Nociceptive Flexion Reflex Threshold in Chronic Pain Patients

A Needed Update for the Current Evidence

Mohammadreza Amiri, PhD, Hamid Esmaili, MD, Abdul Hamid Hamad, MD, Mohammad Alavinia, MD, PhD, Kei Masani, PhD, and Dinesh Kumbhare, MD, PhD, FRCPC, FAAPMR

Background: The nociceptive flexion reflex is a physiological, polysynaptic reflex triggered by a nociceptive stimulus activating a withdrawal response. In chronic musculoskeletal-related pain conditions, a decreased nociceptive flexion reflex threshold has been suggested as a possible recognition evidence for central sensitization that may cause alteration of central nervous system processing.

Objective: The aim of the study was to systematically review reported comparisons of the nociceptive flexion reflex threshold in chronic pain patients and healthy individuals.

Methods: Electronic databases covering studies published between January 1990 and December 2019 were systematically searched. After application of exclusion criteria, 20 studies including 28 trials were included in this review. For meta-analysis, we used a random-effects model and funnel plot for publication bias. This research was registered at PROSPERO (CRD42019140354).

Results: Compared with healthy controls, standardized mean differences in nociceptive flexion reflex threshold were significantly lower in the total sample of chronic pain patients. Subgroup analysis indicated a homogenous decreased nociceptive flexion reflex threshold in studies reporting fibromyalgia, chronic pain, and joint pain while heterogeneity existed in other included pain conditions.

Conclusions: A lower nociceptive flexion reflex threshold in patients experiencing chronic pain conditions may imply hyperexcitability in central nervous system processing. As a preliminary study, the findings would act as a basis for developing a methodology assisting current clinical practices

Key Words: Fibromyalgia, Whiplash, Withdrawal Response, Pain, Musculoskeletal

(*Am J Phys Med Rehabil* 2021;100:750–759)

What Is Known

- Currently, there is no objective, reliable physiological sign for chronic pain conditions. The nociceptive flexion reflex has the potential to be a physiological sign. The literature has not provided a clear answer as to whether this reflex can be used to discern between chronic pain conditions and healthy controls.

What Is New

- We performed an updated systematic review and meta-analysis of the nociceptive flexion reflex in chronic pain conditions and show that the threshold is decreased. This may be used as an objective biomarker but further research would be necessary.

Chronic pain is a major cause of suffering and disability worldwide.[1] Achieving an accurate diagnosis is critical because treatment is multimodal and expensive and does not generally address the underlying pathophysiological mechanisms.[2] The mechanisms responsible for chronic pain include peripheral and/or central sensitization and the interaction between these and psychological, polygenetic, environmental, and other factors.[3,4] The development of a clinically feasible, objective, reliable biomarker would assist with improving the accuracy of diagnosis and predict response to treatment.

The nociceptive flexion reflex (NFR) threshold is proposed as a potential objective candidate that may assist with uncovering pain mechanisms that could play an important role in more homogeneous diagnostic categorization and therefore a better response to treatment.[5] It was originally described to be a direct measure of spinal cord segmental excitability and neuroplasticity and is an objective measure of pain compared with relying on subjective patient reporting.[6] The threshold has been defined as the lowest noxious stimulation intensity required to trigger a reflex motor response.[7,8] The required stimulus intensity can vary across individuals, but the threshold is usually consistent.[9]

Nonetheless, a systematic review was previously published about a decade ago that concluded patients experiencing chronic pain conditions have a decreased level of the threshold compared with healthy controls.[10] Since then, other chronic pain conditions such as joint pain have been investigated for the levels of the NFR threshold. Therefore, an updated review was needed: (1) to include most recent evidence and (2) to provide a more comprehensive meta-analysis by disease subgroups. In addition, to draw a more robust, confident conclusion from the analysis, meticulous statistical methodologies were used. Thus, the main objective of our article was to systematically review the published evidence reporting the comparison of NFR

From the Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada (M. Amiri, AHH, M. Alavinia, DK); Isfahan University of Medical Sciences, Isfahan, Iran (HE); Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada (KM); and Division of Physical Medicine and Rehabilitation, Department of Medicine, University of Toronto, Toronto, Ontario, Canada (DK).

All correspondence should be addressed to: Dinesh Kumbhare, MD, PhD, FRCPC, FAAPMR, 550 University Avenue, Suite 7-131, Toronto, Ontario, Canada M5G 2A2.

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ajpmr.com).

ISSN: 0894-9115
DOI: 10.1097/PHM.0000000000001626

threshold in chronic pain patients and healthy controls. A secondary objective was to report a subgroup analysis (ie, meta-analysis by disease) and draw conclusion from the findings.

METHODS

Registration

To avoid data dredging, aims of this study were registered in PROSPERO (CRD42019140354) at initial stages of literature search and before any data extraction and meta-analysis.

Systematic Search Strategy

This study conforms to all Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[11] and reports the required information accordingly (see Supplemental Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B156). We systematically searched the databases using the methodology outlined by the Cochrane collaboration[12]: Medline, CINAHL, Embase, Cochrane reviews, and Cochrane central registry of controlled trials, and PeDRO. We used the following search terms: nocicept*/flex*/adj7 reflex; NFR; nociceptive withdrawal reflex; flexor withdrawal reflex; flexor reflex; withdrawal reflex; RIII reflex; spinal-mediated reflex; central hyperexcitability; central sensitization; musculoskeletal system; musculoskeletal diseases; and pain. The only limits applied were articles about human subject and literature in English. We included articles in our study if they reported case-control studies comparing NFR threshold in chronic pain patients and healthy control subjects and were published until December 2019.

Selection Agreement and Disagreement Settlement

Titles and abstracts were reviewed and assessed for eligibility by MA and DK, and in the case of disagreements, unanimous decision was reached after providing reasoning to include or exclude the study.

Inclusion and Exclusion Criteria

This systematic review targeted research that compared NFR threshold between patients experiencing fibromyalgia, whiplash, chronic pain, spinal pain, and joint pain and healthy individuals. Studies were included in this review if (1) reporting a case-control of any chronic pain condition, (2) statistics (mean and standard deviation or confidence interval (CI) or median and quartiles/interquartile range) about NFR threshold in both chronic pain patients and healthy controls were provided, (3) human subjects, (4) published in English, and (5) full text was available with reporting of the methodology of the threshold measurements. In addition, if the required statistics could not be extracted, obtained from authors, or calculated, then the study was considered as not satisfactory to the inclusion criteria and therefore was excluded. Exclusion criteria were as follows: (1) studies that did not report the NFR threshold statistics in both patients and healthy control, (2) studies that only reported patients' feedback about pain, (3) studies that lacked healthy controls as comparators, and (4) full text unavailable or abstract only.

Quality Assessment

We used the modified version of the Downs and Black[13] checklist to assess the quality of reporting (Appendix 1, Supplemental Digital Content 2, http://links.lww.com/PHM/B157). Each item received a minimum of zero (if no) to a maximum of 1 (if yes). Note that item number 5 (ie, in our modified version is item 4) has a maximum value of two (no = 0, partially = 1, yes = 2). The scoring maximum value, therefore, was 18 points.

Data Extraction

The following data were extracted from each study: study characteristics such as sample sizes of patient groups and healthy controls; type of chronic pain condition; measurement methodology including setting, stimulation, and recording; and reflex threshold latency (in milliamperes). Furthermore, where the NFR threshold values were presented in plots (eg, see Langemark et al.[14]), values were extracted with the best precision possible and included in the meta-analysis. Finally, if mean and standard error or median and quartiles/interquartile range were reported, proper conversion formulae were used to derive mean and standard deviation statistic.[15]

Meta-Analysis

Extracted data were meta-analyzed using RevMan 5.3 (The Cochrane Collaboration, 2006) by disease subgroups and overall. To estimate a point estimate for the effect and to incorporate the variability of the measurement methodologies described in the literature, we calculated standardized mean differences (SMDs) and 95% CIs.[16] Following the study by Borenstein et al.,[16] because NFR threshold may vary between studies because of different diseases and methodology techniques, a random-effects model was used for the meta-analysis. For studies with multiple trials and a single control group, suggestions by the Cochrane Handbook were followed in which we included each pair-wise comparison separately, but with shared intervention groups dividing the control sample size out approximately evenly among the comparisons.[12]

RESULTS

Selected Trials

Systematic search strategy in electronic databases are presented in Appendix 2 (Supplemental Digital Content 3, http://links.lww.com/PHM/B158). Briefly, we obtained a total of 761 articles from systematic literature search. After removing duplicates, a total of 456 articles passed for screening of which 38 studies were passed for comprehensive full-text information analysis. Three authors (MA, DK, HE) performed this full-text screening that resulted in exclusion of an additional 28 articles. In Figure 1, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for the systematic search, screening, and selection process for the number of literatures included is illustrated. Concluding these procedures, nine studies were included for data extraction. The systematic literature search was performed by our librarian, Ms. Jessica Babineau, who is a professional information specialist and has received training in Cochrane methodology and the search was double checked, reviewed and confirmed by the authors.

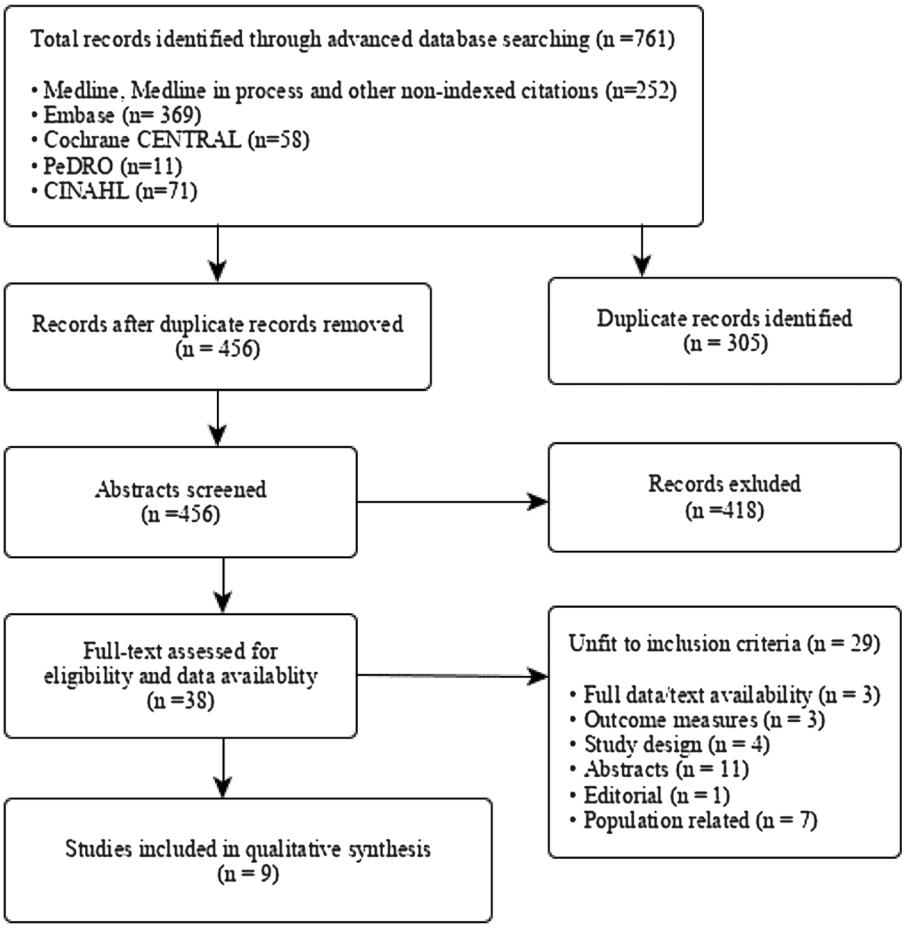

FIGURE 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the studies updating systematic review by Lim et al. (2011).[11]

Quality Scoring

The pooled studies scored a mean (SD) of 10.8 (1.8) of the possible full 18 points score. Studies commonly lacked criteria in reporting of the random variability, external validity, and a priori sample size calculation. Table 1 summarizes the details about the studies included in this systematic review and meta-analysis.

Overall Studies

Overall, 360 patients and 506 healthy control individuals have been included to update the previous systematic review and meta-analysis[10] summing up to a pool of 879 individuals with 828 healthy control individuals. Figure 2 illustrates the forest plot of the disease subgroups for all included studies. The overall pool of studies showed a significant SMD in NFR threshold in chronic pain patients compared with healthy individuals (SMD = −0.89, 95% CI = −1.10 to −0.68, $P < 0.00001$), but the overall difference was heterogeneous ($I^2 = 70\%$, $\chi^2 = 91.17$, $df = 27$, $P < 0.0001$). The funnel plot (Fig. 3) visually confirms that the included studies are symmetrical and may provide proof that publication bias is unlikely. To investigate this further, we excluded studies in a trial-and-error investigation to achieve a homogeneous statistic (please see Appendix 3, Supplemental Digital Content 4, http://links.lww.com/PHM/B159). Interestingly, the overall effect size did not change drastically (SMD = −0.87, 95% CI = −1.02 to −0.72, $df = 23$, $P = 0.10$, $I^2 = 28\%$) indicating that the decreased NFR threshold in chronic pain patients is consistent throughout chronic pain conditions.

Fibromyalgia

Six studies (280 subjects vs 198 healthy controls) were included in the systematic review and meta-analysis about the patients experiencing fibromyalgia. Among fibromyalgia patients a significant pooled SMD in NFR threshold of −0.80 (95% CI = −0.99 to −0.61) with a low level of heterogeneity ($I^2 = 0\%$, $\chi^2 = 4.31$, $df = 5$, $P = 0.51$) when compared with healthy controls. The test for overall effect was also highly significant ($Z = 8.16$, $P < 0.00001$). It must be pointed out here that the fibromyalgia category had a total weight of 31.4%.

Whiplash

Three trials (107 patients and 89 healthy controls) were identified and formed the section of people with whiplash diagnosis. There was a significant lower standardized mean in NFR among patients with whiplash compared with the control group (−0.50 [95% CI = −0.98 to −0.02]). The findings of these studies were not statistically heterogeneous ($I^2 = 62\%$,

TABLE 1. Study details included in this systematic review and meta-analysis

Study	No. Subjects	Medical Problem	NFR (Mean ± SD) Patients vs Healthy Control	Stimuli Site	EMG Site	Explanation	Quality Assessment (n = 18)
Krafft et al.[17] (2017)	31 (16 cases and 15 HC)	Chronic back pain	NR HC: NR	Retromalleolar pathway of the sural nerve	Ipsilateral biceps femoris	The sham group was NR. NFR feedback was reported	9
Rice et al.[18] (2017)	26 cases and 22 HC (total = 48)	Fibromyalgia	15.2 ± 7.5 HC: 22.0 ± 7.9	Sural nerve	Biceps femoris	Test NFR area (mV/ms) was reported.	10
Desmeules et al.[19] (2003)	85 cases and 40 HC	Fibromyalgia	26.0 (13.7) HC: 37.6 (16.8)	Sural nerve	Ipsilateral biceps femoris		12
Desmeules et al.[20] (2014)	137 cases and 99 HC	Fibromyalgia	28.6 ± 25.2 HC: 52.1 ± 31.4	Sural nerve in retromalleolar track	Ipsilateral biceps femoris	Global pain threshold in FM sensitized vs healthy control	9
Smith et al.[21] (2014)	53 cases vs 30 healthy HC	Chronic whiplash associated disorders symptoms	T1: 12 (6–18) T2: 12 (6–20) T3: 18 (10–30) T4: 16 (8–38) HC: 21 10 (38)	Sural nerve	Biceps femoris	Pressure pain threshold was measured	12
Biurrun Manresa et al.[22] (2013)	104 cases (40, chronic neck pain, 40 chronic low back pain, 24 with acute low back pain), 300 pain free subjects as HC	Musculoskeletal pain	9.3 (7.3–12.6) 10.3 (7.3–14.7) 12.0 (10.0–4.3) HC: 16 (14–18)	Sural nerve	Biceps femoris and the rectus femoris	Main end point of the study was RRF. NWR was reported as secondary end point. Median and IQR has been reported in 4 groups. The results for chronic low back pain was reported. Single stimulation NWR threshold was reported.	9
Rhudy et al.[23] (2013)	17 patients with FM, 17 patients with RA, 19 healthy pain free HC	Fibromyalgia	19.86 HC: 17.18	Inferior to the lateral malleolus over the sural nerve	Vicinity of musculotendinous junction biceps femoris	SDs NR. There are 2 groups of cases, RA and FM.	10
Umeda et al.[24] (2013)	8 women with FM and 14 healthy HC	Fibromyalgia	11.88 ± 4.64 HC: 14.82 (7.90)	Sural nerve	Biceps femoris		9
Lim et al.[25] (2012)	16 cases and 31 healthy HC	Lateral epicondylalgia	3.50 (2.56) 4.29 (2.15) HC: 3.56 (2.21)	Inferior to the lateral malleolus over the sural nerve	Proximal to the musculotendinous junction biceps femoris.	Cases was reported, number of subjects in cases = 16	10
Sterling et al.[26] (2008)	30 cases and 30 HC	Whiplash	19.8 (14.8) HC: 37.9 (23.2)	Sural nerve at ankle	Biceps femoris	Significantly lower in the whiplash group	14
Sterling[27] (2010)	20 cases and 22 HC	Acute whiplash	NR HC: NR	Sural nerve	Biceps femoris	Cases were categorized into recovered, mild pain, and moderate/severe/ disability. For each category there are 3 measurements NFR for moderate/ severe at 6 mos was reported. The number of subjects was adjusted for data entered NFR VAS was reported.	12

(Continued on next page)

TABLE 1. *(Continued)*

Study	No. Subjects	Medical Problem	NFR (Mean ± SD) Patients vs Healthy Control	Stimuli Site	EMG Site	Explanation	Quality Assessment (n = 18)
Antonaci et al.[28] (1994)	5 cases and 25 HC	Chronic paroxysmal hemicrania	11.1 (2.7) HC: 11.7 (3.5)	Sural nerve (retromalleolar location)	Supra orbital nerve	Insignificant finding	8
Boureau et al.[29] (1991)	9 cases and 17 HC	Chronic tension/mixed headache	11.3 (4.5) HC: 12.9 (2.8)	Sural nerve	Biceps femoris	Insignificant finding	10
		Myofascial syndrome	12.8 (4.5) HC: 12.9 (2.8)				
Filatova et al.[30] (2008)	69 cases and 18 HC	Chronic migraine, tension-type, or mixed headache	9.0 (2.2) HC: 10.3 (1.7)	Sural nerve	Biceps femoris	NFR significantly decreased in patient group	11
Langemark et al.[14] (1993)	40 cases and 29 HC	Chronic tension-type headache	NR HC: NR	Sural nerve	Biceps femoris	Significantly lower in headache group (median, 10 mA) than in the control group (median, 20 mA)	10
Nappi et al.[31] (2002)	6 cases and 10 HC	Chronic cluster headache	17.0 (6.4) HC: 15.3 (4.2)	Sural nerve (retromalleolar location)	Biceps femoris	Insignificant finding	11
Sandrini et al.[32] (2000)	36 cases and 21 HC 18 cases and 21 HC	Cluster headache (episodic) Cluster headache (chronic)	NR HC: NR	Sural nerve (retromalleolar location)	Biceps femoris	Significantly lower over the symptomatic side during the active phase in cluster headache (episodic) compared with cluster headache (chronic) and HC	9
Sandrini et al.[33] (2006)	24 cases and 20 HC 17 cases 20 HC	Migraine with aura chronic tension type	10.7 (2.1) 9.1 (0.8) HC: 11.4 (3.1)	Sural nerve (retromalleolar location)	Biceps femoris	Significantly lower in CTTH patients than in HC but no difference in migraine	12
Banic et al.[6] (2004)	22 cases and 25 HC	Fibromyalgia	8.9 (6.1) HC: 14.2 (7.4)	Sural nerve	Biceps femoris	Significantly lower in the patients' group	13
	27 cases and 29 HC	Whiplash	10.5 (5.41) HC: 13.9 (7.05)				
Guieu et al.[34] (1994)	18 cases and 12 HC	Fibromyalgia	10.1 (1.19) HC: 10.4 (1.2)	Sural nerve	Medial anterior of biceps femoris	Insignificant finding	11
Courtney et al.[35] (2009)	20 cases and 20 HC	Osteoarthritis	9.8 (3.7) HC: 15.0 (3.1)	Medial foot	Tibialis ant and biceps femoris	Significantly lower in the knee OA group	12
Courtney et al.[36] (2010)	10 cases and 10 HC	Osteoarthritis	9.3 (3.1) HC: 14.5 (3.3)	Medial foot	Tibialis ant and biceps femoris	Significantly lower in the knee OA group	8
Courtney et al.[37] (2011)	10 ACL and 10 HC	Unilateral ACL	Injured limb = 11.8 ± 8 Uninjured limb = 18.6 ± 13 HC: 22.5 ± 3	Sural nerve	Biceps femoris	NFR for ACL patients was reported	8
Peters et al.[8] (1992)	12 cases and 12 HC	Chronic low back pain	NR HC: NR	Sural nerve posterior of lateral malleolus	Biceps femoris bend of the knee	Insignificant finding	12

CTTH, chronic tension-type headache; EMG, electromyography; HC, healthy control; IQR, interquartile range; NWR, nociceptive withdrawal reflex; RA, rheumatoid arthritis; RFN, radiofrequency neurotomy; RRF, reflex receptive fields; WAD, whiplash-associated disorder.

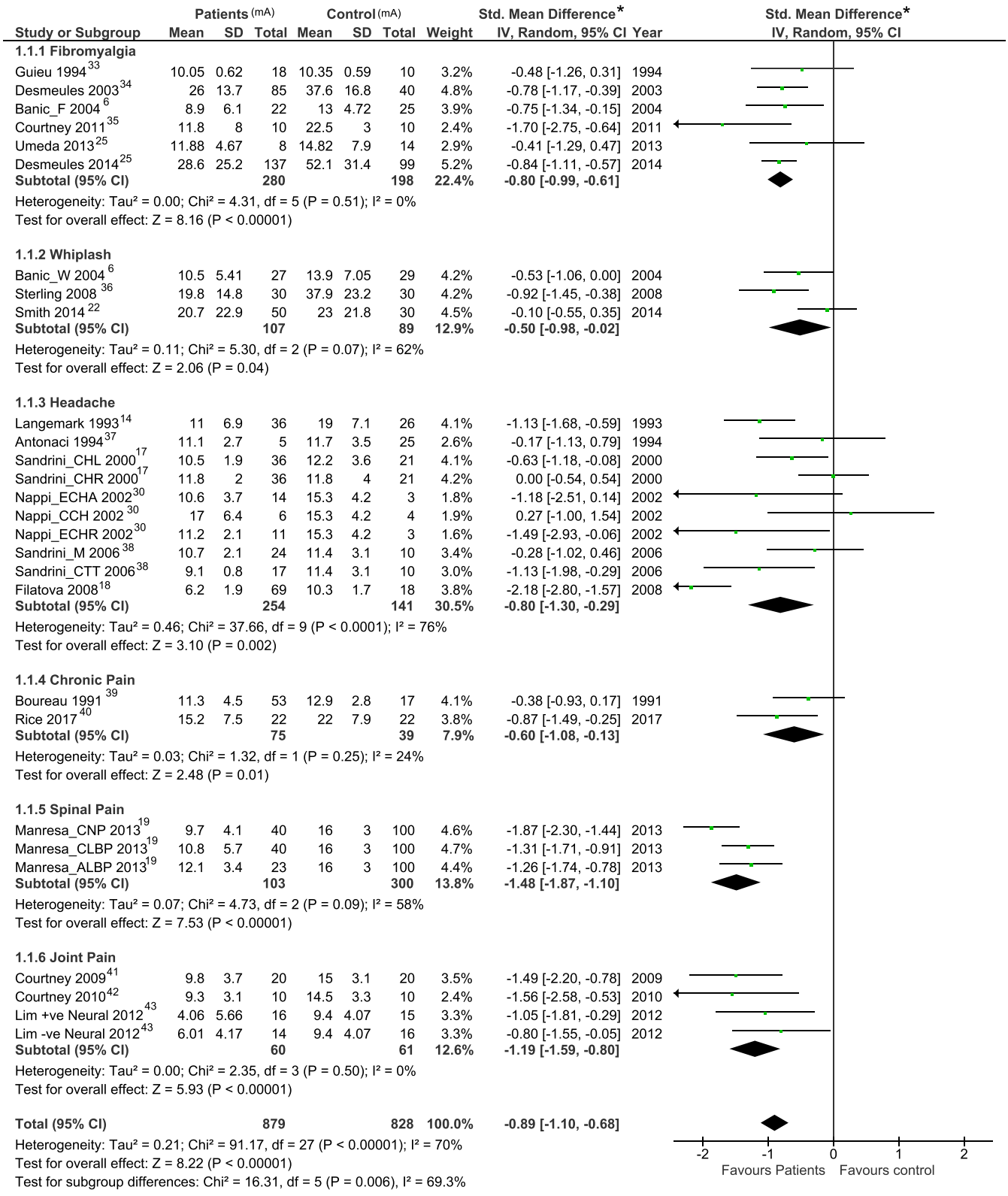

FIGURE 2. Forest plot of the included studies. Nociceptive flexion reflex mean threshold in milliamperes.

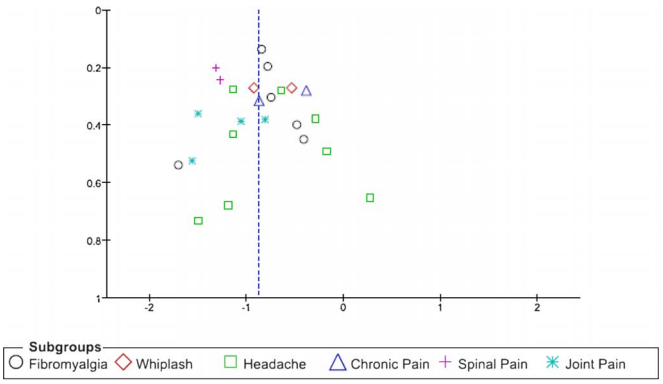

FIGURE 3. Funnel plot of the included studies. The broken line represents the total standard mean difference (−0.89) from the included studies between the total patients (n = 879) and control (n = 828) research participants.

P = 0.07). The test for overall effect was significant (Z = 2.06, P = 0.04). The whiplash stratum weighed 13.8% of the total meta-analysis.

Headache

Ten comparisons (254 patients and 141 healthy individuals) were included in the analysis related to headache. When the NFR threshold was compared between patients with headache and the control participants, we found that the threshold was lower among patients accounting for −0.80 (95% CI = −1.30 to −0.29). There was a statistically significant evidence for heterogeneity among reported NFR threshold findings between chronic headache patients and healthy controls (I^2 = 76%, χ^2 = 37.66, df = 9, P < 0.0001). The test for overall effect: Z = 3.1 (P = 0.002).

Chronic Pain

Two studies (75 patients vs 39 healthy controls) investigated patients experiencing chronic pain found lower SMD in NFR threshold in chronic pain sufferers (SMD = −0.60, 95% CI = −1.08 to −0.13). No significant heterogeneity among studies were identified (I^2 = 24%, χ^2 = 1.32, df = 1,

TABLE 2. Overall heterogeneity of studies

	Included				Excluded			
	Patients Sample Size	Healthy Control Sample Size	Weight	SMD (95% CI)	Patients Sample Size	Healthy Control Sample Size	Weight	SMD (95% CI)
Fibromyalgia	280	198	22.40%	−0.80 (−0.99 to −0.61)	280	198	31.00%	−0.80 (−0.99 to −0.61)
	Heterogeneity: τ^2 = 0.00, χ^2 = 4.31, df = 5 (P = 0.51), I^2 = 0%				Heterogeneity: τ^2 = 0.00, χ^2 = 4.31, df = 5 (P = 0.51), I^2 = 0%			
	Test for overall effect: Z = 8.16 (P < 0.00001)				Test for overall effect: Z = 8.16 (P < 0.00001)			
Whiplash	107	89	12.90%	−0.50 (−0.98 to −0.02)	57	59	10.90%	−0.72 (−1.10 to −0.35)
	Heterogeneity: τ^2 = 0.11, χ^2 = 5.30, df = 2 (P = 0.07), I^2 = 62%				Heterogeneity: τ^2 = 0.00, χ^2 = 1.01, df = 1 (P = 0.31), I^2 = 1%			
	Test for overall effect: Z = 2.06 (P = 0.04)				Test for overall effect: Z = 3.74 (P = 0.0002)			
Headache	254	141	30.50%	−0.80 (−1.30 to −0.29)	149	102	22.30%	−0.73 (−1.08 to −0.37)
	Heterogeneity: τ^2 = 0.46, χ^2 = 37.66, df = 9 (P < 0.0001), I^2 = 76%				Heterogeneity: τ^2 = 0.07, χ^2 = 9.66, df = 7 (P = 0.21), I^2 = 28%			
	Test for overall effect: Z = 3.10 (P = 0.002)				Test for overall effect: Z = 4.05 (P < 0.0001)			
Chronic pain	75	39	7.90%	−0.60 (−1.08 to −0.13)	75	39	9.60%	−0.60 (−1.08 to −0.13)
	Heterogeneity: τ^2 = 0.03, χ^2 = 1.32, df = 1 (P = 0.25), I^2 = 24%				Heterogeneity: τ^2 = 0.03, χ^2 = 1.32, df = 1 (P = 0.25), I^2 = 24%			
	Test for overall effect: Z = 2.48 (P = 0.01)				Test for overall effect: Z = 2.48 (P = 0.01)			
Spinal pain	103	300	13.80%	−1.48 (−1.87 to −1.10)	63	200	14.00%	−1.29 (−1.59 to −0.98)
	Heterogeneity: τ^2 = 0.07, χ^2 = 4.73, df = 2 (P = 0.09), I^2 = 58%				Heterogeneity: τ^2 = 0.00, χ^2 = 0.02, df = 1 (P = 0.88), I^2 = 0%			
	Test for overall effect: Z = 7.53 (P < 0.00001)				Test for overall effect: Z = 8.23 (P < 0.00001)			
Joint pain	60	61	12.60%	−1.19 (−1.59 to −0.80)	60	61	12.10%	−1.19 (−1.59 to −0.80)
	Heterogeneity: τ^2 = 0.00, χ^2 = 2.35, df = 3 (P = 0.50), I^2 = 0%				Heterogeneity: τ^2 = 0.00, χ^2 = 2.35, df = 3 (P = 0.50), I^2 = 0%			
	Test for overall effect: Z = 5.93 (P < 0.00001)				Test for overall effect: Z = 5.93 (P < 0.00001)			
Total	879	828	100.00%	−0.89 (−1.10 to −0.68)	684	659	100.00%	−0.87 (−1.02 to −0.72)
	Heterogeneity: τ^2 = 0.21, χ^2 = 91.17, df = 27 (P < 0.00001), I^2 = 70%				Heterogeneity: τ^2 = 0.04, χ^2 = 31.93, df = 23 (P = 0.10), I^2 = 28%			
	Test for overall effect: Z = 8.22 (P < 0.00001)				Test for overall effect: Z = 11.21 (P < 0.00001)			
	Test for subgroup differences: χ^2 = 16.31, df = 5 (P = 0.006), I^2 = 69.3%				Test for subgroup differences: χ^2 = 12.57, df = 5 (P = 0.03), I^2 = 60.2%			

P = 0.25). Overall, 6.9% of the total meta-analysis were chronic pain studies, and it depicted a statistically significant overall effect (Z = 2.48, P = 0.01).

Spinal Pain

One study including three subgroups (103 patients and 300 healthy participants), which after sensitivity analysis provided two subgroups (63 patients experiencing acute lower back pain, chronic lower back pain, and chronic neck pain) and one shared control group consisting of 200 healthy individuals was thoroughly analyzed in this systematic review. The pooled analysis revealed a significant lower SMD in NFR threshold in patients with spinal pain (SMD = −1.48, 95% CI = −1.87 to −1.10) compared with the control group. This category of patients contributed 13.8% to the total population of the meta-analysis.

Joint Pain

Four trials including 60 patients and 61 healthy controls were included in the subgroup of joint pain. A decreased NFR threshold was observed (−1.19, 95% CI = −1.59 to −0.80) that was homogeneous (I^2 = 0%, χ^2 = 2.35, df = 3, P = 0.50), whereas the test of overall effect indicated a significant value (Z = 5.93, P < 0.00001).

Excluding Heterogeneity Causing Studies

The investigators of the included studies used versatile methodologies to measure the NFR threshold (Appendix 4, Supplemental Digital Content 5, http://links.lww.com/PHM/B160). After a thorough analysis (Table 2), we highlighted the studies that caused an overall heterogeneity, that is, patients with chronic cluster headache remission by Sandrini et al.[32]; patients with headache by Filatova et al.[30]; patients with chronic neck pain by Biurrun Manresa et al.[22]; and patients with whiplash by Smith et al.[38] These exclusions resulted in (I^2 = 28%, χ^2 = 31.93, df = 23, P = 0.10) and the test of overall effect indicated to be still highly significant (Z = 11.21, P < 0.00001). Additional forest plot excluding these studies are presented in Appendix 3 (Supplemental Digital Content 4, http://links.lww.com/PHM/B159). This is significant because the studies that we included had some heterogeneity of the cohorts that were described. We analyzed the effect of the heterogeneity and found that the demonstration of the decreased NFR threshold was maintained.

DISCUSSION

A major issue that faces clinicians and researchers is the lack of objectivity available within many diagnostic criteria used to label a patient with a specific chronic pain condition. For example, common chronic pain conditions including fibromyalgia and myofascial pain syndrome have subjective and self-report–based diagnostic criteria.[38] These criteria are expert opinion, and their ability to create a homogeneous group if applied correctly has not been demonstrated. Furthermore, there has been no association with the underlying disease mechanism or pathophysiology. In addition, the measurement properties of the criteria have not been researched; in fact, the fibromyalgia criteria available to the clinical community since the early 1990s have validity violations.[39] One possible solution would be the development of an objective, reliable, and clinically feasible physiological marker and then using it to develop new diagnostic criteria. With this in mind, we set out to examine the NFR for its utility in chronic pain overall and for specific conditions described in the existing literature. As the first step, we wanted to update the previous systematic review performed by Lim et al.[10] With the addition of new studies and assessing for possible heterogeneity, we wanted to assess whether the NFR threshold still had value in separating out disease from healthy comparison groups.

Updating the synthesis of published studies comparing NFR threshold in chronic pain patients and healthy people was necessary for several reasons. Firstly, the NFR threshold was investigated in new chronic pain conditions such as chronic joint pain. Secondly, scientific literature investigating chronic pain usually aims at the NFR among patients with a specific chronic pain condition (eg, fibromyalgia or whiplash) and investigates it accordingly. We aimed to provide a comprehensive research that encompasses all the evidence that is currently available for chronic pain. The present study's stratified meta-analysis addressed not only such focus to shed light on whether a unanimous conclusion is plausible or further investigations is required, but also juxtaposed a universal patients' NFR and that of the healthy individuals. Having said that, with meticulous analysis, we were able to draw a homogenous conclusion from the meta-analysis indicating that irrespective of the pain-causing factor(s), there is always a lower level of threshold among patients compared with the healthy counterparts.

The analyses reported that the NFR threshold among patients with chronic painful conditions is significantly lower compared with healthy counterparts. This overall finding is in line with all subgroups (ie, fibromyalgia, whiplash, headache, chronic pain, spinal pain, and joint pain). Among all included strata, patients who chronically experienced spinal pain had the largest negative NFR threshold standing at almost −1.5-mA lower threshold compared with the healthy controls in this category (Fig. 2). This may imply the sensitivity of chronic pain related to the spine and how it may impact the NFR magnitude. In addition, in musculoskeletal pain conditions such as whiplash[6,21,27] and fibromyalgia,[6,20,23,24,40] previous tissue damage may cause continuing hypersensitivity and may act as a peripheral mechanism of chronic pain. This implies that a deficit in NFR among patients with chronic pain may infer the presence of central hyperexcitability that may have resulted from peripheral and central sensitization. This may be a significant factor in the transition from acute to chronic pain.[41,42]

Surprisingly, the only trial that had a lower SMD in NFR threshold among patients compared with the healthy controls was Nappi et al.[31] In preliminary meta-analysis, the results from Sterling[27] illustrated that this follow-up study (which we decided to include the 3-mo follow-up instead of 6 mos because of the lack of control group in the latter) may not be relevant to this review's scope as the follow-up period is not long enough comparing the patients with the healthy controls and also the stimuli incorporated for the analysis may vary with that used by the rest of the similar trials.

Null effect among the most recent studies was only present among a couple of the reviewed literature[21,24] of which populations were only women[24] or female percentage was higher,

that is, 69% of the subjects.[21] This finding is not in line with that of previously discussed in Lim et al.[10] They noted more male subject in studies where NFR deficits did not exist. This is an interesting contradiction. As the comprehensive review of NFR determinants by Skljarevski and Ramadan[43] highlighted that the NFR threshold is higher in male patients compared with female patients. This implies that if a study population consists of more of each sex then, statistically speaking, the NFR threshold's average would be biased because the sex, which has more weights, may pull the average in its favor.

In a meta-analysis, a large sample size has a high power to detect small levels of heterogeneity (ie, "*unimportant clinically*" as phrased by the Cochrane Handbook of Systematic Reviews and Meta-analysis).[12] The Cochrane Handbook suggests for the appropriate detection of heterogeneity a larger significance level (ie, $\alpha = 0.10$) should be used.[12] Nonetheless, in the pooled meta-analysis of our review, we detected heterogeneity and were able to analyze for it with a thorough sensitivity analysis of the included studies (see Results). However, we have shown that exclusion of studies that surpassed the threshold did not influence and interfere with the final pooled and/or stratified results. We did not expect otherwise because a general unanimous trend was obvious throughout the trials. This is significant because the diagnostic criteria used within the studies we included in our review most likely did result in some heterogeneity and the impact of this was important to quantify. We have shown that the NFR threshold is still, with heterogeneity accounted for, representative of the disease and can separate it from the healthy comparison group.

This study has limitations, which must be acknowledged. First, advanced data base search techniques resulted in very limited number of studies in some of the clinically relevant strata, for example, chronic pain. In addition, scores of the studies as well as methodologies used varied while objectives were similar. Within this context, the results of the studies we included could have been influenced by confounding variables and as yet unrecognized factors, which could have contributed to the results. This issue was assumed to have a random effect, and thus, we believe that our overall conclusions may not have been significantly affected by it. Next, because heterogeneity is inevitable in meta-analysis with large sample sizes, the best approach could be to investigate each stratification separately, that is, if more robust and trusted homogenous trials existed. At the time we performed our literature search, we did not locate any. Next, although recent and less criticized statistical conversion formula were used to calculate the mission statistics, a scrutiny is advisable. Finally, further studies are required to address reliability and/or validity of measurements for the procedure used in the studies.

CONCLUSIONS

Our meta-analysis revealed that the NFR threshold was lower in the all the clinical group (fibromyalgia, whiplash, headache, chronic pain, spinal pain, and joint pain) when compared with healthy controls. A lower NFR threshold in patients experiencing chronic pain conditions may imply hyperexcitability in central nervous system processing. As a preliminary study, the findings would act as a basis for developing a methodology assisting current clinical practices to help chronic pain sufferers with a more accurate and a much faster diagnosis of the causing factor(s).

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, et al: Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012;380:2163–96
2. Gatchel RJ, Peng YB, Peters ML, et al: The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull* 2007;133:581–624
3. Borsook D, Youssef AM, Simons L, et al: When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain* 2018;159:2421–36
4. Nicholas MK: Why do some people develop chronic, treatment-resistant pain and not others? *Pain* 2018;159:2419–20
5. Smith SM, Dworkin RH, Turk DC, et al: The potential role of sensory testing, skin biopsy, and functional brain imaging as biomarkers in chronic pain clinical trials: IMMPACT considerations. *J Pain* 2017;18:757–77
6. Banic B, Petersen-Felix S, Andersen OK, et al: Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 2004;107:7–15
7. Leroux A, Belanger M, Boucher JP: Pain effect on monosynaptic and polysynaptic reflex inhibition. *Arch Phys Med Rehabil* 1995;76:576–82
8. Peters ML, Schmidt AJ, Van den Hout MA, et al: Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). *Pain* 1992;50:177–87
9. Willer JC: Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain* 1977;3:69–80
10. Lim EC, Sterling M, Stone A, et al: Central hyperexcitability as measured with nociceptive flexor reflex threshold in chronic musculoskeletal pain: a systematic review. *Pain* 2011;152:1811–20
11. Moher D, Liberati A, Tetzlaff J, et al: Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;6:e1000097
12. Cumpston M, Li T, Page MJ, et al: Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;10:ED000142
13. Downs SH, Black N: The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Commun Health* 1998;52:377–84
14. Langemark M, Bach FW, Jensen TS, et al: Decreased nociceptive flexion reflex threshold in chronic tension-type headache. *Arch Neurol* 1993;50:1061–4
15. Luo D, Wan X, Liu J, et al: Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805
16. Borenstein M, Hedges LV, Higgins JPT, et al: *Introduction to Meta-analysis*. West Sussex, England, John Wiley & Sons Ltd., 2009
17. Krafft S, Göhmann HD, Sommer J, et al: Learned control over spinal nociception in patients with chronic back pain. *Eur J Pain* 2017;21:1538–49
18. Rice DA, Parker RS, Lewis GN, et al: Pain catastrophizing is not associated with spinal nociceptive processing in people with chronic widespread pain. *Clin J Pain* 2017;33:804–10
19. Desmeules JA, Cedraschi C, Rapiti E, et al: Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003;48:1420–9
20. Desmeules J, Chabert J, Rebsamen M, et al: Central pain sensitization, COMT Val158Met polymorphism, and emotional factors in fibromyalgia. *J Pain* 2014;15:129–35
21. Smith AD, Jull G, Schneider G, et al: Cervical radiofrequency neurotomy reduces central hyperexcitability and improves neck movement in individuals with chronic whiplash. *Pain Med* 2014;15:128–41
22. Biurrun Manresa JA, Neziri AY, Curatolo M, et al: Reflex receptive fields are enlarged in patients with musculoskeletal low back and neck pain. *Pain* 2013;154:1318–24
23. Rhudy JL, DelVentura JL, Terry EL, et al: Emotional modulation of pain and spinal nociception in fibromyalgia. *Pain* 2013;154:1045–56
24. Umeda M, Corbin LW, Maluf KS: Preliminary investigation of absent nociceptive flexion reflex responses among more symptomatic women with fibromyalgia syndrome. *Rheumatol Int* 2013;33:2365–72
25. Lim EC, Sterling M, Pedler A, et al: Evidence of spinal cord hyperexcitability as measured with nociceptive flexion reflex (NFR) threshold in chronic lateral epicondylalgia with or without a positive neurodynamic test. *J Pain* 2012;13:676–84
26. Sterling M, Hodkinson E, Pettiford C, et al: Psychologic factors are related to some sensory pain thresholds but not nociceptive flexion reflex threshold in chronic whiplash. *Clin J Pain* 2008;24:124–30
27. Sterling M: Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain* 2010;150:501–6
28. Antonaci F, Sandrini G, Danilov A, et al: Neurophysiological studies in chronic paroxysmal hemicrania and hemicrania continua. *Headache* 1994;34:479–83
29. Boureau F, Luu M, Doubrere JF: Study of experimental pain measures and nociceptive reflex in chronic pain patients and normal subjects. *Pain* 1991;44:131–8
30. Filatova E, Latysheva N, Kurenkov A: Evidence of persistent central sensitization in chronic headaches: a multi-method study. *J Headache Pain* 2008;9:295–300
31. Nappi G, Sandrini G, Alfonsi E, et al: Impaired circadian rhythmicity of nociceptive reflex threshold in cluster headache. *Headache* 2002;42:125–31
32. Sandrini G, Antonaci F, Lanfranchi S, et al: Asymmetrical reduction of the nociceptive flexion reflex threshold in cluster headache. *Cephalalgia* 2000;20:647–52

33. Sandrini G, Rossi P, Milanov I, et al: Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. *Cephalalgia* 2006;26:782–9
34. Guieu R, Serratrice G, Pouget J: Counter irritation test in primary fibromyalgia. *Clin Rheumatol* 1994;13:605–10
35. Courtney CA, Lewek MD, Witte PO, et al: Heightened flexor withdrawal responses in subjects with knee osteoarthritis. *J Pain* 2009;10:1242–9
36. Courtney CA, Witte PO, Chmell SJ, et al: Heightened flexor withdrawal response in individuals with knee osteoarthritis is modulated by joint compression and joint mobilization. *J Pain* 2010;11:179–85
37. Courtney CA, Durr RK, Emerson-Kavchak AJ, et al: Heightened flexor withdrawal responses following ACL rupture are enhanced by passive tibial translation. *Clin Neurophysiol* 2011;122:1005–10
38. Kumbhare D, Tesio L: A theoretical framework to improve the construct for chronic pain disorders using fibromyalgia as an example. *Ther Adv Musculoskelet Dis* 2021;13:1759720X20966490
39. Kumbhare D, Ahmed S, Watter S: A narrative review on the difficulties associated with fibromyalgia diagnosis. *Therapeut Adv Musculoskelet Dis* 2018;10:13–26
40. Lidbeck J: Central hyperexcitability in chronic musculoskeletal pain: a conceptual breakthrough with multiple clinical implications. *Pain Res Manag* 2002;7:81–92
41. Arendt-Nielsen L, Graven-Nielsen T: Central sensitization in fibromyalgia and other musculoskeletal disorders. *Curr Pain Headache Rep* 2003;7:355–61
42. Woolf CJ: Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152(3 Suppl):S2–15
43. Skljarevski V, Ramadan NM: The nociceptive flexion reflex in humans – review article. *Pain* 2002;96:3–8