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Evidence for central sensitization in chronic whiplash: A systematic literature review

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Abstract

Background and objectives: It has been suggested that sensitization of the central nervous system plays an important role in the development and maintenance of chronic (pain) complaints experienced by whiplash patients. According to the PRISMA guidelines, a systematic review was performed to screen and evaluate the existing clinical evidence for the presence of central sensitization in chronic whiplash.

Databases and data treatment: Predefined keywords regarding central sensitization and chronic whiplash were combined in electronic search engines PubMed and Web of Science. Full text clinical reports addressing studies of central sensitization in human adults with chronic complaints due to a whiplash trauma were included and reviewed on methodological quality by two independent reviewers.

Results: From the 99 articles that were identified, 24 met the inclusion criteria, and 22 articles achieved sufficient scores on methodological quality and were discussed. These studies evaluated the sensitivity to different types of stimuli (mechanical, thermal, electrical). Findings suggest that although different central mechanisms seem to be involved in sustaining the pain complaints in whiplash patients, hypersensitivity of the central nervous system plays a significant role. Persistent pain complaints, local and widespread hyperalgesia, referred pain and (thoracic) allodynia, decreased spinal reflex thresholds, inefficient diffuse noxious inhibitory controls activation and enhanced temporal summation of pain were established in chronic whiplash patients.

Conclusions: Although the majority of the literature provides evidence for the presence of central sensitization in chronic whiplash, underlying mechanisms are still unclear and future studies with good methodological quality are necessary. In addition, international guidelines for the definition, clinical recognition, assessment and treatment of central sensitization are warranted.

1. Introduction

Chronic whiplash-associated disorders

The term whiplash-associated disorders (WAD) is used for patients who experience complaints due to a whiplash injury. A whiplash injury is often caused by motor vehicle accidents and can result in injuries to bony or soft tissues (Spitzer et al., 1995). Although the majority of patients with whiplash show no physical signs, even when sophisticated imaging techniques are used, up to 50% develop chronic pain and report this as their main complaint (Spitzer et al., 1995; Carroll et al., 2008; Kamper et al., 2008).

Database:
- PubMed and Web of Science, including full text clinical reports.

What does this review add?
- Although narrative reviews regarding central sensitization in whiplash exist, there are no studies that have performed a systematic review of the literature in order to summarize findings regarding central sensitization in chronic whiplash. This systematic review provided evidence for the presence of central sensitization in chronic whiplash.
- Based on the results of this systematic review, recommendations were formulated to steer future studies examining central sensitization in chronic whiplash.

Central sensitization

Acute whiplash injury will induce excitability and hypersensitivity of the peripheral nociceptors, known as peripheral sensitization. In case of prolonged noxious input functional changes, such as enhanced excitability and responsiveness of the neurons within the central nervous system or central sensitization, will appear (Woolf, 1983). These changes can remain long after nociceptive input has disappeared (Woolf and Doubell, 1994; Thunberg et al., 2001). This process and the state of spinal neuron hyperexcitability are referred to as central sensitization (Woolf, 1983; NPC and JCAHO, 2001; Woolf, 2011). Central sensitization encompasses altered sensory processing in the brain (Staud et al., 2007), malfunctioning of descending pain inhibitory mechanisms (Meeus et al., 2008), increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up (Meeus and Nijs, 2007; Staud et al., 2007) and long-term potentiation of neuronal synapses in the anterior cingulate cortex (Zhuo, 2007). The outcome of the processes involved in central sensitization is an increased responsiveness to a variety of stimuli including mechanical pressure (Desmeules et al., 2003), chemical substances (Morris et al., 1997), cold temperature (Kasch et al., 2005), heat temperature (Meeus et al., 2008) and electrical stimuli (Desmeules et al., 2003; Banic et al., 2004). Indeed, when the central nervous system is sensitized, either no or minimal and undetectable tissue damage is required to induce pain. This may explain the discrepancy between the absence of evident tissue damage and persisting pain complaints in chronic WAD (Herren-Gerber et al., 2004).

As pointed out above, different mechanisms contribute to central sensitization. Hence, measuring central sensitization forms a complex challenge for researchers, which may explain why at present there is no gold standard clinical measure for central sensitization in human subjects (Woolf, 2011). Different methods, such as quantitative sensory testing, are used in pain research. These methods are based on the application of standardized (painful) stimuli to cutaneous and musculoskeletal structures to evaluate the sensitivity of these structures to specific stimulus modalities (Graven-Nielsen and Arendt-Nielsen, 2008; Woolf, 2011).

Study aim

It has been suggested that abnormal sensory processing in the central nervous system or central sensitization contributes to the development and maintenance of chronic (pain) complaints experienced by WAD patients (Curatolo et al., 2001; Davis, 2001). Several studies have examined aspects of central sensitization in patients with chronic WAD, but inconsistent results have been presented. For example, some studies have reported the presence of hypoaesthesia or hyperalgesia, while other studies have reported no changes in sensory sensitivity. Currently, it remains unclear whether sufficient evidence is available in favour of central sensitization in chronic WAD. If central sensitization is indeed dominating the clinical picture of patients with chronic WAD, then treatment programmes should be adapted accordingly. Hence, the aim of this systematic review was to review and evaluate the existing clinical evidence in order to establish if there is sufficient evidence for the presence of central sensitization in chronic WAD.

2. Literature search methods

2.1 Search strategy

Using the PRISMA guidelines (Liberati et al., 2009) a systematic search of the existing literature (until 14 March 2012) was performed via the electronic databases PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) and Web of Science (http://apps.isiknowledge.com). Two groups of keywords were listed: (1) central hypersensitivity, central sensitization, sensitization; (2) whiplash, chronic whiplash, whiplash associated disorders, WAD. The keywords from group 1 were combined with the key words from group 2. No limits were used during the search strategy. The results for every database and each combination of keywords are represented in Appendix 1.

2.2 Inclusion criteria

All titles and abstracts were read to identify relevant papers. To be included in this systematic review, papers had to be full text clinical reports, studying central sensitization in human adults (18 years or older) with chronic complaints due to a whiplash trauma. 'Chronic complaints' were described as complaints present for at least 3 months, and no restrictions were made on the type (i.e., pain, stiffness, etc.) or the localization of the complaints (i.e., local, regional, widespread). No limitations were made based on language or year of publication, and all clinical study designs were eligible. Non-clinical reports such as reviews were excluded. The type of outcome measure to evaluate the presence of central sensitization was not an inclusion criterion for this review. Currently, consensus is lacking with regards to a gold standard of outcome measure for central sensitization. In case of uncertainty regarding the eligibility of the paper based on the content of the title and abstract, the full text version of the paper was retrieved and evaluated against the inclusion criteria. The full text version of all papers that met the inclusion criteria were retrieved for quality assessment and data extraction.

2.3 Quality assessment

We expected that the majority of the studies would have used a case-control design to clinically evaluate the presence of central sensitization in chronic WAD. However, to provide a wide overview of all clinical research concerning central sensitization in chronic WAD, we included all clinical reports, regardless of the study design. Therefore, we needed a checklist that contained items that could be used to screen case-control studies, but also other study designs such as cohort studies and randomized controlled trials. Based on the most important methodological issues for each study design and the screening of different existing questionnaires, we composed a checklist with 18 evaluation criteria, presented in Supporting Information Table S1 (see the online version). This questionnaire was used to assess the methodological quality of the full text papers. Two researchers (J.V.O. and J.N.) independently scored the studies. They assessed whether each of the criteria were fulfilled. For the calculation of the total score on quality, only the criteria that were applicable for the study design were taken into consideration. For every evaluated study, a total score was made by summation of all the criteria that were fulfilled, and the score was then transformed into a percentage. For example, when only 15 out of the 18 criteria were applicable to a study, and 9 of the 15 criteria were fulfilled, this resulted in a score of 9/15 or 60%. Besides evaluating the overall quality, the researchers were asked to specify the purpose of the study (aetiology, prevalence, incidence, prevention, treatment, case report, diagnosis), the study design (prospective, clinical trial, case report, hypothetical, cross-sectional) and whether the severity of the complaints of the study subjects was mentioned (for example by using the Quebec Task Force on WAD (QTF-WAD) classification). Where disagreement occurred, a third researcher (M.M.) was called upon to make the final decision. Papers needed to achieve a score of at least 40% on methodological quality to be considered for further appraisal in this review.

3. Results

3.1 Search strategy

The selection process is represented in Figure 1. The initial search resulted in 537 hits. After removal of duplicates, 99 articles remained, and the titles, abstracts or when necessary, the full text paper, were screened for inclusion. Seventy-five articles did not meet the inclusion criteria and were removed. Rejection was mostly based on the participants' conditions

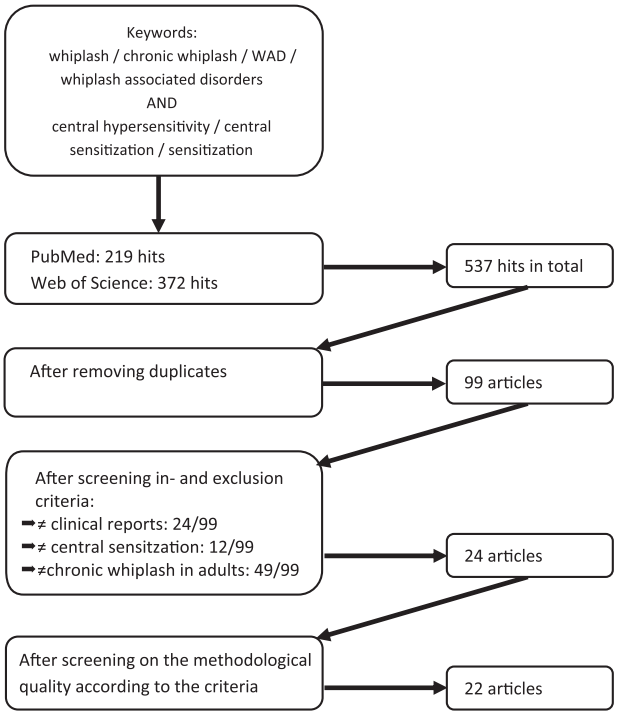

Figure 1 Selection process.

not meeting the inclusion criteria of chronic WAD. Twenty-four articles were eligible for quality assessment, as presented in Supporting Information Table S2 (see the online version).

3.2 Methodological quality

There was 96% (416 out of 432 items) agreement in scoring between the two researchers conducting the systematic review. All disagreements were resolved by a third researcher (M.M.) who made the final decision. Fourteen out of the 24 evaluated studies achieved a score $\geq$ 50%, while eight studies scored between 50% and 30%, and two articles scored <30%. Supporting Information Table S2 (see the online version) provides details regarding the quality criteria that were fulfilled for each evaluated study. Six out of the 24 studies had a sufficient sample size that was statistically justified (criterion 1). In seven studies the groups were comparable at baseline regarding demographic data (criterion 5); 12 studies did not meet this criterion. Remarkably only none of the articles sufficiently described the validity and reliability of the outcome measures used (criterion 6). Only 4 out of 21 studies accounted for co-interventions (criterion 7), and 4 out of 24 included a washout period (criterion 8). The assessor(s) were blinded in five studies (criterion 10). Three studies were eligible for blinding of all the study subjects and all the therapists but only one study fulfilled these criteria (9 and 11) and performed a double-blind study. None of the studies that used blinding reported if the blind procedure was effective (criterion 12). Eight studies made use of a follow-up period (criterion 18). Articles were required to achieve a score of >30% on methodological quality to be considered for further appraisal in this review. The studies of Gunn et al. (2001) and Sterling et al. (2002a) were excluded for this reason, with total scores of respectively 13.3% and 30%.

3.3 Study characteristics

Of the 22 selected papers, four were clinical trials (including two randomized controlled clinical trials), 11 case-control studies, and eight prospective studies (Supporting Information Table S3, see the online version). One out of the 22 studies examined a treatment modality for chronic WAD patients, while 21 studies were performed to investigate the aetiology of chronic WAD.

Fifteen studies included patients with chronic WAD, one study included subacute WAD patients and six studies investigated patients with acute WAD. Although one of the criteria to be included in this systematic review was that studies examined WAD patients with chronic complaints, we did include these seven particular articles that examined acute (Kasch et al., 2001, 2005; Chien et al., 2010; Ferrari, 2010; Sterling, 2010; Kamper et al., 2011) or subacute (Sterling et al., 2003) WAD patients because they were prospective studies examining the role of central sensitization in the transition of (sub)acute to chronic WAD.

Different diagnostic criteria exist for whiplash and it was not always clear which criteria were used. We tried to inventory the severity of the whiplash injuries included in the various studies by classifying each into five grades of severity developed by the QTF-WAD [grade 0 where no neck symptoms or physical sign(s) are present; grade I in case of neck pain, stiffness or tenderness but with absence of physical sign(s); grade II where neck symptoms and musculoskeletal sign(s) such as decreased range of motion and point tenderness are present; grade III in case of neck symptoms and neurologic sign(s); and finally grade IV where a fracture or dislocation is present (Spitzer et al., 1995)]. Not all authors categorized their patient population using this classification. By studying the in- and exclusion criteria and the patient characteristics of the papers, we were able to categorize most of the patients used in the studies with the QTF-WAD classification (Supporting Information Table S3, see the online version). Only two studies did not mention the severity of the symptoms or did not specify the severity within their in- and exclusion criteria. The other studies mainly included whiplash patients with grade II (in 17 articles) and grade III (in eight articles). Patients with grade I were included in eight studies and only one article mentioned including patients with grade IV. In grades III–IV neurological damage, fractures and dislocations might explain the symptoms experienced by whiplash patients, whereas in WAD grades I–II, no physical signs can be identified and central sensitization could explain the sustaining symptoms. In eight studies, whiplash patients were considered chronic when they experienced symptoms for at least 3 months, one study used a margin of 4 months, four studies used a margin of 6 months and one study used a margin of 24 months. One study failed to describe how long the symptoms needed to be present for whiplash patients to be included to the study (Lemming et al., 2005). Chronic WAD can be experienced as local, regional or widespread pain condition. Only two studies reported whether the included WAD patients experienced widespread pain complaints. Kosek and Januszewska (2008) excluded patients who reported pain below the waist and Gerdle

et al. (2008) only included patients without widespread pain although it was not clear how the authors evaluated the presence of widespread pain.

3.4 Evidence for central sensitization

In the following section, the results of this review will be described, structured according to the modes of assessment. We would like to note that although terms like 'pain thresholds' and 'pain detection thresholds' are used mutual in the reviewed literature, they have the same meaning. To avoid confusion, we will use the term 'pain threshold' in this review, which is defined by the International Association of Pain (Merskey and Bogduk, 1994) as the least experience of pain which a subject can recognize. In addition, we will use the terms 'pain tolerance threshold', which has been defined as the greatest level of pain that a subject is prepared to tolerate, and 'perception threshold' to describe the first sensation perceived by a subject.

3.4.1 Mechanical stimuli

3.4.1.1 Deep tissue stimulation

Pressure algometry involves applying mechanical stimuli and is the most commonly used psychophysical quantitative technique to assess pain in myofascial tissues and joints (Fischer and Russell, 1998). A reduction in pressure pain thresholds or increased pain ratings at the area of injury indicates the presence of primary hyperalgesia. But when pressure pain thresholds or increased pain ratings are also detected at remote, asymptomatic sites, this indicates the presence of widespread hyperalgesia, a clinical manifestation of central sensitization. Pressure algometry was used as one of the outcome measures in 16 of the 22 studies (Kasch et al., 2001, 2005; Sterling et al., 2003, 2008, 2010; Banic et al., 2004; Herren-Gerber et al., 2004; Lemming et al., 2005; Scott et al., 2005; Chien et al., 2008, 2009, 2010; Gerdle et al., 2008; Schneider et al., 2010; Sterling, 2010; Kamper et al., 2011). Banic et al. (2004) and Kasch et al. (2005) only assessed the pain and pain tolerance thresholds in response to pressure at local, symptomatic sites (i.e., the neck area) providing evidence for primary hyperalgesia, but not for widespread hyperalgesia and therefore could not judge central sensitization. All remaining studies assessed local, symptomatic and/or remote, asymptomatic sites and established lowered pain thresholds and/or pain tolerance thresholds in response to pressure at both sites demonstrating the presence of widespread hyperalgesia in chronic WAD (Kasch et al., 2001, 2005; Herren-Gerber et al., 2004; Lemming et al., 2005; Scott et al., 2005; Chien et al., 2008, 2009, 2010; Gerdle et al., 2008; Sterling et al., 2008; Schneider et al., 2010; Sterling, 2010; Kamper et al., 2011).

Seven prospective studies were reviewed. In a first study, Kasch et al. (2001) used manual palpation combined with pressure algometry on the neck and jaw muscles, and at a distal control site in acute WAD patients. Assessments were performed after 1 week and 1, 3 and 6 months after injury and the control group existed of patients with an acute ankle injury. Initially, WAD patients had lowered pressure pain thresholds and higher palpation scores in the neck/head, but the distal control site was not sensitized. In addition, the groups were similar after 6 months, and no evidence was found to support the presence or role of central sensitization in the development of chronic pain complaints in whiplash. However, the authors did not differentiate between recovered and non-recovered patients at the follow-up assessments. It is possible that the non-recovered patients presented with lower pressure pain thresholds but that the total effect was offset by the normalized thresholds from the recovered patient group. In a subsequent study, Kasch et al. (2005) took this into consideration. They examined 141 WAD patients, who were divided to recovered and non-recovered, and 40 ankle-injured controls. WAD patients showed a decreased pressure pain tolerance threshold at the masseter muscle 3 to 6 months after the injury when compared to controls. In comparison to recovered WAD patients, non-recovered or chronic WAD patients showed reduced pressure pain tolerance threshold at the masseter muscle 6 months after the injury and a tendency towards a reduced tolerance threshold 3 and 12 months after the injury. Because only a local site was examined, this study provides no evidence for the presence or absence of general, widespread hypersensitivity. Sterling et al. (2003) examined the pain pressure thresholds at local sites (on the neck) and distal, remote sites (on the upper and lower limbs). Local mechanical hyperalgesia was established in the cervical spine at 1 month post-injury, persisting up to 6 months post-injury in those patients who reported moderate/severe symptoms but resolved by 2 months in those who had recovered or reported persistent mild symptoms. In addition, patients with moderate/severe symptoms had lowered pain pressure thresholds at all sites 6 months post-injury, demonstrating generalized hypersensitivity. The findings were confirmed in a second study performed by Sterling (2010). In the study of Chien et al. (2010) the pain pressure thresholds were measured in order to classify whiplash to a low- or high-risk group for poor recovery;

however, the authors did not examine whether the thresholds evolved over time.

Kamper et al. (2011) examined the association between pain pressure threshold measures and neck and general pain. Significant but weak associations were found, both in the acute and the chronic phases of whiplash. This finding is in line with our current understanding of central sensitization (i.e., that symptom changes, such as an increase in neck/general pain complaints, do not correspond to what happens in the tissues).

One study examined the effect of cervical spine manual therapy on pain pressure thresholds in chronic WAD. Although pain pressure thresholds at local and remote sites increased after the experimental intervention, there were no statistically significant differences when compared to the control intervention which existed of manual contact (Sterling et al., 2010).

3.4.1.2 Skin and nerve tissue stimulation

While pressure algometry can be used to examine the sensitivity of muscle tissue, the sensitivity of the skin can be examined by applying mechanical stimuli using Von Frey hairs filaments or a Wartenberg pinwheel. Von Frey testing was used to assess low-threshold mechanoreceptive function or the perception threshold to light touch and punctuate hyperalgesia at the cervical and upper brachial regions. Scott et al. (2005) did not found evidence for the presence of punctuate hyperalgesia in chronic WAD patients. However, we must consider that the authors only based these conclusions on a preliminary analysis, which was performed with part of the data ($n = 20$), not testing the hypothesis on the full sample size of WAD patients ($n = 30$). To the contrary, Kosek and Januszewska (2008) established increased perception thresholds to light touch, demonstrating a decreased sensitivity to light touch in chronic WAD patients. In addition, the authors reported that local anaesthesia did not affect these perception thresholds. The Wartenberg pinwheel was used to examine hypersensitivity in the thoracic dermatomes, and 70% of the examined chronic WAD patients presented thoracic allodynia (Bock et al., 2005).

The Brachial Plexus Provocation Test (BPPT) test involves the application of controlled longitudinal provocative stimuli, which aims to provoke the nerve tissues and to test for mechanical sensitivity of the upper limb nerve tissue (Sterling et al., 2008). The validity of the BPPT as a measure of central hyperexcitability has not been established, but hypersensitive responses to this test have been demonstrated in people with acute and chronic WAD (Ide et al., 2001; Sterling et al., 2003, 2008). Chronic WAD patients demonstrated hyperalgesic responses to the BPPT (lower elbow extension accompanied with higher pain levels during the BPPT) when compared to asymptomatic control subjects (Chien et al., 2008, 2009). Similar findings were reported by Sterling et al. (2002b), who described that the responses were bilateral and occurred in all chronic WAD subjects, regardless of whether or not the subjects reported arm pain as a symptom of their condition. Within the WAD population, subjects whose arm pain was reproduced by the BPPT demonstrated more severe hyperalgesic responses when compared to the WAD subjects whose arm pain was not reproduced by the BPPT and the WAD subjects without arm pain. The BPPT was also used in two prospective studies. In the study of Sterling et al. (2003), WAD patients with moderate/severe symptoms and patients with mild symptoms showed less range of elbow extension and reported more pain during the test than both the control group and the patients who recovered at 6 months. The authors suggested that the decreased threshold to mechanical stimulation evoked by the BPPT is a hyperalgesic sensory response, which is suggestive for the presence of central sensitization. Ferrari (2010) showed that whiplash patients their expectations of recovery in the acute phase can be predictive of the results on the BBPT in the chronic phase. WAD patients with negative expectations reported more arm pain during the BPPT at 6 months follow-up.

Chien et al., 2008, 2009, 2010) also measured the vibration perception thresholds by means of a vibrometer over areas of the hand innervated by the distal aspect of the C6, C7 and C8 nerves. In these studies, chronic WAD patients demonstrated elevated perception thresholds for all sites compared to the control group. In addition, whiplash patients who have a high risk for poor recovery will demonstrate higher perception thresholds to vibration that patients with a low risk (Chien et al., 2010). These findings could be important because altered vibration detection sense is thought to be an early indicator of neural pathology (Greening et al., 2003).

3.4.1.3 Thermal stimuli

Thermal stimuli have also been used to evaluate central sensitization in patients with chronic WAD. Using heat or cold, perception and pain thresholds can be measured. Nine research papers examined the response in chronic WAD patients to thermal stimuli.

A thermode was used in 11 of the studies (Curatolo et al., 2001; Sterling et al., 2003, 2008, 2010; Scott et al., 2005; Raak and Wallin, 2006; Chien et al., 2008, 2009, 2010; Schneider et al., 2010; Sterling, 2010), while one study used the cold pressor test (Kasch et al., 2005). Eight articles reported significantly reduced cervical cold pain thresholds (Sterling et al., 2003, 2008; Scott et al., 2005; Raak and Wallin, 2006; Chien et al., 2008, 2009; Schneider et al., 2010; Sterling, 2010). When chronic WAD patients are categorized using the severity of their symptoms, these reduced cervical cold pain thresholds were only established in patients with more severe symptoms (Sterling, 2010). Three articles reported reduced cervical heat pain thresholds (Sterling et al., 2003; Scott et al., 2005; Raak and Wallin, 2006). In addition, reduced cold and heat pain thresholds were established at remote sites such as the lower limbs (Scott et al., 2005; Chien et al., 2008, 2009). Three studies reported normal heat pain thresholds (Curatolo et al., 2001; Sterling et al., 2008; Chien et al., 2009). Although Sterling et al. (2008) measured heat pain thresholds at different sites, local and remote, one mean value was reported. Therefore, we were not able to study the reactions of the different testing sites to unveil possible reasons, which might explain why no differences were found between the WAD and the control group. In addition, one study used thermal pain thresholds as one of the outcome measures to examine a therapy effect (Sterling et al., 2010). The authors found that cervical spine manual therapy was not able to alter heat or cold pain thresholds in chronic WAD patients.

Even though Chien et al. (2009) were not able to establish decreased heat pain thresholds, the authors did establish decreased heat pain perception thresholds. Heat perception thresholds were higher at the areas of the hand innervated by C6, C7 and C8 (Chien et al., 2008, 2009, 2010) and the thenar (Raak and Wallin, 2006), while cold perception thresholds were reduced in areas of the hand innervated by C8 (Chien et al., 2009). Some studies however did not find any altered cold perception thresholds in patients with chronic WAD (Raak and Wallin, 2006; Chien et al., 2008, 2010). Normal heat pain tolerance thresholds at the neck and the lower limb were established in chronic WAD patients (Curatolo et al., 2001).

Kasch et al. (2005) were interested in examining whether abnormal central pain processing could be responsible for the transition from acute to chronic WAD. Therefore, pain responses after exposure of the hand to cold water (i.e., the cold pressor test) were registered. Patients who had not recovered reported more pain and discomfort in response to the cold pressor test after the injury. In addition, these patients experienced pain earlier during the test compared to the non-recovered patients, when examined immediately after the injury and 6 months after the injury. Because this reduction in pain endurance was established immediately after the injury, it indicates that non-recovery or chronicity may be a result of altered pain processing that occurs very early after injury. In addition, using the cold pressor pain as a counter-stimulation for the induced pressure pain on the right masseter muscle allowed the authors to asses diffuse noxious inhibitory controls (DNIC) functioning. The DNIC, which acts as a filter separating irrelevant stimuli from relevant stimuli, is an important pain inhibitory mechanism used by the human body to modulate pain. DNIC occurs when the response (i.e., pain perception) to a noxious stimulus is inhibited by a second, spatially remote noxious stimulus. Although DNIC seemed to be impaired in chronic WAD patients 6 months after the injury, normal DNIC activation was established in the non-recovered WAD patients.

3.4.1.4 Electrical stimuli

In 10 studies, electrical stimulation was used to evaluate central sensitization in patients with chronic WAD (Curatolo et al., 2001; Banic et al., 2004; Lemming et al., 2005; Chien et al., 2008, 2009, 2010; Kosek and Januszewska, 2008; Sterling et al., 2008, 2010; Sterling, 2010). Electrical stimulation bypasses peripheral receptors and when pain hypersensitivity is observed after stimulation of uninjured body parts evidence is provided for the involvement of central pain mechanisms (Handwerker and Kobal, 1993). The nociceptive withdrawal reflex is a spinal reflex, which can be evoked from the lower limb (nociceptive flexion reflex) by single or repeated (temporal summation) electrical stimulation and allows us to assess the excitability of spinal neurons. In the studies of Banic et al. (2004), Sterling (2010) and Sterling et al. (2008, 2010), the nociceptive withdrawal reflex threshold responses to single electrical stimulation on the sural nerve were registered using EMG. The stimulus intensity necessary to evoke a spinal reflex was significantly lower in patients with chronic WAD than in healthy subjects (Banic et al., 2004; Sterling et al., 2008), which demonstrates a state of hypersensitivity of spinal neurons to peripheral stimulation in these patients. Sterling (2010) found that the nociceptive withdrawal reflex threshold were decreased in the acute phase unregarded patients their symptom severity. However, in the chronic phase, only patients with

moderate to severe symptoms presented decreased nociceptive withdrawal reflex thresholds. Sterling et al. (2008) found no relationships between psychological factors and the nociceptive flexion reflex responses. The authors were able to demonstrate that cervical spine manual therapy can be used to increase nociceptive flexion reflex thresholds measured in the lower limb sites (Sterling et al., 2010). However, pain ratings during the test did not change. These findings suggest that cervical spine manual therapy could be used to influence nociceptive processing and to modulate spinal cord hyperexcitability.

Temporal summation or wind-up occurs when repeated stimuli of constant intensity evoke an increase in the intensity of perception during repeated stimulation, so that the latter stimuli are perceived as painful (Price, 1972). The pain evoked by temporal summation is believed to result from a temporary hyperexcitability of spinal cord neurons (wind-up), a process that probably contributes to central sensitization (Mendell and Wall, 1965; Mendell, 1966). The efficacy of temporal summation of pain can be assessed by measuring pain thresholds during repetitive electrical stimulation. Curatolo et al. (2001) established decreased pain thresholds or hypersensitivity at the neck and the lower limb sites in response to single and repeated intramuscular, and repeated transcutaneous electrical stimulation. Lemming et al. (2005) reported that intramuscular and cutaneous pain thresholds at the lower limbs of chronic WAD patients were significantly lower in response to repeated electrical stimulation compared to single stimulation. In these studies, central hypersensitivity was demonstrated as it is clear that when pain hypersensitivity is observed after electrical stimulation of healthy areas, it is caused by hyperexcitability of the central nervous system. The facilitated temporal summation, which was established in chronic whiplash patients, further supports this theory.

Electrical detection thresholds were studied by Chien et al., 2008, 2009, 2010). The electrical detection threshold is calculated as the mean of the perception and the disappearance threshold. Chien et al., 2008, 2009, 2010) established elevated electrical detection thresholds, which demonstrated the presence of hypoaesthesia at the upper limb sites but not at the lower limb sites. When the authors accounted for the prospect of recovery, they found that a high risk of poor recovery was predictive for increased electrical detection thresholds at distal sites, i.e., the index finger (Chien et al., 2010). Although it was examined whether elevated levels of somatization, depression and psychological depression in chronic WAD patients had an influence on any of the outcomes, no differences were established (Chien et al., 2008).

This hypoesthesia to light touch and electrical current reported by Chien et al., 2008, 2009, 2010) reminds us of the numbness in the referred pain area, which is often reported by chronic WAD patients in the clinical practice. And because hypoesthesia has not been reported in asymptomatic and remote areas, but rather in symptomatic and referred pain areas, it has been suggested that prolonged nociceptive input may have an inhibitory effect on the perception of touch (Chien et al., 2008; Kosek and Januszewska, 2008).

Kosek and Januszewska (2008) investigated pain referral in patients with chronic WAD using intramuscular electrical stimulation. Chronic WAD patients showed increased sensitivity to noxious intramuscular stimulation and required lower intensities of conditioning stimulation to induce referred pain. During the same subjectively painful conditioning stimulation, chronic WAD patients' perceived referred pain was more frequently induced and spread to larger areas compared to healthy subjects. In addition, WAD patients reported proximal referral of pain, which was never perceived by the healthy subjects. Because chronic WAD patients reported an abnormally increased spread of pain during the same subjectively painful stimulation as used in healthy subjects, this study provided evidence for altered central nervous system processing of nociceptive input in whiplash.

3.4.1.5 Injection of local anaesthetics

Local injections with mediators such as local anaesthetics or hypertonic saline can be used to examine the role of nociceptive input and the association with symptoms and central hypersensitivity, and to investigate referred pain, a central phenomena that is of clinical relevance. Curatolo et al. (2001) used an injection of a local anaesthetic into tender and painful muscles of the neck to examine the role of nociceptive input. Local anaesthesia did not influence pain thresholds or hypersensitivity at the neck and the lower limb sites in response to single and repeated intramuscular and transcutaneous electrical stimulation, nor did it influence neck pain intensity. These study results suggest that generalized hypersensitivity is not dependent on nociceptive input arising from the painful and tender muscles. Herren-Gerber et al. (2004) also injected a local anaesthetic into tender and painful muscles of the neck and expected an increase in the pain thresholds measured at the injected point and decreased neck pain. However, they observed both a decrease in pain thresholds and an increase in neck

pain. This was a local effect, as no change was detected at the remote testing site (i.e., the second ipsilateral toe). The authors proposed that injection and infiltration produced a local transient trauma with peripheral and central sensitization that increased neck pain and decreased pain pressure thresholds. It seemed likely that the painful and tender points were areas of referred pain, and these findings suggest that the underlying mechanisms of hyperalgesia at areas surrounding the site of injury are different from the ones that determine generalized hyperalgesia to distant body areas. Instead of influencing the nociceptive input of the muscles, Schneider et al. (2010) anaesthetically blocked the nociceptive input from the zygapophyseal joints. Consequently, the elevated cold pain thresholds in the neck decreased and the decreased pain pressure thresholds increased at local and remote sites (i.e., neck, upper and lower limbs), which suggests that nociceptive input arising from the zygapophyseal joints has an influence generalized hypersensitivity in chronic WAD.

In another study, some chronic WAD patients reported widespread areas of referred pain with proximal spread, after infusion of hypertonic saline into the tibialis anterior muscle (Lemming et al., 2005). In addition, the authors examined the response to intravenous treatment with morphine, lidocaine, ketamine and a placebo. The pharmacological drugs had short-term analgesic effects (up to 120 min after administration) on general pain and neck pain intensity. Although subgroups of patients with chronic WAD were identified based on treatment response, the authors were unable to identify the cause of this differentiation. Nevertheless, they considered the role of different pain processing mechanisms and dysfunctions of nociceptive pathways in chronic WAD as the basis for the differentiation. The pattern of response to the pharmacological challenges did not show any clear relationships with pain duration or the experimental pain tests.

3.4.1.6 Sympathetic vasoconstrictor reflex

To examine the involvement of the sympathetic nervous system in the symptoms of chronic WAD, the sympathetic vasoconstrictor reflex has been measured using laser Doppler flowmetry during a provocation manoeuvre (i.e., an inspiratory gasp). Sterling et al. (2003) found that WAD patients with moderate/severe symptoms showed a tendency for diminished sympathetic reactivity 6 months post-injury, although these effects were not statistically significant. Chien et al. (2009), however, compared the results of chronic WAD patients and healthy people, and demonstrated reduced vasoconstriction in the chronic WAD group.

4. Discussion and conclusions

Persistent pain complaints, local and widespread hyperalgesia, referred pain and (thoracic) allodynia were established in chronic WAD patients and are clinical manifestations of the hyperexcitability of the central nervous system (Coderre et al., 1993; Graven-Nielsen and Arendt-Nielsen, 2002; Staud and Smitherman, 2002). It has been shown that the cervical area is not the sole source of nociceptive input (Curatolo et al., 2001; Herren-Gerber et al., 2004), and the whole body has become sensitized and reacts to harmless stimuli (such as touch, pressure, heat, cold, vibration and innocuous electrical current). Although the majority of the evidence suggests that the central nervous system is hypersensitized, different reactions have been observed in response to the application of innocuous light stimuli (measured by registration of perception thresholds) and noxious stimuli (measured by registration of pain and tolerance thresholds) in the symptomatic area. For instance, hypoesthesia to light touch and electrical current has been established at the upper limbs. It is possible that prolonged nociceptive input has an inhibitory effect on the perception of touch in the symptomatic and referred pain areas (Chien et al., 2008, 2009, 2010; Kosek and Januszewska, 2008). It is clear that the central nervous system plays an important role in chronic WAD. The coexistence of sensory hypersensitivity and hypoaesthesia in chronic WAD indicates that both central facilitatory and inhibitory processes are affected in these patients.

One of the body's pain inhibitory mechanisms used to modulate pain is DNIC. Inefficient DNIC (Kasch et al., 2005) activation and enhanced temporal summation of pain or wind-up (Curatolo et al., 2001; Lemming et al., 2005) in chronic WAD were established. In addition, decreased spinal reflex thresholds in chronic WAD demonstrated hypersensitivity of the spinal neurons (Banic et al., 2004; Sterling et al., 2008; Sterling, 2010). These findings further support the presence of altered central pain processing and central sensitization in chronic WAD. Additional evidence can be provided by future studies examining malfunctioning of descending pain inhibitory mechanisms. Examining DNIC activation in response to different types of stimuli (cold, heat, mechanical), descending endogenous pain inhibition and DNIC activation during exercise can provide more insight in the mechanisms of central processing in chronic WAD.

Attempts have been made to identify other central mechanisms that are involved in sustaining the pain complaints. A reduced sympathetic vasoconstrictor reflex was seen in chronic WAD patients (Sterling et al., 2003; Chien et al., 2009). Although it seems that the sympathetic nervous system is affected in chronic WAD patients, from this review, it is not possible to conclude how this is related to central sensitization. Further, supraspinal descending facilitatory influences such as psychological factors are able to modulate central hypersensitivity and may influence the results of sensory testing (Rhudy and Meagher, 2000; Zusman, 2002). Three studies aimed at examining these psychological factors but two could not find any direct influence on pain responses using quantitative sensory testing (Chien et al., 2008; Sterling et al., 2008). One study found that expectations of recovery were predictive of the results on the BBPT achieved in the chronic phase (Ferrari, 2010). Still, it needs to be examined whether these expectations are also predictive for the outcomes established using other quantitative sensory measures. Recent findings from a study (Wallin et al., 2012), which was not retrieved using our search strategy, suggest that psychological factors are associated with alternations in thermal detection thresholds. Nonetheless, it is clear that more research is warranted to examine the precise influence of psychological factors on the processing of sensory input. Besides using questionnaires to assess these psychological factors, quantitative sensory testing can be performed in combination with functional magnetic resonance imaging in order to visualize activity in brain areas, which are responsible for processing and regulating emotions and stress.

It is not clear when the central nervous system starts sensitizing and when general, widespread hypersensitivity appears, but abnormal nociceptive processing occurs very early after injury (<7 days) and is predictive for the development of chronic WAD (Kasch et al., 2005). Four studies suggest that central sensitization occurs 3 to 6 months after the initial whiplash injury (Sterling et al., 2003; Kasch et al., 2005; Chien et al., 2010; Sterling, 2010). It needs to be examined what determines recovery or chronicity in this crucial (sub)acute period. However, we must take into consideration that the chronic WAD population is a heterogeneous patient group (Herren-Gerber et al., 2004; Bock et al., 2005; Lemming et al., 2005) and that central sensitization is not present in all whiplash cases (Nijs et al., 2010). This heterogeneity may explain why some inconsistent results were found (for example, regarding the cold perception thresholds), and efforts should be made to identify subgroups in the (chronic) WAD population. Attempts have been made by performing prospective studies examining the differences in sensory processing between patients who have recovered and who have not recovered (Sterling et al., 2003; Chien et al., 2010; Sterling, 2010). Therefore, patients can be categorized according to their symptom severity. Other possible reasons for the inconsistent results are the different criteria that were used to diagnose chronic WAD patients in these studies. Therefore, we recommend authors to report the severity of the whiplash injuries, for instance, by using the QTF-WAD classification (Spitzer et al., 1995), and to report whether the WAD patients, which are studied, experience widespread pain complaints, for instance, by checking the criteria for chronic widespread pain (Wolfe et al., 1990) or using the widespread pain index (Wolfe et al., 2010).

There is a need to examine which is the best combination of quantitative sensory measures to determine the presence of central sensitization and can be used to predict chronicity. A first attempt was made by Chien et al. (2009) who found that a combination of pain sensitivity (mechanical hyperalgesia in the neck and upper limbs; electrical pain/detection ratio) and detection thresholds (heat, electrical detection in the C6 innervated area) measures best predicted if subjects were chronic whiplash patients or healthy controls. The authors reported a high classification rate of 90.32% after cross-validation. Although reference values for different sensory tests are available (Rolke et al., 2006; Neziri et al., 2010; 2011), and a first attempt to develop clinical guidelines for the recognition and assessment of central sensitization was made by Nijs et al. (2010), international consensus and guidelines are warranted.

Only one study evaluated the ability of a treatment modality to influence central sensitization, and the results suggest that cervical spine manual therapy can be used to modulate spinal cord hyperexcitability in the short term (Sterling et al., 2010). Although care should be taken with the interpretation of the results as patients were not blinded, only short-term effects were studied and no effects on patients their pain levels and thresholds were found. Clearly, studies on therapy effects are lacking and future studies should examine the effect of treatment modalities and their influence on chronic pain and central sensitization since the presence of sensory hypersensitivity influences the outcomes of physical rehabilitation in chronic WAD (Jull et al., 2007). Based on the mechanisms of central sensitization and on the existing evidence regarding treatment of chronic WAD, Nijs et al.

(2009) wrote a review that explains how rehabilitation strategies for chronic WAD patients can account for the processes involved in central sensitization.

Based on the methodological issues identified in the existing studies, it is recommended that future study designs use a sufficient and justified sample size and reliable outcome measures of which the validity and reliability is reported to the readers. Bias must be prevented by blinding study subjects, assessors and therapists, and providing a washout period before starting data collection is required. Finally, care must be taken to account for co-interventions in order to prevent the treatment paradox, which is a frequent confounder in case-control studies.

In conclusion, the majority of the literature suggests that the central nervous system is becomes hypersensitized in patients with chronic WAD, and that this process of central sensitization plays a crucial role in the persisting pain complaints experienced by these patients. Although evidence suggests that pain facilitatory and inhibitory processes are impaired, the precise underlying mechanisms of central sensitization are still unclear and future studies with a good methodological quality are warranted to resolve this issue. In addition international guidelines for the definition, clinical recognition, assessment and treatment of central sensitization are warranted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Evaluation criteria on methodological quality.
Table S2. Evaluation scores on methodological quality.
Table S3. Characteristics of included studies.

Appendix 1

Total of hits for every keyword combination that was used at the Pubmed Web of Science search engines

PubMed	Whiplash	Chronic Whiplash	Whiplash Associated Disorders	WAD
Central hypersensitivity	20	16	14	10
Central sensitization	18	16	10	4
Sensitization	22	19	11	5
Total hits		165		

Web of Science	Whiplash	Chronic Whiplash	Whiplash Associated Disorders	WAD
Central hypersensitivity	57	38	21	13
Central sensitization	56	38	15	9
Sensitization	61	40	15	9
Total hits		372		