Brain Responses during provoked pain in Patients with Chronic Primary Pain: A systematic review and meta-analysis of fMRI studies

Brain Responses during provoked pain in Patients with Chronic Primary Pain: A systematic review and meta-analysis of fMRI studies

Short running title: fMRI Meta-analysis of Chronic Primary Pain

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Abstract

Chronic pain involves complex mechanisms that remain poorly understood. To address this, the International Association for the Study of Pain introduced the Chronic Primary Pain (CPP) framework in ICD-11 to reflect advances in pain research. In this pre-registered systematic review and meta-analysis, we examined the neural substrates of CPP compared to pain-free individuals during provoked pain. A literature search identified 48 whole-brain fMRI studies (*N* = 2,052) involving experimental pain stimulation in CPP patients (e.g., migraine, fibromyalgia, irritable bowel syndrome), with or without pain-free controls. A conjunction meta-analysis revealed robust activation in the dorsal anterior insula, mid-cingulate gyrus, and medial

frontal gyrus during provoked pain across 39 within-subject experiments. Using cluster- and voxel-level corrections, we observed consistent activity in the mid-cingulate and medial frontal gyrus, with the dorsal anterior insula and mid-cingulate gyrus implicated in pain processing in CPP. PERSPECTIVE: This study indicates the need for a new generation of methodologically harmonised studies integrating within- and between-subject effects before the CPP framework can be translated into a clinical tool. Achieving this translation requires significant methodological consistency in neuroimaging research to precisely identify the CPP neural substrates and advance diagnosis.

Keywords: *Chronic Primary Pain, fMRI, ALE, provoked pain, meta-analysis.*

Introduction

Unlike spontaneous or resting-state activity, provoked pain paradigms allow for controlled comparisons between patient and control groups under matched sensory input, isolating how chronic pain modifies central pain processing. However, identifying reliable brain markers of provoked pain in chronic pain remains challenging due to methodological inconsistencies and heterogeneous samples. Recent research highlights the importance of establishing shared neural mechanisms underlying provoked pain to improve consistency and comparability across studies.[1,2,3,4,5,6,7] Addressing these gaps in pain research is essential to resolving pathophysiological inconsistencies, which in turn will improve the diagnostic application of the newly established chronic primary pain (CPP) classification system.[10] This meta-analysis addresses three key limitations of previous studies.[8]

First, many prior studies did not account for differences between chronic pain conditions,[2,5,6] leading to discrepancies likely caused by condition-specific pathophysiological mechanisms.[9] To mitigate this, the International Association for the Study of Pain (IASP) proposed the CPP classification, which includes conditions such as fibromyalgia, chronic low back pain, migraine, and irritable bowel syndrome.[10] Despite its clinical importance, only one meta-analysis has applied the CPP framework to explore resting-state neural correlates across these conditions.[11]

Second, earlier studies frequently conflated within- and between-subject designs.[2,5,6,6,12,13] Within-subject effects capture individual pain processing, whereas between-subject comparisons examine differences between patients and controls.[8,14] Collapsing these effects may conflate variability due to individual differences with group-level effects,[8,14] potentially masking or misrepresenting key findings. This distinction is particularly critical in studies with smaller sample sizes,[6] where variability in individual brain responses can have a

disproportionate impact on observed effects. Prior research has shown neural activation patterns can differ substantially when analysing within and between individuals with chronic pain.[6] To avoid this, the present study separates within- and between-subject analyses, enabling a clearer, more accurate interpretation of neural responses to pain.

Third, inconsistencies in reported brain activation patterns—such as the insula, striatum, and supramarginal gyrus,[2,3,11]—are common. Such variability is further compounded by gender bias, varied statistical thresholds, heterogeneous pain paradigms, and small sample sizes. These challenges highlight the intricate and multifaceted nature of chronic pain research.

Many past meta-analyses used False Discovery Rate corrections, raising concerns about spurious findings when compared with strict cluster- and voxel-level Family-Wise Error (FWE) corrections,[2,15,16] which are believed to improve spatial accuracy and reliability of the Activation Likelihood Estimation (ALE).[17,18,19] By addressing these methodological issues,[8,10,18,20] the meta-analysis offers a more robust evaluation of neural correlates of provoked pain in CPP, aiming to improve interpretability, enhance diagnostic precision, and guide future research.

Methods

We conducted a systematic review and meta-analysis that followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) reporting guidelines.[21] The procedures and analyses for this meta-analysis were pre-registered on PROSPERO and Open Science Framework. The PRISMA flowchart depicts the literature search and screening (Figure 1). Inclusion criteria and keywords can be found in the eMethod in S1. The literature search was conducted before April 22, 2025, in the following databases: APA PsychInfo, APA PsychArticles, CINAHAL, MEDLINE and Scopus. After a rigorous selection process involving multiple raters (see eMethod), 75 experiments from 48 articles were included in the meta-

analysis.[22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69]

Pain Perception

We performed a multilevel random-effects meta-analysis to manage within- and between-study variances. Details on how the diverse dataset was handled, publication bias, and moderator effects, are found in the eMethod under “Pain psychophysics”.

Meta-analytic Groupings

We ran nine ALE meta-analyses across within-subject and between-subject experiments using cluster- and voxel-level corrections. Eight meta-analyses were conducted for within-subject data using two different cluster- and voxel-level corrections, including patients (k=21), controls (k=18), conjunction, and contrasts (k=39), using cluster-level and voxel-level FWE correction. We ran one meta-analysis on pooled between-subject experiments (pooled, k=36) using cluster-level correction. We conducted single meta-analyses when more than 17 experiments per group were available per group. We pooled smaller groups (<17 experiments). [17] We combined patients and controls datasets for between-subject analyses.[14]

The ALE meta-analyses followed standard procedures.[8] We applied a cluster-forming threshold of P <0.001 and a cluster-level corrected threshold of P<0.01 to control for FWE.[17,20 ,70] On a separate meta-analysis with the same datasets, a voxel-level corrected threshold of P<0.05,[8,16,17,18] was applied to assess the robustness of findings under stricter, more spatially specific criteria. Using both methods allowed us to balance sensitivity and specificity—cluster-level correction offers broader pattern detection, while voxel-level correction provides greater spatial specificity and reduces false positives. The eMethods S1 (ALE section) contains a full description.

The ALE meta-analyses identified brain regions that were consistently active across studies involving patient and control groups. By implementing both cluster-level and voxel-level FWE corrections and including data from within-subject and between-subject experimental designs, we aimed to enhance the sensitivity and robustness of the findings. The subsequent section details the included datasets, participant characteristics, and the spatial patterns of brain activation revealed through coordinate-based meta-analyses.

Results

We included data from 75 experiments reported in 48 articles, comprising 1,206 patients and 846 controls. Following CPP classification, we included studies recruited patients with irritable bowel syndrome (15), migraine (14), fibromyalgia (12), and chronic low back pain (7).[10] We also included studies that used pain paradigms of thermal pain (18), visceral pain (14), mechanical pain (13), and electrical pain (5). Table 1 lists the characteristics of the 48 studies, and Table 2 shows the behavioural data extraction.

Neural Data: Cluster Summary

The ALE analysis identified significant clusters when both cluster-level and voxel-level corrections were applied to within-subject experiments. The insula and cingulate gyrus contributed the most to these clusters (cluster-level, P=0.01). The between-subject analyses did not yield any significant clusters.

Unlike the voxel-level analysis, the cluster-level analysis of within-subject experiments revealed multiple clusters. Figure 2 illustrates the percentage of experiments with overlapping foci that contributed to the structures identified within each cluster. The conjunction analysis showed that Cluster 1 accounted for 93.6% of the clusters identified in the cingulate gyrus, with a maximum activated likelihood estimation value of 0.017, k = 9 foci, and k = 8 experiments (Brodmann Area 32 at 61.7%). Cluster 2 included 81.8% of the clusters located in the insula, with a maximum ALE value of 0.012, k = 5 foci, and k = 5 experiments (Brodmann Area 13 totaling 81.8%).

The contrast analysis identified one cluster in experiments where controls experienced greater pain than patients. In Cluster 1, 44.4% of foci were located in the medial frontal gyrus, with a maximum ALE value of 0.005, k = 3 foci, and k = 3 experiments (Brodmann Area 6 totaling 44.4%). Additionally, the contrast analysis identified two clusters in experiments where patients experienced greater pain than controls. In Cluster 1, 81.4% of foci were in the insula, with a maximum ALE value of 0.001, k = 2 foci, and k = 2 experiments (Brodmann Area 13 totaling 81.4%). In Cluster 2, 45.5% of foci were also in the insula, with a maximum ALE value of 0.006, k = 1 focus, and k = 1 experiment (Brodmann Area 13 totaling 45.5%).

In patients, the cluster-level analysis of within-subject experiments revealed three clusters across several studies. Cluster 1 contained 57.2% of foci in the insula, with a maximum ALE value of 0.020, k = 16 foci, and k = 13 experiments. Cluster 2 included 95.4% of foci in the cingulate

gyrus, with a maximum ALE value of 0.023, k = 10 foci, and k = 8 experiments. Cluster 3 showed 77.5% of foci in the insula, with a maximum ALE value of 0.020, k = 11 foci, and k = 7 experiments. Each cluster predominantly comprised the following: Brodmann Area 13 (57.2%) in Cluster 1, Brodmann Area 32 (77.8%) in Cluster 2, and Brodmann Area 13 (73.8%) in Cluster 3.

In controls, Cluster 1 contained 71.9% of foci in the cingulate gyrus, with a maximum ALE value of 0.025, k = 10 foci, and k = 7 experiments. This cluster was composed mainly of Brodmann Area 24 (53.9%). Cluster 2 included 93.5% of foci in the insula, with a maximum ALE value of 0.014, k = 6 foci, and k = 6 experiments (Brodmann Area 13 totaling 80.6%). The cluster-level analysis did not identify any clusters in the between-subject experiments.

The voxel-level analysis of within-subject experiments (P = 0.05) identified one cluster in controls, where 73.7% of foci were in the cingulate gyrus, with a maximum ALE value of 0.025, k = 4 foci, and k = 4 experiments (Brodmann Area 24 at 73.7%). The voxel-level analysis did not identify any clusters in the conjunction, contrast, or patient analyses. Similarly, the voxel-level analysis of between-subject experiments did not reveal any clusters for patients, controls, conjunction, or contrast. Figure 2 and Table 3 provide a more detailed description of all identified clusters.

Meta-analyses using cluster-level and voxel-level: Within-subject experiments

For within-subject meta-analyses, cluster-level conjunction analysis showed convergence in the right dorsal anterior insula and the mid-cingulate gyrus (Figure 3; Table3; eResults).

Contrast analysis indicated greater convergent activity in patients compared to controls in the dorsal anterior insula $P<0.007$ and ventral anterior insula $P<0.01$, and greater activation in

controls compared to patients in the superior frontal gyrus $P<0.005$ (Figure 4). Patients showed activity in the ventral dorsal anterior insula $P<0.001$, anterior cingulate cortex $P<0.001$, and mid-cingulate gyrus $P<0.001$, while controls exhibited convergence in the dorsal anterior insula $P<0.001$ (Figure 5; Table 3).

With voxel-level, one meta-analysis revealed significant convergence, with control group activity in the mid-cingulate gyrus $P<0.001$ (Figure 5; Table 3). However, conjunction and patients' group were non-significant.

Pain perception

A multi-level random-effects meta-analysis found that patients reported higher pain ratings than controls (Hedges' g = 0.71, 95%-CI [0.29, 1.14], 95%-PI [-1.16, 2.56], *SE* = 0.21, *p*-value < 0.001). The heterogeneity was substantial (I^2 = 85.39%), suggesting high variability in pain ratings between groups and across studies (Figure 6).

Additional analyses

Pain scores were significantly higher for visceral stimuli compared to electrical stimuli (*B* = 1.05, *SE* = 0.55, *p* < 0.05). Egger's test revealed no evidence of publication bias. Additional analyses of potential moderating variables—including depression, anxiety, gender, age, and other methodological factors—showed no significant effects on pain scores (detailed results available in eResults, “Pain psychophysics”).

Discussion

The present meta-analysis provides novel insights into the neural underpinnings of CPP, by adopting this classification of ICD-11 framework and separating within- and between-subject analyses to improve sample representation,[8,9] an approach not used in previous meta-analyses. This methodological refinement enabled a more precise identification of clinically relevant pain-related neural patterns.[10]

Our within-subject findings suggest consistent pain-related neural patterns associated with provoked pain in CPP compared to controls. However, pooled results from between-subject experiments results revealed no convergence.[14] These null results are unlikely to be due to insufficient statistical power (>17 experiments) or the dominance of single studies.[16,17] Altogether, inter-individual differences in pain-related brain activation, variations in pain paradigms across studies, the wide distribution of neural patterns, and methodological

heterogeneity may contribute to obscuring spatial convergence in between-subjects' analyses, even with an adequate number of experiments and sufficient statistical power. These sources of heterogeneity highlight the need for more between-subject experiments in CPP research using standardised methodologies.[8]

Consistent with previous research, within-subject findings using cluster-level correction demonstrated convergence in key brain structures in patients, such as the right ventral dorsal anterior insula, mid-cingulate gyrus, anterior cingulate gyrus, claustrum, precentral gyrus, medial frontal gyrus, and lentiform nucleus.[2,5,7,13,40,71] However, no convergent activity was observed in the posterior insula and thalamus.[5,11,13,72] Controls demonstrated convergence in distinct regions, such as the right dorsal anterior insula, medial frontal gyrus, and mid-cingulate gyrus (Figure 5).

Conjunction analyses revealed overlapping activity between patients and controls, with notable convergences in the right mid-cingulate gyrus, medial frontal gyrus, dorsal anterior insula, and claustrum (Figure 3), challenging previous findings.[6] Contrast analyses revealed differences in convergences between groups, with patients exhibiting stronger convergences in the ventral anterior insula, claustrum, and inferior frontal gyrus,[73] while controls showed greater differences in the superior frontal gyrus, mid-cingulate gyrus, and medial frontal gyrus (Figure 4). These findings suggest group differences in pain processing, indicating stability and consistency in one group compared to the other group.[8] Thus, demonstrating the most contributing experiments to the identified structures.

These findings challenge previous research.[6] The discrepancy may be due to the adoption of a stricter sample population, conservative statistical approaches, and specification of experiment-type and -number. Whereas previous meta-analyses,[6] combined various chronic pain conditions, applied a lenient $P<0.05$ cluster-level correction, and included both within-

subject[23] and between-subject[69] designs. Together, these methodological differences likely contribute to the divergence between our results and prior findings.

Using, voxel-level correction, within-subject findings revealed no convergence.[6] In contrast, control groups showed consistent convergence in the mid-cingulate and medial frontal gyri, aligning with previous meta-analyses,[13] and supporting prior findings that implicate the cingulate gyrus in pain-related activation.[2,5,13]

The ongoing debate concerns the differential involvement of the anterior and posterior insula in pain processing. Specific chronic pain conditions demonstrate distinct insular involvement. For instance, studies on chronic back pain and irritable bowel syndrome emphasise the role of the anterior insula,[73,74,75] whereas fibromyalgia and migraine appear more closely linked to the posterior insula,[5,76,77] aligning with the primary pain matrix.[78]

Research indicates that prolonged exposure to fibromyalgia-related pain leads to notable volumetric, structural, and functional brain alterations.[79] This aligns with our findings on pain perception and neural activity, in which patients reported greater pain than controls and showed more neural clusters. These results underscore the need for further research to reassess the insular cortex's role in CPP.

Our findings may help explain why patients with CPP experience heightened pain sensitivity, even when nociceptive input appears comparable to that of controls. Furthermore, the lack of convergence in the between-subject experiments—despite the application of adequate statistical controls—highlights the urgent need for standardisation in sample selection, experimental design, and pain assessment across neuroimaging studies. This has direct implications for establishing reliable and consistent pain-related neural patterns that are condition-specific for CPP. In turn, this can enhance diagnostic accuracy and inform the

development **of** future clinical applications and personalised treatment approaches, such as targeted neuromodulation or cognitive behavioural interventions.

Lastly, while we acknowledge that some conditions such as CLBP can involve diverse phenotypes, our aim was to capture the shared central mechanisms within the CPP framework, where heterogeneity is conceptualised around functional rather than structural pathology. This approach reflects current diagnostic models,[10] and enhances the relevance of our findings to understanding the generalisable neural features of chronic primary pain.

Overall, our findings clarify both the shared and distinct region-specific contributions observed in patients and controls and advance the understanding of CPP as a distinct neurobiological set of subtypes of this diagnosis, rather than a generalised chronic pain disorder.

Pain perception and additional variables

As expected, CPP patients reported significantly greater pain than controls. Certain chronic pain conditions heighten pain perception due to prolonged hypersensitivity.[80,81] The behavioural findings (Figure 6) are consistent with the neural findings (Figure 2), which demonstrated greater likelihood of activation in key pain-related structures in the insula and cingulate gyrus in patients across multiple studies. The structures involved have been implicated in sensory-discriminative and affective component processing of pain.[82,83] The contrast analysis supported this relationship, with patients showing higher ALE compared to controls, suggesting possible neurobiological substrates underlying magnified pain sensitivity, corroborating the findings of behaviour. However, adaptation theory suggests that chronic pain patients may develop a hyporesponsive state to painful stimulation, where the perception of pain is overshadowed by the ongoing chronic pain experiences.[84,85] This diminished or delayed response in chronic pain conditions may lead to heightened sensitivity

when rating pain.[86] However, previous research reported no significant differences in pain responses between chronic pain patients and controls, suggesting that pain threshold and tolerance may vary across different conditions.[6]

Additionally, pain rating may be influenced by variables such as condition type, gender, and age.[87,88] However, our moderator analyses found no evidence that depression, anxiety, gender, age, confounding variables, or methodological differences influenced participants' pain rating scores. With the exception of visceral stimuli, which significantly impacting pain rating compared to electrical stimuli, due to the substantial number of IBS studies applying balloon distention.[51,69] This reinforces the consistency of our findings across behavioural measures, demographics, and experimental designs.

Limitations and future perspectives

This meta-analysis uncovered several key limitations within the literature, which are crucial for informing future research. While the sample size and diversity of conditions provided an adequate preliminary synthesis, they do not fully capture the full spectrum of CPP conditions. Given the complexity of these conditions, future studies should aim to expand the range of CPP conditions examined, improve methodological standardisation, and identify functional neural networks rather than isolated neural structures. Further research is needed to differentiate the neural substrates of CPP from those of healthy controls, to ensure greater accuracy in pathophysiological mapping. We acknowledge that treating behavioural data as separate entries could inflate the influence of individual studies that report multiple conditions and could violate the assumption of independence if not accounted for properly. However, our multilevel random-effects model accommodates such within-study clustering,[89] allowing us to model both within- and between-study variance, thereby mitigating this concern.

Conclusions

This systematic review and meta-analysis revealed consistent convergence in within-subject experiments using cluster-level and voxel-level correction, but no convergent activity in the between-subject experiments. Importantly, the dorsal anterior insula and mid-cingulate gyrus structures underline their potential significance in pain processing across CPP conditions. Additionally, our findings highlight substantial neural heterogeneity in CPP-related pain processing, supporting the need for further neuroimaging research. Future studies should continue investigating the neural substrates of chronic pain conditions using the International Classification of Diseases 11th Revision.

Author's contributions

Al-Faraj had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization; Validation; Visualization; Roles/Writing - original draft; Writing - review and editing: Al-Faraj, Hanel, Valentini.

Project administration; Al-Faraj

Formal analysis; Software; Investigation; Statistical analysis; Methodology: Neural data/Behavioural data: Al-Faraj, Behavioural data: Hanel.

Drafting of the manuscript: Al-Faraj.

Critical revision of the manuscript for important intellectual content: Hanel, Valentini.

Administrative, technical, or material support: BrainMap team.

Study supervision: Hanel, Valentini.

Data statement

Data for this work can be found at Open Science framework.

Study pre-registeration

The review in this article was preregistered for transparent practices on Prospero ID: CRD42022303560 and Open Science Framework (url: https://osf.io/xjbg2/).

Open materials and methods

All materials, data, and analytic code used in this study are publicly available (URL: https://osf.io/xjbg2/) to ensure transparency and reproducibility. Full methodological details—including systematic review procedures, ALE meta-analysis results, behavioural data meta-analysis, pain psychophysics, and supplementary materials—are available at the same link and S1.

Disclosures

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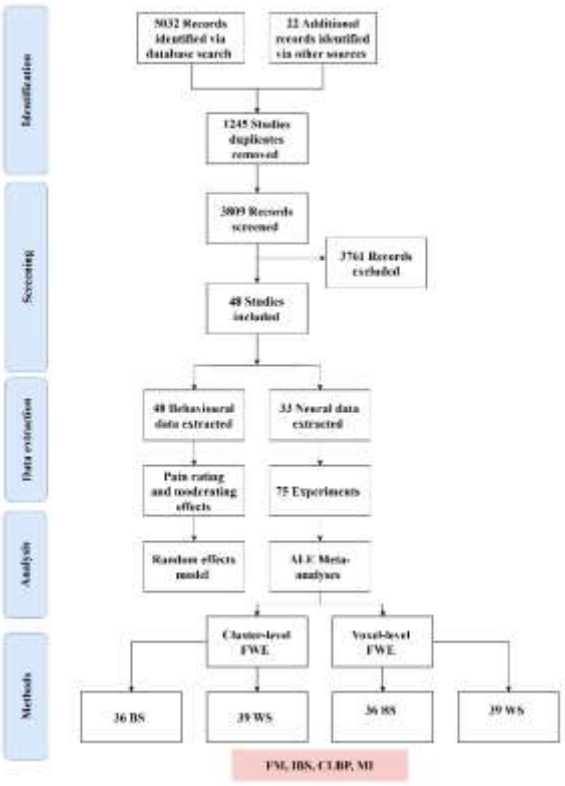

Identification
Screening
Data extraction
Analysis
Methods
5032 Records identified via database search
22 Additional records identified via other sources
1245 Studies duplicates removed
3809 Records screened
3761 Records excluded
48 Studies included
48 Behavioural data extracted
33 Neural data extracted
Pain rating and moderating effects
75 Experiments
Random effects model
ALE Meta-analyses
Cluster-level FWE
Voxel-level FWE
36 BS
39 WS
36 BS
39 WS
FSL, BS, CLBP, MI

Figure 1.

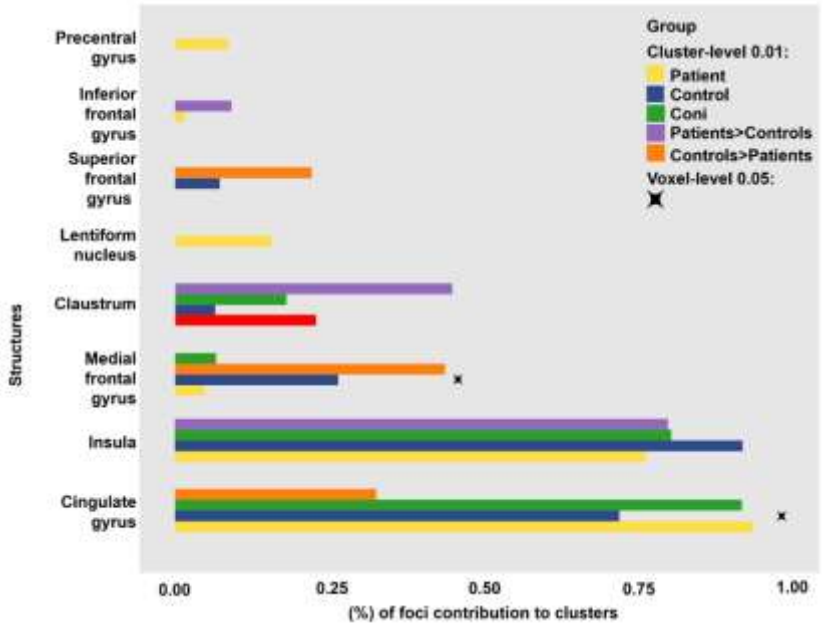

Precentral gyrus
Inferior frontal gyrus
Superior frontal gyrus
Lentiform nucleus
Claustrum
Medial frontal gyrus
Insula
Cingulate gyrus
Structures
Group
Cluster-level 0.01:
Patient
Control
Coni
Patients>Controls
Controls>Patients
Voxel-level 0.05:
0.00
0.25
0.50
0.75
1.00
(%) of foci contribution to clusters

Figure 2.

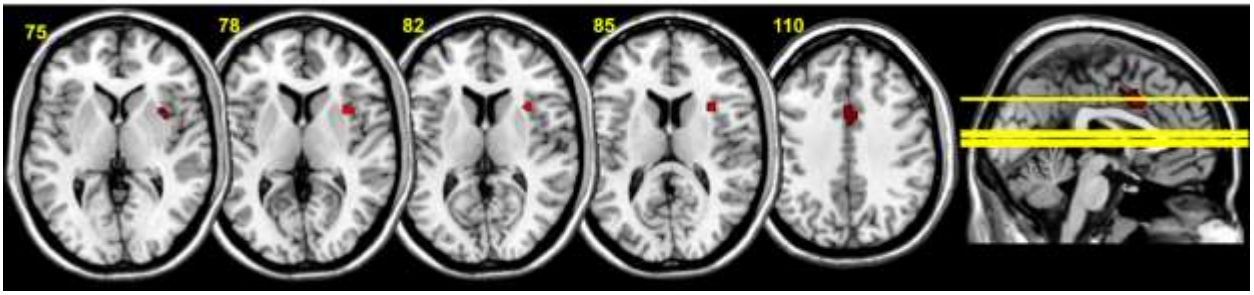
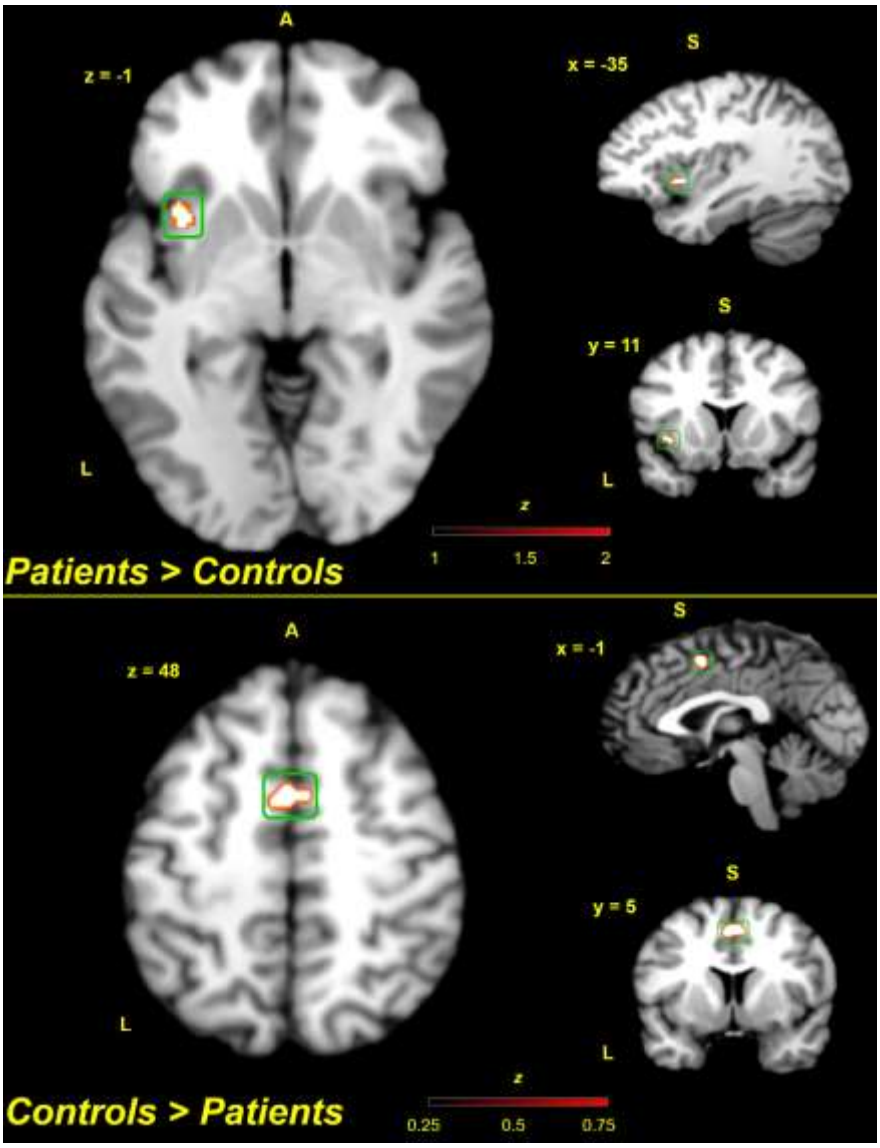


Figure 3.


A
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S
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L
L
z
1
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2
Patients > Controls
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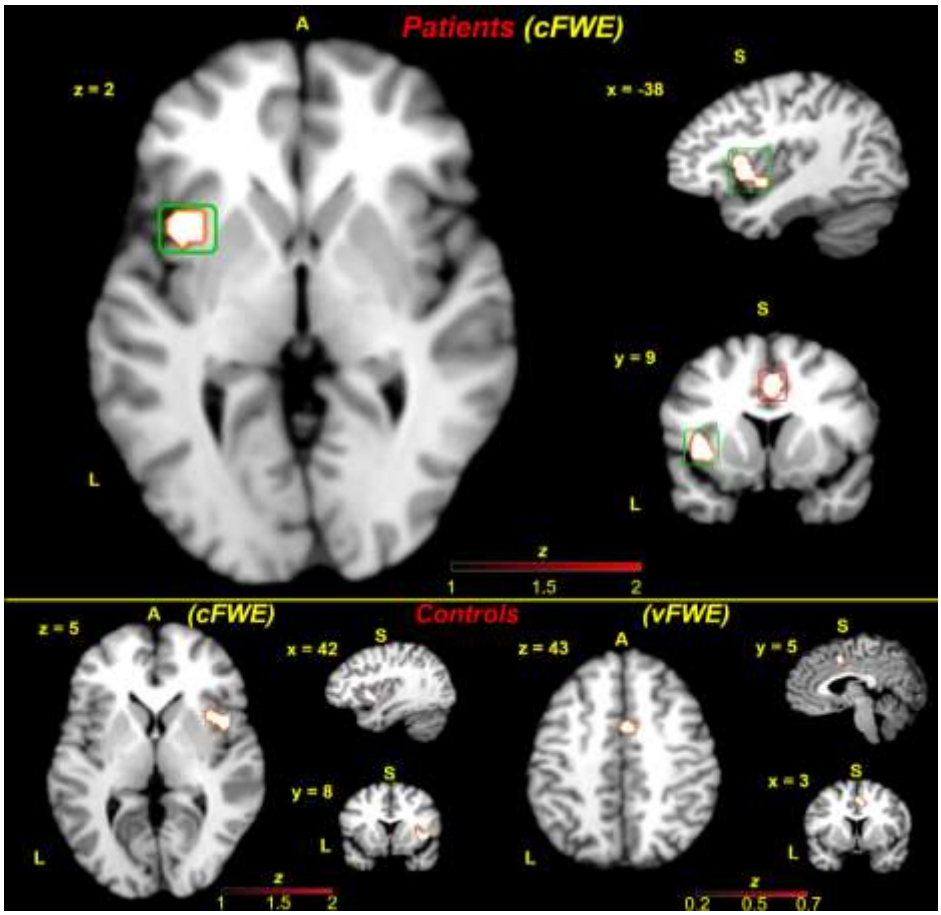
L
L
z
0.25
0.5
0.75
Controls > Patients

Figure 4.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1.5
2
Controls
(cFWE)
A
z = 5
L
S
x = 42
S
y = 8
L
z
1
1.5
2
(vFWE)
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L
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x = 3
L
z
0.2
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Figure 5.

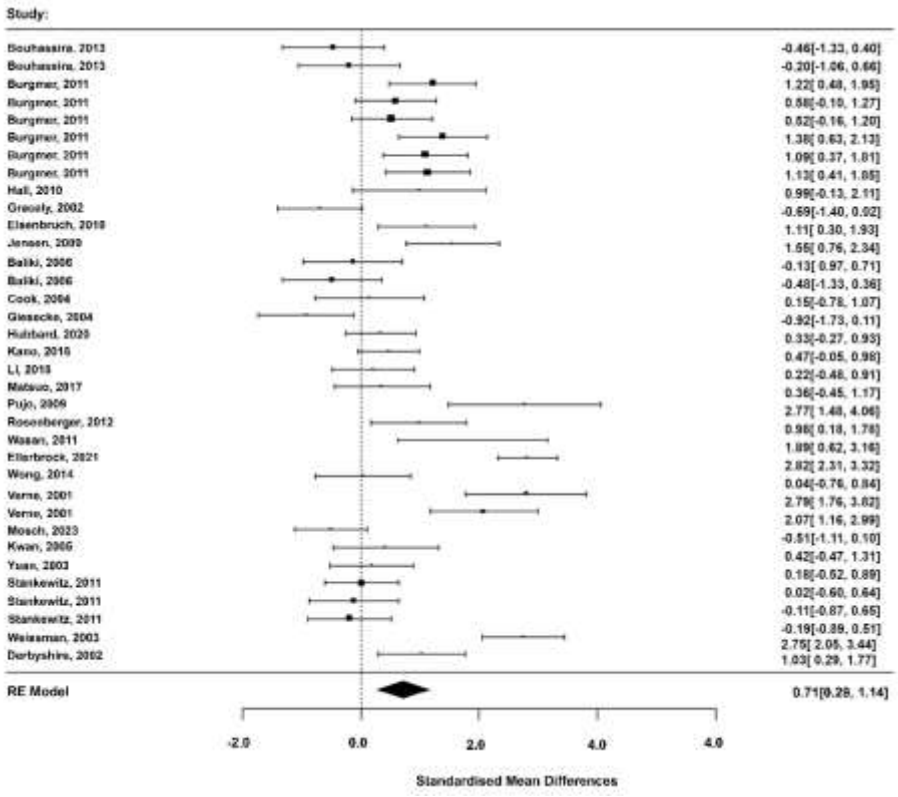

Figure 6

Figure 1. PRISMA flowchart detailing the screening process and meta-analyses methods. 75 experiments from 48 articles were included in the meta-analysis. Abbreviations: ALE, Activated Likelihood Estimation; FWE, Family-Wise Error; BS, Between-subject; WS, Within-subject experiments; FB, Fibromyalgia; IBS, Irritable Bowel Syndrome; CLBP, Chronic Low Back Pain; MI, Migraine

Figure 2. Frequency of reported brain structures across meta-analyses of spatial convergence. Data reflect cluster-level and voxel-level results from within-subject experiments. Each cluster indicates the contribution of a specific brain structure across different groups (e.g., patients or controls). Blue represents controls, yellow represents patients, green represents

conjunction, purple represents patient > control, orange represents control > patient. A star at the end of a bar indicates voxel-level results that survived a threshold of $P<0.05$. Bars without a star represent cluster-level results, surviving a threshold of $P<0.01$.

Figure 3. Conjunction maps of peak coordinates of the within-subject meta-analysis. Spatial convergence identified in patients and controls during provoked pain in the mid-cingulate gyrus (0, 12, 34) and dorsal anterior insula (40, 8, 4). Images were thresholded at $P<0.01$ (cluster-level correction).

Figure 4. Contrast maps of patients and controls. Coordinate based meta-analysis of significant aggregated contrasts between groups between groups [patients > controls] and a significant difference of activated likelihood estimation maps in the dorsal anterior insula (-35, 11, -1), top panel. Contrasts between groups [controls > patients] significant difference in the superior frontal gyrus (-1, 5, 48), bottom panel. Images were thresholded at $P<0.01$ (cluster-level correction).

Figure 5. Thresholded images of within-subject between patients and controls. Coordinate based meta-analysis of neural response to pain vs rest showing convergences for patients in the ventral dorsal anterior insula (-38, 9, 2) in green, anterior cingulate cortex and mid-cingulate gyrus (2, 10, 38) in red, above. Controls in the dorsal anterior insula (32, 16, 14) and claustrum (40, 10, 2). Images were thresholded at $p<0.01$ (cluster-level correction). Single meta-analysis of controls in the MCC (1, 5, 45). Images were thresholded at $P<0.05$ (voxel-level correction)

Figure 6: **Pain rating effect size between patients and healthy controls.** Pain rating effect size between patients and healthy controls. Forest plot displaying the effect size(s) of pain ratings per study. Positive effect size indicates higher pain reporting in patients compared to healthy controls.

Table 1. Chronic Primary Pain (CPP); Studies Description and Experiments Specification That Were Included in the Present Meta-analyses. Description of sample, contrast (experiments), specific characteristics of the patients, and medication and experiment class of included papers.

Study	N (Patients/Controls)	M age (Patients/ Controls)	Pain Condition/ Stimuli	Site of Stimulation	Medication	N of Exp/Sessions (Days)	Experiments (k)
Bouhassira 2013 [23]	10 (11)	41.7 (41.5)	Irritable bowel syndrome/ electrical and visceral	Left lower limb and rectum	NO NE	2/3(1)	3
Burgmer 2011 [24]	17 (17)	52.59 (49.53)	Fibromyalgia/ mechanical	Volar forearm	NO NE	1/4(1)	2
Hall 2010 [25]	8 (6)	39 (45.8)	Irritable bowel syndrome/ visceral	Rectum	NO NE	1/1 (1)	4
Gracely 2002 [27]	16(16)	52.6 (45.8)	Fibromyalgia/ mechanical	Left thumbnail	YES	1/1 (1)	3
Elsenbruch 2010 [26]	15(12)	42.4(31.4)	Irritable bowel syndrome/ visceral	Rectum	NO NE	3/3 (3)	4
Jensen 2009 [28]	16 (16)	44 (33)	Fibromyalgia/ mechanical	Thumbnail	NO NE	1/1 (1)	2

Baliki 2006 [29]	13 (11)	49.2 (48.7)	Fibromyalgia/ thermal	Left forearm	NO NE	4/2 (2)	2
Cook 2004 [67]	9 (9)	37 (35)	Fibromyalgia/ thermal	Left hand	NO NE	2/2(7)	3
Geisecke 2004 [30]	16 (11)	44, 45 (41)	Fibromyalgia/ mechanical	Thumbnail	NO NE	1/2(1)	N/A
Hubbard 2020 [31]	38 (15)	46.1 (45.53)	Fibromyalgia/ mechanical	Leg	YES	1/1(1)	1
Kano 2018 [32]	27 (33)	22 (22.3)	Irritable bowel syndrome/ visceral	Rectum	N/A	3/3(3)	2
Li 2018 [35]	16 (16)	41.6 (31.3)	Chronic low back pain/ mechanical	Lower back	NO NE	1/1(1)	2
Matsuo 2017 [36]	11 (13)	48 (34)	Chronic low back pain/ mechanical	Left low back	NO NE	1/1(1)	2
Pujol 2009 [41]	9 (9)	47.9 (47.2)	Fibromyalgia/ mechanical	Thumb	YES	1/1(1)	3
Schwedt 2014 [68]	25 (27)	36.2 (33.7)	Migraine/ thermal	Left forearm	NO NE	1/3(7)	2
Derbyshire 2002 [69]	16 (16)	45.4 (35.6)	Chronic low back pain/ thermal	Right hand	NO NE	1/1(1)	4

			Irritable bowel				
Sidhu		28.5	syndrome/				
2003 [42]	8 (8)	(28.5)	visceral	Rectum	N/A	1/1(1)	2
			Irritable bowel				
Bonaz			syndrome/		NO		
2002 [43]	12	48	visceral	Rectum	NE	2/2(7)	NC
Callan		51.8	Chronic low back	Lower	NO		
2013 [43]	13 (13)	(48.7)	pain/ electrical	back	NE	1/2(1)	2
Ellerbro							
ck 2021		47.2	Fibromyalgia/				
[45]	84 (43)	(48.1)	mechanical	Left calf	N/A	1/1(2)	NC
			Irritable bowel	Rectum			
Wong		37.2	syndrome/	and left	NO		
2014 [46]	13 (11)	(37.1)	visceral	foot	NE	1/2(2)	NC
Foss			Chronic low back	Lower	NO		
2006 [47]	11 (6)	37 (34)	pain/ thermal	back	NE	4/3(1)	NC
			Irritable bowel	Hand and			
Verne			syndrome/ thermal	foot,	NO		
2001 [48]	12 (17)	31 (31)	and visceral	rectum	NE	1/1(1)	NC
			Irritable bowel				
Bouin			syndrome/				
2002 [49]	86 (25)	44.9 (39)	visceral	Rectum	N/A	2/1(1)	NC
Mosch			Fibromyalgia/	Left	NO		
2023 [50]	22 (21)	50 (47)	thermal	thenar	NE	3/2(3)	4

			Irritable bowel				
Kwan		37.8	syndrome/		NO		
2005 [34]	9 (11)	(31.7)	visceral	Rectum	NE	2/2(3)	NC
Lopez-							
sol		46.27	Fibromyalgia/	Right	NO		
2017 [51]	37 (35)	(43.86)	mechanical	thumbnail	NE	2/1(1)	NC
			Irritable bowel				
Yuan			syndrome/				
2003 [52]	26 (11)	47 (39)	visceral	Rectum	N/A	1/2(1)	NC
			Irritable bowel				
Lawal			syndrome/				
2005 [53]	10 (10)	28.5	visceral	Rectum	N/A	N/A	NC
				Left			
Chen		28.13	Migraine/	medial	NO		
2015 [54]	15 (20)	(28.1)	electrical	forearm	NE	1/1(5)	1
				Maxillary			
Russo		27.83		skin (on	NO		
2012 [54]	16 (16)	(27.5)	Migraine/ thermal	the face)	NE	1/3(7)	4
			Irritable bowel				
Guleria		30.5, 27.5	syndrome/		NO		
2017 [70]	20 (10)	(28.5)	visceral	Rectum	NE	1/1(1)	5
		32.1, 31		Face			
Russo		(28.2,		(trigeminal	NO		
2017 [56]	20 (20)	29.2)	Migraine/ thermal	area)	NE	2/3(3)	2

		30.05,					
Russo	18, 17	32.74		Face	NO		
2019 [57]	(15)	(27.4)	Migraine/ thermal	(cheek)	NE	2/2(4)	1
Stanke				Face			
witz	20, 10,	29.5, 32.5,	Migraine/	(trigeminal	NO		
2011 [58]	13 (20)	33 (27.5)	electrical	area)	NE	1/2(1)	1
Maleki							
2021 [59]	19	42.65	Migraine/ thermal	Hand	YES	2/2(1)	2
Mungo							
ven		29.6					
2022 [60]	25 (29)	(26.4)	Migraine/ thermal	Orofacial	YES	1/1(1)	1
Schulte				Right	NO		
2020 [61]	7	31.29	Migraine/ thermal	hand	NE	N/A	3
Tessito				Maxillary			
re 2011		27.8		skin (on	NO		
[62]	16 (16)	(27.5)	Migraine/ thermal	the face)	NE	3/3(1)	NC
Weissm							
an 2003		25.6	Migraine/ thermal		NO		
[63]	34 (28)	(24.8)	and electrical	Forearm	NE	1/1(7)	NC
Maleki				Dorsum of			
2012 [64]	22 (22)	42 (42.65)	Migraine/ thermal	the hand	YES	1/3(1)	1
Buchgr							
eitz			Migraine/	Somatic			
2006 [65]	60	50.5	mechanical	sites	N/A	1/1(1)	NC

Bogdanov 2019 [66]	14 (24)	33.2 (41.5)	Migraine/ thermal	Right foot and left hand	YES	1/2(1)	1
Rosenberger 2012 [37]	15 (12)	42.4 (31.4)	Irritable bowel syndrome/ visceral	Rectum	NO NE	1/1(2)	2
Wasan 2011 [38]	16 (16)	47.4 (46.7)	Chronic low back pain/ thermal	Leg dermatome	N/A	1/3(1)	1
Jensen 2010 [40]	83 (13)	43.8 2	Fibromyalgia/ mechanical	Thumb	NO NE	1/1(2)	1
Kobayashi 2009 [33]	6 (8)	33 (29)	Chronic low back pain/ mechanical	Lumber region	N/A	2/2(1)	2
Wilder Smith 2004 [39]	10 (10)	35 (31)	Irritable bowel syndrome/ visceral	Rectum	NO NE	8/1(7)	NC

Note. M = Mean, NC = no coordinates, N/A= Not available or not assessed. In the case of study[30], it was unclear whether for both groups neural coordinates represented pain or rest.

Table 2. Behavioural data extraction (e.g., depression and/or anxiety) and pain rating average.

Study	Depression M Patients 1 & 2 (Controls)	SD	Anxiety M Patients 1 & 2 (Controls)	SD	PR (ES)
Bouhassira 2013	2.6 (1.2)	1.3 (4.4)	9.4 (7.4)	4.5 (2.7)	-0.33
Burgmer 2011	21.24 (9.65)	7.87 (4.05)	21.24 (9.65)	7.87 (4.05)	0.98
Hall 2010	N/A	N/A	N/A	N/A	0.99
Gracely 2002	NONE	NONE	NONE	NONE	-0.69
Elsenbruch 2010	3.9(1.7)	3.87(1.38)	7.4(4.6)	3.87(2.42)	1.11
Jensen 2009	NONE	NONE	NONE	NONE	1.55
Baliki 2006	10.9 (6.5)	10.6 (7.7)	12.6 (5.9)	9.5 (6.2)	-0.15
Cook 2004	8.4 (2.4)	7 (2)	30.2 (25.2)	3 (4)	1.01
Geisecke 2004	11.5 (4.8)	7.5 (5.9)	18.5(1.5)	4.4 (4.4)	0.4
Hubbard 2020	NONE	NONE	NONE	NONE	0.22
Kano 2018	38.4 (36)	8.9 (6.4)	42.4 (36.4)	12.3 (6.08)	0.36
Li 2018	NONE	NONE	NONE	NONE	2.77
Matsuo 2017	NONE	NONE	NONE	NONE	0.98

					-
Pujol 2009	13.4 (10.3)	4 (4.7)	13.4 (10.3)	4 (4.7)	0.16
Schwedt					NO
2014	2.8 (4.7)	N/A	25.4 (25.7)	N/A	NE
Derbyshir					
e 2002	4.1 (2.9)	2.4 (2.5)	7.3 (5.6)	2.9 (2.9)	1.03
Sidhu					NO
2003	NONE	NONE	NONE	NONE	NE
Bonaz					NO
2002	63.4	7.4	58.5	8.2	NE
Callan					NO
2013	NONE	NONE	NONE	NONE	NE
Ellerbrock					
2021	7.2 (0.5)	4 (1.4)	7.9 (3.1)	4.3 (2.9)	2.79
Wong					
2014	4.7 (2.8)	NONE	9.3 (4.4)	NONE	2.79
					NO
Foss 2006	NONE	NONE	NONE	NONE	NE
Verne					
2001	7.4 (4.0)	4.6 (5.1)	40.9 (30.4)	14.1 (8.2)	0.78
Bouin					NO
2002	NONE	NONE	NONE	NONE	NE
Mosch					
2023	NONE	NONE	NONE	NONE	0.42

Kwan 2005	NONE	NONE	NONE	NONE	0.18
Lopez-sol 2017	8.89	4.72	11.54	4.15	1.4
Yuan 2003	NONE	NONE	NONE	NONE	0.02
Lawal 2005	NONE	NONE	NONE	NONE	NO NE
Chen 2015	9.2 (2.7)	5.97 (2.43)	6.47 (1.45)	3.87 (1.7)	NO NE
Russo 2012	NONE	NONE	NONE	NONE	NO NE
Guleria 2017	NONE	NONE	NONE	NONE	NO NE
Feitosa Russo 2016	8 4.2 (3.3)	33.3 2.68 (1.34)	42 6.5 (4.8)	43.85 2.68 (1.8)	NO NE
Russo 2019	5.11, 4.79 (N/A)	3.47, 3.13 (N/A)	5.71, 5.94 (N/A)	4.07, 3.66 (N/A)	NO NE
Stankewitz 2011	NONE	NONE	NONE	NONE	- 0.15
Maleki 2021	NONE	NONE	NONE	NONE	NO NE

Mungoven 2022	NONE	NONE	NONE	NONE	NO NE
Schulte 2020	NONE	NONE	NONE	NONE	NO NE
Tessitore 2011	NONE	NONE	NONE	NONE	NO NE
Weissman 2003	NONE	NONE	NONE	NONE	2.75
Maleki 2012	3.8 (2.2)	4.0 (3.8)	NONE	NONE	NO NE
Buchgreitz 2006	NONE	NONE	NONE	NONE	NO NE
Bogdanov 2019	NONE	NONE	NONE	NONE	NO NE
Rosenberger 2012	NONE	NONE	NONE	NONE	1.89
Wasan 2011	NONE	NONE	NONE	NONE	NO NE
Jensen 2010	NONE	NONE	NONE	NONE	0.47
Kobayashi 2009	NONE	NONE	NONE	NONE	2.52
Wilder Smith 2004	NONE	NONE	NONE	NONE	NO NE

Note. Behavioural data extraction and pain rating average. SD: Standard deviation (all reported standard errors were converted to SDs); PR: Pain rating; N/A= Not available or not assessed; ES: Effect size (Hedges' g), positive numerical values mean patients experienced more pain than controls

Table 3: ALE meta-analysis peak clusters

ALE	N	# Foci	# Exp	Clust er	x	y	z	Vol. threshold	Chosen min. cluster size	Region	Max ALE value
Within-subject cluster-level (Conj)	49 4	45 0	39	1	1.6	8.2	37.7			Cingulate gyrus; medial frontal gyrus	0.017
				2	33.6	12.3	8			Insula; claustrum	0.012

Within-subject cluster-level (Contrast P>C)	49	44	39	1	38.7	0.9	10.8	1240 mm3	200 mm3	Insula; claustrum	0.017
				2	-34.92	10.9	-1.7			Insula; claustrum; inferior frontal gyrus	0.068
Within-subject cluster-level (Contrast C>P)	49	44	39	1	-0.6	4.6	47.2	512 mm3	200 mm3	Medial frontal gyrus, cingulate gyrus; superior frontal gyrus	0.055
Within-subject cluster-level (Patients)	64	26	21	1	36.5	5.9	9.4	8008 mm3	936 mm3	Insula; claustrum; lentiform nucleus; precentral gyrus	0.02
				2	12.3	11.4	37.5			Cingulate gyrus; medial frontal gyrus	0.023

					-37.64	8.6	11.6			Insula; claustrum; inferior frontal gyrus; precentral gyrus	0.02
Within-subject cluster-level (Controls)	23	190	18	1	1.3	5.6	41.3	3952 mm3	1016 mm3	Cingulate gyrus; medial frontal gyrus; superior frontal gyrus	0.025
				2	36.5	10.7	2.4			Insula; claustrum	0.014
Within-subject voxel-level (Conj)				NONE							
Within-subject voxel-level (Patients)	264	260	21	NONE				0 mm3	200 mm3		
Within-subject voxel-	230	190	18	1	1.4	4.2	44	3763 mm3	200 mm3	Cingulate gyrus; medial frontal gyrus	0.025

level (Controls)					. 1	
Between-subject cluster-level (Patients)	2 5 9	1 0 8	2 1	NO NE	0 mm 3	1072 mm3
Between-subject cluster-level (Controls)	2 5 5	4 5	1 5	NO NE	0 mm 3	776 mm3
Between-subject cluster-level (Pooled)	5 5 0	1 5 3	3 6	NO NE	0 mm 3	888 mm3
Between-subject voxel-level (Patients)	2 9 5	1 0 8	2 1	NO NE	0 mm 3	200 mm3
Between-subject voxel-level (Controls)	2 5 5	4 5	1 5	NO NE	0 mm 3	200 mm3

Between-subject voxel-level (Pooled)	515	103	56	NO NE	0 mm 3	200 mm3

Note. Conj: conjunction; P>C: patients greater than controls; C>P: controls greater than patients; N: sample size; Vol.: volume

Highlights

- Meta-analysis reveals brain activity linked to provoked pain in chronic primary pain.
- Convergent activation found in mid-cingulate, frontal gyrus, and anterior insula.
- Patients show stronger activity in anterior insula, controls in mid-cingulate gyrus.
- Cingulate gyrus shows consistent activation across patient and control groups.
- Highlights need for standardised fMRI methods to advance CPP diagnosis and treatment.

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