Pain Medicine

Pain Medicine 2011; 12: 110–117
Wiley Periodicals, Inc.

Neuropathic Pain Mechanisms in Patients with Chronic Sports Injuries: A Diagnostic Model Useful in Sports Medicine?

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Abstract

Objective. The pathophysiology of chronic sports injuries such as overuse or tendinopathy remains largely unknown. With this exploratory study, we aim to detect signs of sensitization of the nervous system. Sensitization is an indication of the involvement of neuropathic mechanisms in patients with chronic sports injuries.

Design. Sensory descriptors were assessed by means of a neuropathic pain questionnaire (DN4-interview) and by three methods of sensory testing. The test results were integrated in a scoring system.

Setting. Patients were recruited from an outpatient clinic of a University Medical Centre and at primary care physical therapy practices.

Patients. Fifteen athletes with a unilateral chronic sports injury were included.

Outcome Measures. All subjects filled out the seven-items of the DN4-interview to assess sensory descriptors. Next, the presence of brush-evoked allodynia was assessed and pain thresholds with Von Frey monofilaments and a pressure algometer were measured in all patients to determine signs of sensitization.

Results. Based on the scoring system, in 4 out of 15 patients (27%) the presence of sensitization could be detected. In two other patients, signs of hypoalgesia were observed.

Conclusions. The involvement of sensitization as an explanation for the pain in chronic sports injuries is credible in a considerable proportion of patients. With respect to treatment, the establishment of such neuropathic pain mechanisms is of clinical significance.

Key Words. Chronic Sports Injuries; Sensitization; Allodynia; Hypoalgesia; Diagnostic

Introduction

The prevalence of sports injuries is high; Hootman et al. describe incidence rates of collegiate sports injuries of 13.8 in games and 4.0 in training per 1,000 athletes-exposure [1]. Of the 14 million sports injuries per year in the Netherlands, about 14% become chronic [2]. Tendinopathies [3], shoulder disorders [4], and patellofemoral pain syndrome [5] are common sports injuries that tend to become chronic.

Chronic sports injuries are stressful to athletes and difficult to treat. In the literature, several explanations have been presented that explain the persistence of pain in chronic sports injuries, however the etiology and pathophysiological mechanisms of chronic sports injuries have largely remained unknown [5–7]. Chronic sports injuries can also be referred to as "overuse" injuries or tendinopathy [8]. Throughout the last decade, ideas regarding the pathophysiology of chronic sports injuries vary; from inflammatory and degenerative causes to a failing healing response [9,10]. Jensen et al. investigated the presence of neuropathic pain mechanisms in 91 patients with chronic patellofemoral pain syndrome [5]. They measured sensory detection thresholds by means of quantitative sensory testing (QST) and found significant hypoesthesia on the affected side as opposed to the patients' own unaffected, contralateral side. Recently, Webborn proposed that neuropathic pain mechanisms are a possible source of pain in tendinopathies [11].

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" [12]. In this definition, two major groups can be recognized; a group with *lesions* in the nervous system, such as in patients with diabetic polyneuropathy or postherpetic neuralgia, and a group with *dysfunction* of the nervous system, such as in patients with fibromyalgia and in subgroups of patients with chronic low back pain. Dysfunction of the nervous system could be an explanation for the pain in chronic sports injuries.

The presence of sensitization, in particular modification—a more or less irreversible state of hyperexcitability due to structural changes within neural networks—can be considered as an important neuropathic pain mechanism [13]. Sensitization results in the clinical symptoms *allodynia*—pain due to a stimulus which does not normally provoke pain, e.g., pain upon the light stroking of the skin or pain during normal training or exercise, and *hyperalgesia*—an increased response to a stimulus which is normally painful, e.g., intense pain following a heat stimulus [12,14,15]. The identification of signs of sensitization is important for the management of chronic sports injuries, i.e., education, medication, and treatment modalities.

If nociception and inflammation cannot be regarded as plausible causes for a chronic sport injury, it is reasonable to consider the possibility that sensitization mechanisms may contribute to the persistence of the pain. Currently, little is known whether, or to which degree, such sensitization mechanisms may account for the chronicity of sports injuries. There is no clinical gold standard for the identification of sensitization mechanisms in patients with chronic pain. Although in research setting a quantitative sensory testing protocol has been described [16].

The primary goal of this exploratory study was to investigate if sensitization is a plausible explanation for pain in chronic sports injuries and to introduce a diagnostic model that aids in detecting signs of sensitization in these patients. We aimed to use methods that are simple, and can be employed in day to day sports-medical practice. We use the results from our diagnostic model to also investigate our secondary goal; whether patients in whom sensitization mechanisms have been identified, have suffered from previous injury more frequently; possibly reflecting alterations of neural networks, i.e., sensitization, due to repetitive injury [17].

Methods

Patient Characteristics

The athletes were recruited from the Centre for Sports Medicine of the University Medical Centre Groningen and from primary care physical therapy practices in the North of the Netherlands. All sports physicians and (sports) physical therapists were informed regarding the study by means of a letter and were requested to ask athletes that matched the inclusion criteria to participate in the study (Table 1). An important first step in identifying sensitization is to rule out nociception or inflammation as much as possible. Although it is currently impossible to rule out nociceptive or inflammatory causes of a patient's pain completely, we have minimized the chance of nociception and inflammation through the inclusion of patients with pain that lasts for 3 months or longer (past the time one would normally expect nociception to have healed) [12].

Table 1 Inclusion and exclusion criteria

Inclusion criteria
—Injury occurred during sports game or training
—Age 18 to 65 year
—Nociception or inflammation as possible cause for pain ruled out by physician.
—Pain for more than 3 months
—Written informed consent
Exclusion criteria
—Neurological diseases, know neurological deficits or sensory changes.
—Co-morbidity (diabetes, chronic pain syndrome, cancer, skin infections)
—Previous surgery (arthroscopy) in the area of pain or lower back (in case of pain in the lower extremities)
—Medication interfering with pain and sensation detection
—Mental illness

Prior to participation, the athletes received an informatory letter and signed an informed consent form. The study was executed according to the medical ethical regulations of our hospital, applicable for patients who undergo standard diagnostic procedures and receive standard medical care. From all participating athletes, sociodemographic data (age, gender), history of sports activity (kind of sport, number of years active in that sport) and type and duration of injury, as well as frequency of previous injury (never, seldom, sometimes, regularly, often, very often) were gathered. All athletes filled out a pain drawing and marked their most painful spot. The diagnostic model integrates sensory descriptors (DN4-interview) and three different methods of sensory testing that will be outlined below.

Sensory Descriptors

The "classical" DN4-questionnaire (Douleur Neuropathique 4 questions) contains 10 items. The first seven items, called the DN4-interview, are sensory descriptors that may be applicable to the patient's pain. The other three items are related to physical examination signs (touch hypoestesia, pricking hypoesthesia and brushing). For each positive item on the DN4, one point is assigned. In this study, we only used the DN4-interview (see

Table 2 DN-4 interview in English (and Dutch)

Does the pain have the following characteristics?	
Burning (Branderig gevoel)	Yes / No
Painful cold (Pijnlijk koudegevoel)	Yes / No
Electric shocks (Electrische schokken)	Yes / No
Is the pain associated with one or more of the following symptoms in the same area?	
Tingling (Tintelingen)	Yes / No
Pins and Needles (Prikken)	Yes / No
Numbness (Doof gevoel)	Yes / No
Itching (Jeuk)	Yes / No

The "classical" DN4-questionnaire also contains of the physical examination signs touch hypoesthesia, pricking hypoesthesia, and brushing.

Table 2). The cut-off score for neuropathic pain of the DN4-interview was set at three or more positive items. When results from the "classical" DN4-questionnaire are compared with the diagnoses of expert clinicians, the DN4 showed 83% sensitivity and 90% specificity. The DN4-interview demonstrated similar results [18,19].

Sensory Testing

We replaced 2 items of the DN4 related to physical examination tests; touch hypoestesia and pricking hypoesthesia, since our main interest was to assess sensitization not signs of hypoesthesia. To identify sensitization, three different algorithms of sensory testing were performed in all athletes, with which the three main subtypes of somatosensory afferent fibers (Aβ-, Aδ- and C-fiber) are stimulated. After identifying the most painful spot, a square of 1 cm^2 was drawn on the skin of the affected body part. On exactly the same spot on the nonaffected contralateral side, another 1 cm^2 was drawn. The clinical examination randomly started at either the ipsilateral or contralateral side. All tests were executed by two trained observers in a fixed sequence, i.e., brush, VFM, PPT. Between two successive stimuli, a standard period of 3 seconds was used to avoid temporal summation. Between the three forms of sensory testing, a period of 3 minutes rest was used [20].

In order to compare normal—unaffected—pain thresholds with pain thresholds in the skin area where the chronic sports injury was located, we used the same skin area on the contralateral side. This methodology is common practice in the field of quantitative sensory testing [21]. The examiner assesses sensory function on the affected side and compares the results with the nonaffected side in the same manner, under similar circumstances.

Aβ-fiber mediated allodynia was assessed by means of the light stroking of the skin with a soft brush. The brush was applied with a constant pressure with a single stroke of three seconds over approximately 3 cm in length over the skin, with a speed of 1 cm/s, repeated 3 times [16,22]. Athletes were asked to report if they felt pain during this test. When at least two out of three strokes were reported to be painful, the presence of brush-evoked allodynia was established. Brush-evoked allodynia in a patient with chronic pain is a sign of sensitization of pain modulating systems within the central nervous system [13,17].

Twenty Von Frey monofilaments (VFM) with increasing diameter were used to detect and measure Aδ fiber mediated allodynia. A kit consisting of 20 nylon VFM were used (Touch test™ North Coast Medical, Inc., Morgan Hill, LA, USA). The VFM are calibrated in a logarithmic scale from 0.008 to 300 g (0.08–2,943 mN) within a 5% standard deviation. Numbers on the VFM range from 1.65 to 6.65 and represent the common logarithm of 10 times the exerted force in milligrams. When applied on the skin, monofilaments exert a constant force as the filament bends. This bending reduces measurement artefacts that result from movements or trembling of the examiner's hand. The VFM were applied in increasing thickness until the athlete indicated that the monofilament induced pain thereby indicating that the pain threshold was reached. Each VFM was applied three times, with approximately 10 seconds between two successive stimuli, to avoid temporal summation [20].

The VFM was applied perpendicularly to the skin surface for approximately 2 seconds until a bending of 3–5 mm of the VFM was produced. Patients kept their eyes closed during the investigation to avoid visual feedback concerning the stimuli. The pain threshold was defined as the logarithmic number on the VFM in which at least two out of three applications on the affected side was reported as painful. This algorithm is referred to as the Method of Levels. The procedure was also performed on the contralateral side [21,23,24]. We chose not to integrate the assessment of a sensory perception threshold, in order to limit the amount of time needed to perform the examination [25].

In order to determine (C-fiber-mediated) deep pain sensitivity, a handheld algometer (Microfet Hoggan Health Industries: West Jordan, UT, USA) was used to measure pressure pain thresholds (PPT). The pressure algometer is a device with which a known force—calibrated in Newtons—that can be administered to the skin through a rubber disc at the end of the algometer. The algometer has been demonstrated to yield reliable and reproducible results [26,27]. By pushing the algometer, the force applied to the painful spot gradually increases. As soon as the athlete experienced a painful sensation, he/she said "stop"; the algometer was immediately released and the force was read from the display. The pressure pain threshold, measured in Newtons, is determined as the average of the last two, out of three, consecutive values.

Statistical Analyses

Sociodemographic data (age, gender), history of sports activity (kind of sport, number of years active in that sport)

and type and duration of injury, as well as frequency of previous injury are presented. The data of sensory testing (brush, VFM, PPT) and the outcomes of the DN4-interview are gathered.

We present a scoring system that integrates sensory descriptors and signs of sensitization mechanisms upon physical examination. However, in contrast with the DN4, the current system includes three simple methods of sensory testing, aimed to detect signs of sensitization. Furthermore, two of these methods allow quantification of sensory aberrations.

The scoring system is comparable to the DN4, since the scores of sensory descriptors of the DN4-interview and clinical signs from sensory testing are added to result in a maximum of 10 points. A cut-off score of 5 or higher is regarded to reflect the presence of sensitization in the patient tested. As stated above, maximally 7 points can be scored on the DN4-interview. We assigned one point to every method of sensory testing that is indicative for sensitization. In this manner, a maximum of 10 points can be scored. One point in our scoring system was assigned when brush evoked allodynia was present. With respect to both VFM and PPT testing, one point was assigned for each of these methods of QST when the pain threshold on the affected side was lower than on the contralateral side. For assigning these points, we did not discriminate between the size of the difference of sensory testing for the affected and nonaffected side. Using the Mann-Whitney *U*-test, the relation of the frequency of injury with signs of neuropathic pain (scored 5 points or higher) was analyzed. For all statistical calculations in this study, P values < 0.05 were considered significant.

Results

We included 15 patients with chronic sports injuries (Table 3). The population consisted of four men and eleven female athletes with a mean age of 32 years (SD 11, range 20–59 years) On average, athletes were active in sports for 10 years (SD 9.0 range 1–30 years). The injury had a mean duration of 121 weeks (range 12–676 weeks).

Four subjects (numbers 3, 4, 10, and 11) scored 5 points or higher with the current scoring system. The results of the DN4-interview and the three different algorithms of sensory testing for all 15 subjects are presented in Table 4, in Table 5 the assignment of points is depicted.

Subject numbers 1 and 13 scored 4 and 3 on the DN4-interview, respectively. Noteworthy, the results from QST in these subjects indicated the presence of *hypoalgesia*, as with both VFM and PPT testing increased pain thresholds were found on the affected side compared with the non-affected contralateral side.

For practical reasons, we refer to the group of subjects in whom signs of sensitization have been detected as the group with "sensitization mechanisms" (SM), and the group of remaining subjects as the group with "no-sensitization mechanisms" (n-SM). The reported frequency of injury between SM and n-SM; tended to be higher in the SM group, although this difference was not statistically significant; $P = 0.057$ (2-tailed).

Discussion

Using the current diagnostic model, we found that in 4 subjects (27%) of the small sample of 15, the presence of

Table 3 Socio-demographic characteristics of the population, type and history of injury, pain scores during rest and during sports

Nr.	Sports	Age	Gender	Site of Injury	Duration (weeks)	Pain Rest (NRS†)	Pain During Sports (NRS†)	Injury Frequency before Current Injury
1	Cycling	59	F	Lower-leg	52	8	2	Sometimes
2	Swimming	25	F	Shoulder	272	0	6	Never
3	Tennis	28	F	Shoulder	52	1	4	Often
4	Kickboxing	25	M	Knee	12	3	7	Sometimes
5	Figure skating	25	F	Knee	676	0	2	Seldom
6	Skating	20	F	Lower-leg	16	5	10	Seldom
7	Soccer	27	M	Ankle	12	5	10	Often
8	Fitness	26	M	Knee	104	0	9	Seldom
9	Basketball	21	F	Ankle	23	6	7	Sometimes
10	Gymnastics	22	F	Ankle	104	3	8	Very often
11	Tennis	31	F	Shoulder	40	0	2	Often
12	Soccer	46	M	Upper-leg	26	2	10	Sometimes
13	Fitness	32	F	Knee	364	7	8	Very often
14	Spinning	42	F	Lower-leg	12	4	9	Sometimes
15	Running	43	F	Knee	52	0	10	Sometimes

† NRS = Numeric Rating Scale.

Table 4 Results of 15 patients on the DN4-interview and sensory testing with brush, Von Frey monofilaments (VFM) and pressure algometer (PPT) on the affected and nonaffected side

	Injured side			Noninjured side			DN4-interview
Patient nr.	Brush 1 = allodynia	VFM† Log^{10}*force in mg	PPT‡ (Newton)	Brush	VFM† Log^{10}*force in mg	PPT‡ (Newton)	Score on 7-item DN4-interview
1	0	5.78	124	0	5.10	95	4
2	0	4.65	19.5	0	4.46	25.5	3
3	1	5.07	0	0	5.78	17.5	4
4	1	4.56	15.5	0	4.74	18	3
5	0	5.64	58.5	0	6.45	77	1
6	0	4.74	19.5	0	4.65	8	2
7	0	4.90	34.5	0	4.74	51.5	2
8	0	6.30	74	0	6.55	79	0
9	1	4.80	20	0	5.10	31.5	1
10	1	5.30	3.5	0	5.67	24.5	3
11	0	5.20	0	0	6.40	27	3
12	0	6.65	127	0	6.65	164	0
13	0	5.99	92.5	0	5.88	66	3
14	0	6.10	35	0	5.88	49.5	1
15	0	6.65	54.5	0	6.10	35	0

† VFM = Von Frey Monofilamenten; ‡ PPT = pain pressure threshold.

sensitization may play a role in the chronicity of sports injuries. Sensitization within the central nervous system reflects the involvement of neuropathic pain mechanisms in these patients. In two more subjects, who scored 3 and 4 points on the DN4-interview, signs of *hypoalgesia* were found. The hypoalgesia in these patients reflects a somatosensory aberration, which is also indicative for the presence of neuropathic pain mechanisms [5]. Heterogeneity of neuropathic pain signs and symptoms is frequently described in the literature [13,28,29].

No common pathological somatosensory pattern has been identified in chronic sports injuries or overuse injuries. Normal sensory function is the product of a subtle equilibrium between neurons and their environment [13]. Disruption of this equilibrium can easily lead to profound changes in sensory function and thus lead to pain. Any particular painful condition may cause numerous changes within the nervous system both modulation (reversible state of hyperexcitability) and modification (a more or less irreversible state of hyperexcitability) occur in unpredictable degrees and differ inter-individually. Chronic sports injuries are long-lasting pain states in which, theoretically, sensitization mechanisms are likely to have occurred. The results of this study failed to demonstrate that the "SM" suffered more frequently from previous injury than the "n-SM." However, when the two subjects with signs of hypoalgesia are included in the SM, a new calculation of the Mann-Whitney *U*-test reveals that the difference between SM and n-SM becomes statistically significant; $P = 0.014$. Frequent injuries may cause functional and structural changes within the nervous system, and in turn may aggravate the pain and disability due to new injuries [17]. The majority of the study group (73%) was female; gender

Table 5 Sum of scores with the diagnostic model. Number of points assigned for different elements of the scoring system; The DN4-interview, presence of brush-evoke allodynia, and QST with Von Frey monofilaments (VFM) and pressure algometer (PPT). Patient Numeric Rating Scale 3, 4, 10 and 11 score 5 pts or higher. In patient nrs 1 and 13, apart from a high score on the DN4-interview, signs of hypoesthesia were found with sensory testing

Nr.	DN4	Brush†	VFM‡	PPT§	Sum of scores
1	4	0	0	0	4
2	3	0	0	1	4
3	4	1	1	1	**7**
4	3	1	1	1	**6**
5	1	0	1	1	3
6	2	0	0	0	2
7	2	0	0	1	3
8	0	0	1	1	2
9	1	1	1	1	4
10	3	1	1	1	**6**
11	3	0	1	1	**5**
12	0	0	0	1	1
13	3	0	0	0	3
14	1	0	0	1	2
15	0	0	0	0	0

† Brush: 0 = no allodynia, 1 = allodynia.
‡ VFM = Von Frey Monofilaments.
§ PPT = pain pressure threshold.

can be a potential risk factor for sensitization. Several aspects of this pilot study need further consideration. We used a small sample size in this study. Furthermore we replaced two items of the DN4-questionnaire with 2 different methods of sensory testing for three main reasons. First, we searched for signs of sensitization, not hypoesthesia since sensitization is clinically more relevant in sports medicine. Second, with the three methods of stimulation used, we stimulated Aβ-, Aδ-, and C-fiber afferent nerves, thereby increasing the chance of detecting sensitization. The two different methods of QST in our protocol allow quantification of the somatosensory aberrations, which can be of use for the evaluation of sensory function over time and during therapeutic interventions. Finally, our protocol includes the assessment of punctate or Aδ-mediated allodynia, the DN4 does not. There is ample evidence that input from Aδ-fiber nociceptors is exaggerated by central sensitization, [30,31] therefore we recommend the assessment of Aδ-mediated allodynia.

We adopted the 5 points cut-off score from the DN4 from where we regarded the presence of sensitization likely, considering the similarity between our scoring system and the DN4. However, additional research would be needed, to confirm whether this cut-off score is correct. In this study we compared the results of the sensory tests on the affected side with the results on the contralateral side. This methodology is common practice in the field of quantitative sensory testing [21]. There is evidence that sensibility on the contralateral side may also be affected by central sensitization—and subsequently may not represent the "normal" sensory status [32,33]. An option would be to compare QST results with the results from data bases with cut-off values [16,22]. However, there are several disadvantages of such a data base, the data are gathered by multiple examiners and have a large variability of pain threshold values; QST results of individual patients are nonspecific in many occasions. Another option, for future studies, is to conduct a study with a comparable group of healthy noninjured athletes to rule out the possibility of central sensitization on the contralateral side.

Why is the detection of sensitization mechanisms of clinical value for sports physicians and sports physical therapists? When sensitization mechanisms are present the use of "anti-neuropathic drugs" such as tricyclic antidepressants and anticonvulsants may be considered, instead of classic analgesics. For additional information on the various anti-neuropathic drugs, we refer to the appropriate medical literature [34,35]. The diagnosis central sensitization may give new treatment options. Potentially successful treatments in other chronic pain conditions are behavioral treatments. These treatments aim on improving functionality and do not primarily focus on pain relief [36]. The in sports medicine successfully used eccentric training programs, which are also aiming on functionality instead of pain relief, may have a comparable underlying mechanism, i.e., desensitization of the CNS.

Conclusion

Using the diagnostic model we conclude that in 4 out of 15 athletes (27%) the presence of sensitization as an explanation of the persistence of pain in chronic sports injuries is credible. We found signs of hypoalgesia in two other patients, who also scored high on the DN4-interview, the number of patients with neuropathic pain mechanisms is therefore probably higher than 27%.

Acknowledgments

The authors would like to thank Belinda van Alphen, Mayke Wierenga and Koen Lemmink of the Centre for Human Movement Sciences and University Centre for Sport, Exercise and Health of the University of Groningen and Hans Zwerver, Sport physician; Center for Sports Medicine; University Centre for Sport, Exercise and Health of the University of Groningen for their contribution to the study. The authors also thank Professor Mark Wierda and Dr Marten van Wijhe of the Department of Anesthesiology, for their constructive comments on the manuscript. Furthermore the sport medicine physicians and sport physical therapists of the Centre for Sports Medicine of the University Medical Centre Groningen and from the participating primary care physical therapy practices and the participating athletes.

References

1 Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: Summary and recommendations for injury prevention initiatives. J Athl Train 2007;42:311–9.

2 Schmikili SL, de Wit MJP, Backx FJG. [Report] Sports injuries counted three times. (Dutch). Arnhem: NOC-NSF; 2001.

3 Lian OB, Engebretsen L, Bahr R. Prevalence of jumper's knee among elite athletes from different sports: A cross-sectional study. Am J Sports Med 2005;33: 561–7.

4 Windt van der DA, Koes BW, de Jong BA, et al. Shoulder disorders in general practice: Incidence, patient characteristics, and management. Ann Rheum Dis 1995;54:959–64.

5 Jensen R, Kvale A, Baerheim A. Is pain in patellofemoral pain syndrome neuropathic? Clin J Pain 2008;24: 384–94.

6 Alfredson H, Cook J. A treatment algoritm for managing Achilles tendinopathy: New treatment options. Br J Sports Med 2007;41:211–6.

7 Kingma JJ, de Knikker R, Wittink HM, et al. Eccentric overload training in patients with chronic Achilles tendinopathy: A systematic review. Br J Sports Med 2007;41:e3.

8 Silbernagel KG, Thomeé R, Thomeé P, et al. Eccentric overload training for patients with chronic Achilles tendon pain—a randomised controlled study with reliability testing of the evaluation methods. Scand J Med Sci Sports 2001;11:197–206.

9 Alfredson H, Forsgren S, Thorsen K, et al. Glutamate NMDAR1 receptors localised to nerves in human Achilles tendons. Implications for treatment? Knee Surg Sports Traumatol Arthrosc 2001;9:123–6.

10 Alfredson H, Ohberg L, Forsgren S. Is vasculo-neural ingrowth the cause of pain in chronic achilles tendinosis? An investigation using ultrasonography and colour doppler, immunohistochemistry, and diagnostic injections. Knee Surg Sports Traumatol Arthrosc 2003; 11:334–8.

11 Webborn ADJ. Novel approaches to tendinopathy. Disabil Rehabil 2008;30:1572–7.

12 Merskey H, Bogduk N. Classification of Chronic Pain. Description of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd edition. Seattle, WA: ISAP Press; 1994.

13 Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–64.

14 Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology 2008;70: 1630–5.

15 Svensson P, Wang K, Arendt-Nielsen L, et al. Effects of NGF-induced muscle sensitization on proprioception and nociception. Exp Brain Res 2008;189:1–10.

16 Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German research network on neuropathic pain (DFNS): Standardized protocol and reference values. Pain 2006;123:231–43.

17 Woolf CJ, Salter MW. Neuronal plasticity: Increasing the gain in pain. Science 2000;288:1765–9.

18 Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29–36.

19 Bouhassira D, Lantéri-Minet M, Attal N, et al. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380–7.

20 Price DD, Bennett GJ, Raffii A. Psychophysical observations on patients with neuropathic pain relieved by a sympathetic block. Pain 1989;36:273–88.

21 Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. Pain 2007;129:256–9.

22 Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.

23 Keizer D, van Wijhe M, Post WJ, et al. Quantifying allodynia in patients suffering from unilateral neuropathic pain using Von Frey monofilaments. Clin J Pain 2007;23:85–90.

24 Keizer D, van Wijhe M, Post WJ, et al. Assessment of the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia and neuropathic pain. A pilot study. Eur J Anaesthesiol 2007;24:658–63.

25 Shy ME, Frohman EM, So YT, et al. Quantitative sensory testing. Report of the therapeutics and technology assessment subcommittee of the American academy of neurology. Neurology 2003;60:898–904.

26 Reeves JL, Jaeger B, Graf-Radford SB. Reliability of the pressure algometer as a measure of myofascial triggerpoint sensitivity. Pain 1986;24:313–21.

27 Nussbaum EL, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. Phys Ther 1998;78:160–9.

28 Hansson P. Neuropathic pain: Clinical characteristics and diagnostic workup. Eur J Pain 2002;6(suppl A):47–50.

29 Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1–8.

30 Ziegler EA, Magerl W, Meyer RA, et al. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 1999;122:2245–57.

31 Davis KD, Pope GE. Noxious cold evokes multiple sensations with distinct time courses. Pain 2002;98: 179–85.

32 Jääskeläinen SK, Teerijoki-Oksa T, Forssell H. Neurophysiologic and quantitative sensory testing in the diagnosis of trigeminal neuropathy and neuropathic pain. Pain 2005;117:349–57.

33 Hansson E. Could chronic pain and spread of pain sensation be induced and maintained by glial activation? Acta Physiologica 2006;187:321–7.

34 Finnerup NB, Sindrup SH, Jensen TS. Chronic neuropathic pain: Mechanisms, drug targets and measurement. Fundam Clin Pharmacol 2007;21:129–36.

35 Gilron I, Watson CP, Cahill CM, et al. Neuropathic pain: A practical guide for the clinician. CMAJ 2006;175:265–75.

36 Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: Results of a randomized controlled trial. Pain 2008;15:192–207.