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Shared cortical characteristics in major depressive disorder, anxiety disorder, and chronic pain: a structural MRI meta-analysis study

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Chronic pain (CP) is closely related with major depressive disorder (MDD) and anxiety disorders (ANX), with high comorbidity and shared risk factors. Prior studies have demonstrated common neural correlates across the three disorders, but their neuroanatomic basis is not fully clear. Hence, the preregistered meta-analysis (CRD42019119709) intended to explore common alterations in cortical thickness among CP, MDD, and ANX, a widely used parameter for quantitatively assessing various cerebral conditions with high sensitivity to pathology in neuropsychology. A total of 68 studies comprising 3072 patients and 3427 healthy controls were finally included. Across the disorders, four common clusters with a significant reduction in cortical thickness were identified, including right insula, left anterior cingulate (AC), triangular part of the left inferior gyrus (IFG), and left middle temporal gyrus (MTG). Our findings suggested the shared cortical deficits involving ACC-insula/IFG circuit and left MTG in CP, MDD and ANX, revealing common neural correlates for cognitive and emotional processing in these highly comorbid disorders.

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INTRODUCTION

Chronic pain (CP), a leading cause of disability globally, is a complex disorder characterized by pain that persists beyond the normal tissue healing time (3 months) in the absence of an evident organic lesion, as defined by the International Association for the Study of Pain (IASP) [1]. Prevalence rates of CP vary within the range of 11% to 40%, affecting one in ten adults annually. Long-term pain significant impacts individual's health and well-being, healthcare services, and society as a whole [1, 2].

Affective disorders, such as major depressive disorder (MDD) and anxiety disorders (ANX), are also major contributors to the overall burden of disability [3, 4]. Increasing evidence supports a strong relationship between CP, MDD, and ANX [5]. High comorbidity and shared risk factors, including life stress and adverse childhood experiences, are prevalent among these disorders [6–8]. Depression and anxiety can heighten stress responses, alter pain processing, and increase sensitivity to pain [9, 10]. Conversely, individuals with CP are more vulnerable to developing MDD and/or ANX compared to those without persistent pain [9, 10]. Consequently, recognizing and addressing this bidirectional association is essential for enhancing therapeutic adherence and patient outcomes, given the negative effects of comorbidity.

Pre-clinical studies over the past two decades have provided valuable insights into the transdiagnostic neural procedures underlying in CP, MDD and ANX [9, 11, 12]. Similar findings have also been observed in neuroimaging studies conducted on human beings. Shared structural and functional brain abnormalities are identified in the cortico- and meso-limbic circuit, which consist of the insula, amygdala, hippocampus, anterior cingulate cortex (ACC), and prefrontal cortex (PFC), in all three disorders [11, 13, 14]. A recent meta-analysis of multimodal magnetic resonance imaging (MRI) has further supported these findings, revealing common reductions in gray matter (GM) volume in the insula and medial PFC across MDD, ANX, and CP [15]. However, none of MRI studies and meta-analyses so far have focused on whether changes in surface-based brain morphometry (eg., cortical thickness, CT) consistently overlap in MDD, ANX, and CP.

CT is one of the most widely used biomarker in the field of neuropsychology, known for its ability to quantitatively assess various cerebral conditions with high sensitivity to pathology compared to GM volume [16, 17]. Individual meta-analyses have been conducted for CP, MDD, and ANX, respectively, revealing significant cortical changes for each disorder, and some of these deficits partially overlapped across the three disorders [13, 18, 19] Moreover, the systematic review conducted by Sindermann et al. summarized that a thinner cortex in the ACC and the orbital frontal region was found in both MDD and ANX compared to healthy controls (HCs) [20]. However, the aforementioned cortical abnormalities cannot fully reflect the common neural mechanisms underlying CP, MDD, and ANX, due to the lack of direct statistical analysis among the three disorders.

Therefore, the present study aimed to identify evidence of transdiagnostic neural alterations through meta-analyses of MRI

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studies on CT comparing patients with CP, MDD, and ANX with HCs. We first tested (i) cortical deficits in CP, MDD, and ANX, respectively, and then (ii) for common cortical changes across the three disorders. Also, we explored the disorder-specific cortical alterations for each disorder. This in-depth investigation of cortical alterations related to CP and affective disorders (MDD & ANX) may disentangle transdiagnostic neural underpinnings.

METHODS

Search and study selection

Meta-analysis procedure was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [21] (Supplementaty Table S1). The protocol was registered at PROSPERO (CRD42022361809). English-language literatures were searched until October 30, 2022 in Cochrane Library, Embase, PubMed and Web of Science. The relevant keywords and search strategy were described in detail in Supplementary methods. The studies comparing patients with CP, MDD, or ANX with HCs were selected, and the inclusion criteria were as follows: i) studies published in a peer-reviewed journal rather than theoretical papers, case reports, reviews, and meta-analyses; (ii) analyzed whole-brain CT; (iii) provided the coordinates of significant clusters in Talairach or Montreal Neurological Institute (MNI) space; (iv) individuals without any neurological or severe medical comorbidity in the term of the exclusion of CP and psychiatric comorbidity; and (v) only collected baseline findings in longitudinal or intervention/challenge studies. When the samples overlapped between studies, the study with the larger sample size was included. Furthermore, we made no restrictions on age, duration of illness, medication status and symptom severity of a patient to maximally cover any useful records.

Data extraction

Demographic and clinical characteristics of each study, along with methodological information, were independently obtained by two authors (W.Y and B.T), consisting of sample size, age, gender, illness duration, medication status, symptom severity, strength of MRI scanner, the method used to preprocess imaging data, and peak coordinates and effect sizes of the main brain regions that showed significant between-group differences. Any inconsistencies during the data extraction were discussed by the third person to reach a consensus decision.

Meta-analysis

Seed-based mapping (SDM) software version 5.15 (https://www.sdmproject.com/) was used for meta-analyses of CT studies between patients with CP or affective disorders and control subjects [22]. Here, we briefly described this method as follow. First, peak coordinates of brain clusters with significant between-group differences and their statistical *t* values were extracted from each included study to create an effect-size signed map, and negative findings were also enrolled to get a null effect size. The *Z* and *P* values were converted into *t-statistic* values online once *t* values were not reported (www.sdmproject.com/utilities/?show=Statistics). Studies included that used Talairach coordinates were first converted into MNI space to standardize the coordinate space. Next, a random-effects analysis for the study maps was performed to obtain the mean meta-analytic signed map, accounting for both positive and negative effects. Finally, a threshold of $P = 0.005$ with peak $Z = 1$ and cluster extent $= 10$ was used.

We identified common and disorder-specific deficits of cortical morphology between CP, MDD and ANX via a three-step meta-analytic approach that has been used in other studies [23, 24]. (i) We initially conducted separate meta-analyses for the patient group of each disorder with their respective HCs to characterize robust CT changes for each disorder. (iii) For common CT abnormalities across the three disorders (relative to their respective HCs), a conjunction analysis was performed by computing errors for the estimated *P* value of each vertex from the separate meta-analytic maps. (ii) Disorder-specific CT abnormalities (i.e., CP vs MDD, CP vs ANX, ANX vs MDD, relative to their respective HCs), were determined using a quantitative contrast method, which calculated the difference in each vertex covarying for age and sex, and used standard randomization tests to establish statistical significance. Additionally, we carefully controlled for comorbidity effects when identifying shared and distinct structural alterations in the comparative and conjunctive meta-analysis procedures.

To explore the potential impacts of confounding factors (e.g: age, sex, duration of illness and percentage of comorbidity) on cortical deficits from the separate meta-analyses, a linear random-effects model was used for meta-regression analyses in each patient group and a threshold of *P* value less than 0.0005 was adopted [25]. And at least 9 studies should be required for each meta-regression analysis, as recommended by Radua et al. [26].

Jackknife sensitivity analysis

A whole-brain jackknife sensitivity analysis was performed to examine the reliability of meta-analysis results. It needed to iteratively repeat the analysis each time when one dataset was discarded. The results were considered highly replicable if a given cluster remained significant in 75% or more of the combinations of studies [27]. We conducted jackknife analysis for each pooled meta-analysis.

Analysis of heterogeneity and publication bias

I^2 statistics was used to evaluate the inter-study heterogeneity of individual clusters obtained from the meta-analyses. Publication bias was evaluated by funnel plots. Egger's test and any results with $P < 0.05$ were considered to be significant for publication bias [28].

RESULTS

Included studies and sample characteristics

The PRISMA flowchart of the literature search and selection was shown in Fig. 1. 35 studies comprising 1508 CP patients and 1549 HCs, 22 studies comprising 1133 MDD patients and 1515 HCs, and 11 studies comprising 431 patients with ANX and 363 HCs were included in the present meta-analysis. Demographic and clinical characteristics of these included studies were provided in Supplementary Table S2–S4. One-way ANOVA revealed significant differences in mean age ($F = 16.948$, $P < 0.001$, $\eta^2 = 0.3475$) and female ratio ($F = 4.531$, $P = 0.014$, $\eta^2 = 0.1224$) in the three patient groups. Post-hoc tests revealed that mean age and female ratio of the CP patient group were higher than those of MDD and ANX ($P < 0.001$ & $P < 0.001$).

Meta-analysis

CP, MDD and ANX patients versus HCs, respectively. Compared with HCs, CP patients showed a significant reduction of CT only in the right insula (Table 1, Fig. 2A). MDD patients showed significantly reduced CT in four clusters in comparison with HCs: right middle temporal gyrus (MTG), right supplementary motor area (SMA), left superior temporal gyrus (STG) and left superior frontal gyrus (SFG), dorsolateral (Table 1, Fig. 2B). For ANX, thinner cortex was observed in four clusters: bilateral insula, triangular part of the right inferior frontal gyrus (IFG), and right median cingulate/paracingulate gyri (MG/PC) (Table 1, Fig. 2C). No clusters in each disorder had a greater cortex than that in control subjects. Controlling for comorbidity in the analysis, the cortical results of CP and MDD remained stable in comparison with HCs, with the exception of ANX (Supplementary Table S5).

Given that the complex etiology and clinical presentations of CP, subgroup analysis may be helpful in clarifying distinct

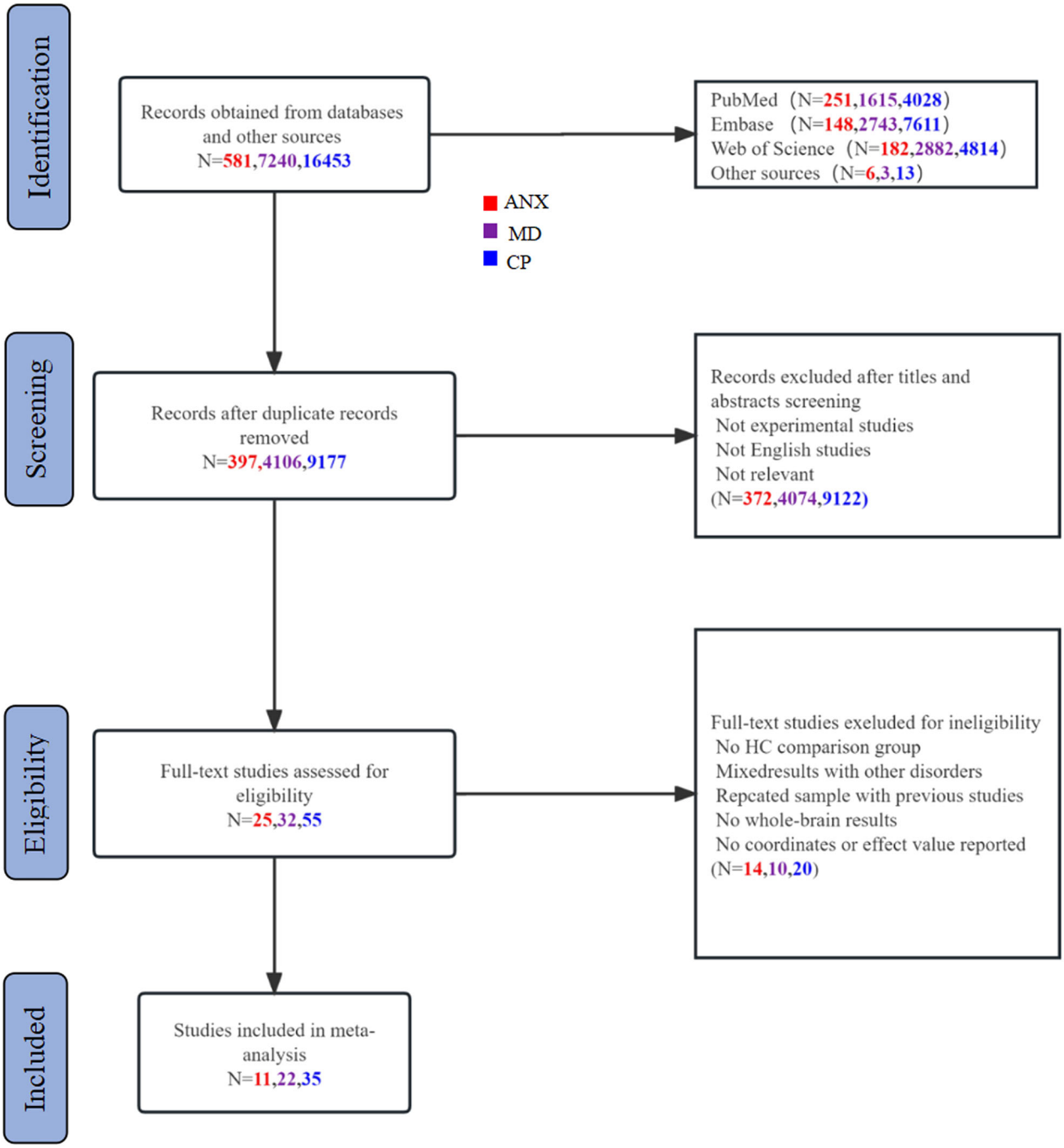

Fig. 1 PRISMA flow diagram of study selection in this meta-analysis. ANX, anxiety disorder; MDD, major depressive disorder; CP, chronic pain; HC, healthy control.

neurological mechanisms involved in different illness conditions. Therefore, CP patients were divided into neuropathic- and non-neurogenic pain groups, the former comprising 21 studies, with 1139 patients and 1040 HCs while the latter including 14 studies with 408 patients and 498 HCs. Subgroup meta-analyses revealed increased CT in a wide range of brain regions including left striatum, right paracentral lobule, and reduced CT in right superior parietal gyrus, left precentral gyrus in neurogenic pain patients (Supplementary Table S6). Patients with non-neurogenic pain showed increased CT in the left precentral gyrus (PreCG), orbital part of the bilateral middle frontal gyrus (MFG), and thinner CT in the right insula, median cingulum, MTG and triangular part of the left IFG compared to HCs (Supplementary Table S7).

Comparative and conjunction analyses of CT between CP, MDD and ANX. Studies with comorbidity were excluded to avoid the confounding impacts of comorbid conditions, further identifying the common and specific CT changes for each disorder. Decreased and increased CT in ANX relative to CP were found in the right angular gyrus (ANG) and the right insula, respectively (Table 2, Fig. 3A). And greater CT was observed in four clusters in CP compared to MDD: right SMA, right MTG, orbital part of the left MFG, and left PreCG (Table 2, Fig. 3B), while ANX patients showed thinner cortex

Table 1. Whole-brain meta-analysis results for CT studies comparing CP, ANX, or MDD with their respective HCs.

MNI coordinates	SDM Z	Voxels	Region	*P* value, uncorrected	BA	Egger's bias	Egger's p
CP < HCs							
36, 10, 4	−1.189	1504	Right insula	0.000283837	48	−0.46	0.243
MDD < HCs							
60, −42, −2	−1.778	596	Right middle temporal gyrus	0.000051618	21, 22	0.93	0.091
−52, −24, 4	−1.374	203	Left superior temporal gyrus	0.000500619	48	1.45	0.004
8, 14, 52	−1.305	180	Right supplementary motor area	0.000898004	6	0.04	0.945
−24, 34, 36	−1.117	45	Left superior frontal gyrus	0.002755880	9	0.13	0.859
ANX < HCs							
−36, 2, 0	−1.230	307	Left insula	0.000278711	48	1.16	0.268
42, 38, 0	−1.263	207	Right inferior frontal gyrus, triangular part	0.000233330	45, 47	1.12	0.286
6, 0, 38	−1.015	186	Right median cingulate/paracingulate gyri	0.001924992	24	−0.31	0.833
32, 26, 0	−1.230	161	Right insula	0.000278711	24	1.16	0.268

BA Brodmann area; *MNI* montreal neurological institute; *SDM* seed-based d mapping; *CP* chronic pain; *MDD* major depression disorder; *ANX* anxiety disorder; *HCs* healthy controls.

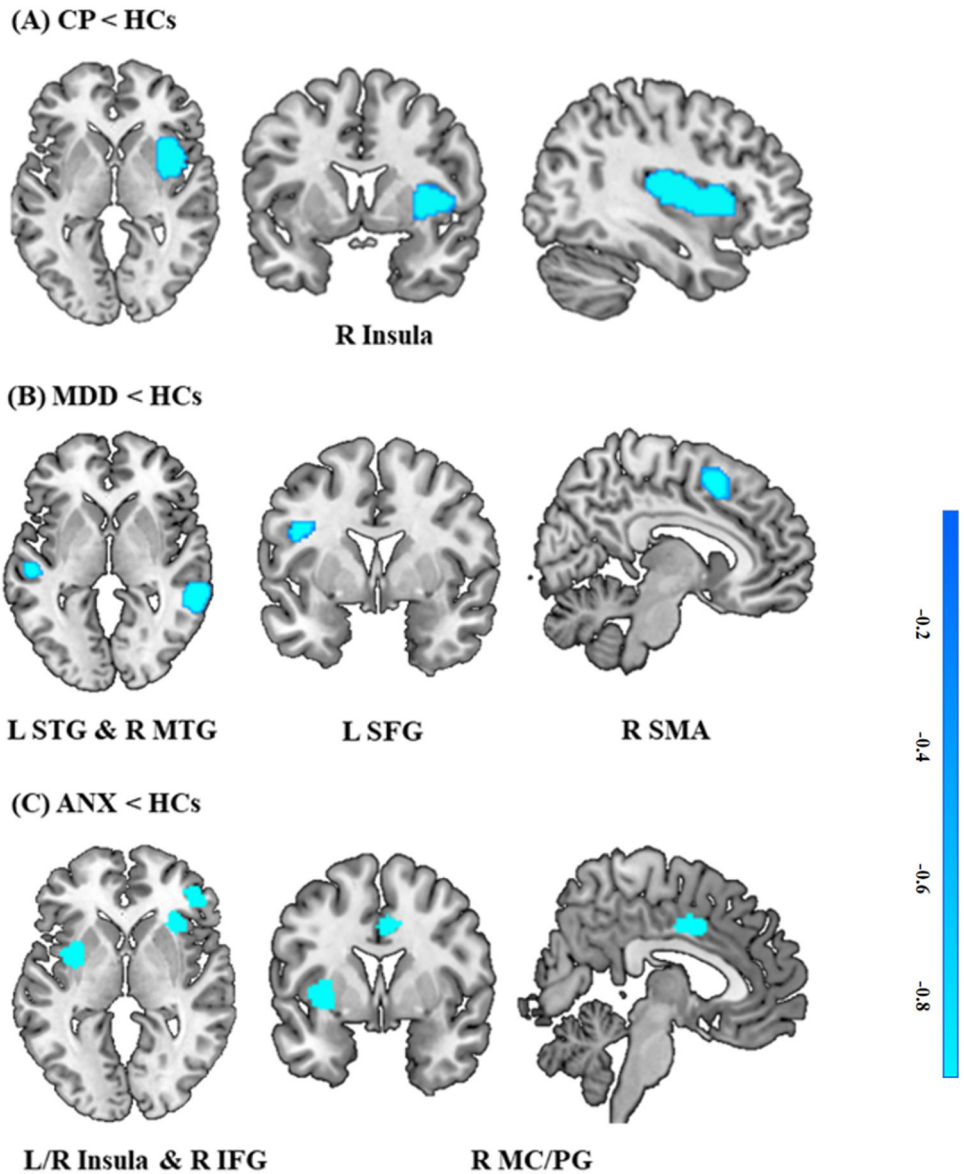

Fig. 2 Cortical changes of CP, MDD and ANX in comparison with HCs. A–C Reduced cortical deficits of CP, MDD and ANX in comparison with HCs, respectively. CP chronic pain, MDD major depressive disorder, ANX anxiety disorders, HCs healthy controls, STG superior temporal gyrus, SFG superior frontal gyrus, SMA supplementary motor area, IFG inferior Frontal Gyrus, MC/PG median cingulate/paracingulate gyri, L left, R right.

Table 2. Comparative meta-analysis results across CP, ANX, and MDD.

MNI coordinates	SDM Z	Voxels	Region	*P* value, uncorrected	BA	Egger's bias	Egger's p
CP > ANX							
32, 26, 0	1.359	71	Right insula	0.000753462	47	−0.12	0.678
CP < ANX							
34, −64, 46	−1.040	836	Right angular gyrus	0.000036120	7	0.12	0.725
CP > MDD							
60, −42, −2	1.210	361	Right middle temporal gyrus	0.000361264	21	0.22	0.319
−30, 52, −6	1.165	218	Left middle frontal gyrus, orbital part	0.000526428	11, 47	0.42	0.058
−32, −28, 58	1.066	224	Left precentral gyrus	0.001032174	3, 4	0.31	0.081
8, 12, 54	1.081	195	Right supplementary motor area	0.000923812	6, 32	0.04	0.875
ANX < MDD							
32, 24, 0	−1.545	258	Right insula	0.000134170	47	0.21	0.617
−8, 56, 6	−1.205	80	Left superior frontal gyrus, medial	0.001966298	10	−0.40	0.404
−34, 2, 0	−1.469	112	Left insula	0.000227094	48	−0.01	0.990
42, 38, 0	−1.515	91	Right inferior frontal gyrus, triangular part	0.000113547	45	0.05	0.895

BA Brodmann area; *MNI* montreal neurological institute; *SDM* seed-based d mapping; *CP* chronic pain; *MDD* major depression disorder; *ANX* anxiety disorder; *HCs*, healthy controls.

than MDD patients in 4 clusters: bilateral insula, left SFG and triangular part of the right IFG (Table 2, Fig. 3C).

Four common clusters with a reduction in CT were identified in conjunction analyses (CP ∩ MDD ∩ ANX): right insula, left anterior cingulate (AC), triangular part of the left IFG, and left MTG (Table 3, Fig. 3D). In addition, conjunction meta-analyses were also performed between any two disorders, and the relevant results were provided in Supplementary Results.

Meta-regression. In MDD, age was positively associated with thinner CT in the right MTG ($r = 0.476$, $p = 0.025$). There were no significant associations between CT deficits and any other confounding factors in CP, MDD and ANX.

Analyses of jackknife, heterogeneity and publication bias. The results of the jackknife sensitivity analysis were highly replicable (Supplementary Table S8–S10). Heterogeneity statistics I^2 extracted from the significant clusters were low heterogeneity ($I^2 < 50\%$). And there was significant publication bias in the left superior temporal gyrus in MDD (Table 1). No significant publication bias was identified by Egger's test for CP and ANX (Table 1).

DISCUSSIONS

This meta-analysis is the first to quantitatively evaluate common cortical changes across CP, MDD, and ANX, in comparison to HCs. Shared decreases in CT were observed in the ACC-insula/IFG circuit and left MTG, shedding light on neural correlates of comorbidity and shared neural mechanisms for cognitive and emotional processing. Also, specific cortical changes for each disorder replicated and extended prior findings, suggesting additional disorder-specific mechanisms.

A recent publication by Brandl et al. found common GM volume reduction in insular and medial-prefrontal cortices across these three disorders, providing powerful evidence of neural correlates for comorbidity and a shared neural basis [15]. According to the 'perception-action' model for pain, the posterior insula, parietal operculum, and the primary and secondary somatosensory cortices form the primary pain unit responsible for pain perception and localization [29, 30]. The anterior insula and ACC, as key components of the second cortical pain unit, are associated with attention to pain [31]. Both pain matrices collaborate to shape the affective experience of pain, without directly initiating behavioral responses. Series of studies have demonstrated abnormalities in the insular-ACC circuit in patients with chronic pain [13, 14, 32]. Also, this neurocircuit is engaged in the perception and attention aspects of negative emotion [33]. Several MRI studies identified disrupted connectivity between the insula cortex and ACC in depression, social anxiety disorder, and panic disorder [34, 35]. Thus, it suggested that the insula-ACC circuit is a pivotal node in the brain governing cognitive and emotional processing and behavior. Similar roles can be also observed in the insula-IFG circuit. Tops and Boksem speculated that the insula and IFG areas within the ventral corticolimbic control pathway first integrate limbic emotion–motivational and sensory inputs, and then produce different responses based on the required level of precision for a stimulus or task [33]. Findings from functional MRI (fMRI), electroencephalogram (EEG) and event-related potential (ERP) studies have confirmed this point [33]. However, the above two common neurocircuits are partially separable due to their respective adaptations to various conditions involving pain and emotion, even though they interact [33]. For example, a PET study identified correlations between an activity shift from the insula-IFG region to the dorsolateral cortex and antidepressant effects of medication in patients with depression [36]. Regarding the left MTG, both CP and affective disorder patients exhibited functional deficits in this region [37–39]. The MTG is responsible for emotional processing, selective attention, working memory, and other cognitive functions [40–42]. Abnormal activity in this area may be associated with negative emotions and cognitive impairment [43]. In conclusion, our research has identified common cortical changes in the insula-ACC/IFG circuit and left MTG among CP, MDD and ANX, offering insights into the development of potential treatment biomarkers for shared neural mechanisms, especially Transcranial Magnetic Stimulation (TMS).

Comparative meta-analyses in our study showed that specific cortical changes for CP, MDD and ANX partially overlapped with not only common CT changes across disorders but also with CT deficits in each disorder when compared to HCs, including the insula, IFG, MTG, and SMA. This implies the need for further

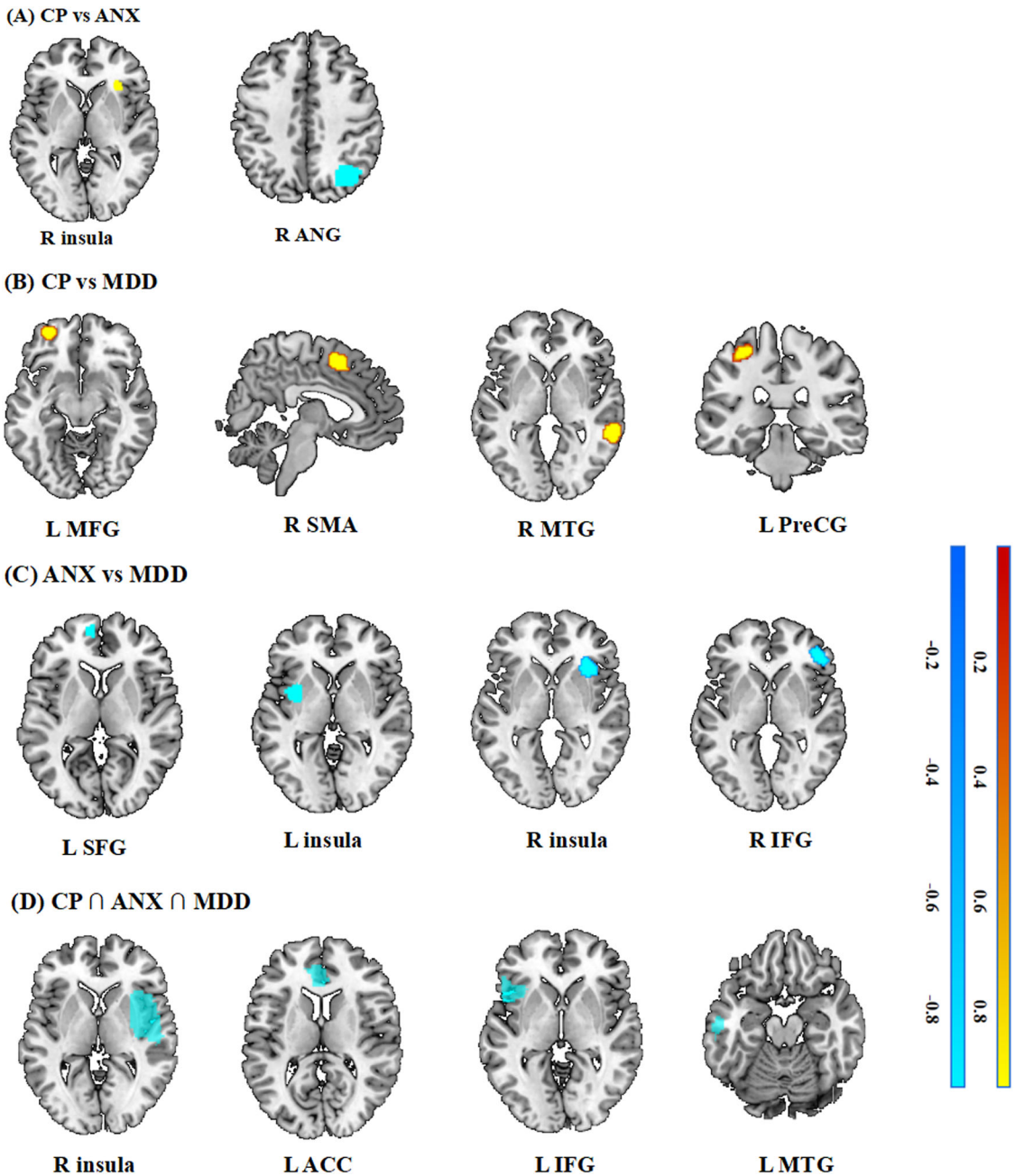

Fig. 3 Disorder-specific and common cortical changes across CP, ANX and MDD. Disorder-specific (**A**–**C**) and common (**D**) cortical deficits across these disorders. The brain regions marked in blue and red indicate decreased and increased cortical thickness, respectively, in patients compared to HCs. CP chronic pain, MDD major depressive disorder, ANX anxiety disorders, HCs healthy controls, ANG angular gyrus, SMA supplementary motor area, MTG middle temporal gyrus, PreCG precentral gyrus, MFG middle frontal gyrus, SFG superior frontal gyrus, IFG inferior Frontal Gyrus, ACC anterior cingulate, L left, R right.

research to uncover the complex neurological processes underlying this finding and to understand its implications for clinical treatment. Thus, here we only discuss CT changes in the angular gyrus specific to CP vs. ANX, as well as in the PreCG and MFG for CP vs. MDD, and the SFG for ANX vs. MDD. The angular gyrus, situated posteriorly in the inferior parietal lobule, serves as a multimodal integrative hub that converges multisensory inputs from multiple brain regions [44]. This area is associated with several cognitive domains, including language processing, memory retrieval, attention, and social cognition [44, 45]. Prior fMRI studies have reported dysregulated connectivity between the angular gyrus and other brain regions in patients with migraine, fibromyalgia, and anxiety, respectively [46–50]. Here, we showed a significant reduction of CT in the angular gyrus in individuals with CP compared to those with ANX, indicating a potential vulnerability of this region to CP. Similar psychopathological mechanisms may underlie cortical deficits between CP and MDD in our study. Taken together, our observation of disorder-specific cortical changes enhances our comprehension of unique neural mechanisms associated with each disorder. Beyond the regional morphological changes associated with clinical conditions, mapping intrinsic brain connectivity networks can provide a potential mechanistic framework for understanding various aspects of human behavior, as reported in numerous studies [51–53]. These

Table 3. Conjunction meta-analysis results across CP, ANX, and MDD.

MNI coordinates	Voxels	*P* value, uncorrected	Region	BA
Common CT-increased: (CP > HCs) ∩ (ANX > HCs) ∩ (MDD > HCs)				
None				
Common CT-decreased: (CP < HCs) ∩ (ANX < HCs) ∩ (MDD < HCs)				
36, 10, 4	899	<0.00005	Right insula	48
−2, 40, 8	533	<0.00005	Left anterior cingulate	32
−52, 18, 8	227	<0.00005	Left inferior frontal gyrus, triangular part	48
−58, −16, −22	229	<0.00005	Left middle temporal gyrus	20

CT cortical thickness; *BA* Brodmann area; *CP* chronic pain; *MDD* major depression disorder; *ANX* anxiety disorder; *HCs*, healthy controls.

networks, which include functional and structural connections within the brain, can provide deeper insights into the neural mechanisms underlying cognitive processes, emotional regulation, and social interactions. In anticipation of future endeavors, we aim to examine the functional networks of these three diseases, thereby delving deeper into the shared and distinct functional network alterations among them.

There were some limitations that are worth highlighting. First, this study was based on summarized data (i.e. reported coordinates) rather than raw original data, and a few results with small or moderate effect sizes may have been neglected. Second, only 11 MRI studies related to ANX was included in this meta-analysis, which is smaller in comparison to those involving CP (35 studies) and MDD (22 studies), although the number of included studies for ANX met the recommended number of studies for performing SDM [26]. Third, some uncontrollable influence of medication on cortical deficits across these three disorders might still exist, as we did not exclude patients using drugs in our study. It was difficult to consistently and accurately record medication usage for all the included studies. The potential effect existed between the different filed strength, as we did not limit the parameters. The reconstruction of cortices will be influenced by field strength and sequence parameters. This factor might subtly affect the contrast between gray and white matter and the extraction of white matter surface and the pial surfaces. Thus, the differences of MRI parameters across studies represent an important consideration when interpreting our findings. Finally, the included disorders were quite heterogeneous; for example, CP encompasses different conditions like chronic back pain or fibromyalgia (see detailed information in Supplementary Materials). This inherent heterogeneity, common in many psychiatric diagnostic categories, could potentially diminish statistical power and elevate the risk of obtaining false-negative results.

As the first meta-analysis quantitatively evaluating cortical characteristics among CP, MDD, and ANX, shared deficits involving ACC-insula/IFG circuit and left MTG suggested common neural correlates for cognitive and emotional processing in these highly comorbid disorders.

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COMPETING INTERESTS

The authors declare no competing interests.

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