141964. Standardized regression weights and squared multiple correlation coefficients are shown for each model. The ordinate values in the bar plots were the residuals controlling for sex and age. ALFF, the amplitude of low-frequency fluctuation; GMV, grey matter volume; IC, independent component; Log-t, log transformed; n.s., not significant; SNP, single-nucleotide polymorphism; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

sensitivity, even if they are not spatially overlapping. These findings not only confirmed findings from previous studies that focused on a single modality but also revealed multimodal covarying brain patterns associated with pain sensitivity in both structural and functional regions. These patterns are not easily detected by analyzing each modality separately, as demonstrated by our analysis in the supplementary material (available at http://links.lww.com/PAIN/B949). Hence, our study underscores the significance of considering multimodal brain patterns when exploring interindividual differences in pain sensitivity.

4.2. Distinct mechanisms underlying different pain sensitivity measurements

Consistent with previous findings,[18] our results revealed that 2 pain sensitivity measurements, threshold and tolerance, were highly correlated. However, the associated brain patterns, genetic factors, and pain catastrophizing were distinct between them: pain tolerance and threshold were associated with psychological factors and genotypes, respectively. The significant association between pain catastrophizing and pain tolerance aligns with previous studies.[47,63] In addition, a recent study revealed the *FAAH-OUT* gene identified in a pain-

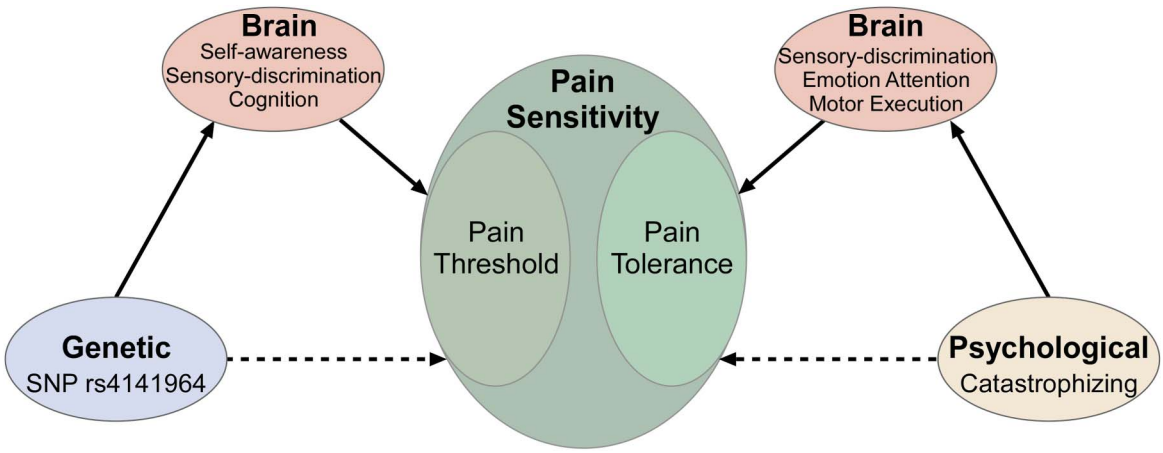

Figure 7. Model to elucidate the mechanism underlying the interplay of brain–gene–psychology interactions in shaping interindividual variations in pain sensitivity. Interindividual variations in pain sensitivity are shaped by the complex interplay of the brain, gene, and psychological factors. One measurement of pain sensitivity, pain threshold is influenced by genotype (ie, SNP rs4141964) through covarying structural and functional brain patterns primarily involving the self-awareness, sensory-discriminative, and cognitive-evaluative processing of nociceptive inputs. In comparison, psychological factors (ie, pain catastrophizing) contribute to pain tolerance by modulating covarying structural and functional brain patterns mainly involving the sensory-discriminative, motivational-affective, and attentional aspects of pain processing, as well as involving motion preparation and execution in response to pain. SNP, single-nucleotide polymorphism.

insensitive patient negatively affected FAAH expression, leading to pain insensitivity.[39] This result aligns with our findings suggesting the important role of the *FAAH* gene (SNP rs4141964) on pain sensitivity.[28] The *FAAH* gene encodes the anandamide-degrading FAAH enzyme, playing a crucial role in the anandamide metabolism. The activity of FAAH might influence nociception and inflammatory responses through its effects on anandamide levels, making it an important contributor to pain sensitivity.[12,20,46,48] These results suggest that pain threshold and tolerance may be influenced by different mechanisms. Pain threshold seemed to be more susceptible to stable physiological factors such as genotype, while pain tolerance was more amenable to psychological variable,[21] such as pain catastrophizing.

We proposed a composite model that highlights the crucial role of brain patterns in the contribution of genetic and psychological factors to pain sensitivity (**Fig. 7**). Specifically, pain threshold is influenced by the SNP rs4141964 through multimodal covarying brain patterns. Unlike pain tolerance, pain threshold is relatively stable within an individual[59] and not easily altered by manipulation,[7,18] which measures the ability to detect sensory quality changes from cold to pain, emphasizing nociceptive quality discrimination.[21] In addition, pain threshold corresponds to the minimum stimulus intensity eliciting pain sensation and often failing to evoke powerful emotional experience. Thus, as a stable physiological factor, the genotype regulated pain threshold by modulating the intrinsic brain features mainly involved the self-awareness, sensory-discriminative, and cognitive-evaluative processing of nociceptive inputs, without involving emotion-related brain regions. On the contrary, pain tolerance indicates unwillingness to receive more intense stimuli.[21] Therefore, individuals may experience heightened unpleasant emotions and a greater propensity to terminate stimulation approaching pain tolerance. Consequently, pain tolerance is more vulnerable to cognitive and affective influences than threshold.[53,59] As a cognitive factor, pain catastrophizing leads to a deficit in attentional disengagement from nociceptive information,[17,66,67] typically accompanied by negative emotions such as pain-related fear and anxiety.[57] Therefore, our model suggests that pain catastrophizing influences brain activity related to emotion and attention, increasing attention and vigilance towards pain and subsequently decreasing pain tolerance.

4.3. Sex differences in the mechanisms of pain sensitivity

Our results showed that the mediation role of multimodal covarying brain patterns in the associations between pain catastrophizing and pain tolerance was pronounced only in male participants. One possible explanation is male and female individuals may have different neural mechanisms of pain modulation, which can be influenced by psychological factors such as pain catastrophizing. In male individuals, we observed that pain catastrophizing was associated with increased activity in the ACC and insula, regions involved in the affective and cognitive aspects of pain, such as emotional distress and attention to pain.[5] Therefore, pain catastrophizing may enhance the negative emotional and cognitive aspects of pain more in male individuals, leading to lower pain tolerance. On the contrary, our analysis of the SNP rs4141964's effects on pain threshold and multimodal covarying brain patterns revealed significant associations in the entire participant group. However, it is possible that the *FAAH* gene has different expression levels or interactions with other genes in male and female individuals.[41] Genetic analyses, especially with single SNP phenotyping, typically require a large sample size. Therefore, although our study did not identify significant associations between the *FAAH* gene and pain threshold within each sex, the role of the *FAAH* gene in regulating pain threshold specifically for each sex remains inconclusive.

Overall, these findings emphasize the importance of considering sex differences when investigating the psychoneural mechanisms of pain sensitivity. Such considerations may have significant implications for developing personalized pain management interventions. Therefore, future research with larger sample sizes is warranted to further elucidate the underlying mechanisms contributing to these sex differences.

4.4. Limitations

This study has several limitations. First, using CPT to measure pain sensitivity may not provide a comprehensive evaluation of pain sensitivity across various sensory modalities such as a standardized assessment using quantitative sensory testing (QST). Future studies that incorporate QST to comprehensively evaluate pain sensitivity are warranted to fully elucidate the underlying mechanisms of pain sensitivity. Second, given the healthy participants enrolled and the relatively modest effect sizes of certain correlations, the generalizability of these findings to patients experiencing painful conditions and their potential clinical relevance warrant further exploration. Third, task fMRI data and genome-wide association analysis should be included in future studies to disclose a more comprehensive pain sensitivity mechanism.

5. Conclusions

In summary, our results suggest that pain threshold may be more susceptible to stable physiological factors such as genotype, while pain tolerance may be more responsive to psychological variables. Mediation analysis emphasizes the critical, pronounced contribution of brain patterns in the associations between genes/psychological factors and pain sensitivity, mainly for male individuals. Our study provides valuable insights into the intricate interplay among the brain, genes, and psychological factors shaping individual differences in pain sensitivity.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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