Systematic Review

Lack of Evidence for Central Sensitization in Idiopathic, Non-Traumatic Neck Pain: A Systematic Review

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Background: Chronic neck pain is a common problem with a poorly understood pathophysiology. Often no underlying structural pathology can be found and radiological imaging findings are more related to age than to a patient's symptoms. Besides its common occurrence, chronic idiopathic neck pain is also very disabling with almost 50% of all neck pain patients showing moderate disability at long-term follow-up. Central sensitization (CS) is defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity," "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input," or "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors." There is increasing evidence for involvement of CS in many chronic pain conditions. Within the area of chronic idiopathic neck pain, there is consistent evidence for the presence and clinical importance of CS in patients with traumatic neck pain, or whiplash-associated disorders. However, the majority of chronic idiopathic neck pain patients are unrelated to a traumatic injury, and hence are termed chronic idiopathic non-traumatic neck pain. When comparing whiplash with idiopathic non-traumatic neck pain, indications for different underlying mechanisms are found.

Objective: The goal of this article was to review the existing scientific literature on the role of CS in patients with chronic idiopathic non-traumatic neck pain.

Study Design: Systematic review.

Setting: All selected studies were case control studies.

Methods: A systematic search of existing, relevant literature was performed via the electronic databases Medline, Embase, Web of Science, Cinahl, PubMed, and Google Scholar. All titles and abstracts were checked to identify relevant articles. An article was considered eligible if it met following inclusion criteria: (1) participants had to be human adults (> 18 years) diagnosed with idiopathic non-traumatic chronic (present for at least 3 months) neck pain; (2) papers had to report outcomes related to CS; and (3) articles had to be full-text reports or original research (no abstracts, case-reports, reviews, meta-analysis, letters, or editorials).

Results: Six articles were found eligible after screening the title, abstract and – when necessary – the full text for in- and exclusion criteria. All selected studies were case-control studies. Overall, results regarding the presence of CS were divergent. While the majority of patients with chronic traumatic neck pain (i.e. whiplash) are characterized by CS, this is not the case for patients with chronic idiopathic neck pain. The available evidence suggests that CS is not a major feature of chronic idiopathic neck pain. Individual cases might have CS pain, but further work should reveal how they can be characterized.

Limitations: Very few studies available.

Conclusions: Literature about CS in patients with chronic idiopathic non-traumatic neck pain is rare and results from the available studies provide an inconclusive message. CS is not a characteristic feature of chronic idiopathic and non-traumatic neck pain, but can be present in some individuals of the population. In the future a subgroup with CS might be defined, but based on current knowledge it is not possible to characterize this subgroup. Such information is important in order to provide targeted treatment.

Key words: Central sensitization, hypersensitivity, chronic pain, neck pain, idiopathic, non-traumatic, pressure pain thresholds, review

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Chronic neck pain is a common problem (1) with a poorly understood pathophysiology. Often no underlying structural pathology can be found (2,3) and radiological imaging findings are more related to age than to a patient's symptoms (2,4). Besides its common occurrence, chronic non-specific neck pain is also very disabling with almost 50% of all neck pain patients showing moderate disability at long-term follow-up (5).

There is increasing evidence for involvement of central sensitization (CS) and impaired endogenous pain modulation in many chronic pain conditions including fibromyalgia (6), low back pain (7), osteoarthritis (8), and rheumatoid arthritis (9). CS is defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" (10), "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (11), or "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors" (12). CS can manifest itself as changes of pressure pain thresholds (PPTs) (13), thermal pain thresholds (14), vibrotactile stimulus detection thresholds (15), and electrocutaneous stimulus detection thresholds (2). Within the area of chronic neck pain, there is consistent evidence for the presence and clinical importance of CS in patients with whiplash associated (or traumatic) disorders (16). In these patients, features of CS like both sensory hypersensitivity (decreased pain thresholds) (11) and hypoaesthesia (increased detection thresholds) (17) can be found.

However, the majority of chronic neck pain patients suffer from complaints which are unrelated to a traumatic (whiplash) injury, and hence are termed chronic idiopathic non-traumatic neck pain. When comparing traumatic with idiopathic neck pain, indications for different underlying mechanisms are found (18). Hence, it is not possible to extrapolate the findings regarding CS from traumatic neck pain to idiopathic neck pain. As it remains unclear which processes lay at the origin of complaints experienced by chronic idiopathic neck pain patients, this review aims to investigate the existing literature on the presence and possible role of CS in these patients. This might lead to more insight in the underlying pathophysiology, giving opportunities to ensure better and more targeted therapy.

Methods

Literature Search Strategy

A systematic search of existing, relevant literature was performed by the authors, including an experienced medical information specialist, in the databases Medline (via OvidSP), Embase (via embase.com), Web of Science, Cinahl (via EBSCOhost), and Cochrance (via Wiley). Extra references were retrieved from PubMed (articles not yet indexed by Medline) and Google Scholar. The databases were searched from inception until March 13, 2014. Two elements were used in the search strategies: neck pain and sensitization. We explicitly chose not to focus the search strategies on non-traumatic neck pain to be as sensitive as possible. Both elements were searched using controlled vocabulary, when available in the databases, combined with exhaustive text words in title and/or abstract. Search results were only limited to human studies. The complete search strategy (with list of key words and total hits) for all databases can be found in the Appendix 1. The articles were imported in the reference software EndNote and checked for duplicates.

Inclusion Criteria

All titles and abstracts were checked to identify relevant articles. An article was considered eligible if it met following inclusion criteria: (1) participants had to be human adults (> 18 years) diagnosed with idiopathic non-traumatic chronic (present for at least 3 months) neck pain; (2) papers had to report outcomes related to CS; and (3) articles had to be full-text reports or original research (no abstracts, case reports, reviews, meta-analysis, letters, or editorials).

Idiopathic was defined as the absence of a relationship between symptoms and objective anatomic findings. In order to facilitate identification of idiopathic neck pain, a list for differential diagnosis was assembled as shown in Table 1. Papers reporting these kinds of disorders were excluded. In case of insufficient information for in- or exclusion to ascertain that the study fit in the review's focus (e.g., whether they focused on non-traumatic neck pain patients solely), an e-mail was sent to the authors of the respective article to gain more information. When no reply was given within the time span of one month, the article was not considered for inclusion.

Quality Assessment (Risk of Bias)

Methodological quality was assessed by 2 inde-

Table 1. *Differential diagnosis.*

Soft tissue lesions (eg., muscle strain, etc.)
Fibromyalgia and/or chronic fatigue syndrome
Psychogenic disorders with sleep disturbance, tender trigger points and more prominent psychological abnormalities
Neurological signs (hyperreflexion, paraesthesia, clumsy hands, etc.)
Inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, etc.)
Metabolic diseases (Paget's disease, osteoporosis, etc.)
Diagnosis of any temporomandibular joint disorder (TMD), according to the Research Diagnostic Criteria for TMD
Concomitant diagnosis of primary headache
History of specific spine surgery
History of whiplash
History of non-specific neck surgery < 3 years ago or a neck fracture

pendent authors who were not acquainted with each other's evaluation of the search results before having a consensus meeting. After rating the selected articles, the results of both researchers were compared and differences were analyzed and discussed. In case of a disagreement, a decisive opinion was provided by a third researcher. The methodological quality was evaluated by using the Newcastle-Ottawa Scale (NOS) for case control studies, which is widely used and recommended by the Cochrane Collaboration (www.cochrane.org). The NOS uses a rating system to evaluate the quality of a study, with a maximum score of 9, which can be transformed into a percentage (19). We did not use the criterion on response rate, as there were no included studies on which this was applicable. Hence, a maximum score of 8 was set to evaluate methodological quality. Because of the small number of selected articles in this review, it was decided not to preface a cut-off value of methodological quality for inclusion.

Based on study design and methodological quality, each individual study received a level of evidence, according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO (www.cbo.nl/Downloads/632/bijlage_A.pdf). Furthermore, a level of conclusion was determined after clustering studies with comparable methods, accounting for the study designs and the risk of bias.

Results

Search Strategy

The selection process of the relevant papers is presented in Fig. 1. The initial search resulted in 2,648 hits. After removing the duplicates, 1,488 hits were screened on title and abstract and 65 articles were selected for

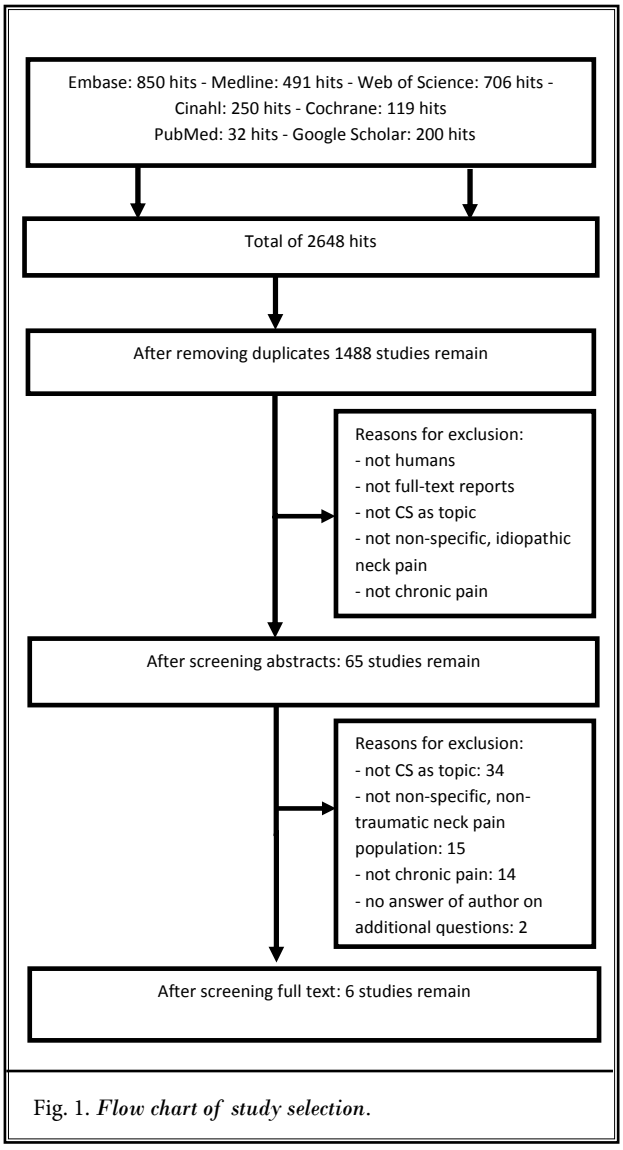

Fig. 1. *Flow chart of study selection.*

Table 2. *Evaluation scores on methodological quality.*

Criteria methodological quality	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8	Total score	%
Chien and Sterling 2010 (17)	0	0	1	1	1	1	0	1	5/8	63%
Chua et al 2012 (20)	1	1	0	0	1	1	0	0	4/8	50%
Javanshir et al 2010 (21)	1	1	1	1	0	0	1	1	6/8	75%
Johnston et al 2008 (23)	0	0	0	0	1	1	0	1	3/8	38%
La Touche et al 2010 (22)	1	1	1	1	1	1	1	1	8/8	100%
Scott et al 2005 (18)	0	1	1	1	1	1	0	1	6/8	75%

0: criterion not fulfilled; 1: criterion fulfilled; –: criterion not applicable
Newcastle-Ottawa Quality Assessment Scale: Case-control studies
Criterion 1: Is the case definition adequate?
Criterion 2: Representativeness of the cases
Criterion 3: Selection of controls
Criterion 4: Definition of controls
Criterion 5: Study controls for age/gender
Criterion 6: Study controls for any additional factor
Criterion 7: Ascertainment of exposure
Criterion 8: Same method of ascertainment for cases and controls

screening the full text for in- and exclusion criteria. This led to the inclusion of 6 eligible articles. Exclusion of articles was mostly because they were not about chronic pain, not giving information about CS, or they studied traumatic neck pain patients or specific causes of neck pain.

Methodological Quality

The 2 researchers achieved a 79% agreement (38 of the 48 items) on scoring the selected papers on methodological quality. After discussing the discrepancies, the reviewers reached a consensus in all items. Detailed information on the scores of methodological quality can be found in Table 2.

Overall, the quality of the articles was acceptable with only one study scoring beneath 50%. In 3 out of 6 studies the case definition was adequate (criterion 1) (20-22). The other studies did not comply with this criterion as they failed to apply independent validation of the cases as they mostly included patients based on self-reported complaints. Representativeness of the cases was sufficient in 4 studies (criterion 2) (18,20-22). Controls were derived from the same community as the cases (community controls) in 4 out of 6 studies (criterion 3) (17,18,21,22), and in 4 studies the definition of the controls was adequate (criterion 4) (17,18,21,22). In all but one study, cases and controls were comparable on the basis of the design or analysis (criterion 5 & 6) (17,18,20,22,23). Additional confounding factors taken into account, were global severity index (17), duration of pain/symptoms (20,23), and STAI-scores (18,22). Four out of 6 studies did not comply with criterion 7 by not stating whether the investigators were blinded to the status (case or control) of the patients (17,18,20,23). However, in all but one study the cases and controls underwent the same method of testing (criterion 8) (17,18,21-23). All included studies were given a level of evidence B, since only case control studies were included.

Study Characteristics

All selected studies were case control studies. The main characteristics of the included studies are presented in Table 3. All studies aimed at investigating the underlying mechanisms of non-specific, non-traumatic neck pain, whether or not in comparison to chronic whiplash. All studies used PPTs to investigate sensory sensitivity. Other used parameters were mechanical stimuli, including cold pain thresholds (CPTs) (4 studies) (17,18,21,23); heat pain thresholds (HPTs) (3 studies) (18,21,23); vibration thresholds (2 studies) (17,23); thermal detection thresholds (2 studies) (17,20); current perception thresholds (one study) (17); electrical pain detection thresholds (one study) (20); and Von Frey hair sensibility (one study) (18). Additional used measurements were wind-up ratio (one study) (20) and

Table 3. Characteristics of included studies.

Article	Purpose	Design	Sample characteristics of NP group	Sample characteristics of control group	Mean duration of symptoms in NP group	Inclusion/exclusion criteria	Assessment regarding CS (outcome)	Time of follow-up assessments	General conclusion regarding CS	Limitations of the study
Chien and Sterling 2010 (17)	Comparing the somatosensory phenotype of ideopathic NP patients with chronic whiplash and healthy controls	Case-control	N = 28 20 F, 8 M Age: 32.3 ± 8.7	N = 32 25 F, 6 M Age: 31.4 ± 8.9	28.3 ± 11.2 months	Inclusion: patients reporting ongoing, insidious-onset (non-traumatic) neck pain, for > 3 months and < 3 years in duration Exclusion: onset of pain related to a MVC or other forms of trauma, neurological or musculoskeletal disorders and/or diagnostic psychiatric disorder that may influence QST results	Pressure Pain Thresholds (cervical spine, median nerve, tibialis ant) Cold Pain Thresholds (cervical spine, hand) Vibration Thresholds (hand: dermatomes C6-C7-C8) Thermal Detection Thresholds (hand: dermatomes C6-C7-C8) Current Perception Thresholds (elbow, index finger, 5th digit, tibialis ant)	No follow-up	General conclusion: Patients with idiopathic neck pain do not demonstrate widespread sensory hypersensitivity. Similary sensory hypoaesthesia is also not a feature of chronic idiopathic neck pain.	Not stated
Chua et al 2012 (20)	To map out the changes in pain sensitivity and modulation present in patients with unilateral chronic neck pain	Case-control	N = 18 31% F, 69% M Age: 55 [50 – 61]	N = 18 Matched to NP Age: matched to NP patients	Not stated	Inclusion: pain on palpation of one or more cervical zygapophysial joint, more pain on extension than on flexion, and more pain on lateral flexion to the painful side Exclusion: radicular pain to the arm, malignancy, epilepsy, trauma, or whiplash injuries, uncontrolled depression or major psychiatric illness, and diffuse pain syndromes like FM	Pressure Pain Thresholds (thigh, trapezius, C4/5 facet joint, SCM, greater occipital nerve, temporalis muscle, face) Cold Detection Thresholds (thigh, trapezius, C4/5 facet joint, face) Warm Detection Thresholds (idem) Electrical Pain Detection Thresholds (idem) Wind-up Ratio (idem) Conditioned Pain Modulation Response (thigh, face)	No follow-up	General conclusion: 1. on-going descending tonic inhibition 2. less effective inhibitory modulation in the trigeminal compared to the spinal sensory system 3. relative segmental sensitization over the chronic nociceptive source in the neck These findings suggest that the descending inhibitory modulation system is intact in dynamic equilibrium with ongoing spinal central sensitization in these idiopathic NP patients.	Relatively small number of subjects
Javanshir et al 2010 (21)	To investigate the differences in pressure and thermal pain sensitivity over symptomatic and non-symptomatic areas between patients with acute and chronic neck pain and healthy subjects	Case-control	N = 7 4 F, 3 M Age: 32 ± 8	N = 6 3 F, 3 M Age: 33 ± 8	6.1 ± 3.0 years	Inclusion: patients with mechanical NP: generalized neck and/or shoulder pain symptoms provoked by maintained neck postures, neck movement or joint and/or muscle palpation; bilateral pain > 12 weeks Exclusion: unilateral NP, diagnosis of FM, previous whiplash, cervical spine surgery, clinical diagnosis of cervical radiculopathy or myelopathy, previous physical therapy intervention for the neck, severe degenerative OA	Pressure Pain Thresholds (supraorbital nerve, infraorbital nerve, mental nerve, median nerve, ulnar nerve, radial nerve, C5/6 zygapophyseal joint, second metacarpal, tibialis ant) Heat and Cold Pain Thresholds (cervical spine, tibialis ant)	No follow-up	General conclusion: Suggestions for central sensitization process. Widespread decreased PPT in patients with chronic mechanical neck pain as compared to controls. Chronic patients also showed cold pain hypersensitivity.	- Small sample size - Results not controlled for psychological factors - Low pain and disability levels of the chronic NP group

Table 3 (cont.). Characteristics of included studies.

Article	Purpose	Design	Sample characteristics of NP group	Sample characteristics of control group	Mean duration of symptoms in NP group	Inclusion/exclusion criteria	Assessment regarding CS (outcome)	Time of follow-up assessments	General conclusion regarding CS	Limitations of the study
Johnston et al 2008 (23)	To document the sensory perception and pain thresholds of symptomatic and asymptomatic office workers	Case-control	2 groups of symptomatic office workers: (Gender not stated) Group with mild pain (NDI: 9 – 29): N = 38 Age: 43.8 ± 9.4 Group with moderate/ severe pain (NDI ≥ 30): N = 14 Age: 45.4 ± 10.3	Office workers without pain (NDI ≤ 8): N = 33 Age: 43 ± 10.6 Healthy controls: N = 6 Age: 37.4 ± 10.4 Gender in both groups not stated	Group with mild pain: 10.7 ± 8.7 years Group with moderate/ severe pain: 8.2 ± 8.7 years	Inclusion: in current job or one similar for a minimum of two years, working at least 4h per day using a VDU; experiencing neck pain with or without arm pain which they relate to their work Exclusion: history of neck surgery or trauma, medical diagnosis of FM, carpal tunnel syndrome, cervical radiculopathy, systemic illness or a connective tissue disorder	Pressure Pain Thresholds (neck, trapezius, levator scapula, median nerve, tibialis ant) Thermal Pain Thresholds (cervical spine) Vibration Thresholds (median nerve, radial nerve, ulnar nerve)	No follow-up	General conclusion: There is evidence of multiple peripheral nerve dysfunction with widespread sensitivity most likely due to altered central nociceptive processing initiated and sustained by nociceptive input from the periphery in office workers with NP.	Not stated
La Touche et al 2010 (22)	To investigate trigeminal sensitization in patients with chronic mechanical neck pain, while controlling for psychological aspects	Case-control	N = 23 13 F, 10 M Age: 28 ± 5	N = 23 13 F, 10 M Age: 28 ± 6	10 ± 4.6 months	Inclusion: generalized neck and/ or shoulder pain with symptoms provoked by neck postures, neck movement, or palpation of the cervical musculature (mechanical NP); bilateral symptoms > 6 months Exclusion: unilateral NP, diagnosis of FM, previous whiplash, cervical spine surgery, clinical diagnosis of cervical radiculopathy or myelopathy, history of previous physical therapy intervention for the cervical region, presence of severe degenerative arthritis, less than 18 years old, diagnosis of any TMD, concomitant diagnosis of primary headache	Pressure Pain Thresholds - Trigeminal Region (Maseter & Temporalis muscle) - Cervical Region (Upper Trapezius Muscle & C5-C6) - Tibialis Anterior Muscle	No follow-up	General conclusion: Pressure-pain hyperalgesia in the trigeminal region in patients with chronic mechanical NP, but not widespread pressure-pain hypersensitivity	Not stated
Scott et al 2005 (18)	To gain insight into the pain processing mechanisms underlying chronic idiopathic NP	Case-control	N = 20 13 F, 3 M Age: 32 ± 11	N = 20 8 F, 12 M Age: 31.25 ± 10	51.5 ± 40 months	Inclusion: experiencing insidious-onset NP > 3 months Exclusion: prior trauma of the neck, head or upper quadrant; neurological symptom; experiencing coexisting pain in other body regions	Pressure Pain Thresholds (C2/3; C5/6; median nerve, radial nerve, ulnar nerve, tibialis ant) Heat Pain Thresholds (Cervical spine, deltoid, tibialis ant) Cold Pain Thresholds (Cervical spine, deltoid, tibialis ant) Von Frey Hair Sensibility	No follow-up	General conclusion: Patients with idiopathic NP showed no sensory abnormalities outside of the cervical spine, indicating that widespread hypersensitivity (suggestive of changes in nociceptive processing) is not a feature of this condition.	Not stated

NP: neck pain; CS: central sensitization; M: males; F: females; QST: Quantitative Sensory Testing; FM: fibromyalgia; OA: osteoarthritis; SCM: sternocleidomastoid musle; NDI: Neck Disability Index; VDU: visual display unit; TMD: temporomandibular disorder; MVC: motor vehicle collisions

conditioned-pain modulation (one study) (20). Test sites for all measurements are listed in Table 3.

Two studies were not considered for this review as the information required for inclusion in this review was insufficient. As stated in the methods, the authors of the studies with insufficient information regarding selection criteria were contacted and given a one month timespan for providing the required information. A short description of measurements and results of these studies can be found in Appendix 2.

Information on Central Sensitization

Mechanical Stimuli

Pressure pain thresholds

All 6 included studies performed PPTs as part of their outcome measures (17,18,20-23). All but one study used the tibialis anterior as the remote site. Chua et al (20) used the thigh as the remote site. In the neck region all studies reported significant lowers PPTs for the neck pain patients when compared to healthy controls. Three studies showed no significant lower PPTs in neck pain patients (when compared to healthy controls) at the remote site, being the tibialis anterior site (17,18,22). However, 3 other studies showed different findings (eg., significant lower PPTs) at the remote testing site (tibialis anterior or thigh) in neck pain patients when compared to healthy controls (20,21,23).

The study of Chua et al (20) also found significantly lower PPTs when comparing the painful neck side to the non-painful reference area (thigh) in neck pain patients.

In summary, there is mixed evidence for secondary hyperalgesia measured by PPTs (strength of conclusion 2). There are as many studies providing evidence for secondary hyperalgesia as there are studies that are not.

Cold pain thresholds (CPTs)

Four studies used CPTs. Three studies did not find any significant differences between neck pain patients and healthy controls at any site (17,18,23). In contrast, Javanshir et al (21) found significantly lower CPTs in neck pain patients when compared to healthy controls at the cervical and tibialis anterior sites. Johnston et al (23) found office workers with mild pain significantly more sensitive to cold stimuli when compared to office workers without pain. In summary, evidence is in favor of no decreased CPTs and thus no secondary hyperalgesia in neck pain patients (strength of conclusion 2).

Heat pain thresholds (HPTs)

No significant differences were found by Javanshir et al (21) and Scott et al (18) between the neck pain group and healthy controls for any sites. Johnston et al (23) found significantly decreased HPTs in office workers with mild pain when compared to healthy controls and office workers without pain. In summary, evidence is in favor of no decreased HPTs and thus no secondary hyperalgesia (strength of conclusion 2).

Thermal (cold and heat) detection thresholds

In the study by Chien and Sterling (17) no significant differences between the neck pain group and the healthy controls were found for thermal (cold and heat) detection thresholds at either tested sites (cervical spine and hand). Chua et al (20) found a significant lower cold detection threshold at the reference area when compared to the primary pain site. In contrast, no significant differences were found for the heat detection threshold. Overall, no clear evidence can be found for increased thermal detection thresholds (strength of conclusion 2)

Vibration thresholds

Two studies used vibration thresholds. Chien et al (17) found no significant differences between neck pain patients and healthy controls at any sites. In general, Johnston et al (23) found a decreased sensitivity over each tested site (neck, trapezius, levator scapula, median nerve, and tibilais anterior site) in office workers with moderate/severe pain in comparison to healthy controls and office workers without pain. Nevertheless, the vibration threshold was only significantly higher at the medial nerve site (23). In summary, no explicit evidence for primary or secondary hypoaesthesia was found (strength of conclusion 2).

Other measurements

Determining current perception thresholds, Chien et al (17) found no significant differences between the neck pain group and the healthy controls at any site, with the exception of the elbow site which showed an increased threshold for the neck pain group compared to the controls. No evidence for secondary hyperalgesia was found (strength of conclusion 3).

Chua et al (20) found no differences in electrical pain detection thresholds (EPTs) over the reference area (thigh) between neck pain patients and healthy controls. However, the EPTs were significantly higher over the neck site on the painful side compared to the non-painful side in neck pain patients. The trapezius

site had significantly higher EPTs, and the face had significantly lower EPTs when compared to the non-painful reference area (thigh) in neck pain patients. This study gives evidence for primary hyperalgesia, but gives no evidence for the presence of secondary hyperalgesia (strength of conclusion 3).

When comparing neck pain patients and healthy controls, Scott et al (18) found no significant differences in the Von Frey Hair sensibility at any site (neck and tibialis anterior site). No evidence for increased sensitivity was found (strength of conclusion 3).

Enhanced Temporal Summation of Pain

Wind-up is defined as the perceived increase in pain intensity over time when a given painful stimulus is delivered repeatedly at frequencies greater than 0.5 Hz (24,25). It is created by repeated stimulation of group C peripheral nerve fibers, leading to progressively increasing electrical response in the corresponding spinal cord dorsal horn neurons (25). Wind-up ratio is a measure derived from comparing the perceived intensity of a single electric stimulus at 120 percent of the previously measured pain detection threshold with that of a series of 5 repetitive electric stimuli of the same intensity. Chua et al (20) determined the wind-up ratio and did not find significant differences when comparing side-to-side differences at the reference area (thigh) in neck pain patients. Still, in patients with unilateral neck pain, the wind-up ratio of the neck at the painful site was significantly higher compared to the non-painful reference site (thigh). In summary, no strong evidence for secondary hyperalgesia was found (strength of conclusion 3).

Dysfunctional Endogenous Nociceptive Inhibition

One study used the conditioned pain modulation (CPM) response (20). CPM makes use of the "pain-inhibits-pain" principle, as an additional painful (conditioned) stimulus should suppress the initial experienced pain through adequately working descending and inhibiting pathways (26). CPM is computed by calculating the volume of pain decrease in the test stimulus before/during/after the administration of a painful conditioning stimulus. The pain sensation during/after this conditioning stimulus should normally be lower than before, as this stimulus should activate the endogenous pain inhibitory system (26,27). No significant difference in CPM response was found over the reference area (thigh) between neck pain patients and healthy controls. They did, however, find a strong trend towards significance for a lower CPM response in the face compared to the non-painful reference area (thigh) in neck pain patients (20).

Again, no evidence for dysfunctional endogenous nociceptive inhibition and thus CS is presented (strength of conclusion 3).

Discussion

Based on the available scientific evidence, it was recently concluded that CS is an important feature of patients with chronic idiopathic traumatic neck pain (16). The goal of the present study was to review the existing scientific literature on the role of CS in patients with chronic idiopathic, non-traumatic neck pain. This is the first systematic literature review regarding this topic in this specific subgroup of patients. All included articles in this review used different methods and measurements for evaluating the presence of CS characteristics. This hampers the formulation of a straightforward conclusion regarding the presence of CS in this population as results are divergent. This is in contrast to the results in traumatic neck pain (i.e., whiplash associated disorders) where a clear picture of CS is seen (16). Hence, based on the available evidence it is concluded that CS is not a feature of chronic idiopathic neck pain, but rather appears to be present in a subgroup of patients. More high-quality research is necessary as only 6 studies were included in the present review.

Sensory hypersensitivity, which is known as a feature of CS, does not appear to be an "all or nothing" phenomenon (17). It rather seems a continuum of altered pain processing mechanisms in which greater symptoms of a certain condition are accompanied by more profound changes (17). Pressure pain hyperalgesia in the cervical spine is a common feature of chronic idiopathic non-traumatic neck pain, but widespread pressure hyperalgesia is less present in this population (21,23). Pressure pain hyperalgesia in the cervical spine can be categorized as primary hypersensitivity and is probably reflecting peripheral (i.e., nociceptor) and/or segmentally related (i.e., in the neuroanatomical region corresponding to the primary source of nociception, if any) spinal cord sensitization (22). This primary hyperalgesia is not only limited to the cervical joints, but can also be found in the cervical muscles (like the upper trapezius) (22). The fact that widespread hyperalgesia is far less present in these patients, compared to traumatic chronic neck pain patients, may be explained by the course of primary origin of the neck problem. In traumatic chronic neck patients an injury lays at the basis, which is a far greater determinant of

CS than an idiopathic cause (28). In many cases, chronic idiopathic non-traumatic neck pain is episodic in nature (29), which might lead to interruptions in nociceptive input, which in turn may prevent the development of the pathophysiological processes in the central nervous system that are involved in CS.

The differences in results in the included studies can find their origin in many elements. First, there is no clear definition of the target population described in this review. A consensus should be made, by better defining which patients can be included in this population, in order to avoid the giving of nonsense diagnoses. Not only a clear description of possible pain characteristics (like laterality of the pain, idiopathic, mechanical) is necessary, there is also need of defining criteria for exclusion. This can lead to more adequate and validated selection of patients, which was a methodological element where 4 out of 6 included articles scored negatively.

Second, all studies used different protocols and methods to objectify the presence of CS. Even when using the same test measurement, different testing sites were applied, potentially leading to differences in results and interpretation. Although Chien and Sterling (17) state that all used pain threshold measures and detection threshold measures have an established validity and reliability, there is currently no gold standard in the measurement and evaluation of CS, which is reflected by the large differences in applied protocols in the included studies. It Is also described in literature that CPM is an advanced measurement with high clinical relevance (30), but there is no information on the validity of CPM in the evaluation of CS. The same applies to the wind-up ratio. Perhaps what is needed, is a well validated device or procedure to measure CS.

Third, one of the included studies (17) attributed the discrepant findings in the idiopathic neck pain group by the low levels of pain intensity and disability in comparison to the chronic whiplash patients, as there is some evidence of correlations between the extent of some central processes and pain levels (31). When levels of pain and disability vary between studies, different results on CS outcome measurements could be seen. Javanshir et al (21) proposed the possibility that the discrepancies in results between the studies may be explained by the differences of the PPTs seen in the control group. Additionally, there is the possibility that the population described as chronic idiopathic non-traumatic is still too heterogeneous and requires subgrouping, of which only a few might display CS (21). Future studies might want to focus on this aspect by dividing patients from this population in groups with and without signs of CS and looking into the characteristics of both groups. Lastly, there is still no consensus about the PPT that is needed to consider differences as real clinical changes (22).

Studies using neuro-imaging for examining the role of CS in this population are essentially lacking, which is an important shortcoming in this field. Likewise, with respect to laboratory investigations, there are currently no studies examining the presence of altered cytokine and neuropeptide concentrations suggestive of CS, or exploring the efficacy of centrally acting drugs in patients with chronic idiopathic non-traumatic neck pain. More high-quality research is necessary and should focus on whether or not CS is present in this population by making use of effective protocols and large sample sizes. The use of reliable outcome measures is required and bias must be prevented by blinding of patients, assessors, and – if applicable – therapists.

Not only a clear-cut definition of chronic, idiopathic, and non-traumatic neck pain is lacking, also an internationally accepted set of criteria for CS remains to be established. Therefore, very recently a clinical method for the classification of any pain as either CS pain, neuropathic, or nociceptive pain was developed, based on a body of evidence from original research papers and expert opinion from 18 pain experts from 7 countries (32). When applying these criteria for CS pain to the findings of the present literature review, it is again concluded that conflicting evidence for CS pain in patients with chronic, idiopathic, and non-traumatic neck pain is available. Studies reporting decreased PPTs not only in the painful region, but also at remote sides (e.g., the lower limbs), provide evidence for CS in patients with chronic, idiopathic, and non-traumatic neck pain (21,23). However, as much as 3 selected studies reported the reverse, finding normal PPTs at sites remote from and neuroanatomically unrelated to the cervical spine (17,18,22). Also the lack of clear evidence for dysfunctional CPM (20) supports the view that CS in not a characteristic feature of chronic, idiopathic, and non-traumatic neck pain.

Conclusion

To conclude, literature about CS in patients with chronic idiopathic non-traumatic neck pain is rare and results from the available studies provide an inconclusive message. While the majority of patients with chronic traumatic neck pain (i.e., whiplash) are

characterized by CS, this is not the case for patients with chronic idiopathic neck pain. The available evidence suggests that central sensitization is not a major feature of chronic idiopathic neck pain, but can be present in some individuals of the population. In the future a subgroup with CS might be defined, but based on current knowledge it is not possible to characterize this subgroup. Such information would be important for steering the content of the treatment (i.e., local treatment in nociceptive neck pain and desensitizing treatment in predominant CS pain) (33). Further research is required, including studies using neuroimaging, for providing direct evidence of CS in these patients.

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Appendix 1. Complete search strategy for all databases.

Key Words		
Group 1: Neck Pain	**Group 2: Sensitization**	
Neck pain	Central Nervous System Sensitization	Nerv* plasticit*
Neck pain*	Hypersensitiv*	Neur* plasticit*
Cervical pain*	Neuronal plasticity	Nerv* inhibit*
Cervical disorder*	Hyperalgesia	Neur* inhibit*
	Hyperestesia	Nerv* depress*
	(4) aminobutyric acid	Neur* depress*
	Pain threshold*	Neuroplasticit*
	Sensitiz* / Sensitis*	Summation*
	Sensibilizat* / Sensibilisat*	Long Term Potentiat*
	Windup	Hyperalg*
	PPT(s)	Allodynia*
	Hyperpath*	Hyperesthe*
	Oxysthe*	Cortical reorgani*
	Modificat* pain*	Synap* strengthen*
	Endogen* inhibit*	Nocicepti* inhibit*
	Pain processing	GABA
	Gamma aminobutyr*	Hyperexcitabil*
	Pain modulat*	Disinhibit*
	Nocicept* threshold*	Pain toleran*
		Nocicept* tolerance

Appendix 1 (cont.). Complete search strategy for all databases.

Overview of hits per database		
Database	**Hits after initial search**	**Hits after removing duplicates**
Embase	850	844
Medline	491	91
Web Of Science	706	351
Cinahl	250	48
Cochrane	119	3
Pubmed publisher	32	29
Google Scholar	200	122
Total	**2648**	**1488**

Duplicates removed: 1160

Embase.com 850
('neck pain'/de OR (((neck OR cervical) NEAR/6 (pain* OR disorder*))):ab,ti) AND (sensitization/de OR hypersensitivity/de OR 'nerve cell plasticity'/de OR 'nerve cell inhibition'/de OR 'spatial summation'/de OR 'temporal summation'/de OR 'long term potentiation'/de OR 'long term depression'/de OR hyperalgesia/de OR allodynia/de OR hyperesthesia/de OR '4 aminobutyric acid'/de OR 'pain threshold'/de OR 'sensitivity and sensibility'/de OR sensibility/de OR (sensitiz* OR sensitis* OR sensibilizat* OR sensibilisat* OR hypersensitiv* OR (hyper NEXT/1 sensitiv*) OR hypersensib* OR sensibility* OR ((nerv* OR neur*) NEAR/3 (plasticit* OR inhibit* OR depress*)) OR neuroplasticit* OR summation* OR ('long term' NEAR/3 (potentiat* OR depress*)) OR (Heterosynap* NEAR/3 facilitat*) OR Windup* OR hyperalg* OR allodynia OR hyperpath* OR hyperesthe* OR Oxyesthe* OR (Corticol NEAR/3 reorgani*) OR (Modificat* NEAR/3 pain*) OR (Synap* NEAR/3 strenghthen*) OR ((Endogen* OR nocicepti*) NEAR/3 inhibit*) OR 'aminobutyric acid' OR gaba OR (gamma NEXT/1 (aminobutyr* OR 'amino butyric')) OR (pain NEAR/3 modulat*) OR disinhibit* OR ((pain OR nocicept*) NEAR/6 (threshold* OR toleran*)) OR PPT OR PPTs OR Hyperexcitabil* OR (Pain NEAR/3 processing)):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP) 491
("neck pain"/ OR (((neck OR cervical) ADJ6 (pain* OR disorder*))).ab,ti.) AND ("Central Nervous System Sensitization "/ OR hypersensitivity/ OR exp "Neuronal Plasticity "/ OR "Neural Inhibition"/ OR "Postsynaptic Potential Summation"/ OR hyperalgesia/ OR hyperesthesia/ OR "4 aminobutyric acid"/ OR "pain threshold"/ OR (sensitiz* OR sensitis* OR sensibilizat* OR sensibilisat* OR hypersensitiv* OR (hyper ADJ sensitiv*) OR hypersensib* OR sensibility* OR ((nerv* OR neur*) ADJ3 (plasticit* OR inhibit* OR depress*)) OR neuroplasticit* OR summation* OR ("long term" ADJ3 (potentiat* OR depress*)) OR (Heterosynap* ADJ3 facilitat*) OR Windup* OR hyperalg* OR allodynia OR hyperpath* OR hyperesthe* OR Oxyesthe* OR (Corticol ADJ3 reorgani*) OR (Modificat* ADJ3 pain*) OR (Synap* ADJ3 strenghthen*) OR ((Endogen* OR nocicepti*) ADJ3 inhibit*) OR "aminobutyric acid" OR gaba OR (gamma ADJ (aminobutyr* OR "amino butyric")) OR (pain ADJ3 modulat*) OR disinhibit* OR ((pain OR nocicept*) ADJ6 (threshold* OR toleran*)) OR PPT OR PPTs OR Hyperexcitabil* OR (Pain ADJ3 processing)).ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane 119
((((neck OR cervical) NEAR/6 (pain* OR disorder*))):ab,ti) AND ((sensitiz* OR sensitis* OR sensibilizat* OR sensibilisat* OR hypersensitiv* OR (hyper NEXT/1 sensitiv*) OR hypersensib* OR sensibility* OR ((nerv* OR neur*) NEAR/3 (plasticit* OR inhibit* OR depress*)) OR neuroplasticit* OR summation* OR ('long term' NEAR/3 (potentiat* OR depress*)) OR (Heterosynap* NEAR/3 facilitat*) OR Windup* OR hyperalg* OR allodynia OR hyperpath* OR hyperesthe* OR Oxyesthe* OR (Corticol NEAR/3 reorgani*) OR (Modificat* NEAR/3 pain*) OR (Synap* NEAR/3 strenghthen*) OR ((Endogen* OR nocicepti*) NEAR/3 inhibit*) OR 'aminobutyric acid' OR gaba OR (gamma NEXT/1 (aminobutyr* OR 'amino butyric')) OR (pain NEAR/3 modulat*) OR disinhibit* OR ((pain OR nocicept*) NEAR/6 (threshold* OR toleran*)) OR PPT OR PPTs OR Hyperexcitabil* OR (Pain NEAR/3 processing)):ab,ti)

Web-of-science 706
TS=(((((neck OR cervical) NEAR/6 (pain* OR disorder*)))) AND ((sensitiz* OR sensitis* OR sensibilizat* OR sensibilisat* OR hypersensitiv* OR (hyper NEAR/1 sensitiv*) OR hypersensib* OR sensibility* OR ((nerv* OR neur*) NEAR/3 (plasticit* OR inhibit* OR depress*)) OR neuroplasticit* OR summation* OR ("long term" NEAR/3 (potentiat* OR depress*)) OR (Heterosynap* NEAR/3 facilitat*) OR Windup* OR hyperalg* OR allodynia OR hyperpath* OR hyperesthe* OR Oxyesthe* OR (Corticol NEAR/3 reorgani*) OR (Modificat* NEAR/3 pain*) OR (Synap* NEAR/3 strenghthen*) OR ((Endogen* OR nocicepti*) NEAR/3 inhibit*) OR "aminobutyric acid" OR gaba OR (gamma NEAR/1 (aminobutyr* OR "amino butyric")) OR (pain NEAR/3 modulat*) OR disinhibit* OR ((pain OR nocicept*) NEAR/6 (threshold* OR toleran*)) OR PPT OR PPTs OR Hyperexcitabil* OR (Pain NEAR/3 processing))) NOT ((animal* OR rat OR rats OR mouse OR mice OR rodent* OR rabbit* OR horse* OR cat OR cats) NOT (human* OR patient*)))

Cinahl 250
(MH "neck pain+" OR (((neck OR cervical) N6 (pain* OR disorder*)))) AND (MH "Central Nervous System Sensitization +" OR MH hypersensitivity OR MH "Neuronal Plasticity +" OR MH "Neural Inhibition+" OR MH "Postsynaptic Potential Summation+" OR MH

hyperalgesia+ OR MH hyperesthesia+ OR MH "4 aminobutyric acid+" OR MH "pain threshold+" OR (sensitiz* OR sensitis* OR sensibilizat* OR sensibilisat* OR hypersensitiv* OR (hyper N sensitiv*) OR hypersensib* OR sensibility* OR ((nerv* OR neur*) N3 (plasticit* OR inhibit* OR depress*)) OR neuroplasticit* OR summation* OR ("long term" N3 (potentiat* OR depress*)) OR (Heterosynap* N3 facilitat*) OR Windup* OR hyperalg* OR allodynia OR hyperpath* OR hyperesthe* OR Oxyesthe* OR (Corticol N3 reorgani*) OR (Modificat* N3 pain*) OR (Synap* N3 strenghthen*) OR ((Endogen* OR nocicepti*) N3 inhibit*) OR "aminobutyric acid" OR gaba OR (gamma N1 (aminobutyr* OR "amino butyric")) OR (pain N3 modulat*) OR disinhibit* OR ((pain OR nocicept*) N6 (threshold* OR toleran*)) OR PPT OR PPTs OR Hyperexcitabil* OR (Pain N3 processing))) NOT (MH animals+ NOT humans+)

PubMed publisher 32
((((neck[tiab] OR cervical[tiab]) AND (pain*[tiab] OR disorder*[tiab]))))) AND ((sensitiz*[tiab] OR sensitis*[tiab] OR sensibilizat*[tiab] OR sensibilisat*[tiab] OR hypersensitiv*[tiab] OR hyper sensitiv*[tiab] OR hypersensib*[tiab] OR sensibility*[tiab] OR ((nerv*[tiab] OR neur*[tiab]) AND (plasticit*[tiab] OR inhibit*[tiab] OR depress*[tiab])) OR neuroplasticit*[tiab] OR summation*[tiab] OR (long term AND (potentiat*[tiab] OR depress*[tiab])) OR (Heterosynap*[tiab] AND facilitat*[tiab]) OR Windup*[tiab] OR hyperalg*[tiab] OR allodynia[tiab] OR hyperpath*[tiab] OR hyperesthe*[tiab] OR Oxyesthe*[tiab] OR Corticol reorgani*[tiab] OR pain Modificat*[tiab] OR Synaptic strenghthen*[tiab] OR ((Endogen*[tiab] OR nocicepti*[tiab]) AND inhibit*[tiab]) OR "aminobutyric acid"[tiab] OR gaba OR gamma aminobutyr*[tiab] OR gamma amino butyric*[tiab] OR (pain AND modulat*[tiab]) OR disinhibit*[tiab] OR ((pain[tiab] OR nocicept*[tiab]) AND (threshold*[tiab] OR toleran*[tiab])) OR PPT[tiab] OR PPTs[tiab] OR Hyperexcitabil*[tiab] OR Pain processing[tiab])) AND publisher[sb]

Google Scholar
"neck|cervical pain|disorder" sensitization|hypersensitivity|"nerve cell plasticity|inhibition"|summation|"term potentiation|depression"|hyperalgesia|allodynia|hyperesthesia|gaba|"pain threshold"|sensibility|neuroplasticity -rodent -rat -mice -mouse

Appendix 2. Articles excluded by insufficient patient information.

Although the results of these articles are not considered for this review because of inadequate information, a short description of measurements and results are given here in order to be complete. In the article of Rosendal et al[1], it was not stated whether or not the patients experienced a fracture of the neck or underwent neck surgery. This paper only investigated sensory sensitivity by comparing the PPT's at the neck and tibialis anterior muscle sites in between neck pain patients and controls. No signs for generalized hypersensitivity were found.
The second doubtful article, written by Tampin et al[2], didn't tell if patients were non-traumatic, which implies a possible inclusion of chronic whiplash patients. This paper investigated pain thresholds (thermal, pressure, and mechanical), detection thresholds (thermal, mechanical, and vibration), and wind-up ratio. No differences were found in between neck pain patients and controls, except for cold pain thresholds at the maximal pain area (neck) and the foot. Except for general cold pain hypersensitivity, this paper gives no further evidence for generalized pain hypersensitivity or detection hyposensitivity.

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