Meta-Analysis

# Gray Matter Abnormalities in Patients with Chronic Primary Pain: A Coordinate-Based Meta-Analysis

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Disclaimer: Zuxing Wang and Minlan Yuan contributed equally to this work. See pg. 11 for funding information.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-24-2021
Revised manuscript received: 10-10-2021
Accepted for publication: 10-27-2021

Free full manuscript: www.painphysicianjournal.com

**Background:** Many structural magnetic resonance imaging (MRI) studies have used voxel-based morphometry (VBM) to identify gray matter abnormalities in patients with chronic primary pain (CPP), but the findings have been inconsistent.

**Objectives:** To identify (a) gray matter differences between CPP patients or female patients and healthy individuals and (b) the effects of symptom duration and pain scores on gray matter.

**Study Design:** We conducted a meta-analysis.

**Methods:** VBM studies in PubMed, Cochrane Library, and Google Scholar, from November 2005 to June 2020, were thoroughly collected and carefully reviewed. Manual searches were performed using title and citation information. Gray matter VBM study comparing adult patients (18-65 years) with CPP to healthy controls was reviewed, and results, presented in Talairach or Montreal Neurological Institute coordinates, were included. The t value, peak coordinates, and basic clinical information of each study were reported in detail. Anisotropic effect-size signed differential mapping was used for voxel-based meta-analyses.

**Results:** Patients with CPP had decreased gray matter in the left anterior cingulate (z value = 2.950, $P < 0.001$), right median cingulate (z value = 1.858, $P = 0.001$), and the insula bilaterally (left: z value = 2.441, $P < 0.001$; right: z value = 2.113, $P < 0.001$ ), and increased gray matter in the right striatum (z value = 1.194, $P < 0.001$). Subgroup meta-analysis showed female patients with CPP also had decreased gray matter in the left anterior cingulate gyrus (z value = 2.622, $P < 0.001$). Meta-regression analyses revealed that pain symptom duration was positively associated with a large right brain region (z value = 2.110, $P < 0.001$), a negative association between pain symptom duration and gray matter was found in the right anterior cingulate (z value = 1.969, $P < 0.001$) and right middle frontal gyrus (z value = 1.849, $P < 0.001$).

**Limitations:** Due to the lack of data from male patients, we were unable to perform a male subgroup analysis; therefore, we cannot thoroughly explore the difference in CPP from the perspective of gender.

**Conclusion:** We identified gray matter changes in CPP patients and female patients, as well as a close relationship between CPP and mental disorders. With the chronicity of pain leads to changes in relevant brain regions, which makes treatment more challenging and may have synergistic effects with affective disorders. More prospective longitudinal structural MRI studies of CPP examining the associations between those variables and gray matter in a larger population should be conducted. Additional prospective longitudinal structural MRI studies of CPP with larger sample sizes to confirm the relationships between these variables and gray matter are needed as well as gender differences of CPP in brain structure and function.

**Key words:** Chronic primary pain, gray matter difference, SDM meta-analysis, gender difference, mental disorder

**Pain Physician 2022: 25:1-13**

Currently, the World Health Organization (WHO) defines pain as the "fifth vital sign" after blood pressure, respiration, pulse, and body temperature (1). A new diagnosis of chronic primary pain (CPP), which has been proposed by the International Association for the Study of Pain (IASP), is associated with significant functional disability and/or significant emotional distress that persists or recurs for longer than 3 months and has symptoms that are not better accounted for by another diagnosis (2). Long-term pain stimulation can promote pathological remodeling in the central nervous system, making the progression of pain diseases more difficult to control (3,4). From the patients' perspective, chronic pain is not only an excruciating experience but also seriously affects physical and social functions such that some patients cannot participate in normal life and social activities (5).

Currently, CPP is referred to chronic pain conditions covered by labels such as fibromyalgia, complex regional pain syndrome (CRPS), temporomandibular disorder (TMD), trigeminal autonomic cephalalgias (TACs), irritable bowel syndrome (IBS), and chronic primary low back pain (CLBP) (2). Although CPP is classified into different subgroups, CPP patients are a highly homogeneous group, potentially reflecting the many etiological pathways to CPP. The genesis of CPP has been explained in the context of a biopsychosocial model. It is hypothesized that an interdependency between environmental and genetic factors provokes aberrant long-term changes in biological and psychological regulatory systems (6). Changes in pain sensitivity have revealed an important contribution of central sensitization to the different pain phenotypes in patients (7). In addition, pain signals are processed in the thalamus, midbrain, and several cortical regions that form the pain matrix, a constantly shifting set of networks and connections that supports the conscious perception of pain (8). Magnetic resonance imaging (MRI) can well detect the pain processing of the central nervous system.

Many structural MRI studies in those with CPP have used automated and unbiased methods, such as voxel-based morphometry (VBM), to investigate gray matter abnormalities in CPP. Patients with CPP exhibit reduced gray matter volume (GMV) or gray matter density (GMD) in a number of cortical and subcortical brain regions, including the insula (9-14), anterior and median cingulate cortex (10,12,13,15,16), thalamus (17-19), putamen (17), medial frontal cortex (10), orbitofrontal cortex (12,15,19), precuneus (20,21), amygdala (22,23), primary somatosensory cortex (14,17,24,25), and hippocampus (9,14,23,26). However, there are marked inconsistencies across studies, even in studies of the same disease. These studies have reported increased gray matter in the thalamus (21,25,27), putamen (25,27), insula (17,28), hippocampus (28,29), anterior cingulate cortex (26,28), precuneus (30), amygdala (27,31,32), primary somatosensory cortex (20), and orbitofrontal cortex (28). There are also some VBM studies in those with CPP that have failed to identify significant differences in gray matter.

These inconsistent findings with low chances of replication success across studies reflect possible variations in data analytic strategies and sample characteristics within and across studies. Moreover, the relatively small sample sizes in most studies could have resulted in low statistical stability and increased risk of false-positive results. Finally, gender differences might also have contributed to these inconsistencies (33). In many CPP studies, patients were mainly women (19,34), and in fact, only women were included in some studies (30,35).

Given this variability, we applied seed-based d mapping (SDM), a voxel-based meta-analytical method (36), to publish whole-brain VBM studies in patients with CPP. The inclusion of only whole-brain VBM studies means that the results were not biased or restricted by previous findings to a priori regions of interest (36). Reliability analyses were performed to assess the robustness of the findings. To examine the contribution of gender to differences in gray matter, we conducted an additional subgroup meta-analysis investigating studies in which only female patients were included. Based on the differences between GMD and GMV, we also conducted a subgroup meta-analysis of GMD and GMV. Given the evidence that patients with CPP present with different pain scores, meta-regressions were also conducted to examine the effect of pain scores on gray matter. Finally, the effect of symptom duration was also examined, given its influence on gray matter.

## Methods

### Search and Study Selection

Published studies that measured brain structure using VBM in patients with CPP and controls were included in the database. A literature search of PubMed, the Cochrane Library database, and Google Scholar databases for VBM studies published from November

2005 through June 2020 was conducted. Titles, abstracts, citations, and references were evaluated to determine relevance and to identify additional studies for inclusion. The inclusion criteria regarding CPP diseases were based on the IASP standards in 2019 (2). The following inclusion criteria were established: (1) the study compared gray matter VBM in adult patients (18-65 years) with CPP to healthy controls; (2) the results were presented in Talairach or Montreal Neurological Institute (MNI) coordinates; and (3) the study was included only if a whole-brain analysis, rather than a small volume correction, was performed to ensure no bias in the regions reported. Studies were excluded if they (1) failed to use VBM to report a voxelwise gray matter comparison between CPP patients and healthy controls, (2) included duplicated datasets, and (3) did not provide peak coordinates. A total of 7972 publications were identified, of which 45 met the inclusion criteria and were included in the database. Further details on the search terms and the inclusion flow chart (Fig. S1) are provided in the supplementary materials.

### Comparison of Regional Gray Matter Differences

We used anisotropic effect-size signed differential mapping (SDM) software (version 5.15; http://www.sdmproject.com/software/) to conduct the voxelwise meta-analysis (36,37) that compared gray matter abnormalities in patients with CPP and healthy controls. All the analytical processes in this study were conducted with reference to the SDM tutorial (http://www.sdmproject.com/software/tutorial.pdf), which uses a restricted maximum-likelihood estimation of the variance, a fitting method to achieve a good balance between unbiasedness and efficiency (36,37). First, peak coordinates of gray matter differences between CPP patients and healthy controls were extracted from each included study. Second, an effect-size signed map and variance map for each dataset within a gray matter mask based on the peak coordinates and their effect sizes were obtained by an anisotropic unnormalized Gaussian kernel of 20-mm full-width at half-maximum (FWHM) to optimize the sensitivity and specificity of the analysis. Third, a mean map was created by the voxelwise calculation of the mean of the dataset maps, weighted by the squared root of the sample size of each dataset, so that studies with large sample sizes contribute more. Finally, statistical significance was determined using the standard permutation tests and a threshold of $P = 0.005$ with a cluster-level threshold of 10 voxels and SDM z score = 1 in the present voxelwise meta-analysis (36,38). Underlying publication bias was evaluated with Egger's test (39).

### Reliability Analysis, Subgroup Meta-analysis, and Meta-Regressions

Considering that individual studies may have affected the results, we performed a jackknife sensitivity analysis to investigate the reliability of the results, which was achieved by excluding one study in each of the analyses (40). A subgroup meta-analysis was also performed on studies that included only females diagnosed with CPP or included only GMV and GMD studies.

We also performed a meta-regression analysis using a random effects general linear model to explore potential confounding effects. For example, the effects of the mean pain scores for patients with CPP and the symptom duration of patients with CPP on gray matter were examined.

For the collection of pain severity indicators, we included 1-10 scoring system studies, mainly the visual analog scale (VAS) and numeric rating scale (NRS). Because the VAS and NRS are very similar in sensitivity and reliability for pain assessment and their score values are the same, we directly combined the VAS and NRS data in our meta-regression analysis.

## Results

### Study Characteristics

The database comprised 45 studies that included 1,036 patients with CPP and 1,085 healthy control patients. Two studies used 2 different CPP diagnoses: one used TMD and TACs (17), and the other utilized CRPS and CLBP (9). In another 2 studies, the patients were divided into 2 groups according to the age when the disease was diagnosed (41) and the duration of the disease (32). In 19 studies, the included patients were all females. Among all the CPP patients included in the studies, the number of women was 801, accounting for 77.3%, and the number of healthy female controls was 815, accounting for 75.1%. Moreover, 33 studies focused on GMV, and the other 12 focused on GMD. Table 1 summarizes the variables extracted from the studies. Although many studies have evaluated the depressive and anxious symptoms of CPP patients (13,19), all of them declared that the included patients did not have comorbid mental disorders. Further details are provided in the supplementary materials (Supplemental Table S1).

Table 1. *Demographic and clinical data from study patients in a database of 45 voxel-based MRI studies comparing patients with CPP to healthy control patients.*

| Variable | Pooled Number of Patients in Database | Number of Studies Reporting Variable | Mean Value |
|---|---|---|---|
| Number of CPP patients | 1036 | 45 | 23.02 |
| Female patients | 801 | 44 | 18.20 |
| Number of healthy controls | 1085 | 45 | 24.11 |
| Female healthy controls | 815 | 43 | 18.95 |
| Patients in GMV studies | 746 | 33 | 22.61 |
| Healthy controls in GMV studies | 814 | 33 | 24.67 |
| Patients in GMD studies | 290 | 12 | 24.17 |
| Healthy controls in GMD studies | 271 | 12 | 22.58 |
| Studies only involving female patients | 363 | 19 | 19.11 |
| Studies only involving healthy female controls | 363 | 19 | 19.11 |
| Age (years) | | | |
| Patients, mean | 1024 | 44 | 43.25 |
| Patients, SD | 999 | 42 | 8.78 |
| Healthy controls, mean | 1016 | 42 | 42.09 |
| Healthy controls, SD | 991 | 40 | 8.36 |
| Duration of illness (years) (patients) | 936 | 39 | 8.78 |
| Duration of illness (years) (healthy controls) | 1033 | 39 | NA |
| Total pain score (patients) | 657 | 33 | 5.94 |
| Total pain score (healthy controls) | 748 | 33 | NA |
| Pain score (VAS) (patients) | 425 | 20 | 5.96 |
| Pain score (VAS) (healthy controls) | 504 | 20 | NA |
| Pain score (NRS) (patients) | 138 | 8 | 5.64 |
| Pain score (NRS) (healthy controls) | 150 | 8 | NA |
| Pain score (unknown 1-10) (patients) | 94 | 5 | 6.34 |
| Pain score (unknown 1-10) (healthy controls) | 94 | 5 | NA |

Abbreviations: CPP, chronic primary pain; VAS, visual analog scale; NRS, numeric rating scale; GMV, gray matter volume; GMD, gray matter density; NA, not applicable.

## Patients with CPP vs. Healthy Controls: Regional Gray Matter Differences

Anisotropic effect-size SDM analyses revealed decreased gray matter in the patients with CPP compared with the healthy patients in the left anterior cingulate gyrus, right median cingulate gyrus, and bilateral insula. The CPP patients had significantly increased gray matter in the right striatum (Table 2 and Fig. 1). There was no obvious evidence of publication bias by Egger's tests ($P = 0.484$).

## Reliability Analysis

A jackknife sensitivity analysis revealed that the gray matter decrease in the left anterior cingulate gyrus and bilateral insula was preserved throughout all 45 study combinations. Reduced gray matter in the right Heschl gyrus failed to emerge in only one of the study combinations, with reduced gray matter in the right median cingulate gyrus failing to emerge in only 3 of the study combinations. In addition, an increase in gray matter in the right striatum failed to emerge in only 2 of the study combinations (Supplemental Table S2). Most of the study combinations (39) found no additional significant cluster in either the positive direction or the negative direction.

## Subgroup Analyses: Female Patients, GMV, and GMD

A subgroup meta-analysis was carried out on studies that included only females diagnosed with CPP. Nineteen studies included a comparison between female patients with CPP and healthy controls. This subsample included 363 patients with CPP and 363 healthy controls. Female patients with CPP also had decreased gray matter in the left anterior cingulate gyrus and right median cingulate gyrus. In addition, this comparison found significant increases in the right superior parietal gyrus and left precuneus and reductions in the right putamen and left middle frontal gyrus (Supplemental Table S3 and Fig. S2).

Subgroup meta-analyses were also performed on only the studies that examined GMV and only those that examined GMD. Among them, 33 studies on GMV included 746 patients, and 12 studies on GMD included 290 patients. In the studies on GMV, the subgroup meta-analysis revealed increased GMV in the right striatum and decreased GMV in the left insula, anterior cingulate gyrus, inferior temporal gyrus, precentral gyrus, and superior occipital gyrus (Supplemental Table S4 and Fig. S3). In the studies on GMD, the subgroup

Table 2. *Meta-analysis results of gray matter volume or density in patients with CPP compared with healthy controls.*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Gray matter change |
|---|---|---|---|---|---|---|
| Striatum | Right | 8, 8, -2 | 1.194 | < 0.001 | 748 | Increase |
| Anterior cingulate gyrus (BA 24) | Left | 0, 26, 30 | 2.950 | < 0.001 | 3145 | Decrease |
| Insula (BA 47) | Left | -36, 16, -6 | 2.441 | < 0.001 | 1524 | Decrease |
| Insula (BA 47) | Right | 30, 20, -12 | 2.405 | < 0.001 | 89 | Decrease |
| Median cingulate gyrus | Right | 4, -30, 44 | 1.858 | 0.001 | 218 | Decrease |

Abbreviations: CPP, chronic primary pain; BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

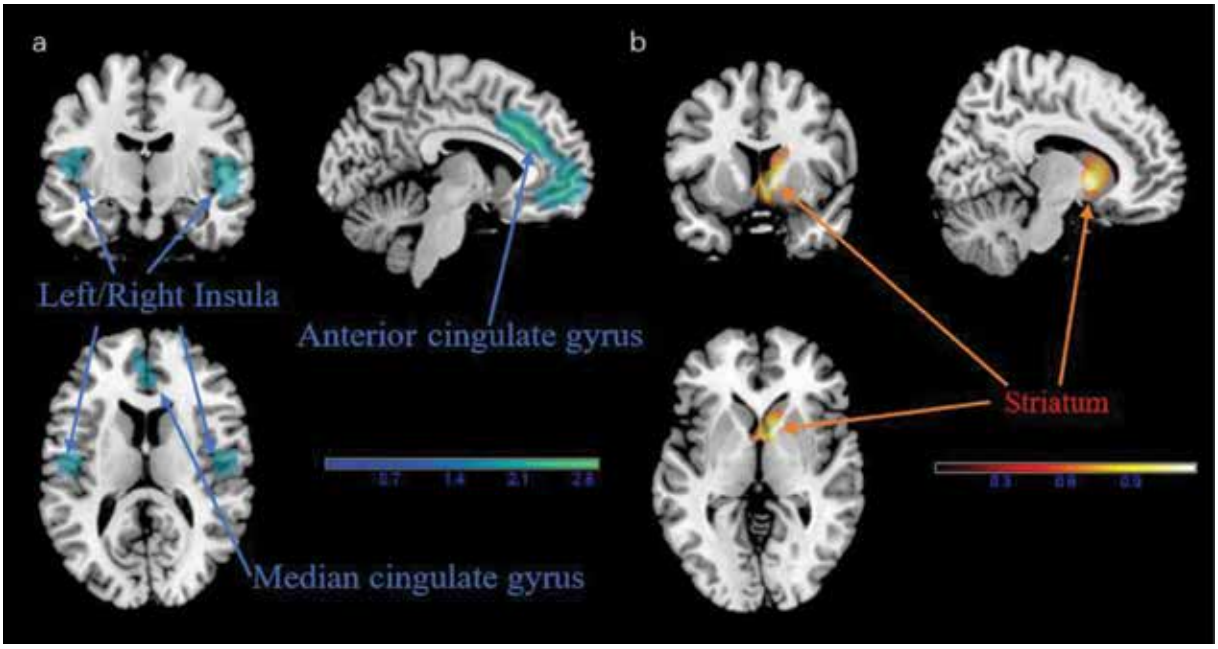


Fig. 1. *Seed-based d mapping (SDM) meta-analysis of 45 voxel-based morphometry studies showing significantly decreased (a) and increased (b) gray matter in patients with chronic primary pain compared with control patients.*

Color bar indicates SDM z scores. (a) Coordinates: 85, 112, 85. Maximum SDM z score = 2.44. (b) Coordinates: 82, 141, 83. Maximum SDM z score = 1.19.

meta-analysis indicated decreased GMD in a brain cluster that encompassed the right insula, left anterior cingulate gyrus, bilateral median cingulate gyrus, left gyrus rectus, and left superior frontal gyrus (orbital part) (Supplemental Table S5 and Fig. S4).

## Meta-Regression Analyses: Effects of Pain Score and Symptom Duration

A total of 33 studies on CPP reported patient pain scores on a 1-10 scale, involving 657 patients and 748 healthy controls. Meta-regression analyses indicated that higher pain scores of the patients with CPP were associated with lower reductions in the gray matter in the left anterior cingulate gyrus and right insula. In addition, lower pain scores of the patients with CPP were associated with lower reductions in the gray matter in the left thalamus and left postcentral gyrus (Table 3 and Fig. 2).

A total of 39 studies on CPP reported pain symptom duration, involving 936 patients and 1033 healthy controls. Symptom durations were positively associated with gray matter in a large right-lateralized cluster that encompassed the insula, striatum, putamen, and amygdala. The longer the pain symptom durations were,

Table 3. *Meta-regression results showing an association between the pain scores of CPP patients and gray matter differences.*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Association |
|---|---|---|---|---|---|---|
| Postcentral gyrus (BA 4) | Left | -54, -8, 28 | 1.020 | 0.003 | 95 | Positive |
| Thalamus | Left | -8, 24, 6 | 1.005 | 0.003 | 22 | Positive |
| Anterior cingulate gyrus (BA 11) | Left | -6, 32, -10 | 1.782 | 0.001 | 83 | Negative |
| Insula (BA 48) | Right | 38, 16, 8 | 1.824 | 0.001 | 67 | Negative |

Abbreviations: CPP, chronic primary pain; BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

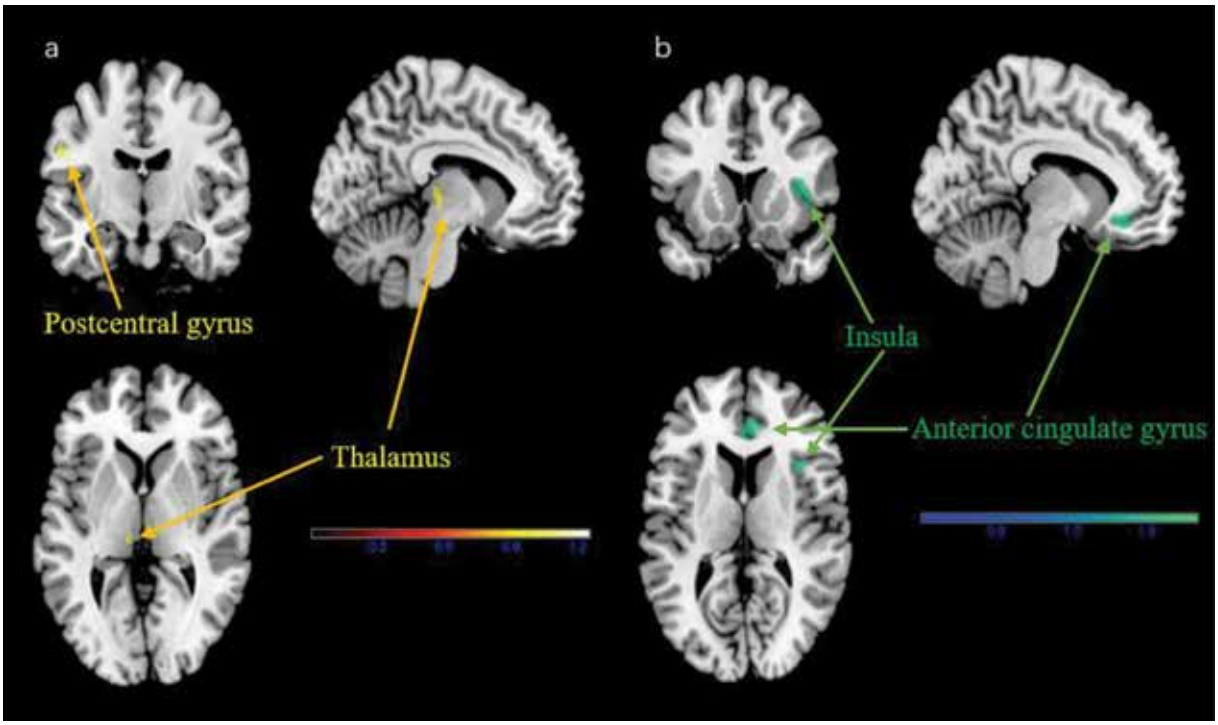


Fig. 2. *Seed-based d mapping (SDM) meta-regression analysis of 33 voxel-based morphometry studies showing significant positive (a) and negative (b) associations between gray matter and pain scores in patients with chronic primary pain.*

Color bar indicates SDM z scores. (a) Coordinates: 83, 115, 75. Maximum SDM z score=1.02. (b) Coordinates: 102, 131, 72. Maximum SDM z score=1.82.

the smaller the gray matter in the right/left anterior cingulate gyrus, left superior frontal gyrus, left inferior frontal gyrus, and right middle frontal gyrus (Table 4 and Fig. 3).

## Discussion

To our knowledge, this is the first meta-analysis of VBM studies on gray matter examining differences between CPP patients and healthy controls to date. We found that compared with the healthy controls, those with CPP exhibited significantly reduced gray matter in the left anterior cingulate gyrus, right median cingulate gyrus, and bilateral insula. Increased gray matter was also observed among the patients with CPP in the right striatum. A subgroup meta-analysis revealed that studies that included only female patients revealed decreased gray matter in the left anterior cingulate gyrus, right median cingulate gyrus, right putamen, and left middle frontal gyrus, and increased gray matter in the right superior parietal gyrus and left precuneus. Regarding the GMV and GMD subgroup meta-analysis, we found that the main results were the same as

Table 4. *Meta-regression results showing an association between the pain symptom duration with chronic primary pain patients and gray matter difference.*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Association |
|---|---|---|---|---|---|---|
| Undefined (BA 48) | Right | 36, -8, -10 | 2.110 | < 0.001 | 858 | Positive |
| Cluster breakdown | | | | | | |
| Putamen (BA 48) | Right | 32, -6, -4 | 2.092 | < 0.001 | 233 | Positive |
| Striatum | Right | | | | 95 | Positive |
| Insula | Right | | | | 94 | Positive |
| Amygdala | Right | | | | 44 | Positive |
| Anterior cingulate gyrus (BA 32) | Right | 4, 46, 24 | 1.969 | < 0.001 | 970 | Negative |
| Cluster breakdown | | | | | | |
| Anterior cingulate gyrus (BA 32) | Right | 4, 46, 24 | 1.969 | < 0.001 | 173 | Negative |
| Superior frontal gyrus, medial (BA 32) | Left | 0, 44,26 | 1.935 | < 0.001 | 204 | Negative |
| Anterior cingulate gyrus (BA 32) | Left | -4, 44, 26 | 1.931 | < 0.001 | 137 | Negative |
| Middle frontal gyrus (BA 46) | Right | 38, 28, 40 | 1.849 | < 0.001 | 206 | Negative |
| Inferior frontal gyrus | Left | -60, 10, 16 | 1.426 | < 0.001 | 27 | Negative |

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

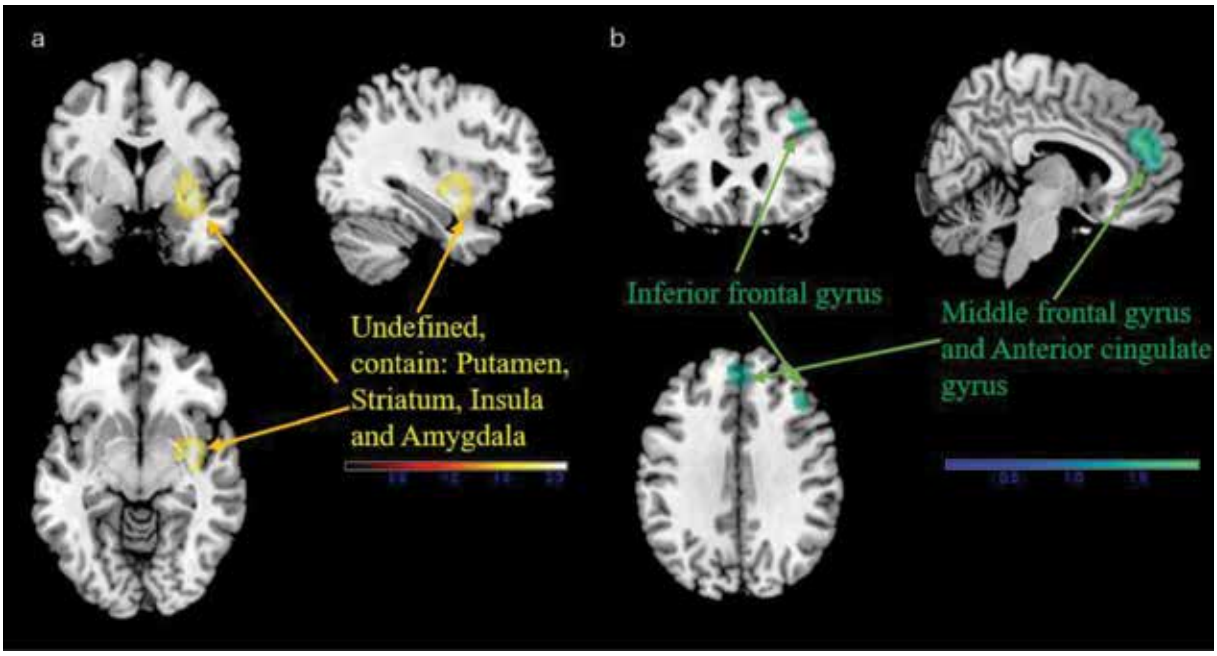


Fig. 3. *Seed-based d mapping (SDM) meta-regression analysis of 39 voxel-based morphometry studies showing significant positive (a) and negative (b) association between gray matter and pain symptom duration in patients with chronic primary pain.*

Color bar indicates SDM z scores. (a) coordinates: 125, 126, 65. Maximum SDM z score = 2.11. (b) coordinates: 97, 152, 106. Maximum SDM z score = 1.97.

those from the analysis of the whole database. Meta-regression analysis also revealed a significant association among symptom duration, pain scores, and some brain regions related to pain processing and emotion regulation.

## Gray Matter Differences in Patients with CPP

### *Cingulate Gyrus and Insula Difference*

The cingulate gyrus is involved in a host of different processes, including connecting sensory input to emotions and emotional responses to pain (42-44). In the cingulate gyrus, the anterior cingulate gyrus and posterior median cingulate gyrus are the most important components of the pain matrix (45). The gray matter reductions in the anterior and median cingulate gyrus observed in patients with CPP support previous functional and behavioral MRI evidence of impairments and atypical cingulate gyrus responses in tasks probing those processes (46,47). Patients with CPP exhibit reduced gray matter in the bilateral insula, which is also part of the pain matrix and can elicit pain when stimulated, and lesions encompassing the insula can alter pain perception (45). Our result fits well with functional MRI studies reporting atypical bilateral insula responses with consistent painful stimulation (48), suggesting that abnormalities within this structure might partly underpin impaired pain perception.

### *Striatum Difference*

Single-photon emission computed tomography (SPECT) studies focusing on fibromyalgia, a kind of CPP, have revealed altered regional blood flow in the striatum (49). This finding may reflect an increase in neuronal activity or a decoupling of neuronal activity from regional cerebral blood flow. Moreover, previous studies have noted somatosensory activation of the striatum in response to pain stimuli (50). Subsequent studies have consistently shown that increased dopamine acting on striatal dopamine D2/D3 receptors contributes to abnormal top-down pain regulation in humans (4,51). Wood et al (52) postulated that a dysfunctional dopamine system may be related to chronic pain. The fact that other disorders associated with the dopamine system, such as anxiety disorder and major depressive disorder, are significantly more common in CPP patients supports this hypothesis (53,54). Our finding of increased gray matter in the striatum was the same as what Schmidt-Wilcke et al (19) found in fibromyalgia patients and supports previous neurophysiological findings of the relevant neuroanatomy. The morphological changes could be explained by the alterations in neural plasticity after the increase in noxious input.

### *GMV and GMD Difference*

When we performed subgroup meta-analyses based on measures of GMV and GMD, which are different indicators of gray matter morphological changes, we found that the main results from the GMV and GMD subgroup meta-analyses were the same as those from the analysis on the whole database. These results reinforced the robustness of our study.

### *Differences from Previous Studies*

Some previous investigations have shown that patients with CPP, in addition to the regions discussed above, exhibited changes in the thalamus (17,21), putamen (17,25), orbitofrontal cortex (12,28), amygdala (22,31), primary somatosensory cortex (14,20), and hippocampus (9,29). However, our results did not reveal similar changes. In addition to differences in sample size and patient gender, these differences may also be caused by the different durations of CPP; its impact on gray matter in relevant brain regions may also be different. Moreover, the characteristics and location of chronic pain in different subcategories are also different, which may be reflected in the difference in cerebral gray matter.

## Gender Differences in Gray Matter

Our subgroup meta-analysis of females indicated that gray matter in the anterior and median cingulate gyrus was decreased, which accounted for most clusters and was in agreement with the main results. In addition, we also observed increased gray matter in the superior parietal gyrus, also known as the primary somatosensory cortex.

### *Primary Somatosensory Cortex*

Studies have shown that the primary somatosensory cortex has functional and structural changes in chronic pain (55,56). However, it should be noted that previous studies that found abnormal changes in the function and structure of the primary somatosensory cortex were studies in which the patients were mostly or all females (17,20,55-57). This can explain the results of our study to some extent: an abnormality in the primary somatosensory cortex was observed only in the subgroup meta-analysis of the female patients and not

in the main meta-analysis where all the patients were included.

### *Putamen and Medial Frontal Cortex*

There is evidence that the putamen plays a role in the sensory aspects of pain (58). Previous studies have shown that many neurons in the putamen are activated differentially or exclusively by nociceptive stimulation, and some of them even encode stimulus intensity (50). Accordingly, activation of the putamen has been observed in previous pain neuroimaging studies (59). Our subgroup meta-analysis found structural changes in the putamen of female patients with CPP, which provides morphological evidence of pain perception and the regulation of the putamen found in functional MRI studies (50,58,59). We also found reduced gray matter in the medial frontal cortex, a brain region responsible for pain processing (60), which might reflect its role in chronic pain. Because the prefrontal cortex is implicated in pain inhibition and facilitation (60), cognitive deficits characteristic of CPP also appear consistent with gray matter atrophy in the frontal cortex (61). Structural changes in this brain region could contribute to the symptom chronification and maintenance of pain in CPP. However, we found a decrease in medial frontal cortex and putamen gray matter only in female patients, and we did not find a similar change in the mixed results involving male patients. Due to hormone secretion and social and cultural factors, experimental and clinical investigations have consistently confirmed gender-specific differences in pain threshold and pain sensitivity (33). Our results may be brain structural expressions of gender differences in pain response, and the brain regions that change only in female patients have potential as biomarkers for female patients.

### *Precuneus*

We also found increased gray matter in the precuneus in the female subgroup, which is involved in affective responses to pain (47). There are great differences in the prevalence and tolerance of chronic pain between men and women (33,62). Many studies have confirmed that women have lower pain thresholds than men and vary from men in their sensitivity to pain. In addition, descending pain control seems less effective in women (63,64). Furthermore, females are more likely to be emotionally affected when coping with chronic pain (64). Therefore, the increase in precuneus gray matter found only in the subgroup meta-analysis of female patients indicated that the emotional responses of women affected by chronic pain are reflected in the precuneus, resulting in structural changes in this brain region. The gender differences in CPP shown in various brain regions need to be further studied and compared in a controlled study of healthy men and women.

## Effects of Symptom Duration and Pain Scores on Gray Matter

### *Effects of Pain severity on Gray Matter*

The severity of pain was negatively associated with the gray matter in the anterior cingulate gyrus and insula. It was mentioned in the previous discussion that these 2 brain regions are deeply involved in pain perception and processing (44,45). Both the anterior cingulate gyrus and insula show individual differences in pain sensitivity, and they may be particularly implicated in heightened pain expectancy and heightened pain anticipation (45). Previous studies also found a negative association between GMV in the insula and anterior cingulate gyrus and pain ratings (14,26). Our study is a further confirmation and supplement to previous studies. Subsequent meta-regression analyses showed that the gray matter in the thalamus and postcentral gyrus was positively associated with pain scores. The thalamus and posterior central gyrus, also known as the primary somatosensory cortex, are brain regions that receive pain signals (8), and damage to the primary somatosensory cortex can be the cause of sensory pain disorders related to chronic pain (65). Moreover, neuropathic pain is related to a decrease in GABA content in the primary somatosensory cortex, which is associated with the functional connectivity of the thalamic cortex (66). GABA has neurotoxic effects and can lead to apoptosis of nerve cells. Therefore, the decrease in GABA in the primary somatosensory cortex of CPP patients may lead to an increase in gray matter volume or density. The positive association between the primary somatosensory cortex and pain severity may be mediated by related pain neurotransmitters. Our exploratory meta-regression results further confirmed the critical role of these brain regions in the occurrence and development of CPP and provided reliable biological targets for the diagnosis and treatment of CPP.

### *Effects of Symptom Duration on Gray Matter*

Pain symptom durations were positively associated with the gray matter in the insula, striatum, putamen, and amygdala. A negative association between pain symptom duration and gray matter was found in the

right anterior cingulate gyrus and frontal gyrus. A large number of previous studies have shown that these brain regions not only play an important role in pain perception and processing (8,43,51), but also present significant structural and functional changes in patients with major depressive disorder (67) and anxiety disorder (68). Most patients with CPP have emotional problems (69), and there is a tendency to attribute unexplained primary pain to mental and psychological problems (2). In many studies on CPP, some of the brain regions mentioned above are found to be related to the duration of pain and to the anxious and depressive symptoms of CPP patients (25,70). Moreover, many studies have shown that antidepressants and psychotherapy have significant effects on CPP (71,72). These findings suggested that with pain chronicity, the brain structure of regions involved in emotion regulation will be affected. More importantly, our results indicated that CPP, which has been attributed more to psychosocial factors, was closely related to mental disorders such as major depressive disorder and anxiety disorder.

### *Inspiration from Previous Studies*

Previous studies have indicated that the brain areas in chronic and acute pain stages are different (73). However, these associations between CPP and certain brain area alterations are never one-dimensional since these changes in the brain can be associated with other factors such as affective comorbidity and medication intake (74,75). Because it has been proven that the brain areas serving the processes of emotion, learning, reward, and memory are the key factors of chronic development, these mechanisms themselves may be the driving force or catalyst of this transformation (76). Moreover, genetic, epigenetic factors (77), physiological, and psychosocial expressions of stress (78) have also been implicated in the development of CPP. Some longitudinal brain imaging studies have found that with the improvement of chronic pain symptoms before and after treatment, the structure of relevant brain regions recovered (79), and the functional indexes of the brain areas also recovered (73). However, these recoveries before and after treatment only occurred in specific brain regions, such as the dorsolateral prefrontal cortex (DLPFC) (79) and emotion-related regions (73). Similar changes have not been found in other brain regions. This may be due to the different plasticity of different brain regions. The high plasticity of some brain regions may recover with the improvement of chronic pain symptoms, while it is difficult to find this change in brain regions with low plasticity. On the other hand, this may be due to the difference in treatment methods. A specific treatment method may only act on a specific brain region so that the corresponding brain region can be restored. It should be noted that there are few studies on brain changes before and after chronic pain treatment, and more attention should be given to this field in future research.

### Limitations

There are some limitations in the study. First, we did not include unpublished studies, but Egger's tests indicated that potential publication bias was unlikely. Second, our results are inherently tied to the limitations of VBM that cannot detect spatially complex and subtle group differences in other brain metrics, such as cortical thickness and surface area. However, our results of decreased gray matter in the cingulate cortex and insula are broadly consistent with some surface-based morphometry studies that examined cortical thickness and surface area (80-82). Third, due to the lack of data from male patients, we were unable to perform a male subgroup analysis; therefore, we cannot thoroughly explore the difference in CPP from the perspective of gender. Fourth, in our meta-analysis, all the studies included depression, anxiety, and other mental diseases as the exclusion criteria. It should be pointed out that many patients with chronic pain have emotional symptoms even if they are not diagnosed with emotional diseases, which may affect the results. However, many studies have evaluated depression and anxiety and analyzed them as covariates in voxelwise-based gray matter analysis to exclude the impact of emotional problems on the main results as much as possible. Finally, pain severity and pain symptom duration in patients with CPP were available in only some studies, weakening the robustness of conclusions drawn from the meta-regression analyses.

## Conclusions

This meta-analysis showed that patients with CPP presented significantly reduced gray matter in the left anterior cingulate cortex, right median cingulate cortex, and bilateral insula, and increased gray matter in the right striatum. These findings help build a more coherent account of structural abnormalities in patients with CPP. Through our meta-analysis of a large sample, it was confirmed that the symptoms of patients with CPP are not only subjective disclosure but also changes in brain-related structures objec-

tively. For a long time, patients with CPP have been criticized by the general population because they cannot find a clear reason for their pain, which makes some CPP patients feel ashamed. Our research results can eliminate the sense of shame of these patients to a certain extent. Subgroup analyses of GMD and GMV further demonstrated the robustness of our main findings, and the subgroup analysis of females provided a possible neurophysiological explanation for the different incidence rates of CPP in different genders. The meta-regression analysis of pain severity provided reliable biological targets for the diagnosis and treatment of CPP and for pain symptom duration. Our results confirmed that the chronicity of pain leads to changes in relevant brain regions, which makes treatment more challenging and may have synergistic effects with affective disorders. There are similar brain structural changes between CPP and mental disorders such as major depressive disorder and anxiety disorder, which may be the pathophysiological mechanism of effective antidepressant and antianxiety therapy for CPP. Additional prospective longitudinal structural MRI studies of CPP with larger sample sizes are needed to confirm the relationships between these variables and gray matter as well as gender differences in brain structure and function in patients with CPP.

## Funding

This study was supported by research grants from the National Key Research and Development Plan (grant number 2017YFC0113907), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2019PT310020), and the Improvement of Clinical Symptoms in Patients with Alzheimer's Disease by Modified Cognitive Stimulation Therapy (2021-YF05-01749-SN).

## Author Contributions

Zuxing Wang, Minlan Yuan, and Bo Zhou had full access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: All authors. Acquisition, analysis, or interpretation of data: Zuxing Wang, Minlan Yuan. Drafting of the manuscript: All authors. Administrative, technical, or material support: All authors. Supervision: All authors.

## Acknowledgment

We thank all the authors from the VBM studies included in this meta-analysis for their advice and for sharing their data. At the same time, we would like to thank Tao Zheng for his help in revising and polishing the manuscript.

Supplemental material available at www.painphysicianjournal.com

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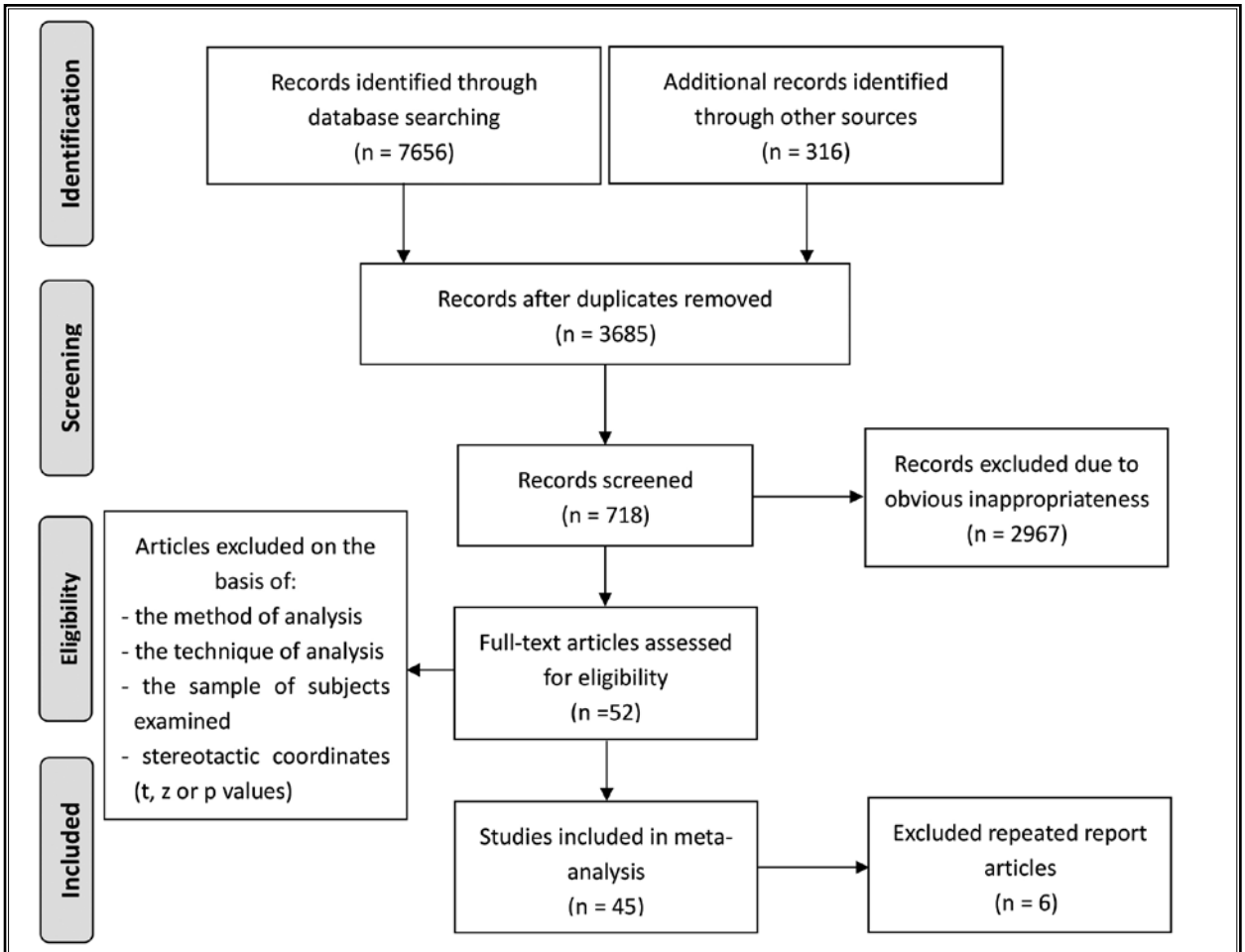


Table S1. *Adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing study inclusion.*

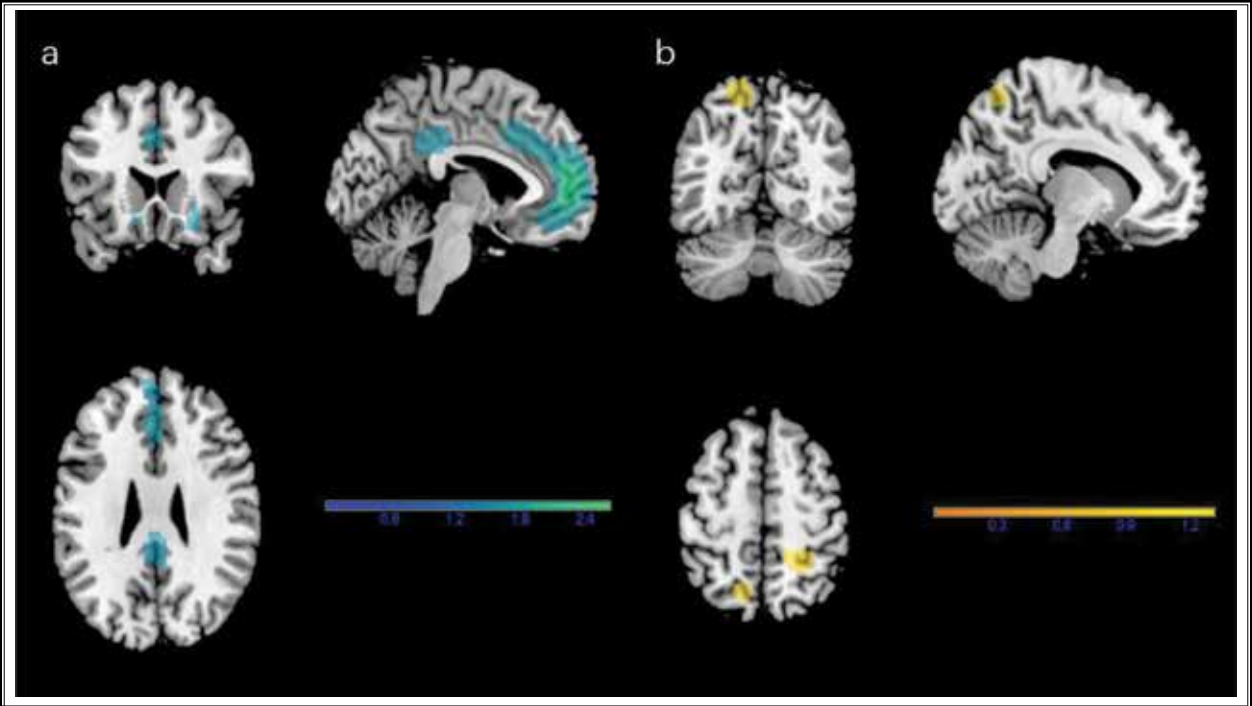


Fig. S2. *Seed-Based d Mapping (SDM) Meta-Analysis of 19 Voxel-Based Morphometry Studies Showing Significant Decreased (a) and Increased (b) Gray Matter in the Female Patients with Chronic Primary Pain Compared With Control Patients*

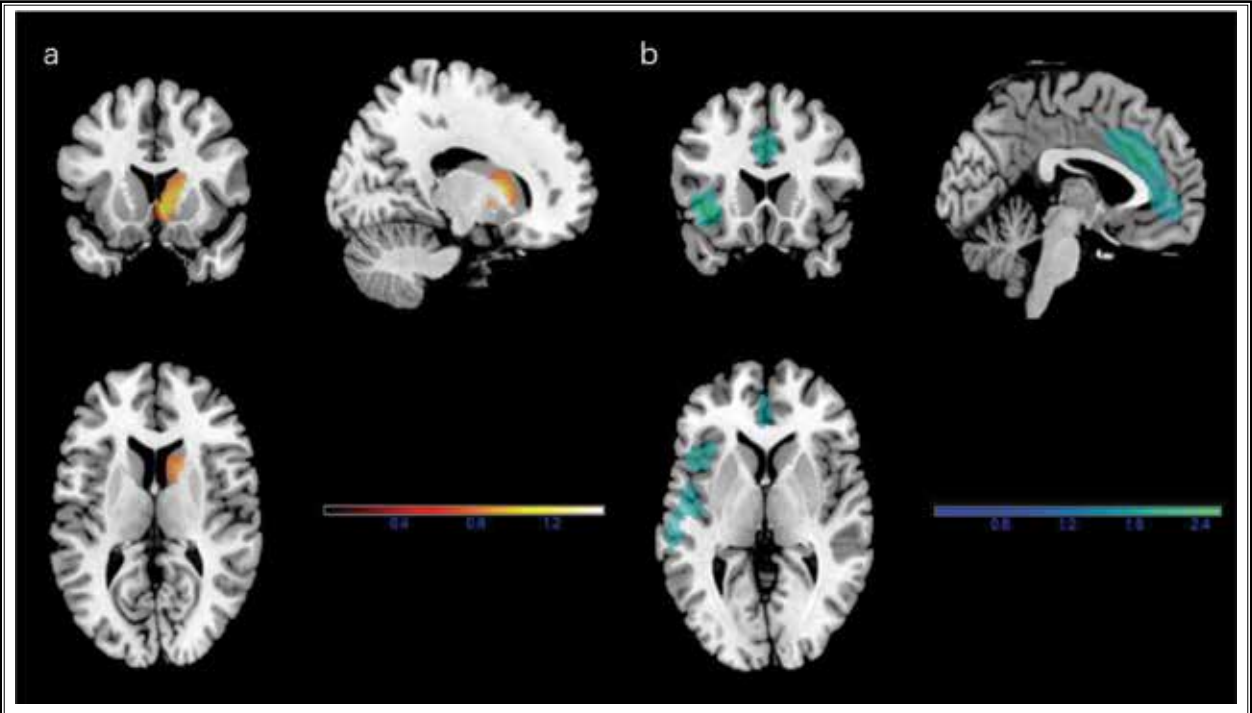


Fig. S3. *Seed-Based d Mapping (SDM) Meta-Analysis of 19 Voxel-Based Morphometry Studies Showing Significant Increased (a) and Decreased (b) Gray Matter Volume in the Patients with Chronic Primary Pain Compared with Control Patients*

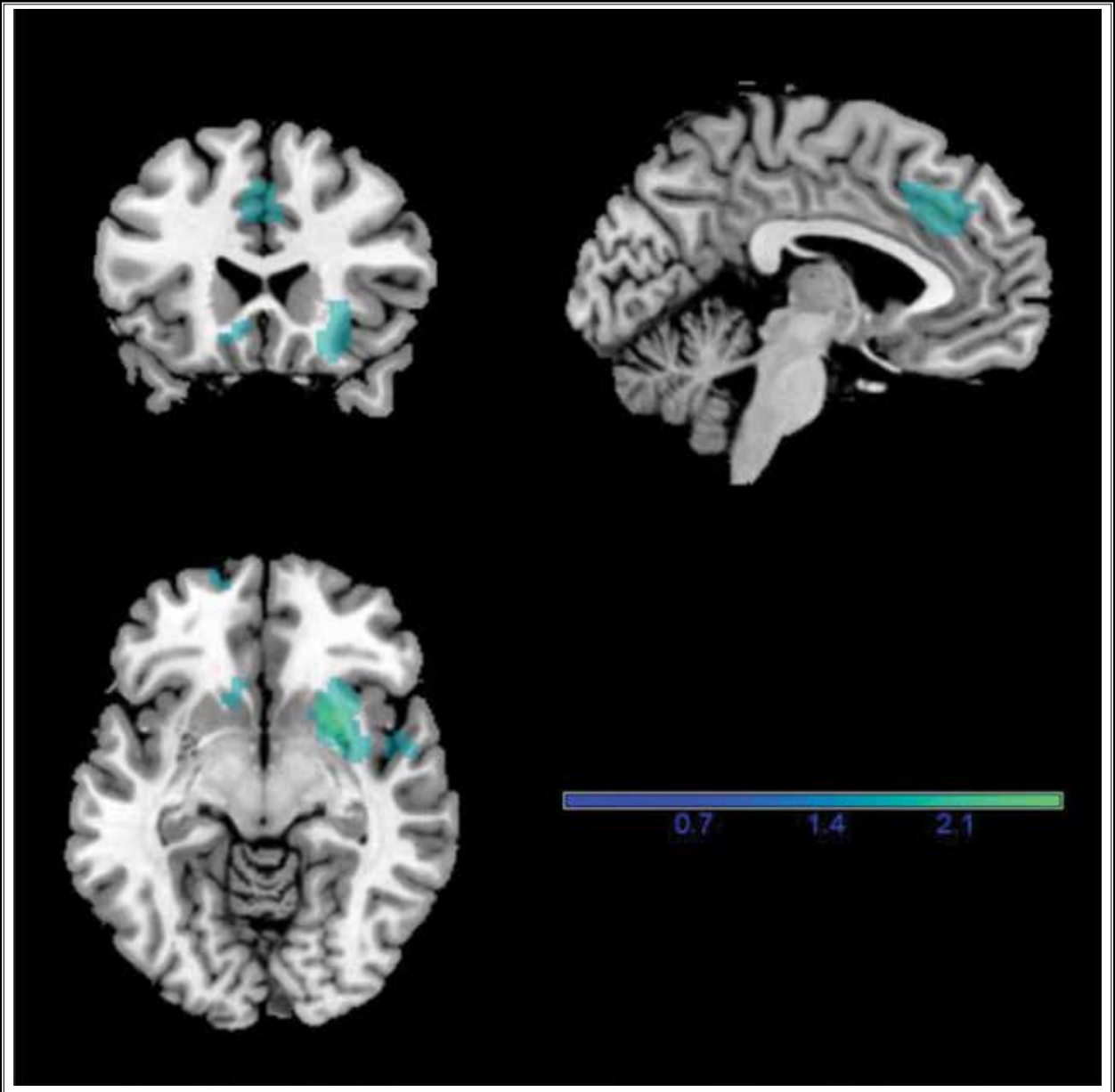


Fig. S4. ***Seed-Based d Mapping (SDM) Meta-Analysis of 19 Voxel-Based Morphometry Studies Showing Significant Decreased Gray Matter Density in the Patients with Chronic Primary Pain Compared with Control Patients***

***Methods. search terms strategy***

Potential studies were identified in PubMed, Cochrane library database and Google Scholar. All available peer-reviewed records were searched using the following terms: "chronic widespread pain," "fibromyalgia," "complex regional pain syndrome," "chronic headache," "chronic migraine," "migraine," "chronic tension-type headache," "tension-type headache," "TTH," "trigeminal autonomic cephalalgias," "TACs," "trigeminal neuralgia," "chronic temporomandibular disorder pain," "temporomandibular joint disorder," "chronic burning mouth syndrome," "burning mouth syndrome," "chronic primary orofacial pain," "orofacial pain," "visceral pain," "chest pain," "epigastric pain syndrome," "EPS," "chronic primary abdominal pain syndrome," "functional dyspepsia," "functional gastrointestinal disorder(s)," "FGIDs," "postprandial distress syndrome," "PDS," "irritable bowel syndrome," "IBS," "chronic primary bladder pain syndrome," "interstitial cystitis," "pelvic pain syndrome," "pelvic pain," "musculoskeletal pain," "cervical pain," "thoracic pain," "low back pain," "back pain," "limb pain" OR "pain disorder(s)" AND "magnetic resonance imaging," "MRI" "neuroimaging," "voxel-based morphometry," "VBM," "morphometry," "concentration" OR "gray matter."

Table S1. *Overview of the Chronic Primary Pain VBM Studies Included in the Meta-Analysis*

| Study | Case Sample /female | Control Sample /female | Mean age ± SD Case | Mean age ± SD Control | Symptom duration (years) | Pain score (VAS/NRS) | MR Scanner | Software | FWHM (mm) | Statistics | Gray matter change | Tal or MNI | Diagnose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kuchinad et al.,(1) 2007 | 10/10 | 10/10 | 52 | 45 | 9.1±6.8 | NA | Siemens 1.5T | NA | 10 | $p<0.05$ corrected | Decrease (density) | Tal | fibromyalgia |
| Schmidt-Wilcke et al.,(2) 2007 | 20/19 | 22/20 | 53.6±7.7 | 50.7±7.3 | 14.4±7.2 | NA | Siemens 1.5T | SPM2 | 10 | $p<0.05$ corrected | Decrease/ Increase (volume) | Tal | fibromyalgia |
| Wood et al.,(3) 2009 | 30/30 | 20/20 | 42.0±8.4 | 40.1±20.0 | Na | 6.6±1.6 (VAS) | GE 1.5T | SPM2 | 12 | $p<0.05$ corrected | Decrease (density) | Tal | fibromyalgia |
| Hsu et al.,(4) 2009 | 29/29 | 29/29 | 42.6±3.7 | 42.2±3.8 | 12.8±8.3 | NA | GE 1.5T | SPM5 | 10 | $p<0.05$ corrected | NA (volume) | MNI | fibromyalgia |
| Fallon et al.,(5) 2013 | 16/16 | 15/15 | 35.5±8.5 | 39.4±8.7 | 9.1±6.8 | NA | Siemens 3T | SPM8 | 12 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | fibromyalgia |
| Ceko et al.,(6) 2013[a] | 14/13 | 14/13 | 55.0±2.9 | 55.4±3.7 | 12.1±9.0 | 2.4±2.3 (VAS) | Siemens 3T | SPM5 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | fibromyalgia |
| Ceko et al.,(6) 2013[a] | 15/14 | 15/14 | 42.4±5.9 | 43.1±5.3 | 8.8±7.1 | 2.8 ±3.0 (VAS) | Siemens 3T | SPM5 | 8 | $p<0.05$ corrected | Increase (volume) | MNI | fibromyalgia |
| Diaz-Piedra et al.,(7) 2015 | 23/23 | 23/23 | 41.6±4.4 | 39.7±5.4 | 8.6±6.3 | NA | Phillips 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | fibromyalgia |
| Burgmer et al.,(8) 2009 | 14/14 | 14/14 | 51.0±7.3 | 46.9±6.8 | 10±6.0 | NA | Phillips 3T | SPM5 | NA | $p\leq0.001$ uncorrected | Decrease (volume) | MNI | fibromyalgia |
| Velzen et al.,(9) 2016 | 19/19 | 19/19 | 48.1±11.6 | 49.4±14.3 | 8.4±8.3 | 7.1±1.5 (NRS) | Phillips 3T | FSL5 | 6 | $p<0.05$ corrected | NA (volume) | MNI | CRPS |
| Pleger et al.,(10) 2014 | 20/11 | 20/11 | 41.8±9.8 | 41.6±9.6 | 1.0±1.2 | 4.4±1.0 (NRS) | Siemens 1.5T | SPM8 | 7 | $p<0.05$ corrected | Increase (density) | MNI | CRPS |
| Geha et al.,(11) 2008 | 22/19 | 22/19 | 40.7±2.3 | 40.5±2.3 | 3.1±3.5 | 5.8±2.5 (VAS) | Siemens 3T | FSL4 | 9.2 | $p<0.05$ corrected | Decrease (density) | MNI | CRPS |
| Shokouhi Et al.,(12) 2018[b] | 12/10 | 16/10 | 51.1±12.7 | 44.4±11.6 | 0.5±0.2 | 6.0±2.2 (VAS) | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | CRPS |
| Shokouhi Et al.,(12) 2018[b] | 16/11 | 16/10 | 43.3±9.3 | 44.4±11.6 | 7.1±4.2 | 4.4±2.1 (VAS) | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | NA (volume) | MNI | CRPS |
| Barad et al.,(13) 2014 | 15/15 | 15/15 | 44.0±12.5 | 44.1±12.0 | 3.7±4.5 | 7.3±Na (VAS) | GE 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | CRPS |
| Baliki et al.,(14) 2011[c] | 28/24 | 46/26 | 40.6±7.4 | 38.8±12.5 | 5.7±2.2 | 5.7±2.2 (VAS) | Siemens 3T | FSL4 | 8 | $p<0.05$ corrected | Decrease (density) | MNI | CRPS |
| Coppola et al.,(15) 2017 | 20/14 | 20/13 | 31.3±10.2 | 28.5±4.1 | 15.0±13.1 | 7.6±1.6 (VAS) | Siemens 3T | SPM12 | 8 | $p<0.001$ uncorrected | Decrease (volume) | MNI | CM |

Table S1 (cont.). *Overview of the Chronic Primary Pain VBM Studies Included in the Meta-Analysis*

| Study | Case Sample /female | Control Sample /female | Mean age ± SD Case | Mean age ± SD Control | Symptom duration (years) | Pain score (VAS/NRS) | MR Scanner | Software | FWHM (mm) | Statistics | Gray matter change | Tal or MNI | Diagnose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lai et al.,(16) 2016 | 33/27 | 33/27 | 39.7±10.7 | 39.7±11.1 | 16.1±10.6 | 6.6±2.1 (NRS) | GE 1.5T | SPM8 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | CM |
| Neeb et al.,(17) 2017 | 21/15 | 21/15 | 49.4±7.46 | 49.4±7.8 | 24.4±8.3 | 7.1±1.6 (NA) | Siemens 3T | SPM8 | 10 | $p<0.05$ corrected | Increase (volume) | MNI | CM |
| Yu et al.,(18) 2020 | 17/8 | 35/20 | 49.6±14.6 | 34.9±10.9 | NA | 7.2±1.9 (VAS) | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | CM |
| Rocca et al.,(19) 2006 | 16/15 | 15/13 | 42.7 | 38.6 | 24.8 | NA | Phillips 3T | SPM2 | 8 | $p<0.05$ corrected | Decrease (density) | Tal | CM |
| Schmidt-Wilcke et al.,(20) 2005 | 20/10 | 40 | 33.9±16.2 | NA | 8.5±7.6 | NA | Siemens 1.5T | SPM99 | 12 | $p<0.05$ corrected | Decrease (volume) | Tal | CTTH |
| Li et al.,(21) 2017 | 28/13 | 28/13 | 45.9±11.2 | 44.9±7.7 | 8.4±3.7 | 8.7±1.2 (Na) | Phillips 1.5T | SPM8 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | TACs |
| Gustin et al.,(22) 2011d | 21/17 | 30/24 | 55.0±2.1 | 53.6±3.2 | 8.5±2.1 | 3.5±0.4 (VAS) | Phillips 1.5T | SPM5 | 6 | $p<0.01$ corrected | Decrease/ Increase (volume) | MNI | TACs |
| Wang et al.,(23) 2019 | 40/23 | 40/23 | 55.8±8.2 | 55.8±8.1 | 7.1±5.3 | 5.8±1.7 (VAS) | GE 3T | SPM12 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | TACs |
| DeSouza et al.,(24) 2013 | 24/15 | 24/15 | 48.5±12.7 | 47.6±12.3 | 6.3±3.0 | NA | GE 3T | FSL4 | 4.6 | $p<0.05$ corrected | Increase (volume) | Tal | TACs |
| Gustin et al.,(22) 2011d | 20/16 | 31/25 | 45.7±2.9 | 46.8±3.3 | 11.5±3.4 | 3.7±0.5 (VAS) | Phillips 1.5T | SPM5 | 6 | $p<0.01$ corrected | NA (volume) | MNI | TMD |
| Wilcox et al.,(25) 2015 | 22/18 | 40/33 | 46.5±2.6 | 48.3±2.1 | 10.4±10.9 | 3.7±2.1 (VAS) | Phillips 3T | SPM8 | 3 | $p<0.05$ corrected | Decrease (volume) | MNI | TMD |
| Younger et al.,(26) 2010 | 14/14 | 15/15 | 38.9±14.1 | NA | 4.4±2.9 | 4.3±2.2 (NRS) | GE 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | TMD |
| Gerstner et al.,(27) 2011 | 9/9 | 9/9 | 25.4±2.5 | 24.8±1.4 | 2.5±2.1 | 2.2±1.4 (VAS) | GE 3T | SPM5 | 8 | $p<0.001$ uncorrected | Decrease (volume) | MNI | TMD |
| Moayedi et al.,(28) 2011 | 17/17 | 17/17 | 33.1±11.9 | 32.2±10.1 | 9.8±8.2 | 4.3±1.8 (Na) | GE 3T | SPM5 | 10 | $p<0.05$ corrected | NA (volume) | Tal | TMD |
| Khan et al.,(29) 2014 | 9/9 | 9/9 | 54.0±7.7 | 56.0±8.2 | 4.0±4.8 | 3.3±3.4 (NRS) | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | BMS |
| Tan et al.,(30) 2019 | 26/21 | 27/25 | 52.1±8.8 | 51.1±5.4 | 0.7±0.8 | 4.2±1.6 (VAS) | GE 3T | FSL | 3 | $p<0.05$ corrected | Decrease (volume) | MNI | BMS |
| Lee et al.,(31) 2019 | 12 | 14 | NA | NA | 0.9 | NA | Phillips 3T | SPM12 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | BMS |

Table S1 (cont.). *Overview of the Chronic Primary Pain VBM Studies Included in the Meta-Analysis*

| Study | Case Sample /female | Control Sample /female | Mean age ± SD Case | Mean age ± SD Control | Symptom duration (years) | Pain score (VAS/NRS) | MR Scanner | Software | FWHM (mm) | Statistics | Gray matter change | Tal or MNI | Diagnose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schmidt-Wilcke et al.,(32) 2010 | 11/9 | 11/9 | 55.2±8.9 | 51.3±8.6 | NA | 4.3±2.2 (NRS) | Siemens 1.5T | SPM5 | 8 | $p<0.001$ uncorrected | Decrease (volume) | Tal | Orofacial pain |
| Kairys et al.,(33) 2015 | 33/33 | 33/33 | 39.5±12.0 | 39.0±11.6 | 9.1±9.0 | NA | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | Increase (volume) | MNI | IC |
| As-Sanie et al.,(34) 2012 | 6/6 | 12/12 | 24.2±1.9 | 24.8±1.2 | NA | NA | GE 3T | SPM5 | 8 | $p<0.05$ corrected | Decrease (volume) | MNI | CPPP |
| Mordasini et al.,(35) 2012 | 20/20 | 20/20 | 40.0±14.0 | 43.0±19.0 | NA | NA | Siemens 3T | SPM5 | 10 | $p<0.001$ uncorrected | Decrease (volume) | Tal | CPPP |
| Farmer et al.,(36) 2011 | 16/16 | 16/16 | 36.9±11.5 | 36.2±11.2 | NA | 4.6±1.7 (VAS) | Siemens 3T | FSL4 | 9.2 | $p<0.05$ corrected | NA (volume) | MNI | CPPP |
| Schweinhardt et al.,(37) 2008 | 14/14 | 14/14 | 25.7±5.1 | 25.6±6.0 | 5.0±2.9 | 6.4±1.5 (NA) | Siemens 1.5T | NA | 10 | $p<0.05$ corrected | Increase (density) | MNI | CPPP |
| Nan et al.,(38) 2015 | 34/19 | 33/24 | 22.4±1.7 | 22.0±0.9 | 3.2±2.3 | NA | Siemens 3T | FSL | 6 | $p<0.05$ corrected | Decrease (density) | Tal | EPS |
| Seminowicz et al.,(39) 2010 | 55/55 | 48/48 | 32.2±12.3 | 31.1±12.3 | 11.1±7.7 | NA | Siemens 3T | NA | 8 | $p<0.05$ corrected | Decrease/ Increase (density) | MNI | IBS |
| Valet et al.,(40) 2009 | 14/14 | 25/25 | 51.1±11.1 | 51.7±7.2 | 9.8±7.2 | 8.8±0.9 (NRS) | Siemens 1.5T | SPM2 | 8 | $p<0.05$ corrected | Decrease (density) | MNI | Pain disorder |
| Li et al.,(41) 2018 | 16/4 | 16/0 | 41.6±13.6 | 31.3±11 | 10.2±9.8 | 5.2±2.4 (VAS) | GE 3T | SPM12 | 8 | $p<0.001$ uncorrected | Decrease/ Increase (volume) | MNI | CBP |
| Dolman et al.,(42) 2014 | 14/9 | 14/9 | 46.9±14.6 | 45.9±12.9 | 8.2±2.1 | 5.2±1.8 (NA) | Siemens 3T | SPM8 | 8 | $p<0.05$ corrected | NA (volume) | MNI | CBP |
| Baliki et al.,(14) 2011[c] | 36/13 | 46/26 | 48.2±11.4 | 38.8±12.5 | 12.3±11.5 | 5.2±2.7 (VAS) | Siemens 3T | FSL4 | 8 | $p<0.05$ corrected | Decrease (density) | MNI | CBP |
| Schmidt-Wilcke et al.,(43) 2006 | 18/9 | 18/9 | 50.4±6.8 | 49.9±8.7 | 14.7±7.3 | 6.3±2.4 (NRS) | Siemens 1.5T | SPM99 | 10 | $p<0.001$ uncorrected | Decrease/ Increase (volume) | Tal | CBP |
| Mao et al.,(44) 2013 | 30/20 | 30/20 | 51.6±8.6 | 50.2±5.8 | 7.8±7.2 | 5.2±2.6 (VAS) | GE 3T | FMRIB | 3 | $p<0.05$ corrected | Decrease/ Increase (volume) | MNI | CLBP |
| Ung et al.,(45) 2014 | 47/22 | 47/22 | 37.3±12.2 | 37.7±7.8 | 8.6±7.8 | NA | GE 3T | SPM8 | 8 | $p<0.05$ corrected | NA (density) | MNI | CLBP |

[a] Patients were divided into two groups according to the age of onset; [b] Patients were divided into two groups according to the duration of disease; [c, d] According to the different diagnoses, patients were two divided into two groups.

Abbreviations: VAS, visual analogue scale; NRS, numeric rating scale; CRPS, complex regional Pain syndrome; CM, chronic migraine; CTTH, chronic tesion-type headache; TACs, trigeminal autonomic cephalalgias; TMD, temporomandibular disorder; BMS, burning mouth syndrome; IC, interstitial cystitis; CPPP, chronic primary pelvic pain; EPS, epigastric pain xyndrome; IBS, irritable bowel syndrome; CBP, chronic back pain; CLBP, chronic Low back pain; MNI, Montreal Neurological Institute; Tal, Talairach.

Table S2. *Results of the Jack-knife Reliability Analyses of the Main Meta-Analysis Findings*

| **Clusters**[a] **Studies** | **Right Rtriatum (8, 8, -2)** | **Left Anterior cingulate/ paracingulate gyrus (0, 26, 30)** | **Left Insula (-36, 16, -6)** | **Right Heschl gyrus (52, -10, 8)** | **Right Insula (30, 20, -12)** | **Right Median cingulate / paracingulate gyrus (4, -30, 44)** |
|---|---|---|---|---|---|---|
| Baliki et al.,(14) 2011[b] | Yes | Yes | Yes | Yes | Yes | Yes |
| Baliki et al.,(14) 2011[c] | Yes | Yes | Yes | No | Yes | Yes |
| Barad et al.,(13) 2014 | No | Yes | Yes | Yes | Yes | Yes |
| Burgmer et al.,(8) 2009 | Yes | Yes | Yes | Yes | Yes | Yes |
| Ceko et al.,(6) 2013[d] | Yes | Yes | Yes | Yes | Yes | No |
| Ceko et al.,(6) 2013[e] | Yes | Yes | Yes | Yes | Yes | Yes |
| Coppola et al.,(15) 2017 | Yes | Yes | Yes | Yes | Yes | Yes |
| DeSouza et al.,(24) 2013 | No | Yes | Yes | Yes | Yes | Yes |
| Diaz-Piedra et al.,(7) 2015 | Yes | Yes | Yes | Yes | Yes | Yes |
| Dolman et al.,(42) 2014 | Yes | Yes | Yes | Yes | Yes | Yes |
| Fallon et al.,(5) 2013 | Yes | Yes | Yes | Yes | Yes | Yes |
| Farmer et al.,(36) 2011 | Yes | Yes | Yes | Yes | Yes | Yes |
| Geha et al.,(11) 2008 | Yes | Yes | Yes | Yes | Yes | Yes |
| Gerstner et al.,(27) 2011 | Yes | Yes | Yes | Yes | Yes | Yes |
| Gustin et al.,(22) 2011[f] | Yes | Yes | Yes | Yes | Yes | Yes |
| Gustin et al.,(22) 2011[g] | Yes | Yes | Yes | Yes | Yes | Yes |
| Hsu et al.,(4) 2009 | Yes | Yes | Yes | Yes | Yes | Yes |
| Kairys et al.,(33) 2015 | Yes | Yes | Yes | Yes | Yes | Yes |
| Khan et al.,(29) 2014 | Yes | Yes | Yes | Yes | Yes | Yes |
| Kuchinad et al.,(1) 2007 | Yes | Yes | Yes | Yes | Yes | Yes |
| Lai et al.,(16) 2016 | Yes | Yes | Yes | Yes | Yes | Yes |
| Lee et al.,(31) 2019 | Yes | Yes | Yes | Yes | Yes | Yes |
| Li et al.,(21) 2017 | Yes | Yes | Yes | Yes | Yes | Yes |
| Li et al.,(41) 2018 | Yes | Yes | Yes | Yes | Yes | Yes |
| Mao et al.,(44) 2013 | Yes | Yes | Yes | Yes | Yes | Yes |
| Moayedi et al.,(28) 2011 | Yes | Yes | Yes | Yes | Yes | Yes |
| Mordasini et al.,(35) 2012 | Yes | Yes | Yes | Yes | Yes | Yes |
| Nan et al.,(38) 2015 | Yes | Yes | Yes | Yes | Yes | Yes |
| Neeb et al.,(17) 2017 | Yes | Yes | Yes | Yes | Yes | Yes |
| Pleger et al.,(10) 2014 | Yes | Yes | Yes | Yes | Yes | Yes |
| Rocca et al.,(19) 2006 | Yes | Yes | Yes | Yes | Yes | Yes |
| As-Sanie et al.,(34) 2012 | Yes | Yes | Yes | Yes | Yes | Yes |
| Schmidt-Wilcke et al.,(20) 2005 | Yes | Yes | Yes | Yes | Yes | No |
| Schmidt-Wilcke et al.,(43) 2006 | Yes | Yes | Yes | Yes | Yes | Yes |
| Schmidt-Wilcke et al.,(2) 2007 | Yes | Yes | Yes | Yes | Yes | Yes |
| Schmidt-Wilcke et al.,(32) 2010 | Yes | Yes | Yes | Yes | Yes | Yes |
| Schweinhardt et al.,(37) 2008 | Yes | Yes | Yes | Yes | Yes | Yes |
| Seminowicz et al.,(39) 2010 | Yes | Yes | Yes | Yes | Yes | Yes |
| Shokouhi et al.,(12) 2018h | Yes | Yes | Yes | Yes | Yes | Yes |
| Shokouhi et al.,(12) 2018i | Yes | Yes | Yes | Yes | Yes | Yes |

Table S2 (cont.). *Results of the Jack-knife Reliability Analyses of the Main Meta-Analysis Findings*

| Clusters[a]<br><br>Studies | Right Rtriatum (8, 8, -2) | Left Anterior cingulate/ paracingulate gyrus (0, 26, 30) | Left Insula (-36, 16, -6) | Right Heschl gyrus (52, -10, 8) | Right Insula (30, 20, -12) | Right Median cingulate / paracingulate gyrus (4, -30, 44) |
|---|---|---|---|---|---|---|
| Tan et al.,(30) 2019 | Yes | Yes | Yes | Yes | Yes | Yes |
| Ung et al.,(45) 2014 | Yes | Yes | Yes | Yes | Yes | Yes |
| Valet et al.,(40) 2009 | Yes | Yes | Yes | Yes | Yes | Yes |
| Velzen et al.,(9) 2016 | Yes | Yes | Yes | Yes | Yes | Yes |
| Wang et al.,(23) 2019 | Yes | Yes | Yes | Yes | Yes | Yes |
| Wilcox et al.,(25) 2015 | Yes | Yes | Yes | Yes | Yes | Yes |
| Wood et al.,(3) 2009 | Yes | Yes | Yes | Yes | Yes | No |
| Younger et al.,(26) 2010 | Yes | Yes | Yes | Yes | Yes | Yes |
| Yu et al.,(18) 2020 | Yes | Yes | Yes | Yes | Yes | Yes |

[a] $P < 0.005$, requiring a peak Z > 1 and a cluster extent of 10 voxels.
[b] Chronic primary back pain.
[c] Complex regional pain syndrome.
[d] Older Fibromyalgia patients.
[e] Younger Fibromyalgia patients.
[f] Trigeminal autonomic cephalalgias
[g] Chronic temporomandibular disorder pains
[h] Complex regional pain syndrome patients in early stage
[i] Complex regional pain syndrome patients in late stage

Table S3. *Meta-Analysis Results Comparing Gray Matter Volume or Density for Female Patients with Chronic Primary Pain and Health Controls*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Gray matter change |
|---|---|---|---|---|---|---|
| Superior parietal gyrus (BA 2) | Right | 20, -48, 64 | 1.257 | < 0.001 | 92 | Increase |
| Precuneus (BA 7) | Left | -14, -64, 60 | 1.239 | < 0.001 | 243 | Increase |
| Anterior cingulate gyrus (BA 32) | Left | -4, 50, -10 | 2.622 | < 0.001 | 2966 | Decrease |
| Median cingulate gyrus (BA 23) | Right | 2, -34, 36 | 1.811 | < 0.001 | 715 | Decrease |
| Putamen (BA 48) | Right | 24, 12, -8 | 1.817 | < 0.001 | 80 | Decrease |
| Middle frontal gyrus (BA 45) | Left | -44, 44, 16 | 1.683 | 0.001 | 85 | Decrease |

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

Table S4. *Meta-Analysis Results Comparing Gray Matter Volume for Patients with Chronic Primary Pain and Health Controls*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Gray matter volume change |
|---|---|---|---|---|---|---|
| Striatum | Right | 8, 8, -4 | 1.472 | < 0.001 | 880 | Increase |
| Insula (BA 47) | Left | -38, 18, -6 | 2.571 | < 0.001 | 1992 | Decrease |
| Anterior cingulate gyrus (BA 24) | Left | 0, 26, 30 | 2.176 | < 0.001 | 1460 | Decrease |
| Inferior temporal gyrus (BA 20) | Right | 50, -26, -24 | 2.267 | < 0.001 | 466 | Decrease |
| Precentral gyrus (BA 6) | Right | 40, -16, 52 | 1.604 | 0.003 | 50 | Decrease |
| Superior occipital gyrus | Left | -16, -66, 28 | 1.629 | 0.003 | 14 | Decrease |

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

Table S5. *Meta-Analysis Results Comparing Gray Matter Density for Patients with Chronic Primary Pain and Health Controls*

| Anatomical location | Hemisphere | MNI coordinates (x, y, z) | SDM z value | *P* value | No. of voxels | Gray matter density change |
|---|---|---|---|---|---|---|
| Lenticular nucleus, putamen (BA 48) | Right | 28, 8, -4 | 2.646 | < 0.001 | 2774 | Decrease |
| Cluster breakdown | | | | | | |
| Insula | Right | | | | 618 | Decrease |
| Rolandic operculum | Right | | | | 390 | Decrease |
| Lenticular nucleus, putamen | Right | 28, 8, -4 | 2.646 | < 0.001 | 315 | Decrease |
| Superior frontal gyrus, medial (BA 32) | Left | -4, 28, 36 | 1.906 | < 0.001 | 472 | Decrease |
| Cluster breakdown | | | | | | |
| Superior frontal gyrus, medial (BA 32) | Left | -4, 28, 36 | 1.906 | < 0.001 | 148 | Decrease |
| Anterior cingulate gyrus (BA 32) | Left | | | | 51 | Decrease |
| Median cingulate gyrus (BA 23) | Left/Right | | | | 130 | Decrease |
| Gyrus rectus (BA 11) | Left | -14, 20, -12 | 1.777 | 0.002 | 73 | Decrease |
| Superior frontal gyrus, orbital part (BA 11) | Left | -16, 60, -10 | 1.950 | < 0.001 | 62 | Decrease |

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, signed differential mapping.

## Supplemental References


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