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Review Article

Role of non-invasive objective markers for the rehabilitative diagnosis of central sensitization in patients with fibromyalgia: A systematic review

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Abstract.
BACKGROUND: Central sensitization cannot be demonstrated directly in humans. Therefore, studies used different proxy markers (signs, symptoms and tools) to identify factors assumed to relate to central sensitization in humans, that is, Human Assumed Central Sensitization (HACS).

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OBJECTIVE: The aims of this systematic review were to identify non-invasive objective markers of HACS and the instruments to assess these markers in patients with fibromyalgia (FM).
METHODS: A systematic review was conducted with the following inclusion criteria: (1) adults, (2) diagnosed with FM, and (3) markers and instruments for HACS had to be non-invasive. Data were subsequently extracted, and studies were assessed for risk of bias using the quality assessment tools developed by the National Institute of Health.
RESULTS: 78 studies ($n = 5234$ participants) were included and the findings were categorized in markers identified to assess peripheral and central manifestations of HACS. The identified markers for peripheral manifestations of HACS, with at least moderate evidence, were pain after-sensation decline rates, mechanical pain thresholds, pressure pain threshold, sound 'pressure' pain threshold, cutaneous silent period, slowly repeated evoked pain sensitization and nociceptive flexion reflex threshold. The identified markers for central manifestations of HACS were efficacy of conditioned pain modulation with pressure pain conditioning and brain perfusion analysis. Instruments to assess these markers are: pin-prick stimulators, cuff-algometry, repetitive pressure stimulation using a pressure algometer, sound, electrodes and neuroimaging techniques.
CONCLUSIONS: This review provides an overview of non-invasive markers and instruments for the assessment of HACS in patients with FM. Implementing these findings into clinical settings may help to identify HACS in patients with FM.

Keywords: Fibromyalgia, central sensitization, nociplastic pain, non-invasive markers, pain threshold, electrophysiological techniques, human assumed central sensitization

1. Introduction

The term nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pai" [1]. Central sensitization (CS) can be described as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" and can therefore be an expression of nociplastic pain [2]. CS results in an enhanced nociceptive neural signaling, meaning that the stimulus intensity necessary to elicit the pain response is lowered, resulting in pain hypersensitivity [3]. This alteration in sensory processing systems is observed in animal experiments [4], and this phenomenon is supposed to be of value to explain multiple chronic pain conditions such as low back pain, osteoarthritis, temporomandibular disorders and fibromyalgia (FM) [5]. FM, with a worldwide prevalence of 2–4%, and temporomandibular disorders are among the most common causes of pain and disability related to CS [6]. Both disorder share features and are influenced by genetic, biological, and psychosocial factors, such as diet, obesity and stressful events [6,7,8]. Because there is no gold standard for the assessment of CS, the presence of it cannot be demonstrated directly in humans. Instead, studies used different proxy markers (signs, symptoms and tools) to identify factors assumed to relate to CS in human, that is, Human Assumed Central Sensitization (HACS). A proxy marker for HACS can be defined as an indirect measurable indicator of the assumed presence of CS. These proxy markers will further be referred to as 'marker' in this review. The term HACS has previously been defined in a review on HACS in patients with chronic low back pain [9]. As FM is related to CS, rehabilitative therapy could play a useful role in the improvement of pain-related and mobility symptoms [7]. Thus, improving the accuracy of FM diagnosis can aid in the rehabilitation process of patients with FM.

Because of the absence of a typical physiological abnormality specific to FM, the diagnosis of FM is based on clinical presentation only, with a diagnostic criterium using a list of eighteen body sites and experiencing pain in at least 11 of the 18 tender points [10]. The 1990 American College of Rheumatology (ACR) classification for diagnosis comprises the assessment of pain in eighteen body sites combined with the average scores of a self-administered questionnaire [11]. The revised 2010 ACR classification includes a calculation of the widespread pain index, a symptom severity scale and does not contain a tender point examination. Diagnostic studies in patients with FM were conducted with the aim of identifying HACS markers, varying from cerebrospinal fluid (CSF) and serum concentrations [12,13, 14] to urinary metabolites such as creatine [11]. Simple clinical tests to objectively identify HACS markers may, however, contribute to setting more suitable and objective diagnosis which are clinically feasible. While there appear to be several studies available, an overview of the current state is missing. The aim of this study was to review the literature to determine non-invasive markers for the presence of HACS in patients with FM and the instruments needed for the assessment of these markers.

Table 1
Eligibility criteria for study selection

	Inclusion criteria	Exclusion criteria
Population	1. Human population	1. Animals
	2. Adults (age 18 or above)	2. Children (age below 18)
Target condition	3. Fibromyalgia diagnosis	3. Pain due to malignancy
		4. Psychosocial problems part of the DSM-5 classification
Type of studies	4. Cross-sectional, cohort, case-control, observational diagnostic, validation studies	5. Systematic reviews
		6. Meta-analyses
	5. Studies published between 01/01/1994 to 01/04/2022	7. Studies before 01/01/1994 OR after 01/04/2022
Outcomes	6. Neurophysiological and non-invasive markers for central sensitization	8. Use of only invasive markers (blood, urine tests)

2. Methods

The search strategy started with a broad search regarding non-invasive markers of HACS for three chronic musculoskeletal pain diagnoses: fibromyalgia, chronic low back pain and osteoarthritis. Due to the vast amount of hits provided by the search, the authors decided to split it in three parts. Therefore, the current study constitutes the first part of a larger review about pain processing in chronic musculoskeletal pain disorders and is focused on markers for HACS in patients with FM. A second part is focused on HACS in patients with chronic low back pain and a third study focusses on HACS in patients with osteoarthritis and other painful syndromes. The current systematic review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] and has been prospectively registered in Prospero (October 2020: CRD42020172382).

2.1. Search strategy

Three electronic databases (PubMed, EMBASE and PsycINFO) were searched on 01/04/2022. MeSH terms in PubMed were incorporated in the search string. Keywords were divided into the three following categories: the target *population* consisted of patients with "Musculoskeletal Pain" OR "Chronic Pain". The target *condition* was HACS. Because there is no consensus or uniformity in terminology, we used the following search terms for HACS conditions: "Central Sensitizatio" OR "Centralized Pain", "Hypersensitivity" and synonyms. Finally, the *outcome* measures "Neurophysiological Biomarker" were related to non-invasive HACS markers. Non-invasive markers are defined as markers determined through a procedure that does not cause a break in the skin, nor creates contact with the mucosa or an internal body cavity. Synonyms of the different keyword groups constituted the search request. The entire search string is presented in Appendix A.

2.2. Eligibility criteria

The eligibility criteria for the article selection are presented in Table 1. The following inclusion criteria were applied: (1) participants had to be adults (age 18 years or older; (2) patients had to be diagnosed with FM according to the American College of Rheumatology (ACR) criteria of 2010 and with the ACR criteria of 1990 for papers published before 201; (3) HACS markers had to be neurophysiological and non-invasiv; (4) the selected studies were published between 01/01/1994 and 01/04/2022. Articles were excluded if (1) included participants suffered from other forms of pain besides FM (but when patients with FM were compared to patients with other forms of pain besides FM these studies were included); (2) participants suffered from psychiatric comorbidity following specified DSM criteria; (3) the study designs were systematic reviews or meta-analyse; (4) the articles used only invasive markers such as blood tests.

2.3. Study selection

The studies were screened (based on title and abstract) by three independent reviewers to exclude studies that were not specific to FM and the study aim. YS screened all, RS screened the first hal; and HT screened the second half. The reviewers subsequently selected articles for inclusion based on full text ($n = 112$). The reviewers discussed this list of studies to resolve disagreements. In the end, there were 78 papers included and 34 studies excluded (see Fig. 1).

2.4. Data extraction

The data extraction process was performed by YS. Two researchers (RS and HT) reviewed the extracted data. The following information was extracted from each study and documented into a table: (1) the study (author names and publication date), (2) the population

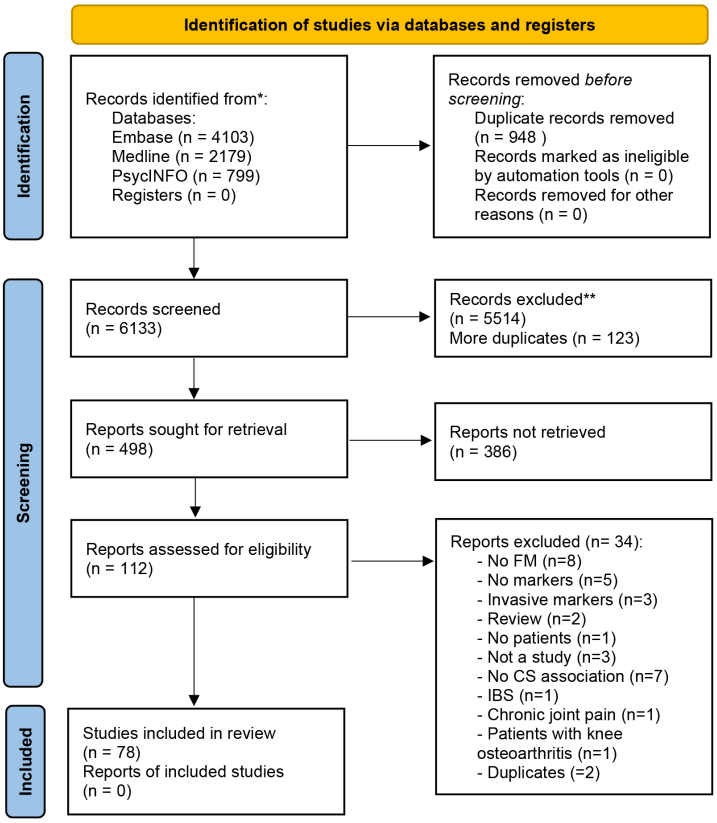

Fig. 1. Flow diagram of study selection process. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

(number of participants with FM, number of healthy controls (HC) if applicable, age, gender and country, (3) study design, (4) aim of the study, (5) hypotheses, (6) inclusion/exclusion criteria, (7) assessment methods, (8) main findings and (9) definitions of HACS, nociplastic pain or hypersensitivity, when stated in the article.

2.5. *Risk of bias and quality assessment*

Quality assessment of the included articles was carried out using the National Institute of Health (NIH) Quality Assessment Tool for case-control studies, observational cohort and cross-sectional studies, and randomized controlled trials (RCTs) [16]. The NIH tool consists of 13 questions for case-control studies, 14 questions for cross-sectional studies and 14 questions for RCTs. Before assessing all the articles, YS, RS and HT first assessed 6 randomly chosen articles and then discussed it together to determine whether they all deduced the same understanding of the assessment questions. Possible answers for each question of the quality assessment were "ye", "no", "cannot determine, not applicable or not reported". The answer 'ye' gave one point, whereas the other answers gave zero points to the study. An overall score between 0 and 13 for case-control studies or 0 and 14 for cross-sectional studies and RCT's, was then calculated for each included study and the studies were subsequently judged as "good" (score of 75% or above), "fair" (score of 50–75%) or "poor" (score below 50%) quality [17]. Discussions between the three authors were held to solve any encountered disagreements.

The quality of the studies was taken into consideration when interpreting results. Markers identified from studies with a quality of at least 'fair' were interpreted as more reliable markers than those identified from studies ranked as 'poor' quality. Furthermore, conflicting outcomes from papers studying the same po-

tential marker were considered as inconsistent results, consequently weighing the marker as 'not valid'.

2.6. Study descriptives

The study descriptives of included articles are population (age and sex), country and number of included participants (patients and healthy controls). The results were divided into two main categories based on whether markers were detected by using measurements to assess peripheral or central manifestation of HACS.

3. Results

3.1. Search and selection

A total of 78 studies fulfilled the eligibility criteria (Table 1) and were included in this study. Peripheral manifestations of HACS include quantitative sensory testing. Central manifestations of HACS include electrophysiological techniques, conditioned pain modulation, pain anticipation and catastrophizing. Contrary to the peripheral manifestation of HACS, central manifestations are measurements of the CNS, such as brain perfusion using electrophysiological techniques and imaging.

3.2. Study characteristics

The study characteristics are shown in Table 2. In total, 2383 patients with FM, 1766 Healthy Controls (HC), and 1085 patients with other chronic pain conditions were included.

Peripheral manifestations of HACS were shown in the following studies: temporal summation of secondary pain (TSSP) and pain after-sensations (AS) were studied in eleven studies [18,19,20,21,22,23,24,25,26,27,28], the autonomic nervous system and slowly repeated evoked pain (SREP) sensitization were studied in five studies [29,30,31,32,33], quantitative sensory testing (QST) measures (heat, pressure and mechanical and sound 'pressure' pain thresholds) were used in thirteen studies [21,23,34,35,36,37,38,39,40,41,42,43,44] and the motor activity and FM was studied in four studies [36,45,46,47].

Central manifestations of HACS were shown in the following studies: pain anticipation was studied twice [48,49], conditioned pain modulation (CPM) was studied nine times [27,29,38,43,50,51,52,53,54], and three studies reported on the effect of distraction on pain [44,55,56], electrophysiological techniques were used in twenty-two studies [28,44,48,49,53,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71], laser-evoked potential (LEP) amplitudes were applied in four studies [72,73,74,75], and brain region activation to stimuli and brain region connectivity were studied in sixteen studies [28,33,44,60,61,62,63,64,66,69,76,77,78,79,80,81].

3.3. Risk of bias and quality assessment

The average risk of bias assessment scores was 39% for case control studies ($n = 65$, Table 3a), 43%, for cross-sectional studies ($n = 9$, Table 3b), and 93% for randomized controlled trials (RCTs, $n = 4$, Table 3c). The higher the assessment score, the lower the risk of bias. All four RCTs were ranked good quality [82,83,84,85], 16 studies were ranked fair quality [21,23,27,30,31,41,42,49,51,61,73,75,78,81,86,87] and 58 studies were ranked poor quality [18,19,20,22,24,25,26,29,32,33,34,35,36,37,38,39,40,43,44,45,46,47,48,50,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,74,76,77,79,80,88,89,90,91,92,93,94,95,96].

3.4. Measurements to assess peripheral manifestations of HACS

3.4.1. Quantitative sensory testing (QST)

Temporal summation of second pain (TSSP) and after-sensations (AS): TSSP, also known as windup (WU), is a process evoked by repetitive harmless stimuli supposed to cause higher excitability of the dorsal horn neurons, mediated by C nociceptive fibers. Pressure algometry was used in three studies [23,26,43] and thermodes were used in seven studies [18,19,20,21,25,27,28] for pressure and heat pain stimulation, respectively, to measure TSSP. Higher TSSP ratings [19], no difference in TSSP ratings [28], higher pain AS [18,26], slower rate of AS decline [19,20,21] and lower stimulus temperature and frequency needed to elicit TSSP in patients [18,24,66] were demonstrated and are, according to our division, signs associated with HACS. The authors of eight studies showed higher TSSP sensitivity in patients with FM [19,20,23,25,26,27,28,43] compared to HC. No TSSP difference between groups was reported in two studies [18,21]. Results are shown in Table 4.

Pain thresholds: Statistically significant lower pressure pain thresholds (PPT) [23,34,35,36,37,41,42,43,44], heat pain thresholds (HPT) [34,41,42,43,44], cold pain thresholds (CPT) [34,37,39,43,44], mechanical

Table 2
Characteristics of included studies ($n = 78$)

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Al-Mahdawi et al., 2021 [96]	31 (23F) patients with FM (18–62 years) and 31 (22F) HC (17–55 years) Iraq	CC	Compare patients with FM and HC with different electrodiagnostic testing and to see whether there is any relationship between the measures	NR	Inclusion: ACR, illness duration from 5 m to 10 y. Exclusion: abnormal upper and lower limb NCSs, EMG and SSR, history of distal symmetrical paresthesia or abnormal sensory examination results, muscle disease, neuromuscular junction disorder, peripheral nerve dysfunction disorders	NR	– Distal sensory latency, distal motor latency, CV, sensory nerve APA, compound muscle APA – Motor unit potentials (MUPs) were analyzed for duration and amplitude – Stimulus at wrist contralateral to recording side. SSR was measured and latency was determined – Stimulous on index finger and CSP was recorded with electrode on abductor pollicis brevis muscle. Thumb abduction, 20 consecutive painful electrical stimuli of 80-mA and 0.5 ms duration were applied to index finger	– No significant difference in SSR in FM vs HC ($P = 0.66$) – No significant difference in CSP onset latency in FM vs HC ($P = 0.41$) – CSP duration $>$ in FM vs HC ($P < 0.001$) – CSP $=$ pause during which muscle is under constant contraction, after stimulation of cutaneous nerve – No correlation between CSP parameters and other ED parameters and age in FM
Baek et al., 2016 [89]	24(23F) patients with FM (45.21 ± 14.38) and 24(21F) HC (48.54 ± 11.84) South Korea	CC	To compare cutaneous silent period (CPS) in FM and HC to understand pathophysiology of FM		Inclusion: ACR Exclusion: distal paresthesia, sensory loss, medical condition associated with peripheral neuropathy	NR	– CSP recorded by electromyographer – during max voluntary contraction, painful stim until complete silent period – CSP duration $=$ time btw start and end of silent period (EMG activity)	– No group difference in CSP onset latencies – CSP onset latency $=$ affected by A-delta fibers instead of CNS control: if no group difference $\longrightarrow$ FM not related to afferent A-delta fiber dysfunction – CSP duration $>$ FM vs HC ($P = 0.021$) $\longrightarrow$ supraspinal control dysfunction (previous study) $\longrightarrow$ dysfunction of CNS pain regulation in FM

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Banic et al., 2004 [57]	22(18F) patients with FM (mean age 47), 27(19F) whiplash patients (39) and 29(20F) HC (46) Switzerland	CC	To show that Patients with FM and whiplash patients have spinal cord hyperexcitability which causes them to experience severe pain after low intensity nociceptive stimulation	That FM and whiplash patients have facilitated withdrawal reflex ⟶ spinal cord hypersensitivity	Inclusion: ACR for FM Exclusion: pain for < 6 months, peripheral/central neurological dysfunction	Decreased reflex threshold indicates spinal cord hypersensitivity	– Nociceptive withdrawal reflex to test excitability of spinal neurons – VAS for pain at rest – Single and repeated electrical stimuli on sural nerve – EMG reflex response recorded from biceps	– Reflex threshold after single and repeated stimuli < in FM vs HC ($P = 0.01$ and $P = 0.04$) – Same for whiplash vs HC ($P = 0.02$ and $P = 0.03$) ⟶ spinal cord neuron hypersensitivity to peripheral stimulation
Bendsten et al., 1997 [90]	25(F) patients with FM (44.9 ± 1.5) and 25(F) HC (41.4 ± 2.6) Denmark	CC	To investigate the perception of pain in Patients with FM' tender muscles		Inclusion: ACR Exclusion: < 18 years, > 65 years, other somatic/psychiatric disease, analgesics, opiates, benzo, antidep	NR	– Palpometer to check the pressure exerted by examiner during palpation – Palpation at trapezius (highly tender) and temporal (largely normal muscle) (reference study) – Both are pericranial muscles – 7 pressure intensities – Pain intensity recorded (VAS) at each intensity – AUC for stim-response curve = tenderness degree	– Trapezius: patient's muscle > tender than HC ($P = 0.02$) – Temporal: muscle tenderness was not different btw FM and HC – Pericranial musculoskeletal tissues > tender in FM than HC – Stim-response curve was linear (in FM) and approximately linear (power function) (in HC) ⟶ qualitatively (not quantitatively) different in both groups
Blumenstiel et al., 2011 [34]	21(F) patients with FM (50.6 ± 9.5), 23(F) chronic back pain (43.4 ± 8.6) and 20(F) HC (38.3 ± 7.6) Germany	CC	To disclose the similarities and differences in the pathophysiology of FM and CBP		Inclusion: ACR for FM Exclusion: comorbidities (neuropathy, diabetes, infections, disc hernia)	NR	– FM and CBP tested on most painful area on back + hand dorsum (pain-free control) – Mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), pressure PT (PPT), cold&heat pain threshold (CPT, HPT)	– Back: FM had < CPT, HPT, MPT, MPS, PPT vs HC ($P < 0.01, < 0.05, = 0.01, < 0.01, = 0.01$) – FM had < CPT, HPT, MPT, > MPS vs CBP ($P < 0.01, < 0.05, < 0.01, < 0.01$) – CBP had < PPT, > VDT (vibration) vs HC ($P < 0.01, < 0.05$) ⟶ only pressure pain dif ⟶

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								peripheral sensitization **Hand**: FM had < MPT, MPS, PPT, CPT vs HC ($P < 0.01, < 0.01, < 0.05, < 0.01$) – FM had < MPS, MPT, PPT vs CBP ($P < 0.01, < 0.01, = 0.01$) – No difference in hand btw CBP and HC ⟶ CBP has **localized** pain problem – FM had ↑ sensitivity for dif pain types at dif areas ⟶↑ sensitivity **generalized** in space (sup&deep, back&hand) ⟶ **central** disinhibition
Bosma et al., 2016 [18]	20(F) patients with FM (39 ± 4.9) and 20 HC(F) (39 ± 10.2) Canada	CC	To characterize the fMRI responses in the spinal cord and brainstem that correspond with TSSP in FM compared to HC	– No difference in TSSP-related brain response while using pain-sensitivity calibrate T° – ↓ fMRI responses in spinal cord + brainstem, that show alterations in descending control system	Inclusion: ACR Exclusion: opioids, NSAIDs	TSSP evoked at lower frequencies ⟶ CS	– Questionnaires – Stimulus T° calibrated to subject's TSSP sensitivity – TSSP condition: repetitive stim at interstimulus interval of 3 s (0.33 Hz) – TSSP-C: 6 s interstim interval (0.17 Hz) and unlikely to cause TSSP – fMRI + pain ratings during stimuli	– T° used for FM < HC ($P = 0.01$) – No difference in ratings btw FM and HC ($P = 0.43$) (because heat stim was calibrated) – No brain region with more activity in TSSP-C vs TSSP in FM – Dorsal horn ROI: BOLD signal changes > in TSSP vs TSSP-C in HC but no difference btw both conditions in FM ⟶ FM have TSSP at lower freq (0.17 Hz) ⟶ CS – Pain-after sensation > FM vs HC for both conditions ($P = 0.01$) ⟶ altered painprocessing in TSSP-C

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Bourke et al., 2021 [43]	19 (16F) patients with FM (36), 19 (13F) patients with CFS (43) and 20 (14F) HC (34) UK	CC	Investigate possible similarity of CS prevalence in patients with CFS and patients with FM compared to HC	– Inefficient CPM and enhanced TS would be similar and greater in CFS and FM compared to HC – Correlation between the aformention-ed measures and PPT, pain intensity, fa-tigue and physical function	Inclusion: CFS diagnosis by CDC criteria, chronic and peristent fatigue as pri-mary complaint in CFS, ACR for FM Exclusion: current psychiatric disorders, no comorbid idiopathic pain disorder, somatic syndrome or comorbid disorder of interest in CFS and FM, smoking, BMI > 30 kg/m2, use of certain medications	CS is defined by the presence of both enhanced TS and inefficient CPM	– Questionnaire measures (PPI, CFQ, anxiety, SF-36-PF) – QST measures: PPT, TPT (CDT, WDT, CPT, HPT) , CPM measured using PPT with tourniquet cuff, TS – Pain intensity rating on NRS	– Questionnaire: PPI and fatigue (CFQ) > in FM vs HC ($P < 0.01$); ($P < 0.01$) – SF-36-PF < FM vs HC ($P < 0.01$) – No difference in state of anxiety between FM and HC ($P = 0.08$) – PPT < in CFS and FM vs HC ($P = 0.03$), no difference btw CFS and FM – No difference between FM/CFS and HC for CDT ($P = 0.56$) and WDT ($P = 0.78$) – CPT > FM vs HC ($P = 0.01$) – HPT < FM vs HC ($P = 0.03$) – TS > in FM vs HC ($P < 0.001$) – Inefficient CPM in 95% of FM cases and 0 HC cases ($P < 0.01$) – CS (based on definition) present in 95% of FM cases vs 0 HC cases ($P < 0.01$) – No correlation between CS measures and PPI, SF36-PF, CFQ or anxiety
Burgmer et al., 2012 [79]	17(F) patients with FM (52.59 ± 7.95) and 17(F) HC (49.53 ± 8.87) Germany	CC	Differentiate between increased pain ratings and hyperalgesia related to peripheral or	– FM would show ↑ sec-ondary but no primary mechanical hyperalgesia vs HC	Inclusion: ACR Exclusion: psychiatric disorder, other pain origin, pain medication	NR	– Numerical rating scale (NRS): intensity of pain – MPQ: for qualitative aspect of pain – Forearm incision ⟶ in-duce primary&secondary hyperalgesia (pH&sH)	– FM > incision-evoked pain at each timepoint ($P < 0.01$) vs HC (NRS) – No difference at each timepoint ($P > 0.06$) for pH

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
			central sensitization and to correlate with cerebral activation pattern	– FM secondary hyperalgesia would correlate differently with activation of cerebral pain matrix, especially central pain inhibition areas			– Measured at different time points (blocks) fMRI	– No interaction effect btw pH and 2groups ($P = 0.40$) – FM > sH vs HC at each timepoint ($P < 0.01$) and over the time course of pain ($P < 0.01$) ⟶ CS not PS – No group difference for correlation btw pH and brain activity – HC: correlation sH and brain activation (DLPF correlation coef $R = -0.34$, $P = 0.01$, SMC $R = 0.38$, $P = 0.01$) – FM: no correlation sH and DLPFC or SMCs ⟶ pain transmission problem at central levels
Burgmer et al., 2009 [71]	14(F) patients with FM (51 ± 7.3) and 14(F) HC (46.9 ± 6.8) Germany	CC	To investigate whether patients with FM show alterations in brain morphology in areas of the pain matrix vs HC and whether such volumetric changes are consequences of chronic pain	Volumetric changes will be present in brain areas related to medial pain system in FM vs HC	Inclusion: ACR Exclusion: other pain origin, psychiatric disorders	Decreased GMV indicate CS pre-condition	– T1-weighted MRI – Assessed 3 chronic pain-specific clinical markers to check for correlation with areas showing volume differences (pain duration, PDI, pain med intake duration) – VBM analysis: whole-brain technique showing change in gray matter	– FM > PDI and HADS vs HC – FM < gray matter volumes in ACC ($P = 0.01$), inf frontal gyrus ($P = 0.04$) and amygdala ($P = 0.01$) – FM: pain duration and functional disability due to pain (PDI) not correlated w gray matter volume in areas showing grey matter volume differences ⟶↓ volume = possibly CS precondition in FM – Pain med intake duration = positive correlation with GMV ($P = 0.01$) in right ACC. ↑ pain med intake duration = ↑ GMV in ACC

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Chalaye et al., 2012 [29]	10(F) patients with FM (46.7 ± 7.1), 13(F) IBS patients (37 ± 15.8) and 10(F) HC (41 ± 8.5) Canada	CC	To compare descending pain inhibition, pain sensitivity and ANS reactivity to pain in FM, IBS and HC	IBS and FM share common but graded pathophysiol-ogy, both having impaired descending pain inhibition vs HC but greatest in FM. Same for ANS dysfunction	Inclusion: ACR for FM, ROME II for IBS Exclusion: other medical condition, having FM + IBS, neurological problems, CVD, opioid, antidep, other pain origin	NR	– Cold water arm immersion pain – Ascending: first fingers, wrist, elbow shoulder (endogenous pain inhibition is moderately activated at beginning) – Descending: opposite (fully activated) – NRS: ratings – ECG for ANS	– Linear relationship across groups for pain intensity: FM most painful, then IBS, then HC least ($P = 0.02$) – Linear relationship ($P = 0.001$) for descending pain inhibition: HC&IBS felt less finger pain during descending sessions vs ascending ($P = 0.007$, $P = 0.008$) vs FM felt no dif ($P = 0.44$) $\longrightarrow$ no pain inhibition – Only FM $\uparrow$ HR due to finger immersion ($P < 0.02$) (sympathetic) and $\downarrow$ parasympathetic activity – Common but graded pain modulation and ANS dysfunction btw pain conditions
Cook et al., 2004 [62]	9(F) patients with FM (37 ± 5) and 9(F) HC (35 ± 3) USA	CC	To examine the function of nociceptive system in Patients with FM using fMRI	– FM will exhibit neural response in pain -related brain regions vs HC for non-painful stim – FM > response in same areas vs HC for painful stim – similar response for perceptually equivalent pain	Inclusion: ACR and chronic fatigue syndrome in FM Exclusion: pain medication < 3w prior, psychiatric disorder	NR	– Ex1: responses to painful stim – Ex2: fMRI + painful and nonpainful stim for 5 conditions – Condition1: no stim – Cond2&5: nonpainful warm stim – Cond3&4: absolute T° pain stim + perceptually equivalent pain stimulus	– Ex1: FM > sensitive to experimental heat pain vs HC ($P < 0.01$) – Cond2&5: FM > activity in prefrontal, supplemental motor area, ACC vs HC ($P < 0.01$) – Painful stim: FM > activity in contralateral insular cortex vs HC ($P < 0.01$) $\longrightarrow$ FM have > activity in pain-related regions to pain and nonpainful stim – Perceptual eq: no group difference in brain response

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
				– FM: nonpainful stim response remains ↑				– Both groups: self-reported pain correlated to cingulate cortex activity (bilat), sensory cortex (contra), inf parietal and ant insular (ipsilateral) ($P < 0.01$)
Craggs et al., 2012 [63]	13(F) patients with FM (43.4 ± 7.5) and 11(F) HC (42.9 ± 10.3) USA	CC	Examine the effective connectivity among TSSP-related brain regions in FM&HC and compare whether they are connected in a similar manner		Inclusion: ACR Exclusion: abnormal findings, unrelated to FM, analgesic, NSAID, acetaminophen use	Increased influence of brain regions represents CS presence	– Previous study: fMRI + repetitive heat pulses (0.33 Hz) on foot (sensitivity adjusted) – Current study: structural equation modeling (for effective connectivity) – 5 pain-related brain regions: thalamus, S1, S2, P-Ins, aMCC	– Previous study: FM ↓ stimulus intensities to achieve same TSSP as HC + no difference in brain activity btw groups + showed brain areas with ↑ activity when TSSP evoked – Current study (predictions confirmed): thal ⟶ direct influence on P-Ins and indirect on P-Ins via S1&S2 – Functional connection from P-Ins to aMCC – New pathway found: thal ⟶ aMCC ⟶ S1 (in both groups and hemispheres) – TSSP brain activity similar to other pain activity (sensory, cognitive and affective dimensions)
De La Coba et al., 2018 [30]	30(F) patients with FM (52 ± 9.57) and 27(F) HC (51.41 ± 9.94) Spain	CC	To examine whether BP-related pain modulation, indexed by static and dynamic evoked pain responses, is altered in FM vs HC		Inclusion: ACR, HC free of pain Exclusion: CVD, neurological disorders, psychiatric/somatic disease,	NR	– Static evoked pain: pain threshold and tolerance – Dynamic evoked pain: slowly repeated evoked pain (SREP) – BP recorded during 5 min period before pain	– SREP sensitization in FM but not in HC ($P < 0.01$) – +correlation btw static pain and BP in HC ($P < 0.05$) ⟶↑ BP = ↑ pain threshold and pain tolerance – No correlation in FM

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								– Neg correlation btw SREP sensitization & FM and not in HC ($P = 0.001$) – HC: BP-related hypoalgesia (for static) but not FM ⟶no BP-related pain inhibition for static measures
De La Coba et al., 2017 [31]	24(F) patients with FM (52.21 ± 9.59) and 24(F) HC (50.96 ± 10.27) Spain	CC	Evaluate degree of pain sensitization elicited by SREP vs pain threshold and tolerance in terms of associations with clinical FM pain ratings (1) and sensitivity and spec in differentiating btw FM and HC (2)	(1) SREP sensitization in FM but not HC (2) FM < threshold-tolerance vs HC (3) FM: stronger association btw pain and SREP sens than with T-T (4) > sens/spec for SREP sensitization vs T-T to discriminate btw groups	Inclusion: ACR, HC free of pain Exclusion: CVD, somatic/psychiatric disease	NR	– VAS: for pain intensity for pressure stim – McGill Pain Questionnaire (MPQ) – 9 pain stimuli at calibrated pressure level (T-T)	– FM > SREP sensitization vs HC ($P < 0.01$) – FM < T-T vs HC ($P = 0.004$, $P = 0.01$) – FM: pain ratings ↑ as trials happened, not in HC ($P < 0.01$) – + correlation btw SREP sensitization and MPQ in FM ($P < 0.01$) – SREP sensitization is better for group discrimination (FM or HC) vs T-T ($P = 0.01$) (higher specificity) – No association btw SREP sensitization and T-T
De Tommaso et al., 2014 [73]	199 (171F) patients with FM (40.55 ± 10.5) and 109 (89F) HC (40.32 ± 9.9) Italy	CC	Examine the nociceptive pathways at the peripheral to the central level in FM		Inclusion: ACR Exclusion: < 8 years of education, CNS disease, drugs acting on CNS, opioids	NR	– Laser-evoked potentials (LEP): pain stimulus – Skin biopsy	– Normal motor&sensory nerve conduction velocities and action potential amplitudes (FM) – N2-P2 complex amplitude < FM vs HC ($P = 0.01$) but not in migraine Patients with FM – N2P2 habituation index (HI) > FM vs HC (all sites) – No correlation btw HI and amplitude

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
								– +cor btw HI and tender point pain ($P < 0.01$) – −cor btw HI and daily life quality ($P < 0.01$) – biopsy: FM loss of epidermal nerve fibers (ENF) and Meisner corpuscles (MC) – Cor btw ENF density & N2P2 amp – No cor betw ENF &HI or clinical feature
Del Paso et al., 2021 [32]	40 (37F) patients with FM (51.15 ± 6.99) and 30 (28F) HC (49 ± 9.36) Spain	CC	Investigate the cardiac, vasomotor and myocardial branches of the baroreflex function in patients with FM compared to HC	Patients with FM would demonstrate an inverse relationship of BRS and BEI in the 3 branches with clinical pain intensity	Inclusion: ACR Exclusion: cardiovascular, inflammatory, metabolic and neurological diseases, mental disorders	Pain in FM is defined by hypersensitivity of central nociceptive pathways and incomplete pain-inhibiting mechanisms	– MPQ, STAI, BDI, OQS – SBP, IBI, SV, PEP, TPR recorded during cold pressor test and mental arithmetic task	– Inverse correlation btw BRS and BEI with clinical pain, cold pressor pain, depression, anxiety, sleep problems and fatigue – cBRS and cBEI < FM vs HC in rest *($P = 0.01$); ($P = 0.01$)* – cBRS ↑ FM vs HC during task and ↓ in FM vs HC during recovery ($P = 0.01$) – vBRS ↓ during cold pressor test in FM ($P = 0.01$) – cBRS and cBEI ↓ in both groups during cold pressor test – cBRS decreased only in HC during task ($P = 0.01$) – mBRS derived from PEP < FM vs HC at rest *($P = 0.048$)* – positive correlation btw cBEI and IBI *($P < 0.01$)* and HRV ($P < 0.01$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								– Negative correlation btw mBEI derived from PEP and PEP ($P < 0.05$) – ↓ reactivity in cBRS and cBEI during cold pressor test in FM vs HC – ↓ reactivity of SBP, DBP and SV in FM vs HC during cold pressor test – ↓ reactivity of IBI, SBP, DBP, PEP and SV variability during arithmetic task
Desmeules et al., 2014 [58]	137 (92.7%F) patients with FM (50.1 ± 9) and 99 (90.9%F) HC (48.9 ± 10.8) Switerland	CC	Evaluate whether neurophysiological, psychological and genetic factors are related in FM	CS observed in FM could be associated with COMT polymorphism (which is linked to ↓ COMT activity)	Inclusion: ACR, HC free of pain and no CNS disorder Exclusion: analgesics (> 4 1/2 lives), specific medical disorders	NFR < 27 mA indicates CS	– QST: periph T° stim: ice water immersion ⟶ hand withdrawal time (latency) – QST: nociceptive flexion R-III reflex: CS presence	– FM < cold&heat pain threshold vs HC ($P < 0.01$) – Cold pain tolerance (ice) < FM vs HC (shorter latency period) ($P < 0.01$) – NFR threshold < FM vs HC ($P < 0.01$) ⟶ **CS** in 71% of FM (NFR < 27 mA = CS)
Desmeules et al., 2003 [53]	85 (89%F) patients with FM (49 ± 9.3) and 40 (87.5%F) HC (47 ± 12.2) Switzerland	CC	Determine whether abnormalities of peripheral and central nociceptive sensory input processing exist outside spontaneous pain areas in FM vs HC, by using QST and a neurophysiologic paradigm independent from subjective reports		Inclusion: ACR, HC free of pain Exclusion: specific medical disorders, necessary analgesic use	– NFR cut-off of < 27.6 mA = 73% sens and 80%spec for detection of central allodynia – non-painful DNIC lead to decreased NFR: this indicates CS	– QST: periph nociceptive pathway: T° perception & T° PT and T° PTolerance – QST: central nociceptive pathway: NFR(obtained after electrical stim of sural nerve area of nonspontaneous pain) – DNIC: conditioning pain stim leads to ↓ in NFR amplitude. Nonpainful stim should have no effect	– QST periph: FM < cold & heat pain threshold vs HC ($P < 0.01$, $P = 0.01$) – Cold pain tolerance < FM vs HC ($P < 0.01$) – T° detection threshold similar in groups ⟶ **no** peripheral large and small fiber lesion in FM – Subjective pain threshold after electrical sural nerve stim ↓ in FM vs HC – QST central: NRF threshold < FM vs HC (22.7 mA)

Table 2, continued

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								– NFR cutoff of < 27.6 mA = 73%sens and 80% spec for detection of central allodynia in FM ⟶ help chose which FMpatients can benefit from central analgesics – DNIC in FM lead to ↓ NFR amp when non-painful conditioning ⟶ CS and alteration in inhibitory pathways
Donadel et al., 2021 [81]	22 (F) patients with FM (47.14 ± 9.49) and 19 (F) HC (34.68 ± 12.45)	CC	Compare the cortical activation and deactivation patterns in patients with FM and HC after 2 stimuli through the assessment of HbO and BOLD fNIRS	Peak latency and HbO concentration differences before and after stimuli would be shorter and larger, respectively, in patients with FM than in HC (explaining a faster cortical response in FM)	Inclusion: ACR Exclusion: pregnant participants, history of malignancy or uncompensated chronic disease, history of neuropsychiatric comorbidities, use of certain medication	Central sensitivity syndrome defined as widespread pain and a state of high reactivity amplifying nociceptive stimuli	– Hand immersed in water at 25°C (primary stimuli) and 5°C (secondary stimuli) – 2 min rest after both thermal tests – Removal of hand from water after 30 s or at first pain sensation – fNIRS at PFC and MC – GEE models to compare effect of speed of activation/max cortical activation (peak latency) and cortical deactivation based on Δ-HbO and Δ-HbO* respectively – BDI, STAI, BP-PCS – ROC analysis	– Δ-HbO (peak latency) difference at left MC at primary stimulus vs secondary stimulus > in FM vs HC ($P = 0.02$) → cortical activation occurs slower at left MC in FM than HC – Δ-HbO* at left PFC at primary stimulus vs secondary stimulus ↑ by 47.82% in FM and by 76.66% in HC ($P = 0.02$) → cortical late response (at left PFC) is higher in HC than FM – Δ-HbO* at left MC at primary stim vs secondary stim ↑ more in FM than HC ($P = 0.02$) (table 2 shows $p < 0.001$?) → lower deactivation at left MC in FM than HC – CSS score with Δ-HbO* at left PFC showed a ROC analysis with the best discriminatory profile CI 95%, 0.61–100

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Fallon et al., 2013 (Ipsilateral) [60]	19(F) patients with FM (40.01 ± 7.95) and 18(F) HC (39.23 ± 7.99) UK	CC	Evaluate cortical activation patterns during mechanical-tactile stimulation in FM and correlate cortical activation changes with clinical symptoms	Patients with FM would report subjective pain and show alterations in α and β band ERD amplitudes and that these ERD differences would correlate with symptoms	Inclusion: ACR Exclusion: other disorders, CNS medication, analgesics (except paracetamol)	Increased ERD could be a physiological correlate of CS	– Forearm brushing (innocuous) (mechanical brush stimulation) – EEG recorded – At the end: manual tender point scale (MPTS) examination + rated pain during palpation of points – Amplitude changes analyzed in α freq band: (8–13 Hz), β band: (16–30 Hz) – Compared event related desynchronization (ERD) during brushing btw groups	– FM had ERD in β band in ipsilateral (right) hemisphere during brushing (but not HC) $\longrightarrow$ ipsilateral cortical activation in FM during brushing $\longrightarrow$ altered central processing of nonpainful stimuli in FM – Correlation btw MTPS scores (clinical severity) and β band ERD size in ipsilateral central-parietal region ($P = 0.05$) $\longrightarrow\uparrow$ ipsilateral ERD = physiological correlate of CS – Beamformer analysis: FM activation in bilat insula, S1 and ipsilateral S2 cortices but HC only contralateral (left) hemisphere
Fallon et al., 2013 [91]	16(F) patients with FM (38.5 ± 8.45) and 15(F) HC (39.4 ± 8.7) UK	CC	Evaluate whether morphological alterations to subcortical brain regions may contribute to pathophysiological mechanisms and pain in FM	Patients with FM would show subcortical abnormalities in shape and volume and that the degree of these changes would correlate with severity of clinical measures (MPTS)	Inclusion: ACR Exclusion: other disorders, analgesics (except paracetamol), CNS medication	NR	– Subcortical segmentation – Vertex analysis: evaluate group differences in shape – Volumetric analysis – Brain MRI – Correlation btw total GMV and symptom severity (MTPS, BDI, FIQ)	– $\downarrow$ mean brainstem volume of FM vs HC ($P = 0.01$) – Left lateral aspect of lower brainstem (medulla) shape alterations in FM and volume reduction – Correlation btw $\downarrow$ brainstem volume and MTPS scores ($r = -0.45$, $P = 0.04$) – FM: $\downarrow$ grey matter volume in brainstem and left precuneus and $\uparrow$ in bilateral S1 cortices

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								– No significant difference in mean total grey matter V (TGMV) in FM vs HC ($P > 0.05$) but was < in FM – ↓ TGMV = ↑ MTPS in FM ($r = -0.63$, $P = 0.01$)
Gentile et al., 2020 [92]	38(35F) patients with FM (42.1 ± 10.1) and 21(15F) HC (32.6 ± 13.9)	CC	To investigate the motor cortical metabolism and changes of LEPs parameters in patients with FM and HC during movement tasks	NR	Inclusion: ACR, right-handed Exclusion: < 8 years of education, PNS or CNS diseases, other morbidities, history of cancer, use of drugs acting on CNS, chronic opioid therapy	NR	– SFT and FFT tasks repeated during laser stimulation on both moving and non-moving hands – fNIRS-EEF recording during tasks – Mean HbO2 concentrations were calculated	– FM had slower finger tapping vs HC – N1 and N2P2 amplitude ↓ in FM vs HC when stimulation on right hand – No significant LEP parameter changes when stimulation on left hand – FM had ↓ tone of cortical motor area activation (and this finding was more pronounced during fast movement)
Gerdle et al., 2010 [93]	27(F) patients with FM (37 ± 5) and 30(F) HC (40 ± 5) Denmark	CC	Investigate differences in neuromuscular control (differential activation = shifts in activity btw regions in a muscle) within trapezius muscle in FM vs HC	NR	Inclusion: ACR, HC free of pain	NR	– Symmetrical bilateral shoulder elevation – Different weights – Surface EMG recorded – Measured differential activity btw cranial and caudal part of muscle = EMG amplitude differences btw cranial and caudal parts	– 0 kg, 1 kg: freq of differential activation btw cranial/caudal < FM vs HC ($P < 0.04$) – no difference btw FM and HC for 2 kg, 4 kg – ↑load⟶↓median freq of differential activation in HC but no change in FM with load – 0 kg, 1 kg: duration of dif activation > FM vs HC ($P < 0.03$) – No difference btw groups for 2 kg, 4 kg

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Gerhardt et al., 2016 [41]	48(24F) CLP patients (59.7 ± 11.8), 29 (17F) CWP patients (55.2 ± 8.3), 90 (80F) FM (55.1 ± 9.3) and 40 (17) HC (61.6 ± 12) Germany	CC	– To know if patient's sensory profiles distinguish between CLP and CWP subgroups of CBP patients – To see to what extent CLP and CWP patients differ from Patients with FM	NR	Inclusion for CBP: CBP as main symptom for > 45 days. For FM: ACR, chronic back pain even if not primary symptom. HC free of pain Exclusion for CBP: pathologies of CBP (hernia), diseases affecting sensory processing, opioid use	NR	– QST: WDT, CDT, HPT, CPT, PHS, MDT, MPT (pinprick), MPS, WUR, PPT, VDT tested on painful area on back and pain-free area on had – Psychosocial: HADS – body pain diagram	– CLP > sensitivity to PPT in back vs HC, no dif in hand – CWP > sensitivity to HPT, > WUR in back and > sensitivity to CPT and HPT in hand vs HC – FM > sensitivity to HPT, PPT, > WUR in back and > sensitivity to WDT, CPT, HPT and PPT in hand vs HC – Back: – no difference in back between CLP and CWP – FM > sensitivity to HPT, PPT, > WUR vs CLP – FM > sensitivity to PPT vs CWP but not in other modalities – Hand: – CWP and FM > sensitivity to WDT and HPT vs CLP – FM > sensitivity to CPT and PPT vs CLP – No different in hand btw CWP and FM except > sensitivity to PPT in FM vs CWP **Conclusion** CWP and FM: central descending control mechanism Anx, functional impairment, dep > in FM vs CWP

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Goubert et al., 2017 [23]	26(19F) FM (45 ± 9), 23(14F) RLBP (31 ± 10), 15(8F) mild CLBP (34 ± 10), 16(8F) severe CLBP (46 ± 14) and 21(12F) HC (38 ± 13) Belgium	CS	Compare QST assessment in different LBP patient groups with FM and HC, with regard to chronicity	Altered pain processing in severe CLBP but not in RLBP. Mild CLBP in between RLBP and severe CLBP	Inclusion: ACR for FM Exclusion: other specific diseases, antidep or analgesics (except NSAID, paracetamol)	Decreased PPT indicate hypersensitivity	– Manual pressure algometry: evaluate pressure pain threshold and TS of pain – Cuff algometry: evaluate pressure detection pain threshold (cPDT) and pressure pain tolerance threshold (cPTT), spatial summation (SS), conditioned pain modulation (CPM)	– PPT < FM vs HC, RLBP, severe CLBP ($P = 0.01, 0.03, 0.05$) in quadriceps, ($P = 0.01, 0.01, 0.04$) in LB, ($P = 0.01, 0.03, 0.04$) in trapezius⟶ FM hypersensitivity – TS > FM vs HC, RLBP ($P = 0.05, < 0.05$) quad, ($P = 0.02, < 0.05$) trap ⟶ pain facilitation – cPTT < FM vs HC, RLBP ($P = 0.01, 0.04$) and in severe CLBP vs RLBP ($P = 0.04$) ⟶ deep tissue hypersensitivity ⟶ altered pain processing in FM and CLBP – No significant group difference for SS or CPM
Giesecke et al., 2004 [67]	16 (12F) FM (45 ± 12), 11 (8F) CLBP (44 ± 13), 11 (4F) HC (41 ± 7) Germany		To compare sensory testing and fMRI results between idiopathic CLBP patients, patients with FM and HC	NR	Inclusion for CLBP: LBP = dominant symptom, pain for min. 12 w For FM: ACR HC free of pain and morbidities Exclusion: opioid use, pain in areas other than LB (for CLBP), other causes of pain	NR	– Questionnaires: CES-D, STPI, SF-MPQ – Body pain diagram – Experimental pain assessed + fMRI – Stimuli delivered at thumbnail – First: stimuli given in ascending manner of intensity (start at 0.5 kg/cm2) – Second: stimuli given at 20-sec interval in random order	– ↑pain in FM (body map) vs CLBP and HC – ↑tender points in FM vs CLBP and HC – ↑psychological problems in FM vs HC – Similar pain thresholds in FM and CLBP – Signif. lower in FM and CLBP vs HC – Pressure intensity needed to evoke pain ↓ in FM and CLBP vs HC fMRI: – equal pressure condition: ↑ signal in contralat S1&S2, ipsilat S2, IPL and cerebellum (pain processing regions)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								in CLBP and FM, but same stimuli caused less pain in HC and ↑ in controlat S2 only – Equal pain condition: 3 groups showed ↑ signal in contralat S1, S2, IPL, insula, ACC and ipsilat S2 and cerebellum. However, ↑ activation in patients vs HC
Guedj et al., 2007 [70]	18(F) patients with FM (49 ± 11) and 10(F) HC (52 ± 7) France	CC	Investigate brain processing associated with spontaneous pain in FM	Cerebral perfusion abnormalities would show evidence of altered cerebral processing linked to spontaneous pain in FM	Inclusion: ACR Exclusion: psychiatric disease, other medical condition, specific meds	NR	– ^{99m}Tc-ECD SPECT for neuroimaging – VAS pain scores	– Hypoperfusion: bilateral frontal, ant/post cingulate and/or medial temporal lobes, left pontine tegmentum, thalamus and right putamen = affective and attentional dimension of pain – Hyperperfusion: right centroparietal lobe (SI, SII) = sensory dimension of pain – SPECT = tool for follow up of recovery
Hazra et al., 2020 [33]	50 (42F) patients with FM (38.88 ± 10.52) and 50 (40F) HC (37.78 ± 8.56) Italy	CC (CS?)	Assess and compare central sensitization and autonomic activity in patients with FM and HC	Central nervous system hyper-sensitivity in patients with FM will explain the generalized pain symptoms in FM	Inclusion: ACR Exclusion: psychiatric disorder, regional pain syndromes, hypothyroidism, major systemic infection, condition having an effect on ANS, disorder of cerebral vascular system, connective tissue or peripheral nerve	CS assessed by increase in prefrontal cortical activity by means of fNIRS for oxygenation measures and patient history (VAS, WPI)	– Autonomic activity (HRV with ECG, EDA) measured during rest, CPT and DBT – Pre-frontal cortical activity measures with fNIRS measuring cortical oxygenation HbO – VAS during CPT	– HR at rest is significantly > in FM vs HC *($P < 0.05$)* – HR ↑ during CPT and DBT than at rest, no sign difference btw groups – HRV? – ↑ in HbO at PFC at rest and during CPT in FM vs HC *($P < 0.01$ for 15 fNIRS detectors on scalp)* → altered central nervous system processing – During CPT, FM reached peak HbO concentration faster than HC

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								– EDA amplitude > in FM vs HC during rest and CPT ($P < 0.05$) – VAS ↑ during CPT vs rest in FM *($P < 0.05$)* – VAS ↑ during CPT in FM vs HC ($P < 0.05$)
Hurtig et al., 2001 [39]	29(F) patients with FM (46y) and 21(F) HC (39y) Sweden	CC	Investigate whether Patients with FM can be subgrouped regarding thermal hyperalgesia and if these subgroups differ in clinical appearance	NR	Inclusion: ACR, HC free of pain	NR	– VAS pain scores – Cold & warm thresholds (CT, WT): sensation of cold or warmth perceived – T° pain thresholds (CPT, HPT) – Tactile threshold: when feel touch on skin	– HPT, CPT < FM vs HC ($P < 0.01$ both) – 2 FM subgroups (1: HPT = 44.1; CPT = 13.6) (2: HPT = 39.2; CPT = 23.5) – Sub2 is more deviated than HC (sub1: intermediary) – Sub1 vs HC: signif different in CPT ($P < 0.05$) – Sub2 vs HC: signif dif in CPT&HPT ($P < 0.01$) – Sub1&2 differed in hand pain intensity and affective hand pain (signif) (sub2 more local pain intensities)⟶ peripheral sensitization? – Sub2 worse than sub1 regarding sleep quality & tender point number (nonsignif) – ↑ tender point score ⟶ ↑ chance of being in sub2 ⟶ central factor involvement?
Ichesco et al., 2014 [80]	18(F) patients with FM (35.8 ± 12) and 18(F) HC (32.3 ± 11.3) USA	CC	Investigate whether IC-CC connectivity patterns are seen in FM and whether they are related to the	Differences in IC-CC and IC-IC connectivity would be seen in FM and that it might provide	Inclusion: ACR, >18 y, r-handed Exclusion: treatments after consent, opioids, other pain origin, other study, psychiatric illness	NR	– Demographics, clinical pain, experimental pain (noxious pressure stim), mood assessed – Resting state fMRI – IC: insular cortices – CC: cingulate cortices	– FM: > connectivity btw: **right** AIC and right sup temporal gyrus; btw right MIC and right MIC&MPCC; right PIC and left MCC&PCC – HC: > connectivity btw

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
			hyperalgesia in FM	insights into central neural correlates of chronic pain				**left** AIC and r&l MFgyrus; left PIC and right SFgyrus – FM: ↑ PosteriorIC-PosteriorCC and MIC-MCC connectivity associated with ↓ PPT
Ichesco et al., 2016 [64]	12(F) patients with FM (38.5 ± 12) and 15(F) HC (39.9 ± 13) USA	CC	Perturb the central pain system with calibrated pressure pain stimuli and monitor changes in fcMRI induced by this acute pain	Patients with FM would display increased fcMRI in regions involved in pain processing after experimental pain vs HC	Inclusion: ACR, > 18 y, r-handed Exclusion: treatments after consent, opioids, other pain origin, other study, psychiatric illness	NR	– VAS pain ratings – Pressure pain stimuli to thumbnail – Resting state analysis	– FM > resting state connectivity vs HC after painful stimuli btw r AIC and left ACC & btw left AIC and left parahippocampus gyrus (PHG) – FM > connectivity btw thalamus and DMN strucutures (precuneus&PCC) vs HC after pain – thalamus-DMN connectivity related to VAS scores – IC & ACC = affective dimension of pain
Janal et al., 2016 [21]	100(F) TMD-only patients (36.3 ± 17.3), 25(F)TMD + FM (43.4 ± 20.4) patients, 43(F) HC (36.7 ± 14.2) USA	CC	Determine whether CS is found preferentially in myofascial TMD patients that have orofacial pain as regional manifestation of FM	NR	Inclusion: ACR Exclusion: controls with face trauma, dental treatment, facial pain	TSSP and pain AS indicate CS	– QST: warm & pain thresholds (heat stim) – TS and AS evaluation	– Pain threshold and TS similar btw groups – AS (indicator of CS) after summation trials (TS) decayed more slowly in cases vs HC ($P = 0.01$) but similar decay rate in TMD-only and TMD + FM ($P = 0.32$) ⟶no different pain maintenance in TMD with and without FM

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Jespersen et al., 2007 [35]	48(F) patients with FM (49y) and 16(F) HC (45y) Denmark	CC	Evaluate the use of cuff pressure algometry (CPA) in FM and to correlate deep-tissue sensitivity assessed by CPA with other FM disease markers	NR	Inclusion: ACR, HC free of pain Exclusion: other rheumatic disease, psychiatric disorder	Decreased PPT indicate hypersensitivity	– Tourniquet cuff on gastrocnemius muscle and subject stops inflation – VAS pain ratings – Pressure-pain tolerance and threshold – FM markers: isokinetic knee muscle strength (IKMS), tenderpoint count, myaglic score, BDI, FIQ	– PPT and PPtolerance < in FM vs HC ($P < 0.04$) ⟶ hyperalgesia in FM – PPT&tolerance and IKMS correlation ($P < 0.01$): ↓ PPTs associated with ↓ muscle strength ⟶ **tool (CPA)** – No correlation btw CPA and tenderpoints, myalgic scores, BDI
Kosek et al., 1996 (Sensory) [37]	10(F) patients with FM (42.7y) and 10(F) HC (42.3y) Sweden	CC	Examine whether sensory abnormalities in FM are generalized or confined to areas with spontaneous pain	If FM pain is due to dysfunction of central processing of somatosensory input (not peripheral) ⟶ general ↑ in pain sensitivity (not restricted to spontaneously painful areas)	Inclusion: ACR, normal lab results, HC free of pain	NR	– VAS pain ratings – QST performed on 4 sites: max pain, homologous contralateral site, site of no pain and h contralateral site – Von Frey filaments to asses low-threshold mechanoreceptive function – T° sensitivity testing (CT, WT, CPT, HPT) – Pressure algometer	– Light touch perception threshold < FM at max pain site vs homologous site ($P < 0.05$) – WT < FM vs HC at max pain site and homologous ($P < 0.01$) but not at pain free sites ⟶ afferent activity modulation system dysfunction but: – HPT < in FM vs HC at all sites ($P < 0.02$) – CPT < in FM vs HC at all sites ($P < 0.01$) – PPT < in FM vs HC at all sites ($P < 0.01$) – PPT < max pain site vs homologous ($P < 0.01$) ⟶generalized ↑ sensitivity in FM = unrelated to spontaneous pain ⟶ CNS dysfunction

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Kosek et al., 1996 [36]	14(F) patients with FM (45.6y) and 14(F) HC (36.8y) Sweden	CC	Evaluate influence of submaximal isometric contraction on pressure pain thresholds (PPT) in FM and HC before and after skin hypoesthesia	NR	Inclusion: ACR, normal lab results, HC free of pain	NR	– Pressure algometry before, during and after isometric contraction of 22% MVC – PPTs reassessed after anesthetic cream and placebo cream	– PPT $<$ in FM vs HC during contraction (start $P < 0.01$; middle $P < 0.01$; end $P < 0.01$) and during post-contraction ($P < 0.01$) $\longrightarrow$ due to abnormal pain modulation during contraction or ischemia $\longrightarrow$ mechanonociceptor sensitization $\longrightarrow \uparrow$ pain during and after exertion in FM – No difference in either group btw EMLA side and placebo cream side during or after contraction – PPT $\uparrow$ in HC after EMLA at rest but not in FM ($P < 0.01$) $\longrightarrow$ FM have $\uparrow$ deep tissue pressure pain sensibility
Lee et al., 2018 [59]	10(F) patients with FM (45.7 ± 11.4) USA	CS	To analyse resting state EEG of Patients with FM to test whether ES is a mechanism involved in the hypersensitivity of FM brains	Explosive synchronization (ES) can be a mechanism of the hypersensitivity in FM brains	Inclusion: ACR, female, 18–65 age range Exclusion: current psychiatric disorder, HADS > 11, chronic infection, chronic pain causing condition, seizure, BMI > 40, analgesics	ES condition represent brain hypersensitivity	– EEG: 10 min of resting state + clinical pain assessment (VAS) – EEG network configuration for ES conditions	– Positive correlation of FM with ES network condition (Spearmen correlation $= 0.79$, $P < 0.01$) $\longrightarrow$ FM brain shows ES conditions – positive correlation for chronic pain intensity and freq difference (ES condition) (Spearman correlation $= 0.72$, $P < 0.05$) – ES network has larger network sensitivity than the non-ES network ($P < 0.01$) $\longrightarrow$ ES condition networks are more sensitive to stimuli than non-ES network

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Lim et al., 2015 [94]	21(F) patients with FM (49.9 ± 8.7) and 21(F) HC (44.8 ± 8.2) South Korea	CC	To investigate intracortical excitability of primary somatosensory cortex (S1) and its potential role in clinical pain in Patients with FM	– Decreased intracortical inhibition of S1 in Patients with FM – Higher reductions in inhibition = increased clinical pain	Inclusion: ACR, widespread pain > 3 months < 10 years, pain intensity > 40 (0–100), 30–60 age range Exclusion: secondary FM, psychiatric disorder/CNS history, peripheral neuropathy	NR	– Median nerve stimulation to the wrists. – Assessed peak-to-peak amplitudes of N20m–P35m – Paired-pulse suppression (PPS) = ratio of the amplitudes of the second to first response – MEG	– Linear regression analysis – PPS ratio for N20m–P35m in both hemispheres were higher in Patients with FM compared to HC ($P = 0.01$) – Correlation with pain: higher PPS ratio in left hemisphere was associated with higher clinical pain ratings in the sensory dimension of pain (r2 = 0.340, $P = 0.01$)
Loggia et al., 2014 [49]	31(87.1%F) patients with FM (44.0 ± 11.9) and 14 HC (71.4%F) (44.2 ± 14.3) USA	CS	To show potential dysregulation in the neural circuitry related to pain experience (anticipation of pain and pain relief)	NR	Inclusion: ACR Exclusion: HC were free of chronic pain, rheumatic disease Exclusion for both: age < 18, psychiatric, neurologic disorder, opioids	NR	– Cuff pressure pain stimulation – Brain activity: blood oxygen level-dependent (BOLD) fMRI – Visual cues prior to cuff onset and offset (anticipation of pain/relief)	– FM: pressure to elicit target pain rating < HC ($P < 0.01$) – FM and HC: pain anticipation ⟶ brain region activation (S1 and motor cortices) – HC > BOLD signal during pain anticipation than FM ($P < 0.05$). – FM < responses in ventral tegmental area (dopamine-rich region related to reward/aversive signal processing) ⟶ "altered dopaminergic neurotransmission in FM"

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Loggia et al., 2015 [48]	31(4M) patients with FM (44.0 ± 11.9) USA	CS	To investigate the association between catastrophizing and brain responses to pain anticipation in FM	– individual levels of catastrophizing modulate brain responses to pain anticipation in FM – anticipatory brain activity mediates the hyperalgesic effect of higher catastrophizing	Inclusion: ACR Exclusion: age < 18, neurological disorder history, head injury history, CVD, opioids	NR	– fMRI and mediation analyses – Catastrophizing assessed using the Pain Catastrophizing Scale (PCS)	– PCS scores negatively correlated with cuff pressure ($r = -0.37$, $p < 0.05$): less cuff pressure to elicit pain is associated with higher catastrophizing – Right lPFC: negative correlation between PCS score and brain response to anticipation – Mediation analyses: pain anticipatory activity of the ant/vent lPFC mediates association between catastrophizing and cuff pressure – Decreased pain anticipatory activity in LPFC mediates hyperalgesic effect of catastrophizing – Catastrophizing ⟶ less activity of descending pain modulatory systems
Lopez et al., 2014 [77]	35(F) patients with FM (46.55 ± 5.94) and 25(F) HC (44.64 ± 5.94) Spain	CC	To identify brain response alterations to non-painful sensory stimuli (auditory, visual, tactile) and their association with clinical pain severity	– 2 changes in FM 1. Reduced response to non-painful stimulation in early sensory cortices 2. Increased response in insula + areas involved in multisensory integration and affect	Inclusion: ACR, Vision, hearing normal Exclusion HC: neurologic disorders, chronic/acute pain, substance abuse, psych. illness	NR	– Self reported measures of multisensory sensitivities (THS and AASP) – fMRI: alternating 30 s rest and activation(x4) Activation = visual and auditory stimulation + touching the tip of the thumb with other fingers	– FM > subjective sensory sensitivity to acoustic stim. during THS ($P < 0.01$) and visual ($P < 0.0001$) and tactile ($P < 0.01$) of AASP. – FM: decreased activation in primary/secondary visual and auditory cortices – Higher FIQ and pain scores associated with lower activation in visual areas. – FIQ negatively correlated with activation in auditory areas

Table 2, continued

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								– FM: lower activation of S1 is associated with hypersensitivity to non-painful sensory stim in daily life
Lopez et al., 2017 [61]	37(F) patients with FM (46.27 6 7.72) and 35(F) HC (43.86 6 6.05) USA	CC	To identify a neurophysiological signature sensitive to FM	NR	Inclusion: normal vision and hearing, ACR Exclusion HC: neurologic disorders, chronic/acute pain, substance abuse, psych. illness history	increased NPSp response indicates enhanced pain processing	– FIQ, SF-36, HADS – Alternating 30 s rest and activation period (visual, aud, tactile stim)(x4) – + subjects touch tip of thumb with other fingers ⟶ sensory and motor systems – Pressure stimulation task: rate pain intensity after fMRI(NRS) – Studied brain response alterations during pain processing using fMRI based neurological pain signature (NPS) – Logistic regression to combine results from the 3 fMRI-based classifiers (NPS, FM-pain, and multisensory) into one signature of FM status	– Increased pain intensity in FM for low-pressure intensity fMRI task (4.5 kg/cm^2) (P <0.01) – FM + HC (for both intensities): NPSp responses (pain-specific brain regions). – FM response to low pressure > than HC (P = 0.01) ⟶ mechanical pain hypersensitivity – Subjective reports (high pressure for HC and low for FM) of pain = proportional to NPSp responses – Mediation analysis: FM/HC differences in pain intensity = mediated by NPSp brain response. – Greater pain ⟶ activation NPSn regions at low pressure = ID feature for FM – Higher pain-evoked activation in NPSn regions ⟶ greater FIQ scores (P = 0.06) – Higher depressive sympt. predicted by stronger NPSn responses (t = 2.09, P = 0.04).

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Lorenz et al., 1998 [72]	10(F) FM and 10 HC(F) (age-matched) Germany	CC	– Distinguish between hyperalgesia (enhanced pain sensation) and hypervigilance (perceptual amplification of sensations) – Compare amplitudes of laser evoked potentials (LEP) between FM and HC and differentiate between components	NR	NR	NR	– CO_2 laser pulses on hand + auditory stimulus – Verbal pain report ⟶ triggered an auditory evoked potential (AEP). – EEG + t-tests for comparison	– FM < pain threshold ⟶ hyperalgesia – No group difference for sensations⟶ no hypervigilance – LEPs produced higher N1 and P2 amplitudes in FM – N1 and P2 potentials of AEPs were not different between groups.
Maestu et al., 2013 [76]	9(F) patients with FM (36.1 ± 3.6) and 9(F) HC (28.4 ± 3.6) Spain	CC	To characterize brain response differences when stimulation pressure is adjusted to subjective levels of pain in both groups	NR	Inclusion FM: ACR, diagnosis > 12 months prior to study, 18–60 age range Exclusion (FM and HC): other medical conditions	NR	– MEG to investigate brain responses – Device delivered pressure pulses – Amount of pressure adjusted to produce similar subjective pain in both groups – Compared responses evoked by sub and suprathreshold stimulation (using a cluster-based permutation testing)	– FM > activation vs HC in somatosensory, temporal, parietal and prefrontal areas at early (short) latencies and prefrontal areas at late (long) latencies – FM increased brain response after pain threshold adjustments
Maestu et al., 2013 (Reduction) [82]	54(F) patients with FM: 28 simulation group and 26 sham group Age (40.7 ± 6.7) Spain	RCT	To test the effect of very low-intensity transcranial magnetic stimulation (TMS) on FM symptoms	NR	Inclusion FM: ACR, diagnosis > 12 months prior to study, female, 20–60 age range, blood tests results Exclusion: other interfering medical condition	NR	– Stimulation/sham sessions 1/week for 8 weeks – EEG, pressure algometer for pain thresholds	– Pain threshold increase was > for stim. group ($P = 0.01$) (after 1st session) – Improvement in the ability to perform daily activities ($P = 0.03$) and sleep quality ($P = 0.04$), and a decrease in perceived pain ($P = 0.02$) after week 6 for stim. group

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
								– No significant changes for fatigue, anxiety, depression, severity of headaches or serotonin levels
Martinsen et al., 2014 [55]	29(F) patients with FM (mean age 49.8 years, range 25–64) and 31 HC(F) (mean age 46.3 years, range 20–63) Sweden	CC	– To investigate distraction-induced analgesia in Patients with FM using Stroop color word task (SCWT) – Assess reaction times (RTs) and fMRI to investigate cerebral activity patterns in FM and HC during SCWT	Already known: SCWT activates dorsal ACC – HC: reciprocity between dACC and dlPFC (longer RT during SCWT incongruent trials ⟶ higher dACC and lower dlPFC activation and vice versa) – if Patients with FM have dysfunction of ACC ⟶ reduced activation of ACC is expected during SCWT	Inclusion FM: 20–65 age range, ACR Exclusion: high BP (> 160/90 mmHg), osteoarthritis, psychiatric disorders, analgesic use	NR	– PPT assessed using pressure algometer – SWCT had 2 paradigms: congruent and incongruent – PPTs were assessed during SWCT	– PPTs > in FM during congruent SCWT vs baseline ($P < 0.05$) ⟶ FM have normal ability to regulate pain sensitivity while distracted – PPTs > in HC during congruent SCWT compared to baseline ($P < 0.01$) – FM had longer RTs vs HC (⟶ cognitive difficulties) during incongruent ($p = 0.01$) and congruent ($p = 0.03$) SCWT ⟶ cognitive difficulties are associated to less activation of caudate nucleus and hippocampus during incongruent SCWT(FM) – Longer RTs during incongruent compared to congruent in both groups – ↑ activation in caudate nucleus (HC) – No ACC dysfunction during SCWT in FM
Martucci et al., 2019 [65]	16 patients with FM (47.13 ± 9.82) and 17 HC (48.71 ± 11.10) USA	CC	To observe altered frequency-dependent activity in spinal cord in FM using resting-state fMRI of the cervical spinal cord	Observe signals indicative of increased resting-state activity (hyperactivity) within the cervical spinal cord in FM	Inclusion FM: ACR, symptoms present > 3 months, no other disorder causing pain, pain score > 2 Exclusion: opioid medication, depression, anxiety	NR	– Analyzed the amplitude of low-frequency fluctuations (ALFF) which is a measure of low-frequency oscillatory power in CNS, for frequencies of 0.001–0.198 HZ and frequency sub-bands	– Mean ALFF in ventral hemicord of cervical spinal cord > FM vs HC – ↓mean ALFF was observed within dorsal quadrants in FM – At corrected threshold of $P < 0.05$: small region of ↓ mean ALFF in dor-

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
							– Questionnaires: SHS, PROMIS, BPI, WPI and SS scores – Pain ratings before and after fMRI (verbal) – 1st analyses: mean ALFF calculated for low frequencies (0.001–0.198 Hz) – 2nd: mean ALFF calculated for sub-band freq. (0.001–0.027; 0.027–0.073; 0.073–0.198 Hz) – Mean ALFF + correlations with symptom	sal quadrant C7/C6 in FM – Frequency sub-band analyses: similar pattern of mean ALFF group differences (uncorrected threshold $P < 0.01$). At corrected ($P < 0.05$), freq sub-band of 0.073–0.198 Hz revealed cluster of ↓mean ALFF in FM at C7/C6 – Mean ALFF values taken from regions with ↓ ALFF in FM = positively correlated with fatigue ($P = 0.01$) – No correlation with symptoms – Conclusion: unbalanced activity between ventral and dorsal cervical spinal cord in FM
Matthey et al., 2013 [83]	77(F) patients with FM: 39 placebo and 38 MLN all doses Switzerland	RCT	To assess the pharmacodynamic activity of milnacipran (MLN), a serotonin-noradrenaline reuptake inhibitor, at spinal level on Patients with FM by using the NFR procedure and to see whether its properties affect NFR in FM (⟶ nociceptive spinal reflex R-III (NFR) threshold is lower in FM)	NR	Inclusion: women, > 18 years, ACR, reported baseline weekly recall pain over 40 (visual analog scale) Exclusion: CNS-active therapies, treatment with trigger point injections/anesthetics, psychiatric illness, BDI > 25	NR	– 3-week daily dose increase – Visit 4: fixed doses – Visit 5(w7): premature withdrawal, 1st and 2nd criteria assessed – Down-titration period – Pressure algometer – Diffuse noxious inhibitory control (DNIC) activity determined by comparing 2 NFR signals (AUC) elicited by same electrical suprathreshold stimulations. Positive response = reduction of more than 20%	– No influence of treatment on NFR ⟶ MLN has supraspinal analgesic properties – QST DNIC test baseline: AUC ↓ by 10.2% ⟶ low level activity and no change at w7 – Treatment did not influence DNIC or T° allodynia – No influence of treatment on PPT – MLN group: ↓ pain on the weekly-recall VAS score vs placebo. Dose-response relationship – Quality of life+function scores > in MLN group

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
			NFR procedure = tool to evaluate excitability state of spinal neurons					– No influence on fatigue and sleep quality – PGIC and PGI scores showed benefit of MLN over placebo ($P = 0.04$), for PGIC responders and ($P = 0.20$) for PGI
Mcloughlin et al., 2011 [47]	16(F) patients with FM and 18(F) HC Age NR USA	CC	To investigate how physical activity affects brain responses to painful stimulation in FM, using fMRI	Hypothesized that self-reported PA and activity measured objectively (accelerometry) would be negatively related to brain activity in areas involved in sensory and affective pain dimensions, and positively related to areas involved in pain modulation	Inclusion HC: no chronic pain Exclusion both: high-dose anti-depressant psychiatric disorders, ACR Exclusion FM: comorbid pain disorder Prior to testing: no exercise for min 48 h, no alcohol for 24 h, no caffeine for 4 h, no smoking for 2 h	NR	– 1st visit: self-reported physical activity (PA) of past week (IPAQ) – Determine suprathreshold pain sensitivity – Wear ActiGraph GT1M to objectively measure PA – fMRI response to painful heat stimuli – Accelerometer data processed: sedentary, moderate and vigorous – Regression analyses for IPAQ and accelerometer – FM divided into 'high' and 'low' active groups	– FM: pos correlation between responses in pain regulatory brain regions (r&l dorsolat prefrontal cortex DPFC) and self-reported PA – FM: neg correlation between responses in areas involved in sensory aspect of pain and self-reported PA – 'High' group: ↑activity in left DPFC and post insula (pain reg) and ↓ activity in left postcentral gyrus (sensory) than 'low' FM – FM: IPAQ and accelerometer measures were related to changes in pain intensity in scan ($P < 0.05$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Montoya et al., 2005 [56]	12(F) patients with FM (50.58 ± 6.19) and 12(F) HC (51.75 ± 5.66) Spain	CC	To analyze pressure pain thresholds (PPT) and event-related potentials (ERP) elicited by emotional words in FM and HC to evaluate the possibility of a cognitive bias in Patients with FM	Hypothesized that Patients with FM would have increased pain sensitivity and enhanced late positive ERP components triggered by pain-related words compared to neutral ones	Inclusion: no medication 24 h before tests (except 4 FM). FM had tender point assessment assessment), ACR Exclusion: > 18 score on BDI	NR	– BDI, STAI (mood measures) – PPT determined (1st assessment) – EEG – 96 words presented, ERPs recorded – After recording, 2nd PPT was assessed – Visual evoked potentials (VEPs) elicited by trials (words) – Amplitudes of VEP components were taken: N100, P200, N400, P300, late positive component (LPC)	– BDI and STAI ($P < 0.01$ and $P < 0.05$) FM mood was more depressive and anxious – ↓PPT in HC from 1st to 10th trial but no change in FM – PPT in FM ↓ from 1st assessment to the 2nd (not in HC: HC PPT decreased within assessment but was same at beginning of each assessment period) ($P < 0.01$) – ↓ P200 amplitude in FM vs HC ($P = 0.08$) – N400 ($P = 0.05$) and P300 ($P = 0.05$): pain-related words elicit more positive amplitudes than neutral words – Enhanced late positive slow waves in HC for pain-related words (no effect in FM)
Morris et al., 1998 [54]	10(F: M ratio 7: 3) patients with FM (56.5 ± 4.3) and 10(9: 1) RA (48.1 ± 4.7) and 10 HC UK	CC	Show a disturbance of pain modulation in FM by using capsaicin-induced secondary hyperalgesia (CISH) as a marker of abnormal nociceptive processing	NR	Inclusion: ACR Exclusion: drug allergy, eczema or psoriasis	Increased CISH indicates spinal cord hypersensitivity	– Current level of pain (VAS), McGill Questionnaire, HAD – Peripheral joint tenderness assessed	– Area of capsaicin-induced secondary hyperalgesia was ↑ in RA and FM vs HC – Area of mechanical 2nd hyperalgesia due to capsaicin was ↑ in FM vs RA + HC – Correlation between area of CISH and VAS pain score ($P < 0.01$) and joint tenderness score ($P < 0.02$) in FM – FM: area of CISH and coping catastrophizing score correlation ($P < 0.01$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Oliva et al., [44]	20 (18F) patients with FM (mean age 43) and 20 (18F) HC (mean age 35) UK	CC	To analyze whether attentional analgesia was attenuated in patients with FM compared to HC	Patients with FM would show a deficit in attentional analgesia and fMRI would demonstrate where the deficiency originated in the pain modulatory pathway/attentional network	Inclusion: ACR, minimum 6 month diagnosis of FM Exclusion: other chronic painful conditions, pregnancy, history of psychiatric or neurological illness	NR	– Thermal QST with thermode applied on forearm (WDT, HPT, CDT, CPT) – PPT assessment on thenar eminence – fMRI during thermal stimuli (calibrated per individual to evoke pain) – RSVP attentional task and concurrent thermal stimuli – Pain ratings and questionnaires (BPI, painDetect) after tests – Repeated 4 times	– BPI pain ratings $>$ in FM vs HC ($P < 0.01$) – Paindetect questionnaire score $>$ in Fm vs HC ($P < 0.01$) – $\uparrow$ depression anxiety scores in FM vs HC ($P < 0.01$) – $\uparrow$ scores in cognitive, avoidance, fear and anxiety sections of PASS in FM vs HC ($P < 0.01$) – HPT $<$ in FM vs HC ($P = 0.01$) – CPT was at higher temperatures in FM vs HC ($P = 0.001$) – PPT $<$ in FM vs HC ($P < 0.01$) – WDT $>$ in FM vs HC ($P < 0.01$) – RSVP task performance: FM required $\uparrow$ ISI than HC to perform task at 70% of optimal ($P < 0.01$) – No difference in degree of attentional analgesia btw groups: both show decreased pain score during hard task vs easy task ($P = 0.97$) – fMRI showed similar activation patterns in both groups except for $\uparrow$ activation in HC in FC and ILC – Positive correlation btw analgesic effect of task and activity change (on fMRI, BOLD signal) in

Table 2, continued

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Passard et al., 2007 [84]	30(29F, 1M) patients with FM (52.6 ± 7.9) France	RCT	To examine the effects of unilateral repetitive transcranial magnetic stimulation (rTMS) of the motor cortex on chronic widespread pain in Patients with FM	Hypothesized that rTMS of motor cortex can diminish chronic widespread pain in Patients with FM	Inclusion: right-handed, > 18 years, ACR, 4/10 score on mean daily pain intensity numerical scale of BPI during baseline week, complete 4 pain diaries out of 7 Exclusion: other medical condition, depression, psychiatric disorder	NR	– Self-reported pain (BPI) 1w before treatment (baseline), during treatment and until first follow up (day1 to 14), D15, D30 ± 2 and D60 ± 4 – PPT was measured	PAG and RVM in both groups ($P < 0.05$) – Baseline: pain intensity similar in both – D5-D14: average pain intensity in rTMS < sham ($P < 0.01$) – D15: SF-McGill total score and sensory and affective scores < in rTMS – D15: ↑PPTs (2 tender points) correlated with ↓ average pain intensity ($r = 0.49$, $P < 0.05$) – PPT effect did not persist on D30 and D60 – Interference on pain with daily life improved with rTMS – FIQ score + fatigue ↓ in rTMS until D30 – No effect on dep&anx
Potvin et al., 2009 [52]	37 (93%F) patients with FM (50.6 ± 7.4) and 36 (81%F) HC (47.9 ± 5.3) Canada	CC	Investigate the influence of dopamine-related gene polymorphisms on thermal pain thresholds (TPT) and DNIC efficacy in FM and HC	NR	Inclusion: ACR Exclusion: diabetes, lupus, RA, cardiac pathology, substance abuse	NR	– FM symptoms were assessed with FIQ – Pretest: thermode on left arm ⟶ TPTs measured – Compare pain induced by thermode, before and after cold-pressor test (CPT) ⟶ measure inhibitory effect of DNIC response	– ↓ DNIC efficacy in FM ($P = 0.04$) – TPT ↓ in FM ($P = 0.01$)
Pujol et al., 2009 [78]	9(F) patients with FM 47.9 ± 9.4), 9(F) HC 1 (47.2 ± 8.9) and 9(F) HC 2 (48.2 ± 5.5) Spain	CC	Generate fMRI maps adjusted to brain response duration after assessing brain response to painful pressure in patients with	NR	Inclusion: ACR, no analgesics 72 h prior to fMRI Exclusion: relevant medical or neurological disorder, substance abuse, psychiatric disease	NR	– HC 1: 4 kg/cm^2 stim – HC 2: 6.8 kg/cm^2 stim to match FM for perceived pain – PPT were assessed	– During fMRI: mild pain in HC, highest in FM ($P < 0.0001$) and pain comparable to FM in HC 2 ($P = 0.123$) – Maps: 9 components in FM and 3 in HC were activated during stim

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
			FM to show activation patterns and correlation with reported pain					– 2 components = pain-related regions (somatosensory and insular) – somatosensory component ⟶ signals persisted after stim was applied – Insular component: FM was same as for other component: fast initial signal ↑ and duration of 18 s.
Price et al., 2002 [25]	15(F) FM and 14(F) HC 21–65 years age range USA	RCT	First aim: to determine whether cutaneous hyperalgesia of FMS is specific to heat-induced windup of second pain or includes other types of experimental cutaneous pain Second aim: to determine whether the enhanced windup of FMS patients can be modulated by placebo, naloxone, or fentanyl injections	– First pain: lowest effect of placebo and fentanyl – 3 s stimuli: larger effect – Second pain: largest effect	Inclusion: > 18, pain-free HC, ACR Exclusion: medical condition contraindicating fentanyl or naloxone use, other study, opioid use, analgesic use	NR	– Rated 1st pain (A-fiber mediated) felt during 700 ms thermode contact – Individual 3 s T° stimuli ⟶ first peak of pain (mainly A-fiber) – Then, repeated 0.7 s heat tap stimuli ⟶ second pain(C-fiber-mediated) – Repeated cold tap stimuli ⟶ delayed aching cold pain – Mechanical visual analogue scales (M-VAS) measure pain intensity – Pain tests conducted at baseline and 20min after each of interventions (saline, fentanyl or naloxone)	– FM > pain sensitivity to 3s heat test ($P = 0.04$) vs HC – FM > windup of delayed pain vs HC (heat and cold induced WU) ($P = 0.01$; $P = 0.04$) – drug condition effect only in FM ($P = 0.03$). – < VAS ratings for naloxone and saline conditions vs baseline ($P < 0.05$) but did no difference between them ($P > 0.05$) – Cold taps: < VAS ratings for saline and naloxone conditions vs baseline ($P = 0.02$; $P = 0.04$) but did no difference btw them ($P > 0.05$) – **1st pain** FM: low-dose fentanyl ⟶ < lower VAS ratings ($P = 0.04$) – **3s stimuli**: < VAS for low-dose and high-dose fentanyl conditions vs baseline scores – ↑T° stim ⟶ ↑ fentanyl effect ($P = 0.01$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
								– no stat signif between fentanyl and placebo in 1st pain – **2nd pain** FM: ↓ windup by placebo & naloxone ⟶ endogenous pain-inhibitory mechanisms – FM: ↓ VAS ratings from placebo and high-dose fentanyl conditions vs baseline ratings ($P = 0.02$, $P = 0.01$) – **cold pain response:** ↓ pain ratings due to low/high dose fentanyl vs saline placebo ($P = 0.01$ and $P = 0.01$)
Schoen et al., 2016 [50]	16(F) patients with FM (44.9 ± 9) and 14(F) HC (40.3 ± 12) USA	CC	To evaluate a novel method to assess CPM in HC and FM subject	NR	Inclusion: ACR Exclusion: medical and psychiatric comorbidities, major depression, schizophrenia, opioid, analgesics	NR	– Thumbnail pressure – Cold water immersion ⟶ conditioning – CPM magnitude was calculated	– HC pain ratings of test stimulus decreased during conditioning with pressure ($P = 0.01$) and conditioning with cold water stimulation ($P = 0.02$) – No change in FM pain ratings ($P > 0.27$)
Staud et al., 2008 (Cutaneous) [24]	14(F) FM (43.4 ± 8.5) and 19(F) HC (41.2 ± 11) USA	CC	To show the role of alterations in central pain sensitization and not peripheral sensitization or rating bias as responsible for TSSP differences between FM and HC	Hypothesized that FM would have pain thresholds, long duration heat stimuli ratings and repetitive heat pulses ratings similar to HC. But FM would require lower peak T° to evoke same TSSP magnitude	Inclusion: ACR Exclusion: analgesic (NSAID included), acetaminophen use	NR	3 tests: 1. Pain threshold to selective C-fibre stimulation 2. Long duration (30 s) to test contribution of 3 baseline T° (BT) (35°C, 38°C, and 40°C) to pain from heat pulse trains 3. TSSP trains of brief (1.5 s), heat pulses at 0.33 Hz adjusting TSSP of FM and HC – pain magnitude rating: NPS – somatic pain rating: VAS	– HC: no somatic pain before and during experiments – FM: VAS scores 2.9 ± 1.2 before and 3.7 ± 1.4 after – Mean peak heat pulse T° used for TSSP testing < in FM vs HC ($P = 0.01$) – TSSP was elicited in HC and FM and TSSP magnitude depended on BT ($P = 0.02$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Staud et al., 2003 (DNIC) [27]	11(F) patients with FM (52.9 ± 6.3), 22(F) HC (35.8 ± 12) and 11(M) HC (40.2 ± 16.8) USA	CC	Test the effects of DNIC on temporal summation of second pain (previous work has shown that enhanced temporal summation of second pain is a key feature of abnormal central processing in FM + DNIC inhibits C-fiber mediated response of dorsal horn neurons more than A-delta of same neurons)	NR	Inclusion: > 18, pain free HC, ACR Exclusion: other medical condition, other study, analgesic, antidepressants	TSSP indicates abnormal central pain processing	– Conditioning stimuli to left hand (water immersion). – stimulus T° adjusted for similar pain ratings in FM and HC. – Test stimuli to right hand – Also tested effects of distraction on ratings of test stimuli	– WU > in FM-F than HC ($P = 0.01$) – HC-M: both DNIC ($P = 0.02$) and DNIC + distraction ($P = 0.04$) condition $\longrightarrow$ $\downarrow$ pain ratings vs baseline – HC-F: no signif effect for all DNIC condition ($P = 0.48$) – HC-M: greater reduction of WU with DNIC + distraction vs to DNIC only, but difference wasn't signif ($P = 0.07$)
Staud et al., 2015 [85]	46 patients with FM: 23 patients (21F, 2M) (46.9 ± 11.5) receiving milnacipran (MLN) 50 mg and 23 placebo group (22F,1M) (47.5 ± 12) USA	RCT	Use novel QST protocol to characterize effects of milnacipran (which has shown analgesic effectiveness in other clinical trials of FM) on spinal pain pathways, clinical pain and mechanical/heat hyperalgesia in Patients with FM	Hypothesized that milnacipran would reduce clinical pain and mechanical and heat hyperalgesia in FM	Inclusion: > 18 years, ACR Exclusion: analgesic (NSAID also) use, other medical condition, other study, anxiolytic, antidepressant, previous treatment with MLN, signs of depression	NR	– MLN or placebo 2/day for 6 weeks – QST measured during heat and muscle stimulus – After experimental session $\longrightarrow$ daily diary(pain, depression, anxiety, fatigue ratings) – clinical pain rating: VAS – experimental pain rating: eVAS	– Clinical pain ratings of both groups $\downarrow$ during 6 w ($P = 0.01$) – But no group difference ($P > 0.05$) – Fatigue $\downarrow$ ($P = 0.04$) but no group difference – No change in depression&anxiety – Experimental pain ratings to mechanical stim $\downarrow$ overtime ($P < 0.01$) but no group difference ($P > 0.05$) – exp pain ratings to heat stimuli decreased overtime ($P < 0.05$) but no group difference ($P > 0.05$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hypersensitivity definition	Assessment method	Results
Staud et al., 2005 [46]	12(F) patients with FM (48.4 ± 7.1) and 11(F) HC (45.7 ± 10.2) USA	CC	Determine whether central or peripheral mechanisms are predominantly involved in the abnormal pain modulation in FM	Hypothesized that isometric exercise would reduce experimental muscle and heat pain in HC but would have either no effect or opposite effect in FM	Inclusion: ACR Exclusion: analgesics (NSAID), acetaminophen use	NR	– Tested peripheral (ipsilateral to handgrip exercise) vs central (contralateral) effects of isometric exercise on pain inhibition – Squeeze dynamometer at 30% max voluntary contraction for 90s (MVC) = ISOM handgrip exercise – Mechanical pain threshold testing or thermal pain testing during handgrip – mVAS: pain rating – Before and after ISOM, HR and BP were recorded – MCV pain questionnaire	– MCV: high ratings of pain, depression, anxiety – ↑muscle pain ratings for both groups from beginning of exercise to end – Signif difference between experimental pain ratings between groups ($P = 0.01$) – HR&BP did not change signif ($P > 0.05$) – Ipsilat thermal pain rating: ↓ exp heat pain rating in HC ($P = 0.01$) and ↑ pain ratings in FM after 60 s and 90 s ($P = 0.02$ and $P = 0.01$) – Contralat: same as ipsilateral ($P = 0.04$), ($P = 0.04$ and $P = 0.04$) – Ipsilat mechanical PT: ↑ of PPTs after 30, 60, 90 s ($P = 0.01$, $P < 0.01$, $P < 0.01$) in HC Whereas decrease of PPT in FM after 30 and 90 s ($P < 0.01$, $P = 0.01$) – Contralat: same as ipsilat ($P < 0.01$, $P = 0.03$, $P = 0.01$) ($P = 0.02$, $P = 0.02$, $P < 0.01$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Staud et al., 2004 [20]	104 (96F, 8M) patients with FM (47.9 ± 11.7) and 72 (65F, 7M) HC (35.1 ± 12.3) USA	CC	Show evidence of central sensitization in Patients with FM by maintaining windup (WU) of second pain at lower stimulus frequencies that would not produce WU when delivered alone	Hypothesized that similar to WU, WU-M (maintained) would be enhanced in FM compared to HC	Inclusion: ACR Exclusion: analgesics (NSAID), acetaminophen use	NR	– FM tested with single 0.7 s heat tap: painless ratings (NPS < 20) – T° was raised until painful (threshold) – Stim intensity used for testing WU-M and WU-AS was defined by testing FM on achieving max NPS ratings	– Stim T° of heat probe that produced maximal WU pain ratings ($\text{NPS}_{\max} = 50 \pm 5$) $<$ in FM – $\uparrow 2^{\text{nd}}$ pain rating during WU-M(low stim freq) in FM vs HC $\longrightarrow$ central sensitization – FM pain $\downarrow$ more slowly at both freq (0.08 and 0.12 Hz) than HC – WU-AS (15–30 s after $\text{NPS}_{\max}$) decreased more slowly for FM vs HC – Sustained enhanced 2^{nd} pain at 0.08 Hz stim in FM but not HC
Staud et al., 2003 [26]	12(F) patients with FM (45.9) and 24(F) HC (40.3) USA	CC	Determine whether temporal summation of deep muscular pain would occur in HC and would be enhanced in FM	NR	Inclusion: ACR Exclusion: analgesics (NSAID), acetaminophen use	NR	– MCV questionnaire + VAS – repetitive indentation of muscle $\longrightarrow$ sensory testing for temporal summation (TS) – 15 stimuli, each 1 s long, with 3 or 5 s interstimulus intervals (ISI)	– Psychological factors associated with FM $>$ in FM vs HC – Pain threshold $<$ in FM ($P < 0.01$) – $>$ stimuli sensation ratings in FM vs HC ($P = 0.01$) – $>$ rating for each muscle tap in FM vs HC ($P < 0.01$) – $\uparrow$ stimulus ratings during tap trials for FM and HC ($P < 0.001$)$\longrightarrow$ TS of pain due to repetitive muscle indentation – $\uparrow$ sensation intensity ratings in FM ($P < 0.01$) – Decay of aftersensations over 60 s in FM and HC – $\uparrow$aftersensation in FM

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Staud et al., 2007 [19]	26(F) patients with FM (44.6 ± 15.9) and 23(F) HC (35.6 ± 14.1) USA	CC	Evaluate the extent of CS in Patients with FM at both ends of the spinal cord by testing TSSP-M and TSSP-aftersensation of heat pain at the upper extremities and lower extremities	Hypothesized that central pain sensitivity would be not only be abnormal but widespread in Patients with FM	Inclusion: ACR Exclusion: analgesics (NSAID also), acetaminophen, narcotic analgesic use	TSSP-M indicates CS	– TSSP-M testing: repeated heat pain stim on hands and feet – M-VAS: current clinical pain rating – pain intensity rating and 15 s + 30 s pain aftersensations (using NPS)	– Stimulus T° to produce max TSSP pain ratings ($NPS_{max} = 50 \pm 5$) < in FM vs HC at hands and feet ($P = 0.01$) – Hands: TSSP-M stim ratings > in FM vs HC for both frequencies ($P <$ 0.01 for 0.17 Hz and 0.08 Hz) – During TSSP-M, FM experimental pain ratings ↓ more slowly than HC and was dependent on TSSP-M stim freq – TSSP-M pain ratings > and longer in FM than HC except during 0.08 Hz stimuli to feet – TSSP-M stim rating during 0.17 Hz > in FM than HC at hands and feet but not statistically different between 2 locations – TSSP-AS ↓ more slowly for FM
Staud et al., 2008 [66]	13(F) patients with FM (43.4 ± 7.5) and 11(F) HC (42.9 ± 10.3) USA	CC	Compare TSSP-related brain responses in Patients with FM and HC	Hypothesized that FM have increased TSSP sensitivity	Inclusion: ACR Exclusion: abnormal findings, analgesic (NSAID included) and acetaminophen use	NR	– Heat pulses ⟶ TSSP – Pain magnitude rating: used NPS – Somatic pain and anxiety rating: used numerical scales – Heat pulses at 0.17 Hz and 0.33 Hz – Thermal stimuli adjusted to each subject's pain sensitivity – fMRI – BDI questionnaire	– BDI: FM had ↓ levels of depression – Found 19 TSSP-related brain regions common to FM and HC – ↑activation of brain regions during 6-pulse condition at 0.33 Hz ($P < 0.01$) – Pain-related brain regions – This happened in all regions (VOI = volume of interest)

Table 2, continued

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								– Stimulus freq (0.33 > 0.17) and number of stimuli (6 > 2) are important determinants of VOI activation – Adjusted stimuli ⟶ pain-related brain activation was same in both groups ⟶ ↑ TSSP sensitivity in FM is not due to specific ↑ in brain activity (but general)
Staud et al., 2010 [45]	34(F) patients with FM (44.6 ± 12.2) and 36(F) HC (44.7 ± 11) USA	CC	Compare the effects of alternating exercise with rest on clinical pain and thermal/mechanical hyperalgesia in FM and HC	Hypothesized repeated periods of strenuous exercise would activate the endogenous pain inhibitory systems in FM and that this would be most evident during short periods of rest	Inclusion: ACR Exclusion: use of analgesics (NSAID included) and acetaminophen	NR	– Arm exercises until exhaustion twice alternating with 15 min rest periods – Mechanical visual analogue scale (VAS) for pain, anxiety and fatigue rating – Rate level of exertion during exercises – VAS: rate experimental pain during mechanical and heat stimulation	– Overall pain ↑ in both groups during exercise – FM pain > than HC – No different pain ratings between exercise periods (⟶ rest helps) – During rest: pain ↓ faster for FM than HC – Magnitude of pain ↓ were similar during both rest periods in FM and HC ($P > 0.05$) – Sensitivity to mechanical pain ↓ in FM after each exercise and rest session – FM > ↓ in fatigue during rest ($P = 0.01$) – ↓ of anxiety did not differ btw groups
Staud et al., 2012 [40]	36(35F, 1M) patients with FM, 23(20F, 3M) HC and 24(18F, 6M) LMP USA	CC	To examine how quantitative sensory tests of primary (mechanical) and secondary (thermal) hyperalgesia predict clinical	Hypothesized that measures of mechanical and heat hyperalgesia would reflect relevant factors of peripheral and central pain	Inclusion: > 18 years, pain free HC, ACR, LMP patients had to have > 3 months of localized chronic pain Exclusion: other medical condition, other study, analgesics, anxiolytics, antidepressants except	TSSP indicates CS presence	– Tested mechanical and heat hyperalgesia at proximal body locations (shoulders) and distal (hands) – Assessed negative affect (which has shown correlation with pain)	– FM > mechanical pain rating vs other groups in shoulder ($P < 0.01$) and different between groups in hands ($P < 0.01$) – Heat pain rating was different between HC and FM ($P < 0.02$) in shoulder

Table 2, continued

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			pain intensity in patients with chronic musculoskeletal pain disorders	processing and clinical pain	amitriptyline			– FM > heat pain rating vs other groups ($P = 0.01$) in hands – LMP > heat pain ratings vs HC ($P < 0.02$) in hands – Pressure sensitivity of FM and LMP predicted 45.3% and 38% of variance in clinical pain, respectively – Heat pain ratings of FM and LMP predicted 16.9% and 26.8% of variance in clinical pain scores, respectively
Staud et al., 2014 [22]	38(F) patients with FM (49.1 ± 16.6) and 33(F) HC (42.2 ± 12.6) USA	CC	To better assess individuals' pain sensitivity by integrating 3 different WU-trains into a single WU-response function (WU-RF) which is representative of central pain sensitivity. And test whether WU, WU-RFs and WU-aftersensations (WU-AS) could predict clinical pain intensity of FM	NR	Inclusion: > 18 years, pain free HC, ACR Exclusion: other medical condition, other study, analgesics, anxiolytics, antidepressants except amitriptyline,	Steeper WU-RF slopes indice abnormal central pain sensitivity	– Rate single 44°C, 46°C and 48°C heat pulses of 3s duration to hand – Then received 6 trains of 5 repetitive heat stimuli at 0.4 Hz to same areas ⟶ WU elicited – Experimental pain rating: NPS – Clinical (somatic) pain rating: VAS – Tender point testing and questionnaires – WU-AS: 15 s and 30 s after each heat stimulus train	– WU-Δ = difference score between 1st and 5th heat pulse – WU-Δ scores ↑ with ↑ stimulus T° (P <0.01) and this ↑ was > in FM than HC ($P = 0.003$) – FM > 15 s and 30 s WU-AS ratings vs HC (all $P < 0.04$) – Decay of 30s AS slower in FM than HC ($P < 0.01$) – Slope of WU-RF was steeper in FM than HC ($P < 0.003$) ⟶ better assessment of CS? – Clinical pain intensity was predicted by WU-AS in FM (Pearson's $r = 0.4$, $P < 0.04$)

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Staud et al., 2021 (Spinal) [87]	14 (F) patients with FM (37.6 ± 16.0) and 16 (F) HC (48.7 ± 12.8) USA	CC	Analyze spinal cord activation and modulation during TSSP in patients with FM and HC	NR	Inclusion: ACR Exclusion: major medical or neurological illness, major psychiatric disorders and any contraindications for the MRI environment, pregnancy	Enhanced TSSP and pain after sensation	– QST: heat stimuli on thenar eminence – Pain ratings with NRS – TSSP: 18 heat stimuli with 2.5sec ISI – fMRI imaging – TSSP before and during fMRI scans – TSSP stimuli is adjusted to each subject's pain threshold, FM having lower stimulus temperature	– TSSP before fMRI: ↑ stimulus temperature for HC vs FM ($P < 0.01$) – No group difference for increase in pain ratings during TSSP before fMRI ($P > 0.05$) – No group difference for increase in pain ratings during TSSP during fMRI ($P > 0.05$) – Similar spinal cord and brainstem BOLD activity in both groups during TSSP (sensitivity-adjusted stimuli) – Structural equation modeling: spinal activation observed during TSSP is associated with ↑ BOLD activity in brainstem in FM vs HC → different pain modulation in FM
Staud et al., 2021 (Fibro) [98]	23 (F) patients with FM (46.2 ± 12.8) and 28 (F) HC (49.6 10.7) USA	CC	Analyze whether patients with FM also represent hypersensitivity to sound augmentation	Patients with FM are also hypersensitive to the augmentation of sound and not only to painful stimuli	Inclusion: ACR Exclusion: major medical or neuro-logical illness, psychiatric disease, and any known hearing abnormalities	NR	– VAS ratings – Auditory testing with wide-band noise: testing auditory thresholds and loudness sensitivity, MRS (multiple stimuli at random order) – QST: heat and mechanical stimuli	– Average pain ratings ↑ in FM vs HC ($P < 0.01$) – PPT and HPT > in FM vs HC ($P < 0.01$) for both measures – Sound 'pressure' pain threshold > in FM vs HC ($P < 0.01$)
Truini et al., 2015 [95]	20(19F, 1M) patients with FM (aged 27–62) and 15(13F, 2M) HC (aged 25–54) Italy	CC	Compare the excitability in the pain matrices of Patients with FM and HC and to see whether a preceding conditioning C-fibre LEP reduced the	NR	Inclusion: > 18 years, ACR, Exclusion: other pain sources or neurological diseases	NR	– C-Aδ conditioning-test experiment ⟶ studied changes induced by C-fibre input on the Aδ-LEP – Conditioning stimulus elicited warmth sensation (C-fibre input) – Following test stimulus elicited pin-prick sensation (Aδ input)	– In FM: when C-fibre input was used as conditioning before Aδ-fibre mediated LEP, Aδ-LEP amplitude was attenuated

Table 2, continued

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			following Aδ LEP				– Electrodes were used to record	
Van Vliet et al., 2018 [38]	34(24F, 10M) DM2 patients (54 ± 11), 28(22F, 6M) patients with FM (50 ± 11) and 33(21F, 12M) HC (53 ± 12) The Netherlands	CC	To assess pain prevalence, severity and characteristics in patients with myotonic dystrophy type 2 (DM2) and compare them with FM and HC subjects	NR	Inclusion: ACR Exclusion: < 18 years, other illness, depression, malignant disorder, neuropathy, recent (< 6w) major surgery	CS is less prominent in DM2 patients vs FM, which confirms the presence of CS in FM	– McGill pain questionnaire – Pain catastrophizing scale – Anxiety and depression – 36-SF for health status – QST: measure pain and central pain processing – PPT using algometer – Determined EPTT – Determined conditioned pain modulation (CPM) as change in percentages in the PPT and EPTT before and after cold pressor task: positive CPM = ability to produce descending inhibitory modulation	– Questionnaires: pain present in 65% of DM2, 100% of FM and 15% of HC – DM2 < PPT than HC ($P = 0.01$) and FM < PPT than DM2 ($P = 0.01$) – Electric pain thresholds (EST electrical sensation threshold, EPT and EPTT) not different between DM2 and HC but < in FM vs DM2 ($P < 0.01$) – Mechanical hyperalgesia in DM2⟶ peripheral sensitization – PPT and EPT < FM vs DM2 ⟶ CS is less prominent in DM2 (+ confirms CS in FM) – No CPM differences between groups
Vaegter et al., 2016 [51]	400(263F, 137M) chronic pain patients (48 ± 12.5) Denmark	CC	To see if there are different subgroups in a cohort of patients with different chronic pain conditions and to investigate differences in pain and pain hypersensitivity between these subgroups	NR	Inclusion: > 18 years, chronic nonmalignant pain for >6 months Exclusion: pain primarily in genital area	NR	– Leg cuff algometry – Measured: PPT, pressure pain tolerance (PTT), temporal summation of pain, CPM, heat detection threshold, heat detection threshold (HDT), heat pain threshold (HPT) – 4 groups made (based on TSP and CPM) – Group1 ($n = 85$): impaired CPM and facilitated TSP – Group2 ($n = 148$): impaired CPM and normal TSP	– PPT and PTT > than before conditioning ($P < 0.01$) – TSP: VAS > after stim10 ($P < 0.01$) – Group 1: more pain areas than other 3 ($P < 0.04$) – G1 NRS scores > G4 ($P = 0.05$) – G1&2 < HPT and PTT vs G4 – Impaired CPM and facilitated TSP⟶ biomarkers?

Table 2, continued

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							– group3 ($n = 45$): normal CPM and facilitated TSP – group4 ($n = 122$): normal CPM and normal TSP	
Van Assche et al., 2020 [74]	92(63F, 29M) patients with FM (49 ± 11.3) and 39(25F, 14M) HC (45 ± 12.6) Belgium	C	To estimate the prevalence of thermo-nociceptive system dysfunction using LEPs in Patients with FM	Hypothesized that small fibre neuropathy (SFN) is a significant contributor to the pathophysiology of FM (not supported by results)	Inclusion: ACR Exclusion: < 18 years, several LEP examinations in same patient, benzodiazepines use 24 h prior to LEP recording, central or peripheral nervous system disorder	NR	– LEP recordings acquired between 2003 and 2012 (database) – During same time period, LEPs acquired from HC	– No group differences in N2-P2 amplitudes btw groups ($P > 0.5$) – No loss of function of nociceptive response to Adelta-nociceptor activation in FM vs HC – No ↓ LEP ⟶ no SFN ⟶ SFN is not contributor to FM (hypothesis not supported)
Vecchio et al., 2020 [75]	81 (73F) patients with FM (50 ± 10) Italy	C	Analyze the functional changes of central nociceptive pathways measured by LEP's and the correlation with clinical characteristics	NR	Inclusion: ACR, age between 18–75 years Exclusion: education below 8 years and any cause of PNS or CNS diseases, psychiatric conditions other than anxiety and depression disorders according to the DSM V, active malignancies or history of cancer, use of drugs acting on the CNS and chronic opioid therapy	NR	– Nociceptive stimuli by laser pulses – Series of 30 stimuli at each stimulation site at intensity one step above threshold – Interval of 5 min between series – Nerve conduction study: analysis of sural, tibial and peroneal nerve conduction velocity and APA	– No LEP latency or amplitude differences btw groups (patients with or without intraepidermal nerve fiber density) – No association between LEP and clinical characteristics – N2P2 habituation index of LEP at leg was altered in FM (> 0.65 in 97.5% of FM, normal value being between 0.45–0.61)
Wik et al., 2006 [69]	8(F) patients with FM (42–56 years) Sweden	C	Analysis of PET scan measure of regional cerebral blood flow (rCBF) during externally induced acute pain and rest in patients with FM	NR	Inclusion: ACR	NR	– PET scans performed while pressure applied on arm tender point and compared to PET scans taken during rest	– FM > rCBF during acute pain vs rest in the right and left parietal cortex and right frontal cortex – FM < rCBF during acute pain vs rest in left retrosplenial cortex (emotional evaluation and pain encoding ⟶ acute pain ↓ the abnormally high pain signaling evaluation)

Table 2, continued

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Wik et al., 2003 [68]	8(F) patients with FM (42–56 years) and 8(F) HC (27–42 years) Norway	CS	To study the CNS in FM and compare PET scan measures of rCBF in FM and HC subjects at rest	NR	Inclusion: ACR Exclusion: organic brain disorder, somatic disease	NR	– Recorded PET scan measures of FM and HC at rest	– FM > rCBF vs HC bilaterally in retrosplenial cortex (at rest) ⟶ encoding of sensory events (also pain signaling) during rest – FM < rCBF vs HC in 2 left hemisphere clusters: one in fronto-temporal regions and one in tempo-parieto-occippital cortex
Wodehouse et al., 2018 [88]	14(13F, 1M) patients with FM (46.7 ± 10.5) UK	CS	To see whether QST detects changes in pain thresholds of Patients with FM receiving pregabalin treatment	NR	Inclusion: > 18 years, ACR, not taken pregabalin and no participation in cognitive behavioral therapy/pain rehabilitation or psychological support	NR	– QST and questionnaires measured at baseline (BS) and every 4w up to 12w of treatment – QST static measures: PPT measured (change from pressure to pain) – QST dynamic measures: ischemic compression of arm used as conditioning stimulus to evoke CPM and repeat PPTs measured	– FM < efficient CPM at baseline – PPTs improved from BS to 4 w ($P < 0.02$) and further ↑ from BS to 12 w ($P < 0.01$) – CPM efficiency improvement from BS to 4 w ($P = 0.01$) and maintained until 12 w ($P = 0.01$) – Numerical rating scores (NRS) improvement from BS to 12w – Improvement in PainDETECT and FIQ – Pregabalin ⟶ increase in PPT and DNIC – QST measured improvement in CS and PS in treated FM

Table 2, continued

Sources (Author; Year)	Population (Gender F/M + (Age mean ± SD) + country	Study design	AIM	Hypothesis	Incl./excl. criteria	Altered pain processing or cs or hyper-sensitivity definition	Assessment method	Results
Zhang et al., 2015 [86]	121(63F, 58M) chronic pain pt on opioid therapy (46.6 ± 9.5), 172(78F, 93M) chronic pain pt on non-opioid therapy (45.6 ± 13.4) and 129 (54F, 75M) HC (35 ± 14.2) USA	CS	To compare the sensitivity to experimental pain of chronic pain patients on opioid therapy vs chronic pain patients non non-opioid therapy and HC by using QST	NR	Inclusion: pain free HC and no opioid treatment min 6 m, pain non-opioid: stable pain condition but no opioid treatment for min 3 m, pain opioid: stable pain condition for min 3m Exclusion: sensory deficits at a QST site, interventions altering QST response, psychiatric illness	NR	– 4 QST parameters: cold&warm sensation, cold&heat PT, cold&heat pain tolerance, TS to heat stim – DNIC was measured	– Pain opioid group: < HPT vs non-opioid ($P = 0.04$) – Max tolerated heat T° < in opioid vs non-opioid ($P = 0.04$) – Opioid group: < tolerance to supra-threshold heat pain stim vs non op ($P = 0.02$) – TS > in opioid vs non op ($P = 0.03$) – Lower DNIC in opioid vs non op ($P = 0.03$)

ACR: American college of rheumatology FM diagnosis criteria, AIC: anterior IC, ACC: anterior cingulate cortex, aMCC: anterior mid-cingulate cortex, APA: action potential amplitude, AUC: area under the curve, AS: pain after-sensation, ANS: autonomic nervous system, BP: blood-pressure, BOLD: blood-oxygen-level-dependent, BDI: Beck depression inventory, BP-PCS: Brazilian Portuguese Profile of chronic pain: screen, BPI: brief pain inventory, BRS; baroreflex sensitivity, BEI: baroreflex effectiveness, CC: cingulate cortex, C: cohort, cor: correlation, CLBP: chronic low back pain, CPM: conditioned pain modulation, CC: case control, CS: cross-sectional, CLP: chronic localized pain, CWP: chronic widespread pain, CSP: cutaneous silent period, CNS: central nervous system, CBP: chronic back pain, CLBP: chronic low back pain, CS: central-sensitization, C(D)T: cold (detection) threshold, CES-D: Center for Epidemiological Studies Depression Scale, CPT: cold pain threshold, CDC; centers for disease control, CFQ: Chalder fatigue questionnaire, CFS: chronic fatigue syndrome, CSS: central sensitization symptoms, CSI: central sensitization inventory, DM2: myotonic dystrophy type 2, DNIC: diffuse noxious inhibitory control, dif: difference, DLPFC: dorsolateral prefrontal, DEPS: depression scale, DBP: diastolic blood pressure, DBT: deep breathing test, DSM V: diagnostic and statistical manual of mental disorders, ES: explosive synchronization, EQ-5 L-5D: EuroQol The 5-level EQ-5D version, ED: electrodiagnostic, EDA: electrodermal activity, EPTT: electric pain tolerance threshold, EMG: electromyography, freq: frequency, FM: patients with fibromyalgia, fNIRS: functional near-infrared spectroscopy, FSS: fatigue severity scale, FP: frontopolar cortex, GMV: gray matter volume, HADS: hospital anxiety and depression scale, HbO: oxyhemoglobin, HC: healthy controls, HPT, heat pain threshold, HR: heart rate, HRV: heart rate variability, IBI: interbeat interval, ISI: interstimulus interval, IPL: inferior parietal lobule, IC: insular cortex, IPAQ: international physical activity questionnaire, IBS: irritable bowel syndrome, ILC: ipsilateral locus coeruleus, PDI: pain disability index, vs: compared to, pt: patients, y: years, w: weeks, VAS: visual analogue scale, LMP: local musculoskeletal pain, LOC: lateral occipital cortex, lPFC: lateral prefrontal cortex, MC: motor cortex, MPT: mechanical pain threshold, MPS: mechanical pain sensitivity, MVC: maximum voluntary contraction, MCV: medical college of Virginia pain questionnaire, MDT: mechanical detection threshold, MPQ: McGill pain questionnaire, MPFC: medial prefrontal cortex, MRS: multiple random staircase method, M1: primary motor cortex, NFR: nociceptive flexion reflex, NRS: numerical rating scale, NPQ: neuropathic pain questionnaire, OQS: Oviedo quality of sleep questionnaire, OFC: orbitofrontal cortices, stim: stimulation, OP: occipital pole, SF-MPQ: short-form of the McGill pain questionnaire, periph: peripheral, P-Ins: posterior insula, PPT: pressure pain threshold, PPI: present pain intensity, PPC: posterior parietal cortex, PS: peripheral sensitization, PAG; periaqueductal grey, PEP: pre-ejection period, PSQ-3: Pain and Sleep Questionnaire Three-Item, PASS: Pain anxiety symptom scales, PCS: pain catastrophizing scale, PrCG: pre-central gyrus, PCC: posterior cingulate cortex, Precun: precuneus, PL: paracentral lobule, PFC: pre-frontal cortex, QoL: quality of life, rCBF: regional cerebral blood flow, RLBP: recurrent low back pain, RCT: randomized controlled trial, ROI: region of interest, RSVP: rapid serial visual presentation, RVM: rostral ventromedial medulla, RMDQ: Roland-Morris Disability Questionnaire, ROC: receiver operator characteristics, SSR: sympathetic skin response, SREP: slowly repeated evoked pain, SPECT: single-photon emission computed tomography, signif: significant, S1&S2: primary and secondary somatosensory cortices, SMC: sensorimotor cortex, STPI: State-Trait personality Inventory (to assess anxiety), SF-36-PF: physical function subscale of the SF-36, SBP: systolic blood pressure, SPL: superior parietal lobule, STAI: State-trait anxiety inventory, SV: stroke volume, TS: temporal summation, , TSSP: temporal summation of second pain, T-T: threshold/tolerance, thal: thalamus, TMD: temporo-mandibular disorder, TPT: thermal pain threshold, cortex, TPR: total peripheral resistance, TSK: Tampa scale of kinesiophobia, VBM: voxel-based morphometry, VDT: vibration detection threshold, VGEE: generalized estimating equations, W(D)T: warm (detection) threshold, WU: wind up of pain, WU-AS: wind-up pain after-sensation, WPI: widespread pain index, +: positive, -: negative, r & l: right & left, ipsilat/contralat: ipsilateral/contralateral, Δ-HbO: difference in HbO concentration from baseline until maximum cortical amplitude of each stimuli, Δ-HbO*: difference in HbO concentration from baseline until 15s after thermal stimuli endin.

Table 3
Risk of bias assessment of included studies ($n = 78$)

Table 3a. Case control studies ($n = 65$)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Score	%	Quality
Al-Mahdawi et al. [96]	Yes	Yes	No	No	CD	Yes	No	NR	NA	Yes	CD	NR	No	4/13	31%	Poor
Baek et al. [89]	Yes	No	NR	No	NR	NR	No	NA	NR	Yes	No	NR	No	2/13	15%	Poor
Banic et al. [57]	Yes	No	NR	Yes	NR	No	No	NA	NR	Yes	Yes	NR	Yes	5/13	38%	Poor
Bendsten et al. [90]	Yes	No	NR	No	NR	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Blumenstiel et al. [34]	Yes	No	NR	No	No	No	No	No	NR	Yes	Yes	NR	Yes	4/13	31%	Poor
Bosma et al. [18]	Yes	No	NR	No	No	No	Yes	NA	NR	Yes	Yes	NR	No	4/13	31%	Poor
Bourke et al. [43]	Yes	No	No	No	No	NR	Yes	NR	NA	Yes	Yes	NR	No	4/13	31%	Poor
Burgmer et al. [79]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor
Burgmer et al. [71]	Yes	No	NR	No	NR	No	No	NA	NR	Yes	Yes	NR	Yes	4/13	31%	Poor
Chalaye et al. [29]	Yes	No	NR	No	NR	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Cook et al. [62]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Craggs et al. [63]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
De la Coba et al. [30]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	Yes	Yes	8/13	61%	Fair
De la Coba et al. [31]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	7/13	54%	Fair
De Tommaso et al. [73]	Yes	Yes	NR	No	Yes	Yes	No	NA	NR	Yes	Yes	Yes	Yes	8/13	61%	Fair
Desmeules et al. [58]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Desmeules et al. [53]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Del Paso et al. [32]	No	Yes	No	No	NR	Yes	Yes	NR	NA	Yes	Yes	NR	No	5/13	38%	Poor
Donadel et al. [81]	Yes	Yes	Yes	Yes	CD	Yes	Yes	NR	NA	Yes	Yes	NR	Yes	9/13	69%	Fair
Fallon et al. [60]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Fallon et al. [91]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor
Gentile et al. [92]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Gerdle et al. [93]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Gerhardt et al. [41]	Yes	No	NR	No	NR	Yes	Yes	NA	NR	Yes	Yes	Yes	Yes	7/13	54%	Fair
Giesecke et al. [67]	No	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	4/13	30%	Poor
Goubert et al. [23]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	7/13	54%	Fair
Guedj et al. [70]	Yes	No	NR	No	No	No	No	NA	NR	Yes	No	NR	No	2/13	15%	Poor
Hazra et al. [33]	Yes	No	Yes	NR	NR	Yes	NR	NR	NA	Yes	Yes	NR	No	5/13	38%	Poor
Hurtig et al. [39]	Yes	No	NR	No	Yes	No	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Ichesco et al. [80]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Ichesco et al. [64]	Yes	No	NR	No	NR	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Janal et al. [21]	Yes	Yes	NR	Yes	Yes	Yes	Yes	NA	NR	Yes	Yes	No	No	8/13	61%	Fair
Jespersen et al. [35]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Kosek et al. [37]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Kosek et al. [36]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Lim et al. [94]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor
Loggia et al. [49]	Yes	Yes	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	7/13	54%	Fair
Lopez et al. [77]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Lopez et al. [61]	Yes	Yes	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	8/13	61%	Fair
Lorenz et al. [72]	Yes	No	NR	No	No	CD	No	NA	NR	CD	No	NR	No	1/13	7%	Poor
Maestu et al. [76]	Yes	No	NR	No	CD	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Martinsen et al. [55]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Martucci et al. [65]	Yes	No	NR	No	CD	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor

Table 3a, continued

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Score	%	Quality
Mcloughlin et al. [47]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor
Montoya et al. [56]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Morris et al. [54]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Oliva et al. [44]	Yes	No	No	NR	No	Yes	Yes	NA	No	Yes	Yes	NR	Yes	6/13	46%	Poor
Potvin et al. [52]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	Yes	4/13	31%	Poor
Price et al. [25]	Yes	No	NR	No	NR	Yes	Yes	NA	NR	Yes	Yes	Yes	No	6/13	46%	Poor
Pujol et al. [78]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	7/13	54%	Fair
Schoen et al. [50]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Staud et al. [24]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Staud et al. [27]	Yes	No	NR	No	Yes	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	7/13	54%	Fair
Staud et al. [46]	Yes	No	NR	No	No	Yes	No	NA	NR	Yes	Yes	NR	No	4/13	31%	Poor
Staud et al. [20]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Staud et al. [26]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Staud et al. [19]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Staud et al. [66]	Yes	No	NR	No	No	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Staud et al. [45]	Yes	No	NR	No	CD	No	No	NA	NR	Yes	Yes	NR	No	3/13	23%	Poor
Staud et al. [40]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor
Staud et al. [22]	Yes	No	NR	Yes	CD	Yes	Yes	NA	NR	Yes	Yes	NR	No	6/13	46%	Poor
Staud et al. [28]	Yes	No	NR	NR	Yes	Yes	Yes	NA	No	Yes	Yes	NR	Yes	7/13	54%	Fair
Staud et al. [42]	Yes	No	CD	NR	Yes	Yes	Yes	NA	No	Yes	Yes	NR	Yes	7/13	54%	Fair
Truini et al. [95]	Yes	No	NR	No	CD	Yes	Yes	NA	NR	Yes	Yes	NR	No	5/13	38%	Poor
Van Vliet et al. [38]	Yes	No	NR	No	No	Yes	Yes	NA	NR	Yes	Yes	NR	Yes	6/13	46%	Poor

Q: question, NR: not reported, NA: not applicable, CD: cannot determine. The quality of included studies was assessed using the National Institute of Health (NIH) Quality Assessment Tool for Case Control Studies (https: //www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Q1: Was the research question or objective in this paper clearly stated and appropriate? Q2: Was the study population clearly specified and defined? Q3: Target population and case representation, Q4: Did the authors include a sample size justification? Q5: Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? Q6: Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? Q7: Were the cases clearly defined and differentiated from controls? Q8: If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? Q9: Was there use of concurrent controls? Q10: Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? Q11: Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? Q12: Were the assessors of exposure/risk blinded to the case or control status of participants? Q13: Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Table 3b. Cross-sectional studies ($n = 9$)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score	%	Quality
Lee et al. [59]	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	NR	NA	No	6/14	43%	Poor
Loggia et al. [48]	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	NR	NA	Yes	6/14	43%	Poor
Vaegter et al. [51]	Yes	Yes	NR	Yes	NR	No	No	NA	Yes	Yes	Yes	NR	NA	Yes	7/14	50%	Fair
Van Assche et al. [74]	Yes	Yes	No	Yes	No	No	No	No	Yes	No	Yes	NR	NA	Yes	6/14	43%	Poor
Vecchio et al. [75]	No	Yes	Yes	NR	CD	Yes	No	Yes	No	Yes	NR	Yes	Yes	Yes	8/14	57%	Fair
Wik et al. [69]	Yes	No	NR	Yes	No	No	No	No	Yes	No	Yes	NR	NA	No	4/14	29%	Poor
Wik et al. [68]	Yes	No	NR	Yes	No	No	No	NA	Yes	No	Yes	NR	NA	No	4/14	29%	Poor
Wodehouse et al. [88]	Yes	No	Yes	CD	No	No	No	No	Yes	Yes	Yes	NR	NA	No	5/14	36%	Poor
Zhang et al. [86]	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	NA	No	8/14	57%	Fair

Q: question, NR: not reported, NA: not applicable. The quality of included studies was assessed using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https: //www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Q1: Was the research question or objective in this paper clearly stated? Q2: Was the study population clearly specified and defined? Q3: Was the participation rate of eligible persons at least 50%? Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5: Was a sample size justification, power description, or variance and effect estimates provided? Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q10: Was the exposure(s) assessed more than once over time? Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q12: Were the outcome assessors blinded to the exposure status of participants? Q13: Was loss to follow-up after baseline 20% or less? Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Table 3c. RCT studies ($n = 4$)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score	%	Quality
Maestu et al. [82]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	13/14	93%	Good
Matthey et al. [83]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	13/14	93%	Good
Passard et al. [84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	13/14	93%	Good
Staud et al. [85]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13/14	93%	Good

The quality of included studies was assessed using the National Institute of Health (NIH) Quality Assessment Tool for Controlled Intervention Studies (https: //www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Q1: Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? Q2: Was the method of randomization adequate (i.e., use of randomly generated assignment)? Q3: Was the treatment allocation concealed (so that assignments could not be predicted)? Q4: Were study participants and providers blinded to treatment group assignment? Q5: Were the people assessing the outcomes blinded to the participants' group assignments? Q6: Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, comorbid conditions)? Q7 Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? Q8: Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? Q9: Was there high adherence to the intervention protocols for each treatment group? Q10: Were other interventions avoided or similar in the groups (e.g., similar background treatments)? Q11: Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? Q12: Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? Q13: Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? Q14: Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Table 4
Summary of temporal summation of second pain, pain after-sensation and pressure pain threshold findings

	TSSP	Stimulus frequency eliciting TSSP	After sensations	Rate of WU after sensation decline	Pressure pain threshold
Patients with FM	↑	↓ [18,20,24] Poor quality studies	↑ $P < 0.04$ [18,26] Poor quality studies	↓[19,20,21] Janal et al. [21]: fair quality	↓[36,43,44,98]
Healthy controls	↓	↑	↓	↑	↑

TSSP: temporal summation of second pain, WU: wind-up of pain, FM: fibromyalgia, ↑: increased compared to other group, ↓: decreased compared to other group. References [18,10,20,21,22,23,24,25,26,27,41,43,44,87,98].

Table 5
Summary of electrophysiological technique findings in patients with fibromyalgia

EMG	EEG	fMRI	PET	VBM	SPECT	fNIRS
↓ NFR threshold	Explosive synchronization conditions in resting state EEG	↓ mean ALFF in dorsal column pathway ↑ mean ALFF in spinothalamic tract region ↑ signal in contralateral S1&S2, ipsilateral S2, IPL, cerebellum Similar activation patterns in both groups during sensitivity-calibrated stimuli	↑ rCBF in retro splenial cortex at rest ↓rCBF in fronto-temporal and tempo-parieto-occipital cortex	↓ GMV in ACC, inferior frontal gyrus, amygdala ↓ brainstem and left precuneus GMV ↑ GMV in bilateral S1	Hypoperfusion: bilateral frontal, ant/post cingulate, med temporal cerebellar cortices Hyperperfusion: S1 & S2	↑ $\Delta-$HbO between 2 stimuli at MC

FM: fibromyalgia, ↑: higher compared to healthy controls, ↓: lower compared to healthy controls, NFR: nociceptive flexion reflex, ALFF: amplitude of low-frequency fluctuations, rCBF: regional cerebral blood flow, GMV: gray matter volume, ACC: anterior cingulate cortex, S1 & S2: primary and secondary somatosensory cortices. EMG: electromyography, EEG: electroencephalography, fMRI: functional magnetic resonance imaging, fNIRS: Functional near-infrared spectroscopy, MC: motor cortex, PET: positron emission tomography, VBM: voxel-based morphometry, SPECT: single-photon emission computed tomography. References [44,57,59,65,67,68,70,71,81,87,91,93].

pain thresholds (MPT) [34] and electrical pain thresholds (EPT) [38] and sound 'pressure' threshold [42] in patients with FM compared to HC were demonstrated. Janal and co-workers observed no statistically significant differences in thermal pain thresholds between patients with temporo-mandibular joint disorder with FM and patients with temporo-mandibular joint disorder without FM [21]. Patients with FM displayed higher warmth detection thresholds (WDT) compared to HC [44]. Bourke and colleagues however showed no difference for WDT and cold detection threshold (CDT) between groups [43].

3.4.2. Other peripheral measurements

Other markers of HACS include slowly repeated evoked pain (SREP) sensitization, the autonomic nervous system (ANS) response to pain measured with an electrocardiogram, electromyography and measures of the cardiovascular system [32], attentional task performance with concurrent pain stimuli [44], the relation between pain perception and motor activity and cutaneous silent period [96]. Patients showed SREP sensitization, measured as higher difference in VAS pain ratings between the last and first pain stimulation trials [30,31] compared to HC. The stimulation trials consisted of a series of nine low-intensity pressure stimuli with 30 second interstimulus intervals. Patients also showed a positive correlation between clinical pain and SREP sensitization, and a lower pain threshold and pain tolerance compared to HC [31]. Patients demonstrated the need for longer interstimulus intervals (ISI) in order to perform an attentional rapid serial visual presentation (RSVP) task at 70% of optimal, compared to HC [44]. Furthermore, studies conducted with ECG on the ANS have shown that the abnormal ANS response to cold pressor tests in patients with FM is caused by lower effectiveness of the baroreflex responses, a homeostatic mechanism that helps to minimize considerable variations in blood pressure [29]. This was also demonstrated by lower baroreflex sensitivity (BRS) and baroreflex effectiveness (BEI) in patients with FM compared to HC during rest, as well as during the cold pressor test. Additionally, there was a positive correlation between BEI and heart rate variability (HRV). A negative correlation between BRS and BEI with cold pressor pain was also found, as well as between BEI and the pre-ejection period of the heart, the latter representing measures of the sympathetic influences on myocardial contractil-

ity. Furthermore, a reduced reactivity of blood pressure and cardiac stroke volume was demonstrated in patients compared to HC during the cold pressor test [32]. In contrast, one study showed no significant group difference in heart rate increase during cold pressor test but did underline a significantly higher heart rate in patients with FM compared to HC at rest [33]. Finally, one study demonstrated a negative correlation between motor activity and pain intensity [45]. There was a positive correlation between patients with FM who reported participating in regular physical activities and activity in pain regulatory regions of the brain (dorsolateral prefrontal cortex, posterior cingulate cortex, posterior insula) during painful stimulation [47]. On the contrary, lower PPT and higher pain ratings to pain stimulation during handgrip exercise was observed in patients with FM compared to HC [36]. Furthermore, a lower nociceptive withdrawal reflex threshold after stimuli in patients with FM compared to HC was shown in three studies [53,57,58]. Finally, a longer cutaneous silent period after painful electrical stimuli was measured in patients with FM compared to HC [96]. These findings are shown in Table 5 as well.

3.5. Measurements to assess CNS manifestations of HAC

3.5.1. Electroencephalogram (EEG)

Various electrophysiological techniques were used to assess HACS. Resting EEG measurements have shown a positive correlation between having FM and explosive synchronization conditions in patients with FM [59] (explosive synchronization being a condition in which a small perturbation leads to global propagation [59]). Furthermore, EEG has been helpful in demonstrating higher [72], lower [73] and identical [74,75] amplitudes of the N1 and P2 components of laser-evoked potentials (LEP) in patients with FM compared to HC [72]. One study analyzed the biphasic N2P2 component of LEP's and found an altered N2P2 habituation index in patients with FM [75] (habituation index representing whether or not subjects showed a decreased or increased response to stimuli repetition).

3.5.2. Brain activity and perfusion

Furthermore, fMRI was used to demonstrate higher mean amplitude of low-frequency fluctuations in the ventral hemicord, which turned out to be decreased in the dorsal quadrants of patient' cervical spinal cord compared to HC [65]. Higher activation in fMRI-based neurologic pain signature regions was observed in patients with FM compared to HC during painful stimulation [61], indicating that this region is hyperactive in patients, suggesting to be an expression of HACS in patients with FM. fMRI also showed higher brain activity in different brain regions during identical pressure stimulation in patients with FM compared to HC [67]. When the stimulation intensity was adapted to create subjectively equal pain intensity for subjects in both groups, patients and HC showed similar fMRI activity [67]. This suggests that hyperactive regions can be an expression of HACS in patients with FM, as it was not activated in HC during identical pressure stimulation fMRI measures during TSSP, elicited by heat stimuli adjusted to individual's pain threshold, also showed higher blood-oxygen-level-dependent (BOLD) activation patterns in the spinal cord of patients with and without FM. This activation also seemed to be associated with increased BOLD activity in the brainstem of patients with FM compared to HC [28]. Another study also demonstrated similar activation patterns in both groups after sensitivity-adjusted thermal stimuli, except for an increased activation of two brain regions in HC compared to patients with FM [44]. Furthermore, there was a positive correlation between the analgesic effect of the task and the BOLD activity detected on fMRI in both groups [44]. Brain perfusion analysis offered promising results using PET and SPECT neuroimaging. PET scan analysis showed increased regional cerebral blood flow (rCBF) bilaterally in the retrosplenial cortex (area that encodes sensory events, pain included) at rest in patients with FM compared to HC [68], increased rCBF in the parietal cortex and decreased rCBF in the retrosplenial cortex during painful stimulation compared to rest was also observed with PET scans in patients with FM [69], hyperperfusion in S1 and S2 areas of patients with FM was demonstrated using SPECT neuroimaging [70]. Functional near-infrared spectroscopy (fNIRS) measurements at the motor cortex (MO) showed greater hemoglobin-oxygen (HbO) concentration differences between two consecutive thermal stimuli in patients with FM compared to HC, suggesting a slower rate of cortical activation in the motor cortex of patients with FM [81]. In contrast, another study demonstrated a higher increase in HbO concentration in the left PFC between rest and cold pressor test in patients with FM compared to HC [33]. During CPT, patients with FM reached peak HbO concentrations faster than HC [33] and also demonstrated greater electrodermal activity amplitudes than HC [33].

3.5.3. Gray matter volume alterations

As final electrophysiological technique, voxel-based morphometry (VBM) analysis, showing gray matter volume alterations, yielded different results between FM patients and HC. Patients with FM presented with decreased grey matter volume in the anterior cingulate cortex [71] and increased grey matter volume in S1 bilaterally, compared to HC [60]. It was demonstrated that VBM-detected gray matter volume alterations in the anterior cingulate cortex are associated to HACS [71]. In contrast, the anterior cingulate cortex and amygdala volumetric changes are not associated with pain duration or functional disability. This suggests that these volumetric differences are not consequences of FM but could rather be a pre-condition for HACS development in FM [71], potentially making voxel-based morphometry a marker for HACS assessment. Additional results are displayed in Table 5.

3.5.4. Conditioned pain modulation (CPM)

Pain during ascending (fingers first) and descending cold water immersion of the arm (elbows first) in HC and patients with FM was tested. One study demonstrated that HC felt less pain in their fingers during descending sessions compared to ascending, whereas patients with FM felt no difference [29]. Furthermore, it was demonstrated that patients with FM felt no changes in pain ratings after a pressure pain conditioning and a cold-water stimulation condition, whereas HC felt lower pain [50]. When comparing the efficacy of cold pressor test conditioning, one study [38] observed no CPM differences between both groups whereas another study [52] observed lower CPM efficacy in patients with FM compared to HC. When using tourniquet cuff conditioning, a study demonstrated that 95% of patients with FM showed inefficient CPM in comparison with zero HC cases [43]. However, lower PPT, HPT and higher pain ratings after a tourniquet cuff conditioning in patients with FM compared to HC were identified [51]. One study [53] observed that CPM decreases the nociceptive flexion reflex (NFR) amplitude in HC when painful conditioning was applied. However, in patients with FM, the nociceptive flexion reflex amplitudes were lower after applying non-painful conditioning CPM [53]. These findings are also shown in Table 5.

3.5.5. Pain anticipation and catastrophizing

Some studies were conducted on pain anticipation and catastrophizing in patients with FM. It was demonstrated that patients showed lower responses in the ventral tegmental area, a dopamine-rich region, during pain anticipation compared to HC [49]. It was shown that patients who were more prone to catastrophizing had a lower pain threshold with cuff algometry [48]. Loggia et al. demonstrated that patients displaying lower pain anticipation, showed reduced activity in the lateral prefrontal cortex (LPC). By means of mediation analyses, it was shown that this reduced activity mediates the hyperalgesic effect of catastrophizing [48]. Oliva et al. showed no difference in attentional analgesia during concurrent thermal painful stimuli, calibrated to each individual's pain threshold, between groups: both groups demonstrated a decrease in pain score during the hard task compared to the easy task [44]. One study demonstrated lower blood-pressure and cardiac stroke volume reactivity during a mental arithmetic task in patients with FM compared to the reactivity of ANS parameters during the cold pressor test [32].

Table 6 shows an overview of the identified markers, with an asterisk next to the markers identified from fair quality papers.

4. Discussion

In this review, patients with FM showed differences on HACS markers compared to healthy subjects. The markers identified to assess *peripheral* manifestation of HACS are higher pain after-sensation intensity (and lower decline rates), lower mechanical pain threshold detected by pin-prick stimulators,lower sound 'pressure' pain thresholds tested with auditory wideband noise testing, cutaneous silent period duration recorded with electrodes, abnormal autonomic nervous system responses to pain, higher slowly repeated evoked pain (SREP) sensitization (elicited by pressure stimuli) and lower nociceptive flexion reflex detected with electromyography. The markers identified to assess *central* manifestations of HACS are electroencephalogram (EEG) differences observed between FM and HC, brain and spinal activity variations (amplitude of low-frequency fluctuations (ALFF), region connectivity, neurologic pain signature response) detected with fMRI, brain perfusion differences observed on PET and SPECT scans, gray matter volume changes detected with voxel-based morphometry and cuff pressure conditioning.

4.1. Measurements to assess peripheral manifestations of HACS

Peripheral assessments of HACS markers have provided inconsistent results. First of all, higher TSSP sen-

Table 6
Overview of the identified markers

HACS markers	Tools
Peripheral manifestations of HACS	
Pain after sensations and decline rates	Numerical pain scale (NPS)
Mechanical pain threshold	Pin prick stimulators
Pressure pain threshold	Pressure algometry
Sound 'pressure' pain threshold*	Wideband noise auditory testing
Autonomic nervous system response to pain	Electrocardiography
SREP sensitization*	Pressure stimuli
Cutaneous silent period	Electrode
Nociceptive flexion reflex	Electromyography
Central manifestations of HACS	
Explosive synchronization networks	EEG
Brain activity variations (ALFF, neurologic pain signature response)*	fMRI
Brain perfusion differences*	PET, SPECT scans, fNIRS and fMRI
Gray matter volume changes	Voxel based morphometry
Conditioned pain modulation*	Tourniquet cuff pressure conditioning

*Markers identified from fair quality papers.

sitivity in patients with FM compared to HC was shown in seven studies [19,20,23,25,26,27,28], with three of these studies being ranked fair quality [23,27,87], and four ranked poor quality [19,20,25,26]. On the other hand, no TSSP difference between groups was found in two other studies [18,21], with one study being ranked fair quality [21] and one with poor quality. From these findings, we cannot deduce that TSSP is a valid marker for the presence of HACS. However, the demonstrated higher pain after-sensation (AS) intensities [18,26] and lower rates of pain AS decline [19,20,21] can support the suggestion to use them as markers for HACS in patients with FM. This is because HC showed opposite results and the higher pain sensation felt in patients with FM can be expressed through the higher pain AS intensities demonstrated in two studies [18,26]. One study showed lower sound 'pressure' pain thresholds in patients with FM compared to HC, further expanding the noxious sensation spectrum of patients with FM to auditory mechanisms [42]. Regarding measurements of HPT and CPT (thermal sensory devices) [21,34,37, 39,41] in patients with FM, one study [21] did not observe thermal pain threshold differences between patients with FM and HC. From these findings, and considering the fact that the study was only ranked fair quality, we cannot undoubtedly classify thermal pain thresholds as a usable marker for HACS identification in patients with FM. Lower MPT detected with pinprick stimulators [34] in patients with FM compared to HC showed to be a promising tool for pain hypersensitivity detection in patients with FM. It is important to note that two of these studies [31,41], were ranked fair quality. Furthermore, authors of several studies [23,31, 34,35,36,37,38,41,42,43,44] demonstrated PPT measurements with pressure algometry to indicate the presence of hyperalgesia in patients with FM. However, one study found SREP specificity to be 25% higher (0.92) and sensitivity 4% higher (0.79) for discriminating between patients with FM and HC compared to PPT measurements (PPT 0.67) [31]. This may indicate that SREP, evoked by a series of pressure stimuli, is a better marker to discriminate for HACS between patients with FM and HC compared to PPT.The increased cutaneous silent period (CSP) duration after stimulation of the cutaneous nerve in patients with FM compared to HC represents a faster conduction of pain and longer period of sustained muscle contraction in patients [96]. This may suggest the effectivity of CSP as a peripheral marker for altered pain sensitization in FM.

By means of ECG, measuring ANS responses to cold pressor tests could be used in a clinical setting to detect abnormalities in the baroreflex responses in patients [29,32]. The reduced baroreflex sensitivity and effectiveness during cold pressor test in patients with FM can be a manifestation of altered CNS activity. Additionally, the demonstrated reduced heart rate variability could be a result of a decreased baroreflex function in patients with FM [32]. Even though another study [33] showed no difference in heart rate increase during cold pressor test between both groups, results still indicated a higher heart rate and lower heart rate variability in patients with FM compared to HC at rest. Furthermore, the results on the correlation between pain modulation and motor features are inconsistent [36,45,46,47], and we can therefore not deduce that assessing pain modulation during motor activity can be regarded currently as a valid marker.

4.2. Measurements to assess central manifestations of HACS

Feasibility of measurements of central manifestations of HACS in patients with FM was shown in several studies [28,43,44,48,49,53,55,56,57,58,59,60,61, 62,63,64,65,66,67,68,69,70,71]. However, except for three [49,61,87], these studies were qualified as poor quality. Furthermore, an explosive synchronization network is a network where a small perturbation rapidly propagates throughout the whole network. Explosive synchronization (ES) networks detected with EEG have shown to elicit higher sensitivity to external stimulation than non-ES networks [59]. Lee et al. [59] concluded that the presence of ES conditions in the brains of patients with FM can be an underlying mechanism of hypersensitivity. ES conditions may thus be a potential marker for HACS. Studies on LEP, on the contrary, yielded inconsistent results. Therefore, it cannot be concluded that LEP amplitude analysis with EEG is a valid method to assess HACS in patients with FM [72, 73,74,75].

Conditioned pain modulation (CPM) can be described as a painful conditioning stimulus leading to decreased pain intensity of another noxious stimulus [97]. The reduced NFR after non-painful conditioning (mechanical stimulation) in patients with FM points towards the presence of altered pain inhibitory pathways [53]. However, this was performed in a poor-quality study, which suggests that NFR amplitude measured with EMG after the application of a painful conditioning cannot be considered a valid marker for HACS detection. One additional study showed the positive effect of attentional analgesia in patients with FM, putting forward the capability of patients with FM to modulate pain when the given stimulus is sensitivity-adapted and the attentional task difficulty is correctly calibrated [44].

fMRI was used in eleven studies [28,44,48,49,61,62, 63,64,65,66,67] to examine various aspects of HACS in patients with FM. The variations of mean amplitude of low-frequency fluctuations (ALFF) in patients with FM indicate an imbalance between pain and sensory processes [65]. This suggests the presence of altered central nervous system activity in patients with FM [65]. fMRI showed increased connectivity between various brain regions in patients with FM compared to HC [63,64,66], reflecting the expression of HACS in pain processing mechanisms in patients with FM [63]. Furthermore, increased brain activation of pain-related areas during non-painful stimulation in patients with FM indicate physiological evidence of their increased pain perception [62]. Similar patterns of brain activation after sensitivity-adjusted painful stimuli in both groups also suggest increased pain sensitivity in patients with FM [28,44]. The same study found a positive correlation between spinal activation during TSSP and increased BOLD activity in the brainstem, suggesting a different pain modulation mechanism in patients with FM [28]. The higher neurologic pain signature (NPS) responses, an fMRI-based neurologic correlate of physical pain, provides evidence of amplified pain processing and HACS in patients with FM [61]. These studies help us conclude that fMRI is a useful tool to help indicate the following markers of HACS in patients with FM: amplitude of low-frequency fluctuations (ALFF) variations, brain activity and connectivity differences, neurologic pain signature responses and pain anticipation dysfunction. On the other hand, rCBF variations indicate patient' higher attention to innocuous sensory signals at rest. These findings make PET and SPECT imaging potential tools for the investigation of brain perfusion abnormalities [68,69,70]. Lastly, two studies [43,51] point out the potential role of CPM assessment with tourniquet pain conditioning as a marker for HACS in patients with FM [51].

All taken together, seventy-four studies were ranked as poor or fair quality. Those studies indicate a high risk of bias, which should be taken into consideration when interpreting results. The markers identified from studies ranked as poor quality cannot be determined as being as valid as markers identified in higher quality papers. Out of the markers identified in this review, the following were suggested from at least fair quality papers: higher SREP sensitization (elicited by pressure stimuli) [30,31], NPS response detected with fMRI [61], lower sound 'pressure' pain thresholds [42], brain perfusion differences [81,87] and conditioned pain modulation with cuff pressure conditioning [51]. The lower pain AS decline rates were suggested from three papers [19,20,21], out of which only one is fair quality [21].

A limitation to this review is the fact that due to the heterogeneity of the studies, especially in the vast number of markers, measurements and differences in study protocols, a meta-analysis could not be conducted. The current study has implications in the clinical setting, because these findings can be utilized to construct a more objective diagnostic protocol for HACS assessment in patients with FM. Furthermore, assessing HACS development over time as a proxy for disease progression in the day-to-day clinical practice may be valuable. Questionnaires combined with a short battery of

objective tests, grouping the markers and their respective tools could be a solution to objectively quantify patients pain markers. Markers that are best executable and affordable in daily practice are tourniquet cuff pressure conditioning [51] and pressure stimuli, the latter being derived from a fair quality paper [31]. By assessing these markers, HACS may be more objectively quantified Additionally, the diagnosis of HACS development over time can also be combined with methods which do not require questionnaires or markers [10]. Physicians could strengthen the diagnosis by assessing amplified pain distribution (number of pain regions and/or pain intensity per region) compared to previous assessments. This will ultimately help to make a personalized treatment plan for daily clinical practice. Studies have shown that the implementation of physical and pharmacological therapy in patients with temporomandibular disorders has led to the reduction of pain- and mobility-related symptoms [6]. Hence, FM, as an overlapping chronic pain disorder with relations to central nervous system dysfunction due to HACS, could also benefit from physical therapy for the rehabilitation of HACS and, as result, for the improvement of pain. Further research, however, is warranted to validate these hypotheses. It is important to note that there is currently no single test or gold standard that can identify patients with HACS and that a combination of different measurements could formulate a gold standard, possibly also combined with more invasive markers which were left outside the scope of the current study.

5. Conclusion

The current study identified non-invasive markers for peripheral manifestations of HACS in FM including quantitative sensory testing measurements and nociceptive flexion reflex assessment. This study also revealed that various techniques can be used to assess the aforementioned HACS. Among them are markers such as EMG for the assessment of nociceptive flexion reflex. Lastly, conditioned pain modulation by tourniquet cuff pain conditioning and techniques such as EEG, PET, SPECT, fMRI and VBM were also identified to be useful in the assessment of central manifestations of HACS. More studies should be conducted in order to determine which markers can clinically be used to identify HACS in patients with FM.

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Competing interests

None to declare.

Supplementary data

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