THE EFFECT OF PAIN NEUROSCIENCE EDUCATION ON PROCESSES OF CENTRAL SENSITISATION IN CHRONIC PAIN: A SYSTEMATIC REVIEW OF THE LITERATURE

LITERATURE REVIEW

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Preface

Pain as a sensation is something the majority of us understand. Less of us can understand how debilitating it is to suffer chronically with pain, nor do we understand the complexity of it. Patients and their families are left feeling helpless and defeated, as are healthcare workers who often resort to dangerous pharmaceutical treatments. But the problem of chronic pain is universal and common, and the complexity of it's treatment should not overwhelm us or suppress our efforts.

Some believe that pain is like an optical illusion, perceived differently depending on particular circumstances. However, once that optical illusion is explained to us, we are able to perceive it differently. In this systematic review, I aim to see if this theory can be applied to pain, albeit a simple solution for an incredibly complex problem.

Taken from Bill Bryson's book 'The Body: A guide for the occupant' where he discusses that chronic pain, unlike acute pain that exists to warn us of damage, has no purpose:

There is a paradox at the heart of pain that make its treatment particularly intractable. 'When most parts of the body are damaged, they stop working- they switch off.' Irene Tracey syas. 'But when nerves are damaged they do exactly the opposite- they switch on. Sometimes they just won't switch off, and that is when you get chronic pain.' In the worst cases, as Tracey puts it, it is as if the volume knob on their pain has been turned all the way up. Figuring out how to turn that volume down has proved to be one of the greatest frustrations in medical science.

I hope this research is my first personal step to make chronic pain a little less loud.

I. Summary

I. Introduction

Advances in neuroscience and the identification of the new concept of central sensitisation (CS) have increased understanding of the complexity of pain, offered explanations for pain without a source and reasons for its persistence, forcing a more holistic chronic pain (CP) treatment approach. Pain neuroscience education (PNE) and its positive effects on chronic pain have been researched and proven, but the effects on CS remain unclear. This systematic review of randomised control trials (RCTs) aims to investigate the effectiveness of PNE on CS processes in addition to pain perceptions and cognitions in individuals with CP. The results will provide evidence for guiding the treatment of chronic pain with suspected central sensitisation.

II. Method of study design:

9 randomised control trials were identified via systematic searches in 3 databases (PubMed, CENTRAL and PEDro) and a secondary searching (PEARLing) process. All RCTs published in English assessing the effect of PNE on CP were considered and screened against inclusion and exclusion criteria. The PEDro scale was used to assess study quality of the 9 included articles. Data were extracted using the Participants, Interventions, Comparison and Outcomes (PICO) approach. The mean results for baseline and follow-up measurements were extracted for each outcome measure in experimental and control groups. Additionally, 95% confidence intervals, f and p values and Cohen d effect sizes were extracted.

III. Results

Although no consensus was reached across the studies for any of the analysed outcome measures, there is promising evidence that PNE (independently and in addition to other treatments) can result in reduced catastrophising about pain, reduced fear of movement, fewer self-reported CS symptoms as well as improve pain pressure tolerance. There is little evidence that spatial summation procedures or subcortical gray matter volumes can be altered. No effects were found for conditioned pain modulation, temporal summation or cortical gray matter volumes.

IV. Conclusion

No definite conclusions can be drawn regarding the influence of PNE on CS, given the heterogeneity of the results. However, the evidence supports a shift from an anatomical biomedical approach to a biopsychosocial approach. The evidence also supports a multi-modal treatment approach for patients with chronic pain. This is shown by significant results for catastrophising, kinesiophobia, pressure pain thresholds and central sensitisation symptoms. However, these results are not consistently significant across studies, therefore further research regarding moderators and mediators is required.

II. Table of Contents

Key Words:

- Central Sensitisation
- Chronic Pain
- Pain neuroscience education
- Biopsychosocial

Abbreviations:

CP: Chronic Pain

CPM: Conditioned Pain Modulation

CS: Central Sensitisation

CSI: Central Sensitisation Inventory

PCS: Pain Catastrophising Scale

PNE: Pain Neuroscience Education

PPT: Pain Pressure Threshold

QST: Quantitative Sensory Testing

SSP: Spatial Summation Procedure

TSK: Tampa Scale of Kinesiophobia

TS: Temporal Summation

1. Introduction

Chronic pain (CP) is a huge burden for individuals, their family and society. In addition to the reduction of quality of life and the psychological and physical price [1] chronic pain sufferers must pay, the economy and healthcare are also significantly impacted[1]. Back pain disability benefit-claims and analgesic prescription, cost the UK £10.7 billion and £537 million a year respectively [2], in addition to costs arising from workplace absence and decreased productivity[2], primary-care visits, referrals, investigations and interventions. Global prevalence rates of CP are difficult to determine, but there are more CP victims in the US than diabetes, heart disease and cancer combined[3]. Pain remains the biggest contributor to disability measures in 2020[2], yet more than 56% of CP patients in the Netherlands declare that their problem is undertreated[1].

Advances in neuroscience have led to the discovery and investigation of a complex phenomenon that is now considered a significant factor of persistent pain[3–7] and can begin to explain pain without an obvious source[3,8,9]. The International Association for the Study of Pain (IASP) established an entirely new pain category, 'nociplastic pain'[10], to classify this phenomenon as 'pain maintained by altered nociceptive processing'[10], highlighting its clinical relevance and importance as a potential treatment target[9]. This phenomenon is commonly termed 'Central Nervous System Sensitisation' or briefly 'Central Sensitisation'(CS)[9].

Although various definitions for CS exist [6], it was originally defined as an 'amplification of neural signalling within the central nervous system that elicits pain hypersensitivity'[4]. There is consensus that hyperexcitability is a common mechanism in all CS definitions[6] but it is more recently defined by the IASP as an 'increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input'[10].

CS is referred to as an 'umbrella term' consisting of multiple Central Nervous System (CNS) dysfunctions[11,12] that contribute to increased sensitivity[3,4] to various stimuli[9] including pain, light, sound [8,13], temperature [14]. CS dysfunctions include pain faciliatory pathways with increased membrane excitability and synaptic transmission[15–17]; altered sensory processing in the brain[9,15,17,18] potentially due to gray matter morphologic changes in sensory processing regions[19]; and reduced inhibition of descending antinociceptive pathways[9,15,17,20,21].

Changes causing hypersensitivity incite excessive responses to normal and sub-threshold stimuli, which are further aggravated by the inability to activate endogenous pain inhibition mechanisms[4]. Consequently, pain is experienced from non-noxious stimuli, responses to noxious stimuli are further increased and prolonged, and the receptive field is expanded[4], provoking the CS clinical features of hyperalgesia, allodynia and wide-spread pain, respectively[4,5].

Additionally, but not to be used synonymously with CS[5], (negative) behavioural, emotional, social and cognitive factors, potentially as a result of a chronic condition[22], can alternatively/additionally form a vicious cycle and contribute to its persistence[3,23]. Pain-facilitating pathways can be (further) sensitised by emotions, thoughts, attention, and stress such as catastrophising (focus on negative emotions/thoughts/beliefs/expectations) and pain-related anxiety[23,24].

A thorough assessment of patients with suspected CS must therefore include analysis of the patient's perceptions and cognitions[3]. These include pain perceptions, pain catastrophizing thoughts, anxiety, fear of movement, anger, depressive feelings and stress and can be assessed with various outcome measures[3].

CS charateristics are established amongst many CP conditions[25] including fibromyalgia [26–29], chronic whiplash [30], chronic lower back pain [7,31,32], osteoarthritis [7,33–35], rheumatoid arthritis[36], irritable bowel syndrome[29], headaches[37,38] and chronic fatigue sydnrome [39] with some authors believing no CP condition can exclude CS as a contributing factor [7].

CS is not only hypothesized as a potential cause for amplified pain in existing CP conditions[8,9] but also a potential mechanism for chronic pain development[7,8,40] and poorer patient outcomes[8,9], including post-operative outcomes[7].

Despite the recognition of CS features in multiple conditions[14], determining CS prevalence rates poses challenges[7]. No gold standard assessment exists[8,41] and a true CS diagnosis in humans is not currently possible [5,7,42] due to the contribution of the multiple mechanisms [43] previously mentioned. However, CS can be suspected by assessment of clinical features [3,43], the use of diagnostic surrogate markers [44] and a process of exclusion of other causes [3,5]. Nijs et al. advocate that to classify CS, neuropathic pain must first be excluded, according to IASP diagnostic criteria, followed by screening for CS clinical features: 1) Disproportionate pain, compared to the nature and extent of the injury or pathology; 2) diffuse pain distribution, allodynia and hyperalgesia; 3) Hypersensitivity of senses unrelated to the musculoskeletal system[8]. For further classification details suggested by Nijs et al[8], readers are referred to the referenced article.

Additionally, various diagnostic surrogate markers that assess features of CS have been developed, including patient-rated questionnaires, pain area mapping, Pain Pressure Thresholds(PPT), and Quantitative Sensory Testing (QST) of Temporal Summation(TS) and Conditioned Pain Modulation (CPM)[4,7].

Questionnaires include the Central Sensitisation Inventory (CSI)[41] and the Pain Sensitivity Questionnaire (PSQ)[45] which assess hypersensitivity of senses [3] and various clinical symptoms[41]. The CSI is a valid, reliable and relevant [8,46] 25-item questionnaire with a cut-off score of 40 indicating CS as a predominant cause of hypersensitivity[8,47]. It is considered the best self-informed tool to value CS[48] and demonstrates concurrent validity with psychological factors[42].

Pain mapping consists of measuring the location and extent of areas of pain, referred pain and sensory hypersensitivity[49]. This assists in determining increased central contribution if pain spreads beyond the presumed nociceptive neuronal territory or segment[3,7]. This process can be objectified by means of validated and reliable maps such as those developed by McGill[49,50].

When suspecting CS, simply measuring short-term changes in experienced pain severity does not provide sufficient information regarding nociceptive input or (defective) pain mechanisms, hence are an unreliable measure on which to assess treatment efficacy, guide treatment dosage and adapt personal behaviour[9]. Furthermore, it is not yet possible to confirm functional neuroimaging as an objective marker of CS[5]. Therefore, researchers advocate the use of PPT and QST[4].

Measurement of PPT or pressure algometry[51] consists of measuring the threshold of pain at various locations outside the area of presumed nociception[4]. This is an efficient, reliable and valid way to detect widespread hyperalgesia or secondary hyperalgesia [4,51].

QST provides details of the functioning of the nervous system [7,52], in both healthy and pathophysiological circumstances[7]. using experimental methods with different stimulus modalities[4,44]. By implementing repetitive stimuli, clinicians can detect TS, or a 'wind up' of pain, resulting in increased pain as neuron excitability increases with successive stimulation signifying overactive CNS processing[53]. Assessing CPM can measure the functionality of descending tracts responsible for controlling and modulating pain perception[53]. It involves the implementation of a test stimulus and a conditioned stimulus clinicians can detect dysfunctions, as functional descending tracts possess an endogenous analgesic system whereby painful stimuli override the effects of other painful stimuli[53]. Results of these methods can detect dysfunctional pain mechanisms[51], thus determining the severity of CS in multiple conditions[7]; quantify pain sensitivity in clinical studies[7,44] providing data for intervention analysis[54].; and guide treatment parameters[4].

Despite the challenges of CS diagnosis, substantial evidence regarding the presence of central pain-provoking mechanisms[7] and the impact of psychological processes[55] has provoked an increased belief that pain in CP is not just a symptom, but a potential pathophysiological process[9]. This has forced physiotherapists to abandon traditional biomedical treatment approaches for CP, in favour of a more holistic strategy that considers CS and the many psychological, behavioural, and social contributors[5]. The clinical reasoning that pain equals tissue damage[5] is the focus of many biomedical treatment approaches that target local structures[9] and offer traditional education focused on pathoanatomy and biomechanics[56]. Although not to be completely rejected, as removal of peripheral drivers can offer

positive results[5,7], the focus on damage or deviance from "normal" anatomy and omission of more complex pain explanations means these approaches hold little value for reducing pain and disability in CP with signs of CS [57]. In fact, the more processes of CS a patient exhibits, the poorer they will respond to biomedical treatment[9]. This can often enforce negative patient outcomes as the source of the problem is not addressed[57] and negative cognitive-emotional factors develop/worsen[57] due to a lack of improvements and feeling misunderstood. Additionally, pharmacotherapy, such as opioids, risk harmful side-effects and dependency. This highlights the necessity for extensive investigation of interventions that no longer address CP as "just a symptom" but target the umbrella of CS and the reversible mechanisms it encompasses.

One intervention receiving substantial attention is 'Pain Neuroscience Education'(PNE)[58] or 'Explain Pain'[59], which offers a more 'central' approach[11] through educating patients about the multiple components involved in pain perception[58]. By implementing a biopsychosocial approach, PNE aims to assist patients in reconceptualising their opinion that pain is a result of brain and nervous system input signals and not a measure of damage[59]. When effective, PNE assists patients to understand their pain; adapt beliefs regarding their illness; adjust coping strategies and form a stronger therapeutic alliance[57] with their therapist. PNE has been repeatedly scrutinised in systematic reviews and trials, with researchers trying to determine the clinical effects of different PNE techniques and dosages, proving efficacy amongst various CP populations[60]. Promising evidence for the effects of PNE on improving pain and disability[57,60,61] as well as psychosocial factors[57,60] exists, but PNE is frequently administered adjunct to various interventions[62,63]. However, efficacy of PNE is assumed as more promising results occur with the addition of PNE than independent implementation of the interventions[63]. This suggests PNE prior to more active interventions allows for application, and thus consolidation, of neurophysiological knowledge[62] and, considering the complexity of pain treatment, removes potential barriers in further interventions by means of a stronger therapeutic alliance[9] or improved patient cognitions and beliefs[62].

1.1 Study Objective

Despite substantial research surrounding CS and PNE, no systematic reviews specifically analysing the effect of PNE on CS in CP conditions exist to the author's knowledge. Therefore, this review aims to use randomised controlled trials using confirmed CS indices to assess PNE efficacy across various CP conditions. Randomised controlled trials using PPT and QST, will give insight into the effect of PNE on endogenous pain mechanisms. Patient-relevant outcomes to provide a more accurate indication of treatment efficacy[64] can be analysed through use of CS-related questionnaires, including the self-reported CSI or PSQ. Additionally, due to the complex nature of CS and the intertwined influence of psychosocial factors, randomised controlled trials must include any outcome measures that further assess patient pain cognitions. This will provide additional insight regarding patient-specific and clinically relevant outcomes, as QST produces evoked pain that does not directly reflect the pain experienced in specific conditions[5].

Although this review aims to assess the effect of PNE, PNE used adjunct to other interventions will be included. This is justified as an additional intervention may enhance the PNE process. Additional interventions reflect a clinical scenario, in which physiotherapists frequently adopt a multicomponent approach. By determining the effect of PNE on physiological and patient-specific outcome measures, this review aims to aid physiotherapists in the treatment of CP, with suspected signs of CS.

The results of this review, whereby data of existing RCTs is analysed, aim to not only determine the general efficacy of PNE but also the most effective way to employ it. Analysis of expected heterogeneity in the administering of PNE, including dosage, frequency, duration, technique, tools used, the professional delivering PNE and the addition of another intervention amongst others, will assist clinicians in developing a sound understanding of the complexities of pain perception and the most effective way to employ PNE. QST testing is expensive and timely to administer, but physiotherapists can use these results to deliver a treatment that can be tailored to their patients.

2. Methods

2.1 Research Design

The search process was conducted by one reviewer from November 2020-January 2021. A preliminary PubMed search was conducted in November 2020 to establish appropriate search terms, key words and ensure no systematic reviews existed on the topic. This search confirmed the most common variations for 'central sensitisation' and 'pain neuroscience education' [65] and established and reliable outcome measures that detect CS-related improvements in CP. After the preliminary search, the problem was formulated in PICO form:

- **P**opulation: Chronic Pain
- **I**ntervention: Pain Neuroscience Education
- **C**omparison: N/A
- **O**utcomes: PPT, QST, CSI, PSQ, Pain drawings and any outcomes measuring patient pain cognitions.

The methodology of a systematic review was used to establish effects of PNE on CS in CP.
No ethical evaluation was required as no participants were recruited for the purpose of this literature review[66]. The search was limited to selection of RCTs.
The search was done in November and December of 2020 in PubMed, Cochrane Register of Controlled Trials (CENTRAL), and PEDro databases. The choice of these databases was justified for the following reasons. PubMed is a widely accessible resource which is available to the public and provides MEDLINE and other National Library of Medicine (NLM) resources[67]. CENTRAL only includes controlled clinical trials that have been extensively searched for in various databases, other bibliographic databases and hand searching[68]. PEDro provides physical therapy related literature and a corresponding PEDro score for RCTs.

2.2 Search Terms

Alternative terms established in the preliminary search were used for "Central Sensitisation" and "Pain Neuroscience Education" to ensure full inclusion of existing research. Table 1 shows the search terms used.

Table 1 Description of search terms

	Question Term	Search Term	MeSH Term
Population	Chronic Pain	"Chronic pain"	N/A
Intervention	Pain Neuroscience Education	"Pain neuroscience education" "Pain neurophysiology education" "Pain physiology education" "Pain biology education" "Therapeutic pain education" "Explain pain"	N/A
Outcome	Central Sensitisation	"Central Sensitisation" "Central Sensitization" "Central Nervous System Sensitisation" "Nociplastic pain"	Central Nervous System Sensitization

2.3 Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[69] and flowchart() were used to evaluate and ensure good quality reporting.
The search strategy was adjusted according to the individual database's search requirements. Boolean operator "AND" was used between population and intervention to ensure inclusion of both, and "OR was used between alternative terms. MeSH terms were used where appropriate in PubMed.
Appendix 1 demonstrates the search methods used in the individual databases.
PEARLing was conducted, whereby references of included articles were searched for additional articles. This provided one additional article.

A full search in PubMed was as follows:
("chronic pain"[MeSH Terms] OR ("chronic"[All Fields] AND "pain"[All Fields]) OR "chronic pain"[All Fields]) AND ((("pain"[MeSH Terms] OR "pain"[All Fields]) AND ("neuroscience"[All Fields] OR "neurophysiology"[MeSH Terms] OR "neurophysiology"[All Fields] OR "therapeutic"[All fields]) AND ("education"[MeSH Subheading] OR "education"[All Fields])) OR ((("explain"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields])) OR (("pain"[MeSH Terms] AND "education"[MeSH Subheading]) OR "education"[All Fields]))) + Randomised Controlled Trials

2.4 Study Selection

Search results from PubMed, CENTRAL and PEDro were combined and checked for duplicates via an external citation manager and confirmed manually. Inclusion and exclusion criteria (shown in Table 2) were used to exclude articles deemed irrelevant to the research question via screening of abstracts and titles. Full-text articles were retrieved and screened against the same criteria if eligibility required further investigation. Rationale for excluded articles was recorded and methodological quality of included articles was assessed. Reasons for removal were lack of established CS-related outcome measure and a (pain) education invention that did not specifically consist of pain neurophysiology. One article[70] that did not fully meet the inclusion criteria, as there is no CS-related outcome measure, was still included for analysis. This RCT is a secondary analysis of an RCT assessing efficacy of blended-learning PNE on people with Chronic Spinal Pain(CSP) [71]. This secondary analysis provides additional information relevant to the research question as CS-levels are determined at baseline with use of the CSI and outcomes assessing cognitions are present, justifying its inclusion. Figure 1 provides a summary of the search procedure.

Table 2 Inclusion and Exclusion Criteria

	Inclusion	**Exclusion**
Participants	Adults > 18 years old Chronic pain lasting > 3 months.	Pain with no evidence of suspected CS involvement. (Sub)-acute pain.
Intervention	Pain Education, as determined by Moseley, consisting of explanations of the neurophysiology of pain.[59]	(Pain) education related to a biomedical approach: • Related to a specific condition/ postural/ exercise/ behavioural. Alternative pain education: • CBT/ behavioural counselling.
Outcome	CS-related: • QST measuring hyperalgesia, allodynia or TS • 2 different QST together measuring CPM • Questionnaires measuring symptoms and history of functional syndromes - Central Sensitisation Inventory (CSI) - Pain Sensitivity Questionnaire (PSQ) • Outcome measure related to psychosocial factors/ pain cognitions.	
Research Design	RCTs	Protocols of RCTs
Additional	Full-text available English	Poor/moderate methodological quality (PEDro score 0-5)

2.5 Methodological Quality Analysis

Considering the hierarchy of evidence, good quality RCTs offer the highest-level evidence for analysis in systematic reviews to assist in guidance of clinical decisions[72,73]. Levels of evidence as described by Sackett[72] can be seen in Table 3. The PEDro scale, an 11-item scale developed to reliably[74] rate the quality of RCTs, was used to assess the individual methodological quality of the included RCTs. Clear satisfaction of each criterion in the RCT corresponds to 1 point, totalling a maximum of 10 points as the first criterion is omitted from the score[74]. High quality, fair quality and poor quality can be determined if the total score is 6-10, 5-4 or ≤ 3, respectively[74]. A table consisting of the chosen articles and their corresponding PEDro scoring can be found in Appendix 2.

Table 3 Levels of Evidence from Sackett72

Level	Type of Evidence
I	Large RCTs with clear cut results
II	Small RCTs with unclear results
III	Cohort and case-control studies
IV	Historical cohor or case-control studies
V	Case series, studies with no controls

2.6 Data Extraction

Data were extracted using the PICO approach in addition to the name of author(s), publication year and title. *Participants:* age, sex, diagnosis, duration of symptoms and diagnostic criteria. *Intervention*: stand-alone PNE or in combination, method of PNE, duration, intensity, and frequency. *Comparison:* to another treatment, to no treatment or to usual treatment. *Outcomes:* outcome used to assess CS changes and corresponding results, outcome used to assess cognition changes and corresponding results. The extracted characteristics of the included articles that analysed PNE independently are summarised in Table 5, articles that combined PNE with another intervention are summarised in Table 6.

2.7 Data Analysis

The P value, the mean and 95% confidence intervals (CI) for the between-group differences in addition to the mean changes, 95% CI and effect sizes before and after treatment were extracted from the articles to determine the effect of PNE on each outcome measure.

An alpha of $p < 0.05$ was used to define significant differences. This can enable classification of outcomes into four levels of scientific evidence to assist in clinical decision making[72]. Classification determined by Grade Practice Recommendations are shown in Table 4. To be "consistent", at least 75% of the included RCTs must present the same (significant/insignificant) results on the various outcome measures.

Table 4 GRADE Practice Recommendations

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent.	Generally, clinicians should follow a recommendation but should remain alter to new information and sensitive to patient preferences.
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

D	Option	Level V evidence: little or no systematic empirical evidence	Clinicians should consider all options in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial role.

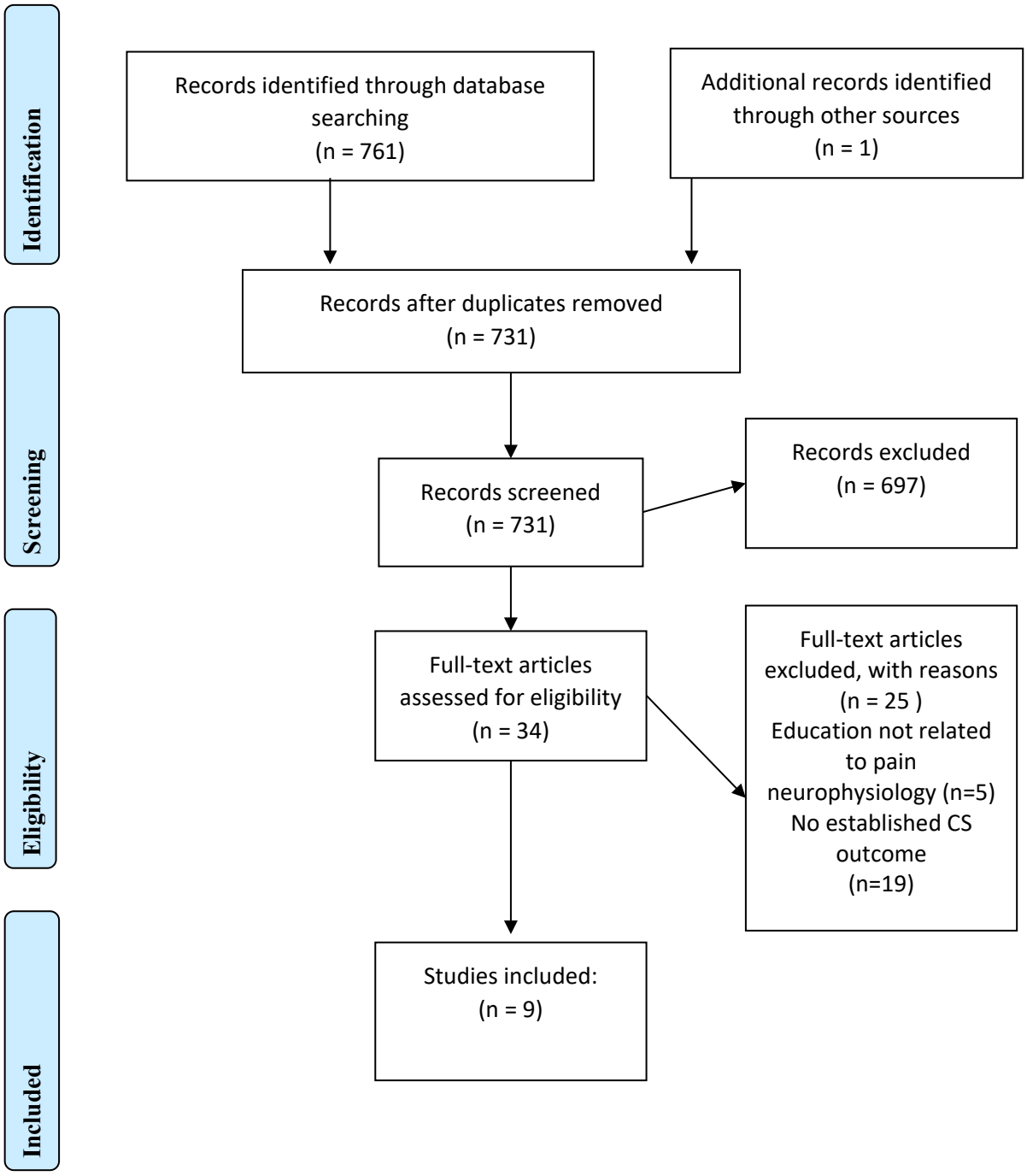

Figure 1 PRISMA flow diagram

3. Results

3.1 Description of the included RCT's

3.1.1 Study selection:

Of the 761 identified articles, 9 studies were included. This process is summarised in a PRISMA diagram (figure 1).

Two[70,75] of the studies, one of which is a secondary analysis of an additional study, are written by the same research group and use the same sample. For the purpose of analysis, the sample included in both of the studies are considered two separate samples.

All of the included studies were RCTs. 4 of the studies were conducted in Belgium[54,70,75,76] and the remaining 5[77–81] were conducted in Spain.

The list of included studies is included in table 5. Gender, age and duration of pain for each study is included in table 6. Study details including methodological quality; participant characteristics; type of intervention and control; and type and time of outcome measure assessment are summarised in Table 7.

3.1.2 Sample characteristics:

The total sum of participants is 643 with the smallest sample of 12[78] and the largest of 170[80]. The majority of the sample were female, totaling 503 (78.2%). Mean ages (and standard deviation) of the total sample of each trial were extracted or calculated from the sub-groups when absent. Mean ages varied from 36 (+-10) years to 53.4 (+-9.08) years. Sample characteristics are summarised in Table 6. Assessed conditions included non-specific chronic spinal pain (nCSP)[70,75,80]; non-specific LBP (nLBP)[78,79]; Fibromyalgia (1990 American College of Rheumatology (ACR) criteria[76]), (1990 and 2010 ACR criteria[77]), (2010 ACR criteria[81]); Chronic Fatigue Syndrome (CFS) with chronic pain.[54]

3.1.3 Recruitment:

4 trials[76–78,80] recruited their subjects sample from referrals from practices.

3 trials [70,75,79] recruited their subjects via promotion such as announcements, adverts and social media in universities, hospitals and physiotherapy practices.

1 trial[54] recruited their subjects via random selection from medical files from a university-based chronic fatigue clinic.

Table 5 List of included studies

Study No	Author	Country	Journal (year)	Type of Study	Intervention	Sample size	% Female	Age (y)
1	Meeus, et al[54]	Belgium	Arch Phys Med Rehabil (2010)	Double blind RCT	PNE only	48	83.3%	18-65
2	Van Oosterwijck, et al[76]	Belgium	Clin J Pain (2013)	Double blind RCT	PNE only	30	86.7%	18-65
3	Malfliet, et al [70]	Belgium	PM R (2018)	Triple blind RCT	PNE only	120	60.8%	18-65
4	Amer-Cuenca, et al[77]	Spain	Pain Med (2020)	Single blind RCT	PNE only	77	92.2%	?
5	Tellez-Garcia, et al[78]	Spain	J Bodyw Mov Ther (2015)	Single blind RCT	PNE & another intervention	12	66%	18-65
6	Bodes, et al [79]	Spain	Arch Phys Med Rehabil (2018)	Single blind RCT	PNE & another intervention	30	86.7%	20-75
7	Malfliet, et al[75]	Belgium	Pain Pract (2020)	Multi-centre RCT	PNE & another intervention	120	60.8%	18-65
8	Galan-Martin, et al[80]	Spain	J Clin Med (2020)	Multi-centre RCT	PNE & another intervention	170	80%	18-70
9	Ceballos-Laita, et al[81]	Spain	J Clin Med (2020)	Feasibility RCT	PNE & another intervention	36	100%	20-65

Table 6 Sample characteristics

	Gender				Age (years)		Duration of Pain (months)	
	Study Group		Control Group		Study Group	Control Group	Study Group	Control Group
Study No	**M**	**F**	**M**	**F**				
1	2	22	6	18	38.3 ±10.6	42.3 ±10.2		
2	3	12	1	14	45.8 ±9.5	45.9 ±11.5	145 ±96	116 ±46
3 High CSI	7	17	8	22	36.58 ±11.03	40.47 ±12.49	111 ±128.3	66.5 ±96.5
Low CSI	15	21	17	13	40.13 ±14.91	42.10 ±11.10	88 ±156.5	70.5 ±141.5
4 HD	3	17			54.75 ±10.14		282.36 ±62.84	
CLD	0	20	1	16	55.20 ± 8.19	51.27 ±10.57	278.16 ±186	251.04 ± 108.24
DLD	2	18			51.67 ±7.38		151.68 ±30.56	
5	2	4	2	4	36 ±5	37 ±13	17 ±9	19 ±8
6	6	22	6	22	49.2 ±10.5	44.9 ±9.6		
7	22	38	22	35	39.1 ±11.95	40.53 ±12.88	121.55 ±100.77	103.41 ± 82.88
8	24	65	10	71	53.02 ±10.7	49.14 ±12.14	93.13 ±83.5	93.86 ±84.91
9	0	16	0	16	52.13 ±10.31	53 ±10.68	148.44 ±103.68	133.44 ±97.2

Table 7 Description of studies

Study	Enrolment Criteria	Intervention	Control	Outcome Measures	Assessments
1	• Chronic Fatigue Syndrome ○ Centers for Disease Control and Prevention criteria (1994) ○ Chronic widespread pain: Pain located axially on L & R of body, above and below waist, lasting >3 months)	• 1 x 30 min interactive PNE	• 1 x 30 min interactive session on pacing and self-management	• CS-related ○ PPT • PS-related ○ PCS ○ TSK	• Baseline • Post intervention
2	• Fibromyalgia ○ (ACR criteria 1990)	• PNE received in oral format. • Encouraged to read written leaflet at home & 1-week later phone call	• Pacing self-management technique education in oral format • Encouraged to read written leaflet at home & 1-week later phone call	• CS-related ○ SSP ○ PPT • PS-related ○ PCS ○ TSK	• Baseline • 2 weeks • 3 months
3	• Non-specific CSP ○ ≥3 days/week ≥3 months ○ High CSI: n=54 ○ Low CSI: n=66 ○ CSI cut off >40	• PNE (3 sessions in 12 weeks) ○ Group: 30-60 min + book for home ○ Online module with 3 videos + questionnaire ○ One-on-one conversation	• Neck and back education sessions (biomedical based) ○ 3 sessions in 12 weeks ○ Group: 30-60 min + book for home ○ Online module with 3 videos + questionnaire ○ One-on-one conversation	• CS-related • PS-related ○ PCS ○ TSK	• Baseline • Post intervention
4	• Fibromyalgia ○ ACR criteria (1990&2010) ○ Stable medication for ≥ 4 weeks ○ Average pain intensity ≥4 on VAS	• PNE: High Dose (6 x 45 min sessions) • PNE: Concentrated low dose (2 x 45-minute sessions) • PNE: Diluted low dose (6 x 15-minute sessions)	• Biomed-Ed ○ 2 x 45 min sessions	• CS-related ○ PPT ○ TS ○ CPM • PS-related ○ PCS	• Baseline • 3 months
5	• Non-specific CLBP (≥3 months) ○ pain symptoms localised below the costal margin and over the gluteus area. • No referral into LE for > 1 year • No PT in last 6 months • 1 active Tr point reproducing symptoms.	• Trigger point dry needling. ○ Once per week for 3 weeks • PNE ○ 30 min after session #2 & #3	• Trigger point dry needling. ○ 1 x week for 3 weeks	• CS-related ○ PPT • PS-related ○ TSK	• Baseline • Post intervention
6	• Non-specific CLBP ○ ≥6 months pain symptoms localised below the costal margin and over	• Multi-modal Therapeutic Exercise ○ 2 sessions 1 month apart • PNE after each session	• Multi-modal Therapeutic Exercise ○ 2 sessions 1 month apart	• CS-related ○ PPT ○ CSI	• Baseline • Post intervention • At 1 month

	gluteus influenced by postures and physical activities. ○ usually accompanied by painful movement limitation and frequent referred pain	• Home exercise program for 3 months after the 2 sessions		• PS-related ○ PCS ○ TSK	
7	• Non-specific CSP ○ ≥3 days/week ≥3 months CLBP ○ Failed back surgery syndrome >3 years prior ○ Chronic whiplash ○ Chronic non-traumatic neck pain	• Cognition-Targeted Motor Control Training ○ Sensorimotor training complying with modern PNE. ○ Graded approach for feared/avoided movement. • PNE (3 sessions in 12 weeks) ○ #1. Group: 30min-1h + book for home ○ #2. Online module with 3 videos + questionnaire ○ #3. One-on-one conversation + 15x one-on-one	• Current best-evidence physiotherapy ○ Traditional (biomedical) neck and back education and general exercise	• CS-related ○ CSI ○ PPT ○ CPM ○ Grey matter morphologic features • PS-related ○ PCS ○ TSK	• Baseline • 3 months • 6 months • 12 months
8	• Non-specific CSP (>6 months)	• Group Physical Exercise (PE) ○ 18 PE + home program • PNE ○ Twice a day for 2 weeks ○ Book for home ○ One 2-hour PNE after 3 months	• Usual physiotherapy supported by current protocols: • 15 x 1-hour sessions of thermotherapy and analgesic electrotherapy in areas of pain and exercises	• CS-related ○ CSI ○ PPT ○ McGill Pain map • PS-related ○ PCS ○ TSK	• Baseline • 3 months • 6 months
9	• Fibromyalgia (ACR classification criteria 2010-11)	• Therapeutic Exercise (60 mins) ○ 3 x week for 10 weeks ○ Warm up, aerobic & strengthening, cool down with stretching, respiratory exercise. • PNE (30-45 mins) ○ 1 x week for 8 weeks ○ Face to face	• Therapeutic Exercise (60 mins) ○ 3 x week for 10 weeks ○ Warm up, aerobic & strengthening, cool down with stretching, respiratory ex	• CS-related ○ PPT • PS-related ○ PCS	• Baseline • Post intervention • 3 months

Abbreviations:

CLBP: Chronic Low Back Pain
CSP: Chronic Spinal Pain
PNE: Pain Neuroscience Education
PT: Physiotherapy
TrP (DN): Trigger Point (Dry Needling)
CS: Central Sensitisation
FM: Fibromyalgia
PPT: Pain Pressure Threshold
SSP: Spatial Summation Procedures
TS: Temporal Summation
CSI: Central Sensitisation Inventory
LE: Lower Extremity
PS: Psychosocial
TE: Therapeutic Exercise
TSK: Tampa Scale of Kinesiophobia
CPM: Conditioned Pain Modulation
PCS: Pain Catastrophising Scale

3.1.4 Medication use:

8 of the 9 included trials referred to the use of medication during the trial. Analgesic and antidepressant use is described in Table 8.

Table 8 Medication use

Study No	Analgesics	Analgesics Non-compliant	Antidepressants	Antidepressants Non-compliant	Other
1	Not <24 hrs before Ax	EG: 2 (8%) CG: 8 (33%)	Not <24 hrs before Ax	EG: 9 (38%) CG: 7 (32%)	No physical exercise <24 hours before Ax.
2	Not <24 hrs before Ax	EG: 11 (73%) CG: 12 (80%)	Not <24 hrs before Ax	EG: 6 CG: 7	No new treatments. Allowed usual meds
3					No new meds <6 weeks prior/during trial
4					Allowed current meds. No new meds/treatment
5					No new meds/ additional treatment during trial
6	Not <24 hrs before Ax				
7					Allowed current meds but not other therapies/ start new meds or therapy during trial
8	May continue (changes in use recorded)				Analgesics baseline: EG: 92% CG: 89% Analgesics 6mo: EG: 46% CG: 78%
9					

3.1.5 Intervention

3.1.5.1 Content of the intervention

Table 9 Content of the PNE intervention

Included Topic	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9
Pain Neurophysiology	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acute Pain Vs Chronic Pain				✓	✓			✓	✓
Pain does not equal tissue damage								✓	

Purpose of acute pain				✓				✓	✓
How acute pain originates			✓	✓			✓		✓
Nociceptive inhibition/facilitation			✓	✓			✓		
Peripheral sensitisation			✓	✓			✓		
Central sensitisation			✓	✓			✓	✓	✓
How pain becomes chronic (neuroplasticity/ modulation/ modification)				✓				✓	✓
Potential sustaining factors of CS (e.g emotion, stress, illness perception, pain cognition, pain behaviour)			✓	✓			✓		✓
Why/ how treatments decrease hypersensitivity of CNS				✓				✓	✓
Consequences of chronic pain (kinesiophobia, fear-avoidance behaviour, social isolation)								✓	

All of the articles made reference to "Explain Pain" by Butler and Moseley. Additional literature to guide the intervention included "Pijn Educatie: een praktische handleiding voor (para)medici" by Paul Van Wilgen[75]; the published guideline "How to explain central sensitisation to patients with 'unexplained' chronic musculoskeletal pain"[77] and content from www.paininmotion.be[79].

3.1.5.2 Dosage and Delivery of the intervention

Table 10 Dosage and means of delivery

Study No	No. of sessions	Duration	Frequency	Type	Educator	Method
1	1	30 mins	1			
2	2	30 mins	Session 1: day 1 Session 2: day 7		Bachelor in physiotherapy (with training from 2 qualified PT's with education experience)	1st: Powerpoint 2nd: phone. Individual tailored
3	3	1: 30-60 mins 2: N/A 3: 30 mins	3 sessions in 2 weeks		PT with clinical experiencein chronic spinal pain	1st: Powerpoint 2nd: online e-learning & Booklet 3rd: 1:1 conversation
4	HD: 6 CLD: 2 DLD: 6	HD: 45 mins CLD: 45 mins DLD: 15 mins		1x group (max 6) 1x online 1x 1-on-1	PNE-experienced PTs	Powerpoint Discussion & Coaching
5	2	30 mins	1 x/week for 2 weeks after session 2 and 3 of TrP DN			Powerpoint & Discussion & Homework
6	2	30-50 mins	2nd session after one month TE after PNE		Experienced PT	Powerpoint & Explanation Discussion Leaflet for home
7	3		12 weeks			
8	6	1-4: 90 mins 5: 120 mins 6: 120 mins	Session 1-4: 1 or 2/week Session 5: after TE program Session 6: after 3 months +18 exercise sessions (+reference to PNE)		PT with 30h training prior with min. 5 years working with CSP	Verbal and visual Discussion
9	8	30-45 mins	1x/week for 8 weeks		Medical doctor expert in pain neurophysiology	

3.2 Outcome measures assessing psychosocial factors

3.2.1 Pain Catastrophising Scale (PCS):

The PCS is a self-reported questionnaire that quantifies an individual's pain experience by scoring how catastrophically they view their pain. It has 3 subscales; helplessness (feel helpless about their pain), magnification (magnify the threat value) and rumination (cannot prevent negative pain-related thinking) resulting in a total score[82]. A decrease in score suggests less tendency to think catastrophically about pain. 8 of the 9 studies used the PCS as an outcome measure.

The data for each study are included in Appendix 3 and summarised as a narrative description below.

Study 1) Immediately post-intervention, the experimental group shows a decrease in PCS-rumination score decreasing significantly compared to the control group. The control group showed constant values.

Study 2) The experimental group showed a non-significantly larger decrease than the control group in all PCS scores at 14 day and 3-month follow-up.

Study 3) Results were recorded in mean and standard error.

A significant difference was seen between baseline scores of the 2 PNE groups (those with high and low self-reported CSI scores) for total, magnification and rumination scores with the high-CSI group showing higher scores. Post-intervention, only the high-CSI group showed significantly larger reductions in these 3 PCS scores than the low-CSI group and control group. PCS magnification scores increased at post-intervention for the low-CSI PNE group with small effect size.

Study 4) Greater reductions were seen in the PNE-concentrated low dose (PNE-CLD) group receiving 6 sessions of 45 minutes at post-intervention and at 3 months follow-up. Biomedical-education (BIOMED-ED) and PNE-high dose (PNE-HD) showed slight reductions. However, PNE-diluted low dose (PNE-DLD) showed a slight increase in scores at both post-intervention and 3-month measurements compared to baseline.

Study 6) The addition of PNE to therapeutic exercise led to significantly greater improvements at 1 month and 3-month follow-up with a high effect size compared to without PNE.

Study 7) Results were recorded in mean and standard error. No significant differences were found. However, greater, but non-significant, reductions were seen in the experimental group at 3-, 6- and 12-month follow-up.

Study 8) Both groups showed significant increases over time at post-intervention and 6-month measurements. However, the experimental group showed significantly greater reductions in all PCS subscales when compared to the control group receiving usual physiotherapy.

Study 9) The experimental group showed greater but non-significant reductions than the control group at post-intervention and 3-month follow-up.

3.2.2 Tampa Scale of Kinesiophobia (TSK)

The TSK is a self-reported questionnaire that quantifies an individual's fear of movement, (re-)injury, fear of work-related activities and fear avoidance. Total scores range from 17-68 with scores equal to/over 37 indicating kinesiophobia[83].

7 of the 9 studies included the TSK as an outcome measure.

The data for each study are included in Appendix 4 and summarised as a narrative description below.

Study 1) Immediately post-intervention, the experimental group presented with a non-significantly larger decrease in TSK score than the control group.

Study 2) Both the experimental and control group decreased from baseline to 3 months follow-up with non-significantly greater decreases in the experimental group. Scores decreased at 14-day follow-up and increased again at 3-month follow-up.

Study 3) Scores are shown in mean and standard error. TSK scores improved at post-intervention measurements with medium effect sizes in patients receiving PNE with both high and low self-reported central sensitisation symptoms (High- and Low-CSI). The control group showed minor reductions.

Study 5) The inclusion of pain neuroscience education to trigger point dry needling (TrP-DN) resulted in significantly greater improvements in the TSK score at post-intervention measurements.

Study 6) Significant differences with high effect size were found at 1 month and 3 months follow-up in the group that received PNE in addition to therapeutic exercise compared to the group without PNE.

Study 7) The experimental group showed significantly greater reduction compared to the control group with a decrease greater than the minimally important change of 5.5 (large effect size). These results were maintained at 6- and 12-month measurements.

Study 8) The experimental group showed significantly greater reductions post-intervention compared to the control group with large effect size. These results were maintained at 6-month follow-up.

3.3 Outcome measures assessing central sensitisation factors

3.3.1 Pain pressure threshold (PPT)/ Pressure algometry:

Pressure algometry quantifies pain thresholds by applying a steadily increasing pressure to a particular point on the body until an unpleasant sensation is felt[84]. An increase in score represents an increase in pain tolerance.

8 of the 9 studies used PPT to assess mechanical pain sensitivity. The data for each study is included in Appendix 5.

Study 1) PPTs were measured with an analog Fisher algometer at the skin web between thumb and index finger, 5cm lateral to spinous process of L3, proximal third of the calf in random order. The mean of last 2 values out of 3 consecutive (10s in between) measurements was used and recorded in kg/cm2

The PPT measurements improved in both groups over time, but with no significant difference between groups.

Study 2) PPTs were measured with an analog Wagner algometer bilaterally at the spine (5cm left and right of the spinous process of T8 and L3), the upper trapezius muscle (pars descendens midway, between the seventh cervical vertebra and the tip of the acromion), proximal third of the calf and the web between finger and thumb. The mean of the last 2 values out of 3 consecutive measurements was used and recorded in kg/cm2.

No significant effect was seen for PPTs over time or between groups.

Study 4) PPTs were measured with an analog Wagner algometer at the finger and trapezius. The average of 3 consecutive measurements was used and recorded in kg/cm2.

No extractable data was available for this study.

There was no significant difference between groups. PPTs measured at the finger showed more significant results compared to the trapezius. All groups and all locations showed an increase in scores at immediate post-treatment measurements and reductions at 3 months.

Study 5) PPTs were measured using an electronic algometer on dominant and non-dominant sides of C5-C6, T process L3, 2nd metacarpal and tibialis anterior. The mean of 3 trials was used and recorded on kPa/cm2.

The addition of PNE to trigger-point dry-needling resulted in significantly greater increases in PPT scores at the transverse process of L3 after the intervention. However, for PPTs at C5/C6, the second metacarpal and tibialis anterior, both groups showed similar increases.

Study 6) PPTs were measured using an analog Fisher algometer at 5cm lateral to spinous process of L3 and 2cm from the lateral epicondyle. Results were recorded in kg/cm2.

Both groups demonstrated an increase in PPTs, but the experimental group showed significantly larger increases with lumbar pressure pain thresholds at 1 month and 3-month follow-up.

Study 7) PPTs were measured using a digital Wagner algometer at the most painful side or dominant side in the case of bilateral pain. The trapezius muscle midway between C7 and the acromion and 5cm lateral of the spinous process of L3 on the symptomatic side and the remote sites quadriceps muscle and the web between the thumb and index finger were randomly tested. Results were recorded in kg force. Significant effects were found for primary PPT sites for the experimental group with a 15% increase which is believed to be clinically relevant.

Study 8) PPTs were assessed at 4 points (midpoint between acromion and spinous process of C7 and midpoint between superior border of the iliac crest and the spinous process at the same height, both bilaterally) with a Wagner algometer. The average of 2 measurements with 30 minutes in between was used.

A significant increase with large effect size was shown in the experimental group for all algometry locations when compared to the control group. Further increases were seen at 6 months follow-up.

McGill's pain maps were also used in this study, with the experimental group showing larger reductions of body areas with pain than the control group.

Study 9) PPTs were measured using a standard pressure algometer (Psymtec, FPK 20). The points assessed were right and left occiput, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter, and knee. A sum of the pressure values for each tender point was used for analysis.

The experimental group showed greater improvements in PPT score, but with no significant difference. The experimental group also showed further increase at 3 months follow-up but this remained insignificant.

3.3.2 Conditioned Pain Modulation (CPM) and Spatial Summation Procedure (SSP)

CPM and SSP are used to show the efficacy of endogenous nociceptive inhibition. Two studies assessed CPM. One study assessed SSP. The data for each study are included in Appendix 6.

Study 2) SSP: The dominant arm was divided into 8 segments, immersed per segment into 46°C water for 2 minutes alternated with 5-minute rest wrapped in a towel. Participants had to rate their pain (out of 100) every 15 seconds of the 2-minute immersion time.

No significant effects were found for either group at the 14-day follow-up. There was a significant difference at 3 months, with pain scores decreasing slightly in the experimental group and increasing for the control group.

Study 4) CPM: 5 minutes after TS was measured, the TS assessment (see below) was repeated with an additional conditioning stimulus. The conditioning stimulus was an occlusion cuff, applied to the left arm, which was inflated at a rate of 20mmHg/s until the subject reported pain. The pain was rated on a numerical rating scale and subsequently increased/decreased until a rating of 3/10 was achieved.

No extractable data was available for this study. All groups showed improvements in CPM at post-intervention and 3 month follow-up but there were no significant changes recorded between groups.

Study 7) CPM was assessed by using a conditioning stimulus (cold-water bath). The hand contralateral to the PPT measurement was immersed for 2 minutes and PPTs were measured again after 30 seconds and the initial PPT score was deducted from the PPT measured with cold water immersion. An impaired inhibitory response is suggested by a negative value (PPT score is lower than the original). An effective inhibitory response is indicated by a positive value (when the PPT score is higher than the original).

No effects on CPM efficacy were detected in either group.

3.3.3 Temporal Summation (TS)

TS tests are used to assess descending nociceptive facilitation. When descending nociceptive facilitatory pathways are enhanced, an increase in TS (or “wind up”) of pain is seen.

Study 4) TS measurements were taken 2 minutes after PPT measurements. The same location as the initial PPT measurements was used (finger and trapezius). 10 pulses of the algometer were applied at a rate of 2kg/s pressure increase and participants were asked to rate the 1st, 5th and 10th pulse on a numeric pain rating scale (NPRS).
No extractable data is available for this study, but no changes were detected over time or between group or location.

3.3.4 Central Sensitisation Inventory (CSI)

The CSI screens for presence of hypersensitivity through evaluation of 25 symptoms and scored out of 100. Higher scores indicate higher prevalence of central sensitisation related symptoms. 2 studies assessed the effect on the CSI. The data for each study are included in Appendix 7.

Study 7) The experimental group exhibited significantly lower CSI scores than the control group with medium effect sizes. Significant reductions were maintained at 6 months and 1 year.

Study 8) There were significantly greater reductions in CSI scores in the experimental group with large effect sizes and these effects were maintained at 6 months. Most of the experiment group established scores at a subclinical level (below 30).

3.3.5 Gray Matter Morphologic features:

Gray matter volume changes are involved in the processing of pain (modulatory, emotional-affective, and sensory-discriminative processing). It is believed that reduced gray matter volumes are associated with chronic pain syndromes and are suggested to be reversible. An increase in volume suggests a better functioning pain processing system.

Study 7) Magnetic resonance imaging was used to assess gray matter morphologic features. The gray matter cortical thickness was measured in cortical regions (caudal middle frontal, inferior parietal, inferior temporal, medial orbitofrontal, parahippocampal, postcentral, precentral, rostral middle frontal, superior parietal, supramarginal gyri) and subcortical regions (amgdala, caudate, hippocampus, putamen, thalamus).

No significant effects were found for changes in gray matter volumes at the subcortical level. However, of the tested cortical regions, the experimental group showed a significant increase in supramarginal thickness at 3- and 12-months follow-up.

3.4 Summary of significant outcome measure scores

Table 11 shows the scores for each outcome measure of the individual studies. Significant improvements, non-significant improvements and no effects are shown.

Table 11 Summary of results on outcome measures

Study	PCS total	PCS rum	PCS help	PCS mag	TSK	PPT	CPM	SSP	TS	CSI	Gray matter	McGill Pain Map
1		XX	X	X	X	X						
2	O	X			O			XX				
3	High CSI: : XX Low CSI: O	High CSI: XX Low CSI: O	High CSI: O Low CSI: O	High CSI: XX Low CSI: O	High CSI XX Low CSI: XX							
4	PNE-CLD: X					XX	X		O			
5					XX	L3 D: XX L3 ND: XX						
6	XX				XX							
7	X				XX	XX	O			XX	O	
8	XX	XX	XX	XX	XX	XX	O			XX		XX
9	O	O	O	O		X						

XX: More significant than control

X: significant but not significantly more than control

O: non-significant

4. Discussion

The results of this systematic review give some supporting evidence for the use of PNE for patients with chronic pain. A significant increase in research on the implementation of PNE suggests increasing interest in the topic, encouraging a shift from a biomedical, anatomically-focused approach towards a more biopsychosocial approach. However, the effect of PNE on central sensitisation processes remains unclear.

It was not possible to pool the data of all the studies due to the heterogeneity of the studies, particularly due to the complexity of pain and the many ways it can be influenced. Different study designs and patient populations were used. Additionally, 4 studies [54,70,76,77] delivered PNE independently, whereas 5[75,78–81] used PNE with an additional treatment. This raises challenges in drawing conclusions, as it cannot be assumed that positive results are due to a more effective PNE program. None of the studies used a control group receiving no treatment, therefore it was not possible to confirm specific treatment effects.

PNE effectiveness is reliant on many variables regarding the intervention itself such as the setting, the educator and the means of delivery, but also regarding the participant such as condition, mood or hormonal influences. In order to allow comparison and enable recognition of the effect of different variables, all other variables must remain the same. As this was not the case in these studies, definite patterns cannot be determined. However, there were some noteworthy observations and shortcomings.

Although no definite conclusions can be drawn, there are indications that PNE (independently and in addition to other treatments) can result in reduced PCS, TSK and CSI scores and improve PPT and CPM measurements. However, no effects were found for TS or gray matter morphologic features.

4.1 Summary of main findings

Study 1 (Meeus)[54] on patients with CFS only found significant differences for decreases in rumination. Only 1 session of 30 mins of PNE was administered to participants, however researchers stated that similar results could be seen in CFS patients receiving a 3 hour session. Considering the concentration problems frequently present in those with CFS[85], a 30-minute session is much more feasible. The lack of follow up (only immediately post-intervention) and small sample size (n=48) could have contributed to the lack of effect. For such a small sample it is also important to mention that more of the control group were non-compliant with analgesic consumption (EG n=2, CG n=8), potentially influencing the results. However, changes in pain cognitions, however small, are important, given their link to physical activity in CFS[86]. Given that patients with CFS usually have a low tolerance to exercise, if a change in cognitions can improve their tolerance this could lead to promising therapeutic effects in terms of their physical capacity.

Study 2 (Van Oosterwijck)[76] assessed patients with fibromyalgia. This study offered 2 one-on-one sessions of PNE in one week with written education for home. PNE was delivered by a physiotherapist who had been trained by PNE-experienced physiotherapists. The sessions were also individually tailored. Despite that, only significant effects for rumination were seen at 2 weeks with no significant effects for the remaining PCS scores, TSK, PPT or SSP at 2 weeks. However, at 3 months significantly greater effects were seen for SSP suggesting that PNE has the potential to improve descending nociceptive inhibition at 3 months. Patients with fibromyalgia tend to score highly on SSP tests. However, at 3 months participants showed similar behaviour to healthy controls with reduced pain, but did not achieve an entirely pain-free status. Again, the sample was small (n=30) and no assessments took place beyond 3 months so it is not possible to see if the significant changes were maintained. On the other hand, no outcome measures were assessed immediately post-intervention.

This could have resulted in short-term effects being missed. The control group (pacing activity management) is also an intervention aimed at patients with fibromyagia. It is worth noting that the PNE intervention was non-inferior to this control intervention as greater improvements were seen in the experimental group without significance.

Study 3 (Malfliet)[70] sub-grouped the original sample of patients with chronic spinal pain of an additional study[71] (n=120) into those with high- and low-level scores on the central sensitisation inventory (CSI). This subgrouping allowed us to see that baseline CSI-scores don't affect the response to PNE for TSK scores as both PNE groups showed significantly greater scores than neck/back school. This encourages a shift from a biomedical approach. However, those with high-CSI scores respond better to PNE for total-, magnification- and rumination-PCS scores with low-CSI scorers showing worsened scores for PCS-magnification. Additionally, high-CSI scorers of the control group also showed improvements in total PCS scores. This is an implication that some patients are better suited for educational interventions (PNE or neck/back school) and should be screened for appropriately. This study offered a larger sample size and slightly lower percentage of females than the other studies(60%). However, it still lacked a substantial follow-up as only post-intervention measurements were taken. Therefore, recognition of longer-term treatment effects was not possible. The intervention was given in groups and one-on-one discussions, allowing for socialisation as well as individualised education, this could have contributed to the positive post-intervention measurements. Regarding CSI scores, the accuracy of the CSI for determining CS in individuals remains questionable, as it refers to the psychosocial aspects without attention to endogenous pain mechanisms. Therefore, this study does not give us a good representation of all CS-mechanisms, such as central nervous system changes. It is also unclear how the same sample can receive different interventions. It is stated that this study is the secondary analysis of an additional study of the same author[71]. However, study 7 (Malfliet)[75] used the same sample but the participants received PNE combined with cognition-targeted motor-control-training. If these studies were carried out at different times, it is possible some participants previously received PNE. This may affect the results as participants will be accustomed to the intervention and some effects may have taken place. This questions both the authenticity and validity of this study.

Study 4 (Amer-Cuenca)[77] administered 3 different dosages of PNE compared to biomedical education. Overall, the results show that PNE in any dosage is not superior to biomedical education for patients with fibromyalgia. All dosages received group, online and one-on-one education. Only the concentrated low dose (PNE-CLD), where participants received 6 sessions of 15 minutes, showed greater reductions for PCS than the other interventions. However biomedical-education proved more effective for PCS scores than high-dose (PNE-HD) and diluted low-dose (PNE-DLD). For PPT and CPM, no significant differences were found with all groups showing improvements. No effects were found for TS in any groups. Therefore, similiar effects occur regardless of dosage or education type (PNE/biomed) for patients with fibromyalgia as all groups showed improvements in PCS, PPT and CPM. More definitive results may have been achieved with a larger sample size (n=77) and a longer (>3months) follow-up to determine the effect of different dosages of PNE. However, it can be assumed that educational interventions prove beneficial for catastrophising, pressure pain thresholds and endogenous pain inhibition in patients with fibromyalgia regardless of the content or dosage.

Study 5 (Tellez-Garcia)[78] had the smallest sample (n=12). Outcome measures were only assessed post-intervention. The experimental group received 2 sessions of PNE in addition to 3 trigger-point dry needling sessions, whereas the control received dry needling alone. Although dry needling lead to improvements in kinesiophobia, the addition of PNE lead to significant improvements in kinesiophobia. Dry needling also improved PPT scores but a significantly greater increase, at the lumbar level, was noted with the addition of PNE. However, the addition of PNE did not result in significant differences for the remaining 3 PPT locations. This implies that trigger point dry needling may be responsible for the majority of the effect on PPTs. A larger sample and a longer-term follow-up may have given more insight into the effects of PNE in patients with chronic low back pain.

Study 6 (Bodes)[79] showed that the addition of PNE to therapeutic exercise (experimental group) was superior to therapeutic exercise alone (control group). PCS, TSK and lumbar pressure pain thresholds at 1- and 3-month measurements all showed significant effects for the experimental group. However, no measurements took place beyond 3 months so long-term effects cannot be seen. Although the effect on CSI scores was not measured, a baseline CSI score was included. Both experimental and control group had high scores (EG=57.8 and CG=57.7), above the cut-off score of 40[87]. High CSI scores could suggest a reason for the positive response to the addition of PNE to exercise. Due to the lack of control, it is difficult to see specific treatment effects and separate these from a natural course of chronic low back pain. It would be interesting to see whether PNE administered without exercise would have different effects. Patients also contacted the researcher to be involved, this could result in the participation of only motivated patients. However, the results support the addition of PNE to therapeutic exercise for PCS, TSK and lumbar PPTs despite only offering 2 sessions of 30-50 minutes which is short considering the chronicity of chronic low back pain. A larger sample size (n=30) could have provided more information.

Study 7(Malfliet)[75] is the only study with a 1-year follow-up. The results showed significant improvements of the TSK and CSI and the primary PPT site for the group receiving PNE with cognition-targeted motor control training. These results were maintained at 12 month follow-up. However, no significant improvements were seen for PCS, CPM or gray matter morphologic features. PCS scores showed a non-significantly greater decrease than the control, with a reduction of 63.4% at 12 months for the experimental group compared to 43.7% for the control at 12-months. This could imply that neck/back school also effects PCS scores. These results could be clarified with a sufficient control group. A lack of change in gray matter volumes could suggest the inability of conservative interventions at changing brain areas. However, further studies are required to confirm this hypothesis. It is not possible to say these significant effects are due to the inclusion of PNE as it was combined with motor control training and compared to biomedical neck/back school. However, the results suggest that the combination of PNE (3 sessions over 12 weeks) and cognition-targeted motor control training appears superior to back/neck school for kinesiophobia, central sensitisation symptoms and pressure pain thresholds in patients with non-specific chronic spinal pain. This is supported by the large sample size (n=120) and long-term follow-up.

Study 8(Galan-Martin)[80] showed that an intervention consisting of group physical exercise combined with PNE is superior to ‘current best evidence physiotherapy’ (thermotherapy and analgesic electrotherapy) for patients with chronic spinal pain. Significant differences were found for the experimental group for PCS, TSK, PPT and CSI with mapping painful body areas (also showing larger reductions. These effects were maintained at 6 months. Additionally, voluntary analgesic intake was recorded. In the experimental group analgesic intake reduced from 92% to 42%, suggesting a reduced demand, whereas the control group only reduced from 89% to 78%. Despite this, pain and disability still limited the functionality of 1/5 of the experimental group. It also cannot be said that these effects are due to PNE as it was combined with physical exercise. But, considering the fact patients with unhealthy pain cognitions can respond negatively to physical exercise, it can be considered that the effective incorporation of PNE into physical exercise contributes to these positive effects. Other reasons for these significant results may have been the format of physical exercise. Exercise involved games and dual-tasking and modification of movement patterns that encouraged distraction and assisted patients to overcome kinesiophobia. The educator also had prior PNE training and 5 years of experience working with patients with chronic spinal pain. The PNE intervention was given in 6 sessions of either 90 or 120 minutes. However, further studies are required to determine the individual effects of the various variables and of PNE itself.

Study 9[81] is a small study (n=36) that shows the addition of PNE made no difference to a therapeutic exercise intervention on women with fibromyalgia. This contrasts with study 6 that showed that

combining PNE to therapeutic exercise was superior to exercise alone for patients with chronic low back pain. However, the reasons for this are unclear, as it could be due to various factors including the difference in conditions, a difference in either component of the intervention or that it is only women. Further research is required to clarify this. Greater improvements were seen for the PNE group for PCS and PPT scores however these findings were not significant. A larger sample and a longer follow-up could have produced more significant results.

Although, no definite relationships can be recognised due to the heterogeneity of the studies, generally speaking chronic spinal conditions (low back pain/neck pain) showed more positive results to PNE than chronic fatigue syndrome or fibromyalgia. Of the studies assessing spinal conditions[70,75,78–80] all 5 showed significantly greater improvements in kinesiophobia, 3 [70,79,80] for catastrophising, 3[75,79,80] for pressure pain thresholds, 2[75,80] for central sensitisation symptoms and 1 for McGills pain maps[80] . These results are in favour of PNE interventions of which 4 of the 5 are combined interventions[75,78–80]. Additionally, not all the mentioned outcome measures were used in all of the mentioned studies. These results show some supporting evidence for PNE interventions in chronic spinal pain. But as most of the studies involve combined interventions, further research is required to clarify the individual effect of PNE. On the other hand, combined interventions reflect usual practice accurately as multimodal treatment approaches are often used in primary care.

8 of the 9 studies showed some effect on pain cognitions (TSK/PCS). This is note-worthy considering the barriers psychological factors form for further interventions, such as exercise. Effects on PCS were increased when participants showed high-levels of CS (on CSI), indicating the importance of an appropriate protocol for CS screening for suitable PNE candidates. It also appeared that larger studies[70,75,80] showed more significant results in favour of a PNE intervention. However, no conclusions can be drawn for definite moderators or mediators and further research is required.

All of the studies lacked a suitable control group, therefore it is not possible to rule out the possibility of natural progression of the various conditions as a cause for the effects. The majority of all subjects were female, meaning that caution should be taken when applying these results to a male population. Additionally, more males in the sample could have lead to alternative results. For example, research on chronic pain has shown that more females have deficient CPM, so assessing males with chronic pain produces more reliable results[7]. The participants often showed motivation during the recruitment stage, which also cannot be controlled in real practice. In addition, the longest follow-up was 1 year so it is not possible to draw conclusions about long-term effects which is vital amongst chronic pain conditions. 3 studies [54,70,78] only measured outcomes directly post-intervention which may be too soon to see treatment effects. Additionally, it is hypothesized that changes in pain cognitions in the short-term may lead to changes in endogenous pain mechanisms in the long term, which is shown by studies with longer follow-up. Scientists are aware of the plasticity of the central nervous system, but longer follow-ups and further research are required in order to understand the extent that pain cognitions can influence endogenous central nervous system pain processing.

Significant effects are given in terms of effect sizes, whereas clinical relevance of these differences remains undefined for the various conditions. Additionally, not all outcome measures used by individual studies were extracted, nor did the studies use all the possible outcome measures. This means that some effects could have been missed by the studies and also during this review. This problem could be addressed by creating a guideline regarding CS assessment determined by further research.

4.2 Relevance

Despite not always producing significant effects compared to alternative interventions, PNE gives the patient an active role in their treatment by educating them about their body, enabling them to make informed decisions about their further treatment protocol. However, these results must be extrapolated with caution as physiotherapists may not be as trained as the educators or be administering these

interventions in the same way as these studies. PNE success is dependent on many factors, with the extent of the influence determined only by further research.

4.3 Strengths and limitations

Multiple databases were searched for the most current articles on the topic, which were all of good quality. Several outcome measures that the studies had in common were analysed, giving an overall view of central sensitisation processes despite a lack of consensus regarding assessment. Despite no conclusions being reached, an overall view can be seen of the results. This is promising despite inconsistencies existing throughout some of the studies, for example contradictions regarding significance of results.

However, not all the outcome measures used in the studies were analysed resulting in missing information. Additionally, only one reviewer assessed the studies and authors were not contacted for missing information.

5. Conclusion

From the results of this systematic review, no definite conclusions can be drawn regarding the influence of PNE on CS, given the heterogeneity of the results. However, the evidence supports a shift from an anatomical biomedical approach to a biopsychosocial approach. The evidence also supports a multi-modal treatment approach for patients with chronic pain. This is shown by significant results for catastrophising, kinesiophobia, pressure pain thresholds and central sensitisation symptoms. However, these results are not consistently significant across studies, therefore further research regarding moderators and mediators is required.

6. Recommendations

Further research with long-term interventions is recommended to obtain information regarding the influence of pain cognitions on endogenous pain mechanisms. Further research is also required to determine the effect of individual factors, such dosage/frequency/appropriate recipient/educator's level of experience, involved in PNE to establish the most appropriate way to administer this intervention. In order to provide a better understanding of CS in addition to its ability to be influenced by PNE, a general consensus should be agreed on CS diagnosis and accurate outcome measures. This will provide a standardisation for future trials and help to determine a more accurate representation on how it can be influenced, who will benefit from PNE and which interventions it is best combined with.