

ORIGINAL ARTICLE

Does acupuncture activate endogenous analgesia in chronic whiplash-associated disorders? A randomized crossover trial

Y. Tobbacx^{1,3,4}, M. Meeus¹, L. Wauters⁴, P. De Vilder⁴, J. Roose⁵, Tom Verhaeghe⁵, J. Nijs^{1,2}

1 Chronic Pain and Chronic Fatigue Research Group (CHROPIVER), Department of Human Physiology, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium

2 Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium

3 De Zuil, Centre for Chronic Pain Treatment and Relaxation Therapy, Westerlo, Belgium

4 Belgian Acupuncture Federation, Schoten, Belgium

5 European Federation of Oriental Medicine, Eigenbilzen, Belgium

Correspondence

Jo Nijs

E-mail: Jo.Nijs@vub.ac.be

Funding sources

Mira Meeus is a postdoctoral research fellow of the Research Foundation Flanders (FWO).

The study was funded by the Belgian Acupuncture Federation and the European Federation of Oriental Medicine. The funders had no role in the study design, data collection and analysis, interpretation of the data or decision to publish.

Conflicts of interest

None declared.

Accepted for publication

25 July 2012

doi:10.1002/j.1532-2149.2012.00215.x

Abstract

Background: Many patients with chronic pain, including those with chronic whiplash-associated disorders (WAD), show features of central sensitization. Randomized trials examining whether treatments are able to influence the process of central sensitization in patients with chronic WAD are emerging. Therefore, the present study aimed at examining whether acupuncture results in activation of endogenous analgesia and relief in symptoms in patients with chronic WAD.

Methods: In this randomized crossover pilot trial with blinded assessors, each patient ($n = 39$) received two treatment sessions of identical duration, with acupuncture and relaxation therapy randomly crossed over in visit 2. Primary outcome measurement included immediate activation of endogenous analgesia i.e., pressure pain sensitivity and conditioned pain modulation. Secondary outcome measurements included pain relief and reduced disability level.

Results: Local pressure pain sensitivity at baseline and during conditioned pain modulation decreased significantly more following acupuncture compared with relaxation (time \times group interactions: $p < 0.001$), both in the neck and at a site distinct from the painful region. When comparing the effects of acupuncture versus relaxation, no differences were observed on conditioned pain modulation, temporal summation of pressure pain, neck disability or symptom severity (all p -values > 0.05).

Conclusion: It was shown that one session of acupuncture treatment results in acute improvements in pressure pain sensitivity in the neck and calf of patients with chronic WAD. Acupuncture had no effect on conditioned pain modulation or temporal summation of pressure pain. Both acupuncture and relaxation appear to be well-tolerated treatments for people with chronic WAD. These findings suggest that acupuncture treatment activates endogenous analgesia in patients with chronic WAD.

Introduction

The term 'whiplash' refers to an acceleration-deceleration mechanism and the associated energy transfer to the cervical region as result of an accident.

This sudden impact at the cervical spine may result in bony and soft tissue injuries (whiplash trauma) and the development of a wide variety of clinical manifestations commonly named whiplash-associated disorder (WAD). Patients with chronic WAD typically

What's already known about this topic?

- Many patients with chronic whiplash-associated disorders show features of central sensitization.
- Acupuncture has been shown to have analgesic effects, probably due to activation of brain regions involved in top-down analgesia and opioid mechanisms.
- Its mechanism of action has been established in animal studies and studies in healthy people rather than patients with chronic pain.

What does this study add?

- This study indicates that acupuncture treatment activates endogenous analgesia in patients with chronic whiplash.
- Both, acupuncture and relaxation are well-tolerated treatments for people with chronic whiplash.
- Acupuncture does not activate conditioned pain modulation.

experience pain and severe disability, but at the same time, they do not present objective signs of tissue damage. However, this does not exclude the presence of minimal nociceptive input arising from minimally damaged tissues in the acute phase (Curatolo et al., 2004).

Many patients with chronic pain, including those with chronic WAD, show features of central sensitization, a process characterized by generalized hypersensitivity of the somatosensory system (Sterling et al., 2002, 2003; Banic et al., 2004; Herren-Gerber et al., 2004; Jull et al., 2007; Nijs and Van Houdenhove, 2009; Nijs et al., 2009, 2010). Central sensitization is characterized by increased activity of pain facilitation pathways, which entails temporal summation of secondary pain (wind-up) (Meeus and Nijs, 2007; Staud et al., 2007). In addition, central sensitization includes malfunctioning of descending pain inhibitory pathways, which results in dysfunctional endogenous analgesia (Meeus et al., 2008).

Assuming the presence of minimal nociceptive input arising from minimally damaged tissues, central sensitization could account for pain and disability in the absence of objective signs of tissue damage in patients with whiplash (Curatolo et al., 2004). Indeed, studies have shown that central sensitization modulates the transition from acute to chronic whiplash, and mediates treatment responses in patients with chronic whiplash. Hence, it seems rational to target the process of central sensitization for the treatment of

chronic WAD (Nijs et al., 2009; Van Oosterwijck et al., 2011). However, studies using endogenous analgesia, sensory hypersensitivity or any other feature of central sensitization as outcome measure are essentially lacking.

Acupuncture is a treatment method widely used for patients with chronic pain. Evidence in support of acupuncture for the treatment of chronic (neck) pain has been provided (Irnich et al., 2001, 2002; Fu et al., 2009; Hopton and MacPherson, 2010), but the effect-sizes are rather small and only short-term effects on pain severity have been shown consistently. Addressing its mechanism of action, acupuncture needles were traditionally thought to channel energy or Qi through body 'meridians', but science failed to identify anatomical structures related to these meridians (Zylka, 2010). Many (Zhao, 2008), but not all (Heine, 1988), acupuncture points are located in deep tissues that are rich in sensory innervations, indicating that acupuncture results in activation of a high number of somatosensory afferents. Such stimulation typically results in release of endogenous opioids (Han, 2004; Lin and Chen, 2008; Wang et al., 2008; Harris et al., 2009). In addition, acupuncture stimulates a complex network of brain regions including the periaqueductal grey (Dhond et al., 2008; Zhao, 2008). Activation of the periaqueductal grey implies activation of several endogenous analgesic mechanisms. Taken together, these findings suggest that the mechanism of action of pain relief via acupuncture entails activation of endogenous analgesia (Lin and Chen, 2008). However, many of the cited studies address animal data or data obtained from studies in healthy people. Hence, studying the mechanisms of acupuncture analgesia in patients with chronic pain and central sensitization (i.e., chronic WAD) is warranted.

A randomized crossover trial comparing acupuncture with relaxation was conducted in order to examine whether acupuncture versus relaxation for patients with chronic WAD results in immediate activation of endogenous analgesia, reduction in temporal summation of pressure pain and relief in symptoms.

Methods

Design and setting

A randomized crossover trial with a blinded assessor was conducted. Randomization was done by an independent person, blinded to the study nature and aims and hence, uninvolved with the present study. For each study participant, the independent person drew a number from a closed envelope. The number indi-

cated allocation to either groups [(1) acupuncture during the first session; (2) relaxation during session 1]. A list with patient numbers and the group allocation that resulted from this randomization procedure was stored in a sealed envelope. Only the therapist had direct access to the randomization list with treatment sequence.

Research has taught us that recruitment of chronic WAD patients solely through patient support groups generates bias with respect to various aspects of health status and personality (Nijs et al., 2011). In order to enhance the external validity of study findings, chronic WAD studies should combine a variety of recruitment procedures (Nijs et al., 2011). Therefore, patients were recruited from the medical database of the local university hospital, the medical database of a peripheral centre for emergency medicine and rehabilitation, calls for study participation published at the website of our research group, and through the local chronic WAD patient support group. To further increase feasibility for study participation (and hence the external validity of the study), patients were able to choose between two distinct locations for treatment participation (in the east or the west of the country).

All study participants were asked to sign the informed consent; written informed consent was obtained from all participants in accordance with the declaration of Helsinki (General assembly, October 2008, Seoul). The study protocol, information leaflet and informed consent were approved by the Human Research Ethics Committee of the Brussels University Hospital. The trial is registered at <http://www.ClinicalTrials.gov> using identifier NCT01512576. All data were collected in two different private practices for acupuncture treatment in Flanders, Belgium. Prior to study participation, patients were instructed not to initiate new treatments during the study period, to refrain from nicotine, alcohol and caffeine 24 h prior to study participation, and to not take analgesic drugs 48 h before study participation. Next, they were asked to fill out a set of questionnaires (see below), followed by assessment of conditioned pain modulation testing performed by a blinded assessor. Afterwards, patients received their first treatment session (either acupuncture or relaxation). Immediately after the treatment sessions, patients were re-evaluated by the same blinded assessor (conditioned pain modulation), and were asked to fill out two questionnaires (Neck Disability Index and Whiplash Associated Disorders Symptom list). Each study participant received two treatment sessions of identical duration, with acupuncture and relaxation therapy randomly crossed over in visit 2 (Fig. 1 displays the flow diagram of the

study). To eliminate carry-over effects, a 1-week wash-out period between the treatment sessions was chosen. Hence, patients were scheduled for a second treatment session 1-week later. During their second visit to the treatment centre, they underwent the same procedure as described above for the first visit (except for the content of the treatment, which was crossed-over).

Patients

Thirty-nine patients with chronic WAD participated in the study. To be included, patients had to comply with the following inclusion criteria: a diagnosis of chronic WAD grades 1–3 according to the criteria as defined by the Quebec Task Force classification (Spitzer et al., 1995); chronic neck pain and WAD persisting for at least 3 months; an age between 18 and 65 years. The Quebec Task Force classification (Spitzer et al., 1995) divides patients who experienced a whiplash trauma into five grades. Grade 0 refers to the clinical picture of patients experiencing no neck pain, stiffness, or any physical sign; grade 1 implies the presence of neck complaints of pain, stiffness, or tenderness only but no physical signs during the clinical examination; grade 2 covers patients having neck complaints plus decreased range of motion and point tenderness in the neck; grade 3 refers to neck complaints plus neurological signs such as decreased deep tendon reflexes, weakness, and sensory deficits; and grade 4 implies neck complaints including fracture or dislocation, or injury to the spinal cord (Spitzer et al., 1995). Subjects were excluded if they were classified as WAD grades 0 or 4; pregnant; initiated a new conventional therapy during the study period; taking analgesic drugs 48 h before testing and/or nicotine, alcohol, and caffeine 24 h before testing.

Sample size and study power

The required sample size was determined by targeting an improvement of 20% in endogenous pain inhibition as the primary outcome (i.e., conditioned pain modulation), a study power of 80% and $\alpha = 0.050$. This implies a mean difference in treatment outcome (acupuncture vs. relaxation) of 0.16, with an estimated standard deviation of 0.24 to generate a clinically important difference. The sample size estimation was conducted using SigmaStat 3.1 (2004; Systat Software Inc., Chicago, IL, USA), and indicated that at least 37 patients with chronic WAD should participate in the study. Accounting for dropouts, the required number of study participants was set at 39.

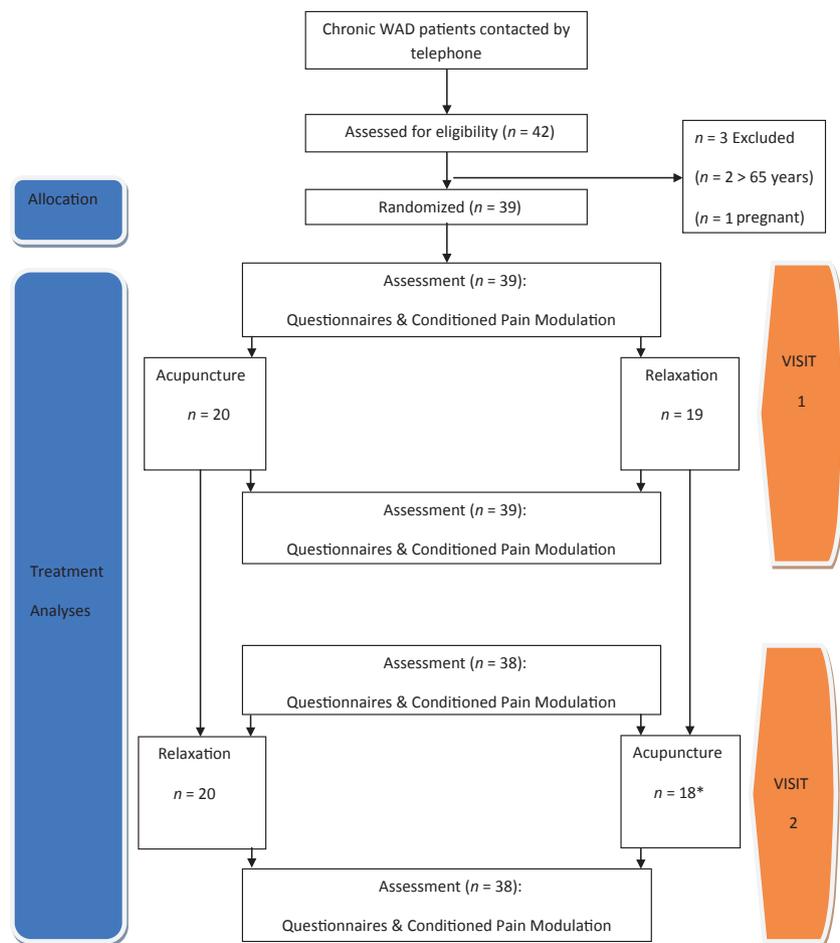


Figure 1 Flow diagram of the study. Assessments were done immediately before and after each treatment. The washout period between the treatment sessions was 1 week. *One dropout: lost after relaxation. WAD, whiplash-associated disorders.

Treatment

Each patient was treated once with acupuncture and relaxation. Both treatments lasted 20 min and were performed by the same therapist. This was possible because the relaxation consisted of listening to an audio CD, so no professional experience was required.

Acupuncture

The therapist had an acupuncture license registered by the Belgium Acupuncture Federation and has more than 15 years of experience in traditional Chinese acupuncture treatment. Technical aspects of both treatments such as patients’ posture and sequence of movements were standardized. The treatment strategy for acupuncture was developed in a consensus process with four acupuncture specialists, together representing two major Belgium societies for acupuncture (i.e., the Belgium Acupuncture Federation and the European Federation of Oriental Medicine). The protocol complies with international guidelines for acupunc-

ture treatment in patients with neck pain (White et al., 2002; MacPherson et al., 2011).

All patients were treated at acupuncture points uni- or bilaterally situated in the local region (neck), distal region (low back, arms and legs) and ear (Fig. 2, Table 1). In addition, acupuncture treatment was performed according to the rules of traditional Chinese medicine and was semi-standardized (Linde et al., 2005). This means that the therapist was allowed to choose from a list of the following acupuncture points: Dazhui GV14, Huatuojiiaji C1–C7, Fengchi GB20, Tianzong SI11, Jianjing GB21, Tianliao TE15, Jianwaishu SI14, Geshu BL17, Xuehai SP10, Houxi SI3, Jinggu BL64, Waiguan TE5, Zulinqi GB41, Shiqizhuixia, Ear Zero point, Ear Jerome point, Ear C0. The combination of acupuncture points was individually tailored, according to the theory of channels of traditional Chinese medicine. Affected channels were indicated by pain localization. Patients had to fill out a Margolis pain diagram (Margolis et al., 1986), and the acupuncturist questioned the patient and performed a traditional Chinese medical tongue- and pulse diagno-

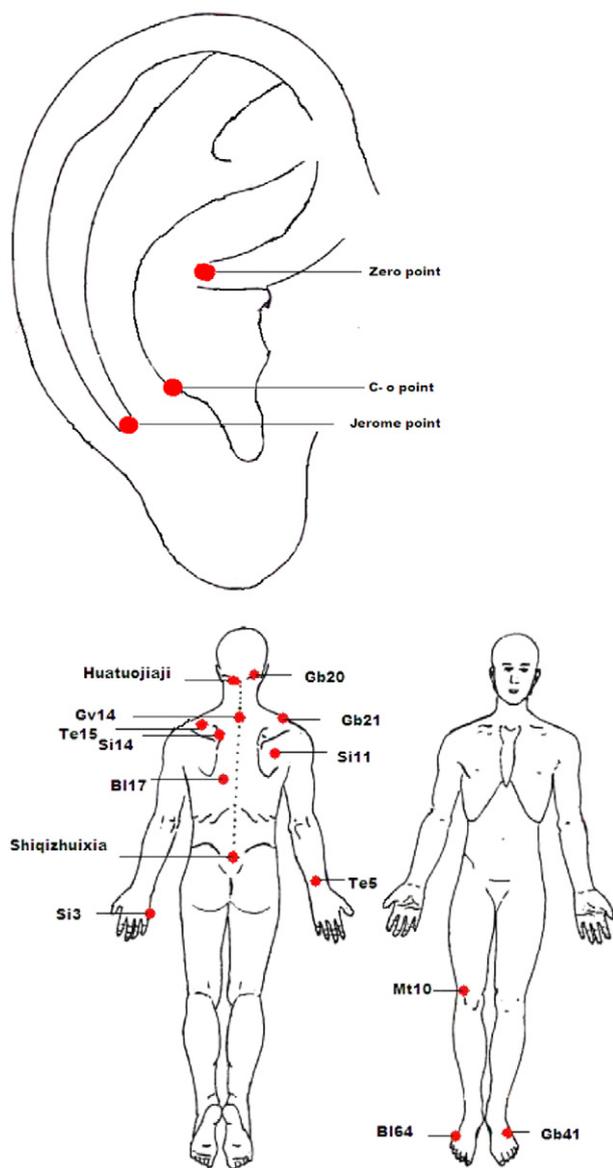


Figure 2 The acupuncture points used for the treatment of patients with chronic whiplash-associated disorders. The therapist was allowed to choose from these acupuncture points.

sis. Local and distal acupuncture points were selected individually on the affected meridians. Additional ear acupuncture points were selected. The frequency of used number acupuncture points are given in Table 1.

Sterile one-time use needles (Euro-acupuncture needles; Herbs and Tough, Nijmegen, The Netherlands) were used, but the therapist was allowed to choose the needle length and diameter. The size of the used needles ranged between 0.22 × 25 and 0.25 × 40 mm; for the ear the needles were standardized: 0.20 × 15 mm. Six to 18 needles per patient were used with an average of 10 needles. When placing the

needles, ‘de Qi’ (an irradiating feeling considered to be indicative of effective needling) was sometimes achieved, but no more than once per needle. No other manipulation of the needles was done during the treatment. At least six needles per patients and per treatment session were inserted. The time between the insertion and removal of needles was 20 min.

Relaxation

For the relaxation treatment, the method of guided imagery was applied. Guided imagery is a system of visualization (Posadzki and Ernst, 2011). During guided imagery relaxation, the patient’s state of consciousness is similar to one that occurs in meditative status. Patients were instructed to listen to a CD with relaxation music (Arcade TV-CD Ad Visser’s Brainsessions, track 3; Arcade TV-CD Ad Visser’s Brainsessions, Den Bosch, The Netherlands). Patients were sitting in an identical position like during the acupuncture treatment (i.e., on a relaxation chair) and listened to the audio CD by headphone. This was done in order to prevent unblinding of the assessor due to hearing of the relaxation music.

Table 1 Acupuncture points, anatomical localization and frequency of acupuncture points treated in acupuncture group.

Acupuncture point	Anatomical localization used frequency
GV 14	Midline of spine between C7 and T1 6
Huatuojiayi C1-C7	Lateral to midline of spine C1 to C7 26
GB 20	In depression between upper ends of sternocleidomastoid and trapezius muscle 21
SI 11	In the middle of the fossa infraspinatus 8
GB 21	Midway between C7 and the acromion 31
TE 15	At the medial end of the supraclavicular fossa 11
SI 14	Lateral to the lower border of T1 (medial border of the scapula) 1
BL 17	Lateral to the lower border of T7 23
SP 10	Superior to upper margin of patella, in the vastus medialis muscle 0
SI 3	On the ulnar side of wrist, between fifth metacarpal bone and carpal bone 6
BL 64	Inferior to the tuberosity of fifth metatarsal bone 4
TE 5	Proximal to dorsal wrist crease between ulna and radius 1
GB 41	In depression between fourth and fifth metatarsal bones 24
Shiqizhuixia	Low border of L5 26
Ear Zero point	Situated at the junction of the conchal ridge and the root of the ascending helix 20
Ear Jerome point	On the line in the postantitragal fossa, at the intersection with the scapha at the transition 13 to the lobule
Ear C0 point	Caudal area of the antihelix, against the antitragus 8

Outcome measurement

Primary outcome measurement included immediate activation of endogenous analgesia (i.e., conditioned pain modulation). Secondary outcome measurements included concomitant pain relief and reduced disability level. Patients were assessed immediately before and after treatment.

Endogenous analgesia

For assessing endogenous analgesia, the method examining the influence of the diffuse noxious inhibitory control system (or spatial summation) on temporal summation was applied. Recently, the term ‘conditioned pain modulation’ was recommended to describe the psychophysical paradigm of diffuse noxious inhibitory control system in humans (Yarnitsky et al., 2010). This term will be further used in this paper. The details and data supporting the test-retest reliability and validity of the experimental protocol for examining conditioned pain modulation are described elsewhere (Cathcart et al., 2009a,b).

The experimental pain assessments before and after each treatment were carried out by the same assessor and consisted out the following four-phase procedure (Fig. 3). The first phase comprised of determination of the pressure pain thresholds at the left trapezius belly (middle between processus spinosus of T1 and lateral part of the acromion) and at the left calf belly (in the middle of the calf’s proximal one-third) with an analogue Fisher algometer (Force Dial model FDK 40 Push Pull Force Gage, Wagner Instruments, Greenwich, CT, USA). In order to determine pressure pain

thresholds at each location, pressure was gradually increased at a rate of 1 kg/s until the subject reported first onset of pain (the subject said ‘stop’ at that point). The pressure pain threshold was taken as the mean of two consecutive (30 s in between) measurements.

The second phase comprised of examination of temporal summation: at each location, temporal summation was provoked by means of 10 consecutive pressure pulses (test stimulus) at the previously determined pressure pain threshold. To preclude bias originating from possible sensitization of pressure pain threshold assessment, temporal summation started 2 min after the last pressure pain threshold measurement. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the predetermined pressure pain threshold and maintained to that point for 1 s before being released. An interstimulus interval of 1 s was taken. The subjects were asked to rate the intensity and unpleasantness of the pain of the first, fifth and 10th pressure pulse on a numerical rating scale (0 = no pain to 10 = worst possible pain). Afterwards, a rest period of 5 min was allowed before investigating conditioned pain modulation.

After the temporal summation procedure, the mechanism of conditioned pain modulation was induced by inflating an occlusion cuff (conditioning stimulus) at the subject’s right arm to a painful intensity (phase 3). The occlusion cuff was inflated at a rate of 20 mmHg/s until ‘the first sensation of pain’ was reported. This cuff inflation was maintained for 30 s. The subject was asked to rate the pain intensity, as a result of cuff inflation at the right arm, on a numerical rating scale (0 = no pain to 10 = worst possible pain). Next, the cuff inflation was increased or decreased until pain intensity at the left arm was rated as 3/10 on the verbal rating scale. The above mentioned temporal summation procedure was then repeated during maintenance of the cuff inflation and relaxation of the right arm (phase 4; Cathcart et al., 2009a,b).

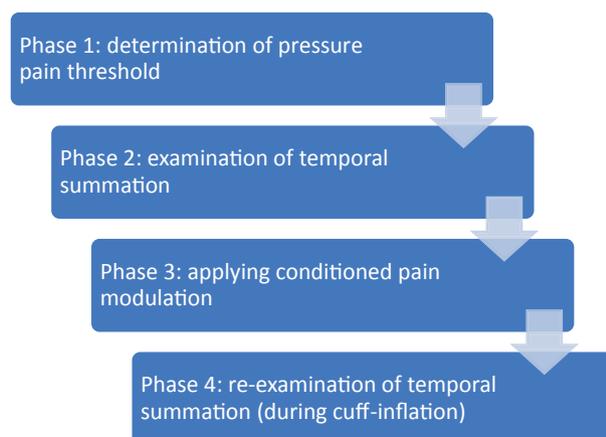


Figure 3 Four-phase protocol for the measurement of endogenous analgesia.

Concomitant pain relief and reduced disability level

Before and after each treatment self-reported measurements were used to assess symptom severity (including pain) and disability. The *Neck Disability Index* was developed in 1991 as a modification of the *Oswestry Back Pain Index* and was the first instrument designed to assess self-rated disability in patients with neck pain (Vernon and Mior, 1991; Vernon, 2008). The *Neck Disability Index* is scored from 0 (good function) to 50 (poor function) and when multiplied by two the percentage of disability can be obtained. The

Neck Disability Index is a valid and reliable instrument, sensitive to measure changes within a population of patient with neck pain (Vernon and Mior, 1991; Vernon, 2008).

The *Whiplash Associated Disorders Symptom List* is a self-reported measure for assessing symptom severity in WAD patients. The questionnaire is composed of the most frequently reported WAD symptoms in the literature and some autonomic symptoms. Every symptom is presented by a visual analogue scale (100 mm), a method that is known for its validity and reliability (Ligjaerde and Foreland, 1998). The WAD symptom has a high internal consistency (Cronbach $\alpha = 0.92$) (Van Oosterwijk et al., 2011).

Statistics

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS Inc., Chicago, IL USA). Appropriate descriptive statistics were used. The normality of data was examined using the one-sample Kolmogorov–Smirnov test. Variables that were not normally distributed were analysed using nonparametric statistics. Baseline group comparability was examined using Fisher's exact test (gender) and independent samples *t*-testing for the remaining variables (or the Mann–Whitney *U*-test when the variable was not normally distributed). Pre- versus post-treatment data per treatment were analysed using paired samples *t*-testing. Two-factor repeated-measures analyses of variances (ANOVAs; group \times time interaction) were used to identify a treatment effect on the dependent variables (i.e., conditioned pain modulation, symptom severity, neck disability index total scores, etc.). In order to account for missing data, all analyses were performed using the 'last observation carried forward' method for intention-to-treat analysis. The level of significance was set at $p < 0.05$, but when appropriate adjusted to the 0.01 level to account for potential type I errors.

Results

Demographic characteristics of the study participants and comparability between groups

Patient recruitment and data collection took place between October 2010 and July 2011; the trial was ended when the required number of patients had completed the trial. Thirty-nine patients with chronic WAD (28 women and 11 men) were randomized into two groups. Twenty participants entered group 1,

Table 2 Baseline characteristics of the two groups.

Variable	Group 1	Group 2	<i>p</i> -value*
	(mean \pm SD)	(mean \pm SD)	
	<i>n</i> = 20	<i>n</i> = 19	
Neck Disability Index	46.7 \pm 10.7	42.6 \pm 13.3	0.297
Neck pain (VAS)	51.2 \pm 24.4	51.4 \pm 22.5	0.971
Headache (VAS)	45.5 \pm 32.2	34.5 \pm 32.6	0.294
Dizziness (VAS)	29.8 \pm 34.7	16.5 \pm 25.1	0.284
Concentration difficulties (VAS)	41.9 \pm 29.5	33.6 \pm 26.9	0.367
Neck mobility (VAS)	45.3 \pm 28.1	44.0 \pm 24.7	0.879
Trouble falling asleep (VAS)	41.3 \pm 30.9	30.2 \pm 27.4	0.246
Trouble staying asleep (VAS)	46.1 \pm 30.3	37.4 \pm 30.9	0.384
Hypersensitivity for bright light (VAS)	49.9 \pm 33.2	35.0 \pm 32.7	0.164
Sweating (VAS)	46.3 \pm 32.2	32.2 \pm 25.8	0.140
PCS helplessness	10.5 \pm 5.7	9.7 \pm 5.6	0.561
PCS magnification	3.3 \pm 2.9	2.4 \pm 1.8	0.267
PCS rumination	8.3 \pm 4.4	6.9 \pm 4.3	0.330
PCS total score	22.1 \pm 11.8	18.9 \pm 10.3	0.396
PVAQ	40.9 \pm 14.2	38.7 \pm 14.4	0.642
TSK	40.0 \pm 8.5	41.4 \pm 8.5	0.631

*The *p*-values are obtained from the independent samples *t*-testing, except for dizziness for which it was obtained from a Mann–Whitney *U*-test. PCS, pain catastrophizing scale; PVAQ, pain vigilance and awareness questionnaire; SD, standard deviation; TSK, Tampa scale kinesiophobia; VAS, visual analogue scale expressed in mm.

implying that they received acupuncture followed by relaxation. The remaining 19 participants received relaxation followed by acupuncture (group 2). In group 1, all patients completed the trial. In group 2, one patient did not return for the second treatment session. The time since whiplash trauma ranged between 6 months and 17 years (mean 4 ± 4 years), and the age ranged between 23 and 57 years (mean 41 ± 10 years). There were no differences in age (independent *t*-test; $p = 0.417$), gender distribution (Fisher's exact test; $p = 1.00$) or time since whiplash (independent *t*-test; $p = 0.532$) between groups. At baseline, the two groups were comparable for disability levels (Neck Disability Index total scores), symptom severity (i.e., neck pain, dizziness, headache, concentration difficulties, neck mobility, sleep disturbances, sweating and hypersensitivity to bright light), pain catastrophizing (i.e., rumination, magnification and helplessness), pain hypervigilance and kinesiophobia (independent *t*-test; $p > 0.05$) (Table 2).

Does acupuncture results in immediate relief in WAD-related symptoms and disability levels?

Disability and pain relief were defined as secondary outcome measures. Looking at the within-group pre-

Table 3 Outcome of the repeated measures ANOVA presenting the effects of acupuncture ($n = 39$) versus relaxation ($n = 39$) on the self-reported measures (intention-to-treat analysis).

Variable	Pre-acupuncture (mean \pm SD)	Post-acupuncture (mean \pm SD)	Pre-relaxation (mean \pm SD)	Post-relaxation (mean \pm SD)	Time \times group interaction effects (F -value; p -value)
Neck Disability Index	44.8 \pm 11.6	42.4 \pm 12.0	44.5 \pm 11.7	42.7 \pm 13.2	0.000; 0.988
Neck pain (VAS)	49.1 \pm 26.5	42.1 \pm 26.6	50.6 \pm 22.7	47.0 \pm 26.8	0.346; 0.588
Headache (VAS)	39.8 \pm 34.1	32.2 \pm 30.6	39.8 \pm 30.8	35.1 \pm 31.9	0.044; 0.835
Dizziness (VAS)	23.9 \pm 29.9	22.2 \pm 29.7	22.0 \pm 28.4	24.2 \pm 30.3	0.000; 0.997
Concentration difficulties (VAS)	39.2 \pm 30.1	39.2 \pm 31.0	40.2 \pm 27.0	36.9 \pm 27.0	0.012; 0.914
Neck mobility (VAS)	48.7 \pm 25.7	42.7 \pm 24.3	47.8 \pm 24.3	45.1 \pm 26.7	0.023; 0.880
Trouble falling asleep (VAS)	35.0 \pm 29.0	28.7 \pm 26.8	30.0 \pm 28.5	25.1 \pm 25.0	0.488; 0.487
Trouble staying asleep (VAS)	41.1 \pm 30.1	34.6 \pm 27.8	36.7 \pm 29.7	32.8 \pm 28.4	0.232; 0.632
Hypersensitivity for bright light (VAS)	44.2 \pm 33.9	38.9 \pm 32.7	37.2 \pm 31.8	36.5 \pm 31.2	0.417; 0.520
Sweating (VAS)	36.5 \pm 32.0	32.0 \pm 30.1	36.5 \pm 27.7	32.9 \pm 28.4	0.005; 0.943

Comparisons were performed using two-way repeated measures ANOVA (time \times group interaction). ANOVA, analysis of variance; SD, standard deviation; VAS, visual analogue scale expressed in mm.

versus post-acupuncture comparisons, immediate improvements in neck disability, neck pain, headache, sweating and hypersensitivity to bright light were observed (paired t -test; $p < 0.05$), but no changes in dizziness, concentration difficulties or neck mobility were found (paired t -test; $p > 0.05$). When comparing pre- versus post-relaxation data, an immediate amelioration in sweating was found (paired t -test; $p < 0.05$), but no changes in any of the remaining main whiplash symptoms (like neck pain, headache, hypersensitivity to bright light or neck disability) (paired t -test; $p > 0.05$). However, when comparing the effects of acupuncture versus relaxation, no differences were observed with respect to the change in neck disability, neck pain, headache, dizziness, concentration difficulties, neck mobility, hypersensitivity to bright light or sweating (ANOVA time \times group interactions: all p -values > 0.05) (Table 3).

Does acupuncture versus relaxation results in immediate activation of conditioned pain modulation and reduction in temporal summation of pressure pain?

Conditioned pain modulation was defined as the primary outcome. Local pressure pain sensitivity decreased significantly more following acupuncture compared with relaxation (ANOVA time \times group interactions; $p < 0.001$), both in the neck and at a site distinct from the painful region (i.e., the calf). Likewise, compared with relaxation acupuncture resulted in stronger improvements in local pressure pain sensitivity during conditioned pain modulation (i.e., during cuff inflation) in the neck and the calf (ANOVA time \times group interactions; $p < 0.001$) (Table 4). When analysing the data of conditioned pain modulation on temporal summation, no changes were observed fol-

Table 4 Outcome of the repeated measures ANOVA displaying the effects of acupuncture ($n = 38$) versus relaxation ($n = 39$) on local pressure pain sensitivity, CPM and TS of pressure pain (intention-to-treat analysis).

Variable	Pre-acupuncture (mean \pm SD)	Post-acupuncture (mean \pm SD)	Pre-relaxation (mean \pm SD)	Post-relaxation (mean \pm SD)	Time \times group interaction effects (F -value; p -value)
Pain sensitivity trapezius	3.92 \pm 1.72	3.16 \pm 1.60	4.13 \pm 1.74	4.10 \pm 1.88	421; <0.001
Pain sensitivity trapezius CPM	3.84 \pm 1.76	2.84 \pm 1.32	3.95 \pm 1.82	3.77 \pm 1.60	425; <0.001
Pain sensitivity calf	3.74 \pm 1.98	3.53 \pm 1.86	3.59 \pm 2.11	3.46 \pm 1.76	307; <0.001
Pain sensitivity calf CPM	3.55 \pm 2.02	3.32 \pm 1.99	3.67 \pm 2.08	3.64 \pm 1.77	288; <0.001
CPM on TS trapezius	0.37 \pm 1.30	0.47 \pm 1.06	0.72 \pm 1.43	0.59 \pm 1.23	1.09; 0.30
CPM on TS calf	0.50 \pm 1.37	0.18 \pm 1.29	0.23 \pm 1.81	-0.03 \pm 1.31	0.835; 0.364
TS trapezius pre-CPM	1.3 \pm 0.755	0.93 \pm 0.718	1.2 \pm 0.700	1.1 \pm 0.568	0.008; 0.928
TS trapezius during CPM	1.1 \pm 0.737	0.85 \pm 0.793	0.99 \pm 0.729	0.86 \pm 0.772	0.281; 0.597
TS calf pre-CPM	1.0 \pm 0.925	0.86 \pm 0.678	0.97 \pm 0.724	0.81 \pm 0.686	0.157; 0.693
TS calf during CPM	0.82 \pm 0.775	0.76 \pm 0.724	0.81 \pm 0.739	0.78 \pm 0.735	0.012; 0.913

Comparisons were performed using two-way repeated measures ANOVA (time \times group interaction). TS data are based on the SDs of the measurements to reflect variability; using the mean values or the raw data did not change the outcome of the analysis (data not shown). ANOVA, analysis of variance; CPM, conditioned pain modulation; SD, standard deviation; TS, temporal summation.

lowing either acupuncture or relaxation for either anatomical locations (calf and neck; ANOVA $p > 0.05$). When comparing the effects (ANOVA time \times group interactions) of acupuncture versus relaxation, no differences in conditioned pain modulation on temporal summation of pressure pain were observed for either anatomical locations (calf and neck; $p > 0.05$) (Table 4). Temporal summation improved (i.e., decreased) following acupuncture for both anatomical locations (ANOVA $p < 0.01$), but remained unchanged following relaxation (ANOVA $p > 0.05$). However, when comparing the effects between acupuncture and relaxation on temporal summation, again no between group differences were found (ANOVA time \times group interactions; $p > 0.05$) (Table 4).

Discussion

This study demonstrated that in patients with chronic WAD, one treatment session of acupuncture compared with one treatment session of relaxation results in stronger improvements in local pressure pain sensitivity in the neck and at a site distinct from the painful region (i.e., the calf). The observation of improved pressure pain sensitivity in the neck and the calf accounts for measurements with and without concomitant ischemic and painful cuff inflation at the right upper arm, suggesting an effect of acupuncture on endogenous analgesia. However, the effects of acupuncture on conditioned pain modulation (i.e., conditioned pain modulation effect on temporal summation) did not differ from that seen in response to relaxation treatment. Likewise, no differences were found between acupuncture and relaxation on temporal summation of pressure pain, either in the painful region (i.e., the neck) or at a distinct location (i.e., the calf).

As evidence in support of central sensitization as a cardinal feature of chronic WAD is cumulating (Sterling et al., 2002, 2003; Banic et al., 2004; Herren-Gerber et al., 2004), studies examining whether treatments are able to tackle the process of central sensitization in patients with chronic WAD are emerging. Central sensitization entails a lack of endogenous analgesia, in addition to many other dysfunctions of central nervous system processing of sensory stimuli. Our group has previously shown a lack of endogenous analgesia following exercise (Van Oosterwijck et al., 2012) and a dysfunctional conditioned pain modulation in patients with chronic WAD (Daenen et al., unpublished data). Using conditioned pain modulation as an outcome measure in randomized trials, as done here, provides opportunities to examine whether treat-

ments are able to activate endogenous analgesia in patients with chronic WAD. Activation of endogenous analgesia might be a crucial step towards diminishing the hypersensitivity of the central nervous system in patients with chronic WAD. Conditioned pain modulation on temporal summation of pressure pain did not respond to either acupuncture or relaxation, which is in line with finding that acupuncture does not activate analgesic effects comparable with diffuse noxious inhibitory control in healthy and pain-free volunteers (Schliessbach et al., 2012) (conditioned pain modulation was previously referred to as diffuse noxious inhibitory control). Yet, local pressure pain sensitivity did improve in response to acupuncture. The fact that local pressure pain sensitivity improved not only in the neck, but also at a site distinct from the painful region, suggests that acupuncture might activate endogenous analgesia in patients with chronic WAD. This notion is further supported by the finding of improved pressure pain sensitivity for measurements with concomitant ischemic and painful cuff inflation at the right upper arm as well (i.e., during conditioned pain modulation stimulation). To the best of our knowledge, this is the first study examining the effects of acupuncture treatment on endogenous analgesia in patients with chronic WAD.

In addition to the lack of endogenous analgesia, increased temporal summation of second pain may contribute to the development or maintenance of central sensitization in patients with chronic WAD. Indeed, central sensitization is characterized by increased activity of pain facilitation pathways, which entails temporal summation of secondary pain or wind-up (Meeus and Nijs, 2007; Staud et al., 2007). Although temporal summation of pressure pain improved following acupuncture and remained unchanged following relaxation, there was no time \times group interaction.

These findings call for further work in this area. It seems appropriate to study the effects of a comprehensive acupuncture treatment (i.e., several sessions of acupuncture spread over a longer period) on local pressure pain sensitivity, conditioned pain modulation and temporal summation of pressure pain in patients with chronic WAD. This applies to further studying of the effects of a comprehensive acupuncture treatment on clinical outcomes (disability and symptoms) as well, as more symptoms improved from pre- to post-acupuncture as compared with the relaxation treatment. The study data presented here will aid in designing future studies in this area, including accurate calculation of the required sample size. Indeed, valid sample size estimations can only be made on the

basis of previous results of studies examining the effects of identical treatments in a similar population, using identical outcome measures. Consequently, the a priori sample size calculation as presented here might be questioned. Still, the study is surely not underpowered for the statistical significant findings.

Addressing the mechanism of action, acupuncture is a complex somatosensory stimulation resulting in activation of a high number of somatosensory afferents. Such stimulation typically results in release of endogenous opioids (Han, 2004; Lin and Chen, 2008; Wang et al., 2008; Harris et al., 2009). Activation of μ -opioid receptors has inhibitory effects, including presynaptic inhibition of primary nociceptive afferents and postsynaptic inhibition of projecting neurons (Kosek, 2009). In addition, acupuncture stimulates a complex network of brain regions including the nucleus raphe magnus, periaqueductal grey, locus coeruleus, amygdala, anterior cingulate anterior and nucleus caudatus (Dhond et al., 2008; Zhao, 2008), and changes the activity in the autonomic nervous system (Dhond et al., 2008; Lin and Chen, 2008; Huang and Tsai, 2009; Kim and Bae, 2010). However, this mechanism of action for acupuncture has been established in animal studies and studies in healthy people. Based on the findings from this study, it is tempting to speculate that acupuncture might activate similar brain-orchestrated mechanism in patients with chronic WAD as observed in animals and healthy people. However, no direct brain observations were done here, precluding to draw firm conclusions with respect to brain mechanisms.

In addition to the above provided interpretation of the study findings in the framework of central sensitization, one should consider alternative explanations as well. For instance, the patients may have had strong expectations regarding the effects of acupuncture, stronger than those associated with relaxation. Expectation of pain relief activates endogenous opioid release and hence, endogenous analgesia (Levine et al., 1978), a mechanism frequently referred to as placebo analgesia (Lyby et al., 2011). In this respect, future studies in the area should control their findings for patients' expectations regarding the treatment effects. Such an approach is preferred over using a placebo control group. Indeed, numerous placebo-controlled studies are available, and studies using an effective treatment as control group are superior over placebo-controlled designs.

The present study is the first to examine the potential benefits of acupuncture in the treatment of chronic WAD. As this was not a clinical trial, it is impossible to conclude whether or not acupuncture is

effective in the treatment of chronic WAD. Further study is required. This study aimed at examining the mechanisms of action of acupuncture versus relaxation, rather than examining its effectiveness. Relaxation was used as a non-needling control intervention to shift research priorities away from asking placebo-related questions (Hopton and MacPherson, 2010). Still, it is important to emphasize that both treatments appear to be well-tolerated by patients with chronic WAD, as they did not result in statistically significant increases in any of the major WAD symptoms or disability level. Moreover, positive short-term effects on symptom severity and disability level were observed when analysing the within-group data, but these changes were similar in both treatment conditions. Future studies should examine the effectiveness of acupuncture and relaxation for the treatment of chronic WAD.

In conclusion, it was shown that one session of acupuncture treatment results in acute improvements in pressure pain sensitivity in the neck and calf of patients with chronic WAD. Acupuncture had no effect on conditioned pain modulation or temporal summation of pressure pain. Both acupuncture and relaxation appear to be well-tolerated treatments for people with chronic WAD. Further work is required to examine whether acupuncture activates endogenous analgesia in patients with chronic WAD.

References

- Banic, B., Petersen-Felix, S., Andersen, O.K., Radanov, B.P., Villiger, P.M., Arendt-Nielsen, L., Curatolo, M. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 107(1–2), 7–15.
- Cathcart, S., Winefield, A., Lushington, K., Rolan, P. (2009b). Noxious inhibition of temporal summation is impaired in chronic tension-type headache. *Headache* 50, 403–412.
- Cathcart, S., Winefield, A.H., Rolan, P., Lushington, K. (2009). Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Res Manage* 14(6), 433–438.
- Curatolo, M., Arendt-Nielsen, L., Petersen-Felix, S. (2004). Evidence, mechanisms, and clinical implications of central hypersensitivity in chronic pain after whiplash injury. *Clin J Pain* 20(6), 469–476.
- Dhond, R.P., Yeh, C., Park, K., Kettner, N., Napadow, V. (2008). Acupuncture modulates resting state connectivity in default and sensorimotor brain networks. *Pain* 136, 407–418.
- Fu, L.M., Li, J.T., Wu, W.S. (2009). Randomized controlled trials of acupuncture for neck pain: Systematic review and meta-analysis. *J Altern Complement Med* 15, 133–145.
- Han, J.S. (2004). Acupuncture and endorphins. *Neurosci Lett* 361, 258–261.
- Harris, R., Zubieta, J.K., Scott, J., Napadow, V., Gracely, R.H., Clauw, D.J. (2009). Traditional Chinese acupuncture and placebo(sham) acupuncture are differentiated by their on μ -opioid receptors(MORs). *Neuroimage* 47(3), 1077–1085.

- Heine, H. (1988). Anatomical structure of acupoints. *J Tradit Chin Med* 8(3), 207–212.
- Herren-Gerber, R., Weiss, S., Arendt-Nielsen, L., Petersen-Felix, S., Di Stefano, G., Radanov, B.P., Curatolo, M. (2004). Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. *Pain Med* 5, 366–376.
- Hopton, A., MacPherson, H. (2010). Acupuncture for chronic pain: Is acupuncture more than an effective placebo? A systematic review of pooled data from meta-analyses. *Pain Pract* 10, 94–102.
- Huang, C.S., Tsai, Y.F. (2009). Somatosympathetic reflex and acupuncture-related analgesia. *Chin J Physiol* 5(Suppl), 345–357.
- Irnich, D., Behrens, N., Gleditsch, J.M., Stör, W., Schreiber, M.A., Schöps, P., Vickers, A.J., Beyer, A. (2002). Immediate effects of dry needling and acupuncture at distant points in chronic neck pain: Results of a randomized, double-blind, sham-controlled crossover trial. *Pain* 99(1–2), 83–89.
- Irnich, D., Behrens, N., Molzen, H., König, A., Gleditsch, J., Krauss, M., Natalis, M., Senn, E., Beyer, A., Schöps, P. (2001). Randomised trial of acupuncture compared with conventional massage and ‘sham’ laser acupuncture for treatment of chronic neck pain. *BMJ* 322(7302), 1574–1578.
- Jull, G., Sterling, M., Kenardy, J., Beller, E. (2007). Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? A preliminary RCT. *Pain* 129, 28–34.
- Kim, S.K., Bae, H. (2010). Acupuncture and immune modulation. *Auton Neurosci* 157(1–2), 38–41.
- Kosek, E. (2009). Medical management of pain. In *Mechanisms and Management of Pain for the Physical Therapist*, Chapter 12. in K. Sluka, ed. (Seattle, WA: IASP Press) pp. 231–255.
- Levine, J.D., Gordon, N.C., Fields, H.L. (1978). The mechanism of placebo analgesia. *Lancet* 2, 654–657.
- Ligjaerde, O., Foreland, A.R. (1998). Direct assessment of improvement in winter depression with a visual analogue scale: High reliability and validity. *Psychiatry Res* 3(81), 387–392.
- Lin, J.G., Chen, W.L. (2008). Acupuncture analgesia: A review of its mechanisms of actions. *Am J Chin Med* 36, 635–645.
- Linde, K., Streng, A., Jurgens, S., Hoppe, A., Brinkhaus, B., Witt, C., Wagenpfeil, S., Pfaffenrath, V., Hammes, M., Weidenhammer, W., Willich, S., Melchart, D. (2005). Acupuncture for patients with migraine: A randomized controlled trial. *JAMA* 293, 2118–2125.
- Lyby, P.S., Aslaksen, P.M., Flaten, M.A. (2011). Variability in placebo analgesia and the role of fear of pain – An ERP study. *Pain* 152, 2405–2412.
- MacPherson, H., Altman, D., Hammerschlag, R., Youping, L., Taixang, W., White, A., Moher, D.; and on behalf of the STRICTA Revision Group(2011). Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement.
- Margolis, R.B., Tait, R.C., Krause, S.J. (1986). A rating system for use with patient pain drawings. *Pain* 24(1), 57–65.
- Meeus, M., Nijs, J. (2007). Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 26, 465–473.
- Meeus, M., Nijs, J., Van De Wauwer, N., Toeback, L., Truijien, S. (2008). Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study. *Pain* 139, 439–448.
- Nijs, J., Inghelbrecht, E., Daenen, L., Hachimi-Idrissi, S., Hens, L., Willems, B., Roussel, N., Cras, P., Wouters, K., Bernheim, J. (2011). Recruitment bias in chronic pain research: Whiplash as a model. *Clin Rheumatol* 30, 1481–1489.
- Nijs, J., Van Houdenhove, B. (2009). From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice (Masterclass). *Manual Ther* 14, 3–12.
- Nijs, J., Van Houdenhove, B., Oostendorp, R.A.B. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice (Masterclass). *Man Ther* 15, 135–141.
- Nijs, J., Van Oosterwijck, J., De Hertogh, W. (2009). Rehabilitation of chronic whiplash: Treatment of cervical dysfunctions or chronic pain syndrome? *Clin Rheumatol* 28, 243–251.
- Posadzki, P., Ernst, E. (2011). Guided imagery for musculoskeletal pain: A systematic review. *Clin J Pain* 27(7), 648–653.
- Schliessbach, J., van der Klift, E., Siegenthaler, A., Arendt-Nielsen, L., Curatolo, M., Streitberger, K. (2012). Does acupuncture needling induce analgesic effects comparable to diffuse noxious inhibitory controls? *Evid Based Complement Alternat Med* 2012, 785613.
- Spitzer, W.O., Skovron, M.L., Salmi, L.R., Cassidy, J.D., Duranceau, J., Suissa, S., Zeiss, E. (1995). Scientific monograph of the Quebec Task Force on Whiplash-associated disorders: Redefining ‘whiplash’ and its management. *Spine* 20(8 Suppl), 1S–73S.
- Staud, R., Craggs, J.G., Robinson, M.E., Perlstein, W.M., Price, D.D. (2007). Brain activity related to temporal summation of C-fiber evoked pain. *Pain* 129, 130–142.
- Sterling, M., Jull, G., Vicenzino, B., Kenardy, J. (2003). Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain* 104, 509–517.
- Sterling, M., Treleaven, J., Edwards, S., Jull, G. (2002). Pressure pain thresholds in chronic whiplash associated disorder: Further evidence of altered central pain processing. *J Musculoskelet Pain* 10, 69–81.
- Van Oosterwijck, J., Nijs, J., Meeus, M., Truijien, S., Craps, J., Van Den Keybus, N., Paul, L. (2011). Pain neurophysiology education improves cognitions, pain thresholds and movement performance in people with chronic whiplash: A pilot study. *J Rehabil Res Dev* 48(1), 43–58.
- Van Oosterwijck, J., Nijs, J., Meeus, M., Van Loo, M., Paul, L. (2012). Lack of endogenous pain inhibition during exercise in people with chronic whiplash associated disorders: An experimental study. *J Pain* 13, 242–254.
- Vernon, H. (2008). The Neck Disability Index: State-of-the-art, 1991–2008. *J Manipulative Physiol Ther* 31, 491–502.
- Vernon, H., Mior, S. (1991). The Neck Disability Index: A study of reliability and validity. *J Manipulative Physiol Ther* 14, 409–415.
- Wang, S.M., Kain, Z.N., White, P. (2008). Acupuncture analgesia: I. The scientific basis. *Anesth Analg* 106, 602–610.
- White, P., Lewith, G., Berman, B., Birch, S. (2002). Reviews of acupuncture for chronic neck pain: Pitfalls in conducting systematic reviews. *Rheumatology (Oxford)* 41, 1224–1231.
- Yarnitsky, D., Arendt-Nielsen, L., Bouhassira, D., Edwards, R.R., Fillingim, R.B., Granot, M., Hansson, P., Lautenbacher, S., Marchand, S., Wilder-Smith, O. (2010). Conditioned Pain Modulation (CPM): Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 14, 339.
- Zhao, Z.Q. (2008). Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol* 85, 355–375.
- Zylka, M.J. (2010). Needling adenosine receptors for pain relief. *Nat Neurosci* 13, 783–784.