Critical Review

Structural Brain Anomalies and Chronic Pain: A Quantitative Meta-Analysis of Gray Matter Volume


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Abstract: The diversity of chronic pain syndromes and the methods employed to study them make integrating experimental findings challenging. This study performed coordinate-based meta-analyses using voxel-based morphometry imaging results to examine gray matter volume (GMV) differences between chronic pain patients and healthy controls. There were 12 clusters where GMV was decreased in patients compared with controls, including many regions thought to be part of the “pain matrix” of regions involved in pain perception, but also including many other regions that are not commonly regarded as pain-processing areas. The right hippocampus and parahippocampal gyrus were the only regions noted to have increased GMV in patients. Functional characterizations were implemented using the BrainMap database to determine which behavioral domains were significantly represented in these regions. The most common behavioral domains associated with these regions were cognitive, affective, and perceptual domains. Because many of these regions are not classically connected with pain and because there was such significance in functionality outside of perception, it is proposed that many of these regions are related to the constellation of comorbidities of chronic pain, such as fatigue and cognitive and emotional impairments. Further research into the mechanisms of GMV changes could provide a perspective on these findings.

Perspective: Quantitative meta-analyses revealed structural differences between brains of individuals with chronic pain and healthy controls. These differences may be related to comorbidities of chronic pain.

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Key words: Chronic pain, voxel-based morphometry, meta-analysis, gray matter volume.

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Understanding the neurobiologic basis of chronic pain is important because it affects 100 million Americans and annually costs more than $500 billion.\textsuperscript{18,95} Chronic pain syndromes represent debilitating conditions that negatively impact quality of life and productivity. The International Association for the Study of Pain (IASP) defines chronic pain as "pain without apparently biological value that has persisted beyond the normal tissue healing time."\textsuperscript{14} It is also associated with increased fatigue and changes in cognitive ability and emotional states.\textsuperscript{18,40,103} Although the most commonly reported finding is regional GMV decrease associated with persistent pain,\textsuperscript{59} increased regional GMV is also found.\textsuperscript{37,38,81,85,96,104,107} Disparate findings across studies make integrative conclusions on the basis of qualitative assessments difficult. Discrepancies between studies likely reflect differences in samples where pain etiology could be a substantial factor. However, the experience of chronic pain could have implications for brain morphology, irrespective of etiology. Only meta-analysis methods are likely to identify trends among heterogeneous chronic pain populations.

Because pain processing is facilitated by complex neural networks involving perception, cognition, and emotion, understanding chronic pain's neurobiology is challenging. Voxel-based morphometry (VBM) has revealed differences in gray matter volume (GMV) of specific brain regions in chronic pain patients compared with healthy controls,\textsuperscript{59,80,81} commonly found in the anterior cingulate cortex (ACC), thalamus, basal ganglia, and insula.\textsuperscript{58,59} Although the above refers to structural investigations of chronic pain versus healthy subjects, there are also functional imaging studies of experimentally induced pain. The relationship between brain function and structural changes is not well elucidated. However, structural and functional changes being somehow related makes sense.\textsuperscript{10,45,46,77} The functional pain network includes somatosensory cortices, ACC, thalamus, insula, basal ganglia, hippocampus, and temporal and parietal cortices.\textsuperscript{16,59,86,93} Given the diverse pain literature, unanimous pain network definitions are difficult. Hence, integration of experimental findings\textsuperscript{26} and comparisons between studies is imminent.

Coordinate-based meta-analysis\textsuperscript{21,48,49} is commonly used for aggregating imaging results across studies. Statistical pooling with activation likelihood estimation (ALE) integrates existing data while avoiding some limitations of single studies, allowing dominant trends to emerge. Here, we performed meta-analyses of VBM imaging results\textsuperscript{26,31,62,63} to investigate GMV differences between brains of healthy controls and patients with chronic pain. We included 23 studies\textsuperscript{4,12,28,29,37,38,47,74,75,78,81,85,87,88,96,99-101,107} with different attributes to identify changes associated with chronic pain that commonly occur, irrespective of etiology, age, sex, etc. We hypothesized that GMV differences in individuals with chronic pain would manifest in regions that are typically associated with pain, such as the ACC, somatosensory cortices, insula, and thalamus. We utilized functional characterization (FC), where we seeded significant clusters as regions of interest and determined the functions that were significantly associated with them in the BrainMap database.\textsuperscript{22} We hypothesized that we would identify the strongest function–location correspondences between regions with altered GMV and perceptual processes. We also hypothesized that we would observe correspondences associated with affective and cognitive processing.

Methods

VBM Literature Search

We conducted a comprehensive PubMed search for structural magnetic resonance images and chronic pain, in addition to examining review papers and tracing references from retrieved papers. Studies were captured up to early July 2012. The employed search terms were “chronic pain and voxel-based morphometry” and “chronic pain and VBM.” Because of the statistical methods employed, coordinate-based meta-analyses have certain requirements for studies to be included. Only studies that analyzed local changes in GMV based on structural magnetic resonance images using VBM were included in our meta-analysis; the reported changes included both increases and decreases in patient GMV relative to control subjects. Of note, VBM preprocessing yields either modulated or unmodulated images. When performing image normalization (warping), gray matter values (within a voxel) can be adjusted (modulated) to the amount of local displacement, such that areas that are expanded/shrunk during the normalization step undergo reduction/amplification in intensity proportional to the alteration in volume; alternatively, gray matter values can be preserved within the normalization step, in which case normalized images are considered “unmodulated.” Modulated images refer to local brain volume, whereas unmodulated images refer to local brain density or concentration. Both analyses based on modulated and those based on unmodulated images were included in this study. As most of the analyses included in this meta-analysis are based on modulated images, we generally refer to GMV.

White matter volume analysis and analyses executed by methods other than VBM were excluded. Furthermore, only whole-brain results reported in stereotactic space (eg, Talairach or Montreal Neurological Institute [MNI]) as standard coordinates (eg, x, y, z) were selected for inclusion. Only between-group comparisons between chronic pain patients and healthy controls were analyzed. Studies were excluded if they 1) did not report stereotactic coordinates of maximal brain structure changes, 2) did not report any comparisons between healthy subjects and chronic
pain patients, 3) only reported coordinates as results of a region-of-interest analysis, or 4) did not report results in English. Using our inclusion criteria, we identified 23 peer-reviewed articles, jointly reporting on 490 patients and 509 healthy controls and 235 foci (see Table 1 for study data and included diagnoses).

The diagnostic criteria for chronic pain syndromes have been diverse, evolving over time and varying between the communities included in the studies, although standardized methods and criteria (eg, IASP criteria, Liverpool criteria, International Headache Society criteria, and American College of Rheumatology guidelines) have recently aided in patient classification. Most diagnoses were determined by clinicians and/or made using previously established, medically accepted diagnostic criteria; the common denominators for inclusion in a chronic pain population were pain duration greater than a specified amount of time (minimum range: 3 months to 1 year) and pain present immediately prior to testing. Because it was our aim to give a quantitative overview of the chronic pain literature, we chose to include all studies that were published in peer-reviewed journals and investigated gray matter differences in patients with chronic pain, regardless of the mode of diagnosis. That is, although the diagnostic criteria are heterogeneous across the included studies, all were accepted by the scientific community as contributing to the knowledge of the neurobiologic substrates of chronic pain and were therefore deemed eligible for inclusion in our meta-analysis.

Anatomic Likelihood Estimation

The meta-analyses were performed using the revised ALE approach for coordinate-based meta-analysis of neuroimaging results. This procedure identifies areas showing a convergence of findings across different experiments whether they are activations in functional studies or morphometric changes in anatomic studies. We use the term anatomic likelihood estimation (ALE) when applying this method to anatomic studies. The studies’ reported coordinates were compiled; those coordinates that were reported in Talairach space were converted to MNI space using the Lancaster transform, and the analysis was performed in MNI space. The ALE analysis treats each focus as the center of a 3D Gaussian probability distribution so as to model the spatial uncertainty associated with the foci. This technique uses the number of subjects to weight the size of the distribution around each point, assuming that a larger sample size should have less associated spatial uncertainty because of the reduction in contributions of interindividual differences.

For each structural magnetic resonance study, this probabilistic approach will yield a modeled anatomic effects map (analogous to a modeled activation map in functional coordinate-based meta-analyses) where each voxel has an associated probability of being a true observed effect. In an ALE meta-analysis, the union of the modeled activation maps is computed at each voxel to provide an unbiased estimate of spatial convergence across experiments. A random effects inference model is used that compares the ALE scores resulting from the union of spatially contingent modeled activation values with the ALE scores derived from a null-distribution permutation procedure reflecting a random spatial association between findings. This comparison filters the “true” ALE scores from those obtained by chance.

We performed separate ALE meta-analyses for reported coordinates associated with increases and decreases in patients’ GMV relative to controls, with inference performed at a cluster-level corrected P < .05 with a cluster-forming voxel-level threshold of P < .01 (uncorrected for family-wise error). Cluster localization and identification was executed using Talairach Daemon via GingerALE cluster analysis.

Functional Characterization

Interpretation and contextualization of regions found to have structural differences can be aided by determining the functional roles those regions play. The ALE analysis yielded a set of regions where structural differences were consistently reported between controls and patients. Using a neuroinformatics approach, we explored the range of functions that have been associated with these regions across the literature using prior results archived in the BrainMap database. When studies are entered into the database, large amounts of descriptor information related to the experiment are also recorded. One of these pieces of data is the behavioral domain that the experiment targets. There are 5 primary behavioral domain categories: cognition, action, perception, emotion, and interoception. Many of these domains are further divided into subdomains. Paradigm classes categorize the specific task employed (see for the complete BrainMap taxonomy and domain and subdomain definitions). In particular, forward inference is the probability of observing activity in a brain region given knowledge of the psychological process, whereas reverse inference is the probability of a psychological process being present given knowledge of activation in a particular brain region. In the forward inference approach, a cluster’s functional profile was determined by identifying taxonomic labels, for which the probability of finding activation in the respective cluster was significantly higher than the overall chance (across the entire database) of finding activation in that particular cluster. Significance was established using a binomial test (P < .05, corrected for multiple comparisons using Bonferroni’s method). That is, we tested whether the conditional probability of activation given a particular label (P(Activation|Domain)) was higher than the baseline probability of activating the region in question per se (P(Activation)). Significance was then assessed by means of a chi-square test. An association of task X to brain region Y obtained in these analyses does not necessarily imply that neural activity in region Y is limited to task X.
Table 1. Studies Used for VBM Chronic Pain Meta-Analysis

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>N SUBJECTS</th>
<th>N COORDINATES</th>
<th>PAIN TYPE</th>
<th>PATIENT DEMOGRAPHICS</th>
<th>PAIN DURATION</th>
<th>SIGNIFICANCE LEVEL (P &lt;)</th>
<th>MODULATED/UNMODULATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apkarian 2004</td>
<td>26</td>
<td>26</td>
<td>0</td>
<td>Chronic back pain</td>
<td>&gt;1 year</td>
<td>.01*</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>As-Sanie 2012</td>
<td>6</td>
<td>12</td>
<td>1</td>
<td>Chronic pelvic pain</td>
<td>&gt;6 months</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Buckalew 2008</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>Chronic low back pain</td>
<td>&gt;3 months</td>
<td>.001</td>
<td>Modulated</td>
</tr>
<tr>
<td>Geha 2008</td>
<td>28</td>
<td>26</td>
<td>1</td>
<td>Complex regional pain syndrome</td>
<td>&gt;3 months</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Gerstner 2011</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>Temporomandibular disorder</td>
<td>&gt;3 months</td>
<td>.001</td>
<td>Modulated</td>
</tr>
<tr>
<td>Gustin 2011</td>
<td>36</td>
<td>21</td>
<td>6</td>
<td>Trigeminal neuropathic pain</td>
<td>&gt;1 year</td>
<td>.01*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Gwilym 2010</td>
<td>16</td>
<td>16</td>
<td>12</td>
<td>Osteoarthritis</td>
<td>Unspecified</td>
<td>.001</td>
<td>Modulated</td>
</tr>
<tr>
<td>Kuchinad 2007</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>Fibromyalgia</td>
<td>&gt;3 months</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Rocca 2006</td>
<td>15</td>
<td>16</td>
<td>21</td>
<td>Migraine</td>
<td>&gt;2 years</td>
<td>.001</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Rodriguez-Raecke 2009</td>
<td>32</td>
<td>32</td>
<td>16</td>
<td>Primary hip osteoarthritis</td>
<td>&gt;12 months</td>
<td>.001</td>
<td>Modulated</td>
</tr>
<tr>
<td>Ruscheweyh 2011</td>
<td>31</td>
<td>45</td>
<td>0</td>
<td>Low back, headache, joint pain</td>
<td>&gt;12 months</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Schmidt-Wilcke 2005</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>Chronic tension-type headache</td>
<td>Unspecified</td>
<td>.05*</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Schmidt-Wilcke 2006</td>
<td>18</td>
<td>18</td>
<td>5</td>
<td>Chronic back pain</td>
<td>&gt;6 months</td>
<td>.001</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Schmidt-Wilcke 2007</td>
<td>22</td>
<td>20</td>
<td>2</td>
<td>Fibromyalgia</td>
<td>&gt;3 months</td>
<td>.001</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Schmidt-Wilcke 2008</td>
<td>31</td>
<td>35</td>
<td>4</td>
<td>Migraine</td>
<td>Unspecified</td>
<td>.05*</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Schmidt-Wilcke 2010</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>Chronic facial pain</td>
<td>&gt;3 months</td>
<td>.001</td>
<td>Modulated</td>
</tr>
<tr>
<td>Schweinhardt 2008</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>Chronic vulvar pain</td>
<td>&gt;6 months</td>
<td>.05*</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Seminowicz 2010</td>
<td>49</td>
<td>56</td>
<td>18</td>
<td>Irritable bowel syndrome</td>
<td>&gt;1 year</td>
<td>.1*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Tu 2010</td>
<td>32</td>
<td>32</td>
<td>9</td>
<td>Primary dysmenorrhoea</td>
<td>&gt;6 months</td>
<td>.005</td>
<td>Modulated</td>
</tr>
<tr>
<td>Valet 2009</td>
<td>25</td>
<td>14</td>
<td>13</td>
<td>Pain disorder</td>
<td>&gt;2 years</td>
<td>.05*</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Vallife 2008</td>
<td>27</td>
<td>27</td>
<td>11</td>
<td>Migraine</td>
<td>20.6 ± 8.9 years</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
<tr>
<td>Vartilainen 2009</td>
<td>28</td>
<td>8</td>
<td>7</td>
<td>Chronic widespread pain</td>
<td>&gt;3 years</td>
<td>.001</td>
<td>Unmodulated</td>
</tr>
<tr>
<td>Younger 2010</td>
<td>15</td>
<td>15</td>
<td>1</td>
<td>Temporomandibular disorder</td>
<td>&gt;1 year</td>
<td>.05*</td>
<td>Modulated</td>
</tr>
</tbody>
</table>

Abbreviations: C, number of control subjects; P, number of patients; C >P, number of foci where GMV was significantly greater in controls than patients; P >C, number of foci where GMV was significantly greater in patients than controls.

NOTE. A 0-count in P >C coordinates indicates that patient increases were tested for, but none were found; a dash indicates that it was unspecified whether patient increases were tested for.

*Study was corrected for multiple comparisons.

| Average duration. |
Results

The largest, most significant region of reduced GMV in patients was observed spanning several structures in the right hemisphere. Cluster 1 began inferiorly in the putamen and claustrum around \( z = -14 \). It then continued from the claustrum to the insula (Brodmann area [BA] 13), moving superiorly and finally extended into the posterior inferior frontal gyrus (IFG; BA 44) on the superior end. The next largest and most significant cluster, cluster 2, began inferiorly in the left ACC (BA 24) and extended into BA 32 in the ACC. It continued superiority into the left cingulate gyrus (BA 32) and began to cross into the right cingulate gyrus (BA 32). It also extended bilaterally into the medial frontal gyri (BA 9). Cluster 3 was found primarily in the left insula (BA 13) and extended slightly into the superior temporal gyrus (STG; BA 38). Cluster 4 was located in the left thalamus, including a submaximum in the medial dorsal nucleus. Cluster 5 contained a submaximum in subgyral gray matter (BA 21), but also included the right posterior STG (BA 22) and the right insula (BA 13). Cluster 6 was located slightly left of midline between \( z = 43 \) and \( z = 53 \) and included the medial frontal gyrus (MeFG; BA 6) and the cingulate gyrus (BA 31). Cluster 7 spanned the left IFG with BA 9 superiorly and BA 44 inferiorly. Cluster 8 was positioned in the right MeFG (BA 6) with a submaximum in the right paracentral lobe (BA 31); it also continued into the posterior midcingulate cortex. Cluster 9’s submaximum was situated in the right superior frontal gyrus (SFG; BA 10), and the cluster descended into the right MeFG (BA 10). Cluster 10 was located primarily in the right anterior middle frontal gyrus (BA 6) with a small extension into the superior frontal gyrus (SFG, BA 6) at \( z = 54 \). Cluster 11 was found in the left posterior middle frontal gyrus. Cluster 12 included a small portion of the left IFG (BA 9), superior to cluster 7, and extended into the insula. Figure 1 and Table 2 display the clusters and their volumes and coordinates.

Figure 2 displays the region in which significantly increased GMV was identified in patients relative to controls. There was only 1 cluster in this comparison (Table 3). It was located in the hippocampus and the parahippocampal gyrus (BA 36).

The FC results in BrainMap (Fig 3) identified a large constellation of domains associated with the abovementioned regions. Only a few of the regions showed significance in the domain of somesthesis; rather, the majority of results were associated with cognitive and emotional domains. These function–location correspondences identified strong associations between cluster 1 and cognition, emotion, pain, and gustation within the perception domain, bladder interception, and anxiety. Cluster 2 was involved in emotion (significantly in fear and sadness), cognition (significantly in knowledge of one’s body and attention), perception (significantly in gustation, olfaction, and pain), sexuality interception, and action inhibition. Cluster 3 showed associations with the domains of action inhibition and speech execution, speech and syntax language cognition, and music cognition. Cluster 4 showed involvement in the action domain, specifically in execution and speech execution. Cluster 5 was associated with audition perception and music cognition. Cluster 6 was shown to be involved in action domains, specifically execution, motor learning, and imagination. Cluster 7 primarily showed association with cognitive domains such as language syntax, language phonology, language orthography, time, working memory, and action imagination. Cluster 8 was involved in action execution and explicit memory cognition. Cluster 9 was associated with vision perception and explicit memory cognition. Cluster 10 showed significant involvement in cognitive processes, including explicit memory and working memory. Cluster 11 showed strong association with explicit and working memory, space, and language semantics cognition, as well as vision perception and action imagination. Cluster 12 was involved with cognition, emotion, pain perception, action inhibition, bladder interception, gustation perception, and emotional anxiety. The cluster in which patient GMV was greater than controls showed association with emotion and cognition, specifically space and explicit memory cognition.

Discussion

The results are discussed by GMV change and cluster groupings with shared regions below.

Decreased GMV in Chronic Pain

Clusters 1, 7, and 12

The IFG present in all 3 clusters is occasionally reported in imaging studies of pain; it shows decreased GMV in pain patients and correlates negatively with pain questionnaire scores. The IFG is active during pain catastrophizing in fibromyalgia patients and contributes to emotional empathy. It is involved in language processing and working memory and contributes to emotional empathy. In an empathy study, IFG activity was increased in chronic pain patients while they rated the pain intensity of characters in pictures or cartoons. The IFG’s involvement in pain may relate to emotional states experienced during pain.

The insula (clusters 1 and 12 here, also 3 and 5) has a significant role in pain processing. Activation in the anterior insula is associated with the affective dimension of pain processing and expectation of pain, whereas posterior activations are associated with the sensation and somatotopy of pain. Work to date has shown that the putamen (cluster 1) has a role in the somatotopic pain processing and likely modulates STG activity. The FC of clusters 1 and 12 confirmed this role in emotional processing. It also revealed that these clusters contain regions involved in cognition, interoception, action, and pain perception. Cluster 7’s FC indicated roles in cognitive language and memory processes.
Cluster 2

Cluster 2 was found in the ACC, a prominent component activated in experimental pain and structurally altered in chronic pain.\textsuperscript{16,17,58,59,70,72,86,92-94} In most pain studies, the ACC appeared to be involved in the affective aspects of pain processing.\textsuperscript{16,17,70,72,94} However, our finding of patient GMV decrease is in an ACC subregion involved in emotion, extending into midcingulate cortex areas involved in pain modulation\textsuperscript{6} and fear and avoidance.\textsuperscript{102} Cluster 2’s FC revealed multiple associations, including emotion, cognition, and pain perception. Given these findings, it appears the ACC is involved in the comorbidity of altered emotional control,\textsuperscript{2} regardless of the precise location. Some of these behavioral domains may be attributed to the MeFG in the cluster; it is part of the dorsolateral prefrontal cortex, shown to modulate pain perception.\textsuperscript{56}

Clusters 3 and 5

Clusters 3 and 5 were found in the left and right STG and insula (discussed above). The STG is typically associated with auditory perception,\textsuperscript{44} speech perception and comprehension,\textsuperscript{11,90} and music processing.\textsuperscript{66} The FC showed involvement in inhibition, speech,
audition, language, and music. However, STG is active in many induced pain studies.\cite{7,23,25,64,76,105} The STG has largely been ignored in pain imaging studies, likely in part because many investigators use region-of-interest analyses and also because a link between STG function and pain is not obvious.

A possible STG role in pain processing is in efference copy.\cite{53} Efference copy and corollary discharge are responsible for monitoring mismatches between predicted and actual sensation.\cite{41,43,57} STG activity is associated with efference copy and is likely mediated by the putamen,\cite{53} a region involved in pain processing. When there is an error signal because of mismatch, subjects try to correct the error and perceive increased sense of effort.\cite{5,91} Research implicates efference copy as driving sense of effort.\cite{60,61,71,73,91} Thus, we hypothesize that STG involvement in pain is due to mismatches between pain expectation and perception and that this constant mismatch leads to central fatigue.

**Cluster 4**

The thalamus is a pain region\cite{16,93} involved in affective and sensory processes related to pain.\cite{13} Its FC, however, showed only association with action and speech execution. This could possibly be due to a bias in the BrainMap database (discussed further below), causing certain study types to be overrepresented. Another possibility is that patients may experience difficulty completing actions and speaking because of their pain, fatigue, and an increased sense of effort.

**Clusters 6 and 8**

Both clusters enter the cingulate gyrus in a subregion that is associated with response selection, the posterior midcingulate cortex; this region is involved in skeletonmotor orientation.\cite{102} This is compatible with cluster 6’s FC results, which indicated a role in action, such as execution, motor learning, and imagination. The 2 clusters entered MeFG in BA 6 with cluster 6 in the supplementary motor area. In a functional study in fibromyalgia, the supplementary motor area showed activations in the high subjective pain condition in controls but not patients.\cite{84} The FCs revealed that cluster 8 was significantly involved in explicit memory and action execution. Cluster 6 was associated with action domains.

**Cluster 9**

The SFG is associated with many cognitive processes and is implicated in introspection,\cite{32} working memory,\cite{9} and spatial processing.\cite{9} Although the SFG has also been associated with pain processing,\cite{29,74,101,107} its role in chronic pain typically is not discussed. The SFG’s emergence in this analysis, its FC in memory cognition, and its involvement in introspection suggest that its role is associated with coping styles. For example, some chronic pain patients are able to adopt an internal
locus of control, which is associated with diminished pain perception.\textsuperscript{19,39} Thus, the SFG may mediate patients’ cognitive attempts to cope with pain.

Clusters 10 and 11

The middle frontal gyrus has been implicated in working memory\textsuperscript{54} and contingency awareness.\textsuperscript{15} These 2 functions are compatible with FC results showing significant associations with cognition and working memory. These clusters were within the premotor cortex known to be positively correlated with pain intensity.\textsuperscript{69} It is likely that these differences are related to patients living with chronic pain and developing the expectation of pain. Cluster 10 also extends into the SFG.

Increased GMV in Chronic Pain

The parahippocampal gyrus is involved in pain modulation and sensitivity.\textsuperscript{35} Also, the hippocampus\textsuperscript{93} is activated during pain while the subjects experience anxiety, leading to greater pain perception.\textsuperscript{67} Accordingly, the FC shows involvement in 2 areas affected by comorbid symptoms of chronic pain, cognition, and emotion. Thus, in addition to a functional role in pain, hippocampal involvement also participates in these comorbidities.

Toward Understanding the Neurobiology of Chronic Pain

The inclusion of many types of chronic pain in this meta-analysis supports that these structural variations are associated with chronic pain in general. There were several clusters of GMV reduction in patients compared to healthy controls. It is logical to hypothesize that regional structural differences are associated with altered pain processing and sensitivity. However, the fact that many regions exhibiting GMV differences are not part of the classic “pain matrix” challenges the existence of such a well-defined matrix and suggests that altered morphology may not be completely related to altered functionality. It is likely that the comorbidities of chronic pain are associated with GMV changes.

The only cluster with increased GMV was found in the hippocampus and parahippocampal gyrus. This is a region of overlap between the functional pain network and regions that are structurally altered in chronic pain. The mechanism by which gray matter changes in either direction is unknown; further research aimed at determining why and how GMV changes could provide much more insight. Perhaps integrating findings from anatomic, functional, resting state, and connectivity analyses of chronic pain could yield a detailed model of the differences in the brains of those with chronic pain and help generate hypotheses about the origin and exacerbation of these differences.

One limitation of this meta-analysis is that the chronic pain conditions are extremely heterogeneous. For example, chronic headache disorders are often distinct from other chronic pain disorders, as are autoimmune and inflammatory disorders. It is possible that pain conditions with a neuropathic etiology are different from painful conditions without damage to the nervous system. Furthermore, many of the disorders were represented in diffuse body regions with diverse somatotopic representations. However, including as many disorders as possible was advantageous for this analysis for increased power and to attempt to identify GMV changes common to all disorder types. Most of the included studies did not control for depression, and many found differences in depression scores between patients and controls. Although this could affect the results, we believe that it supports our conclusions that many of the structural changes observed could be related to comorbidities instead of just the chronic pain. Constraints in meta-analyses are inherent to the methods used in a given set of studies. FCs are limited to those coded in the BrainMap database. Researchers interested in a particular region often use specific paradigms to study that region. Therefore, FCs could be incomplete depending on the focus of the studies. In addition, many VBM studies do not test for gray matter increases in disordered populations (3 of 23 here do not), possibly giving an inaccurate impression of the relative frequency of GMV increases and decreases.
Finally, studies using different scanning parameters and scanner strengths could introduce small spatial errors into the raw data.

In summary, these meta-analyses support that chronic pain is associated with regional GMV changes. Many of the regions were not “pain matrix” regions, which implies that altered brain morphology is related not only to altered pain processing in chronic pain but also to frequent comorbidities. This is further supported by the fact that these comorbidities are present in most chronic pain disorders; therefore, disorder heterogeneity does not discount the results.

<table>
<thead>
<tr>
<th>Cluster No.</th>
<th>Volume (mm³)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>ALE Value × 10³</th>
<th>x₀</th>
<th>y₀</th>
<th>z₀</th>
<th>Label</th>
<th>BA</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1096</td>
<td>27.1</td>
<td>-29.14</td>
<td>-13.06</td>
<td>2.15</td>
<td>28</td>
<td>-30</td>
<td>-8</td>
<td>Hippocampus</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>2806</td>
<td>26</td>
<td>-28</td>
<td>-18</td>
<td>1.87</td>
<td>26</td>
<td>-28</td>
<td>-18</td>
<td>Parahippocampal gyrus</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 3. Chronic Pain Patients GMV > Control Subjects GMV ALE Clusters

Figure 3. Functional characterization results. Behavioral domains in which the region of interest was significantly involved compared to baseline. Significance at \( P < .05 \). A, action; BR, base rate; C, cognition; E, emotion; Ex, execution; I, interoception; L, language; M, memory; P, perception; S, somesthesia.
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