Running title

Neural Mechanosensitivity in Chronic Neck Pain.

Title

Differences in Neural Mechanosensitivity between Patients with Chronic Nonspecific Neck Pain with and without Neuropathic Features. A Descriptive Cross-Sectional Study.

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ABSTRACT

Objective: To assess differences in neural mechanosensitivity between patients with chronic nonspecific neck pain with and without neuropathic features (NF and No-NF, respectively).

Design: Descriptive, cross-sectional study.

Setting: A primary care center, a hospital physiotherapy outpatient department, and a university campus.

Subjects: Chronic nonspecific neck pain patients classified by the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale [S-LANSS; 49 patients with NF (S-LANSS ≥ 12) and 50 patients with No-NF (S-LANSS < 12)] and a healthy control group (n = 48).

Methods: The primary measurements were the mechanosensitivity of the median nerve and cervical region, specifically the assessment of the onset of symptoms and submaximal pain intensity according to the Upper Limb Neural Test 1 (ULNT1) for the median nerve and the Modified Passive Neck Flexion Test (MPNFT) for the cervical region; secondary measurements included pain intensity, neck disability, kinesiophobia, and pain catastrophizing.

Results: Statistically significant differences between the NF and No-NF groups were found with respect to the onset of symptoms of ULNT1 [-15.11 (-23.19 to -7.03)] and MPNFT [-6.58 (-11.54 to -1.62)], as well as the outcomes of the VAS [Mean difference (95% Confidence Interval); 7.12 (1.81 to 12.42)] and NDI [3.72 (1.72 to 5.71)]. Both chronic nonspecific neck pain groups showed statistically significant differences compared to the CG for all outcomes assessed ($P<0.01$) except for the onset of symptoms of ULNT1 in the No-NF group.

Conclusions: The findings of this study suggest that chronic nonspecific neck pain patients with NF have greater neural mechanosensitivity, pain intensity, and neck disability than those with No-NF.

Key words: chronic pain, mechanosensory, psychosocial factors, neck pain, pain catastrophizing.

INTRODUCTION

Neck pain is one of the most significant problems in healthcare [1]. With three-quarters of people worldwide experience pain in this region at some time in their lives [1], this condition has considerable social and economic impact [2,3]. In addition, neck pain is more prevalent in middle-aged women and tends to become chronic [4,5].

Nociceptive pain is defined as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" [6], while neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [6,7]. Conceptually, in neuropathic pain, the excitability of neurons increases as a result of sensitization. Nowadays there is a debate about whether this sensitization occurs in the peripheral or central nervous systems or both [8]. It is also unclear whether chronic neck pain is a neuropathic or nociceptive [9]. A sensory hypersensitivity can be considered a dysfunction of the nervous system [10]. A cervical hypersensitivity has been demonstrated in chronic neck pain conditions, but the existence of a widespread hypersensitivity is still debated. The widespread hypersensitivity in chronic whiplash is supported by several investigations [11–15]; however, in chronic nonspecific neck pain the literature is limited and controversial [13,16–19]. Some research has shown that whiplash may have a neuropathic features (NF) [12,20,21], which could explain the difference in the pain processing mechanism found with chronic nonspecific neck pain. In addition, patients with whiplash have a higher neural mechanosensitivity in the upper limb nerve trunks in neurodynamic tests [21,22], potentially contributing to the appearance and perpetuation of widespread hypersensitivity. However, there is a lack of evidence regarding the neural

mechanosensitivity in chronic nonspecific neck pain. The neural mechanosensitivity is believed to be a protective mechanism that occurs when nerves are subjected to mechanical stress during movement [23]. Hence, considering the information presented above, it is possible that patients with chronic nonspecific neck pain with NF will present higher neural mechanosensitivity than those without NF (No-NF).

In the literature, several authors consider the classification of nociceptive pain and neuropathic pain as relatively simple; however, this organization is useful for selecting the optimal treatment for reducing pain [10,24–27]. Among the diverse tools to discern between the two types of pain, the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) score is a reliable and valid tool for the differential diagnosis of pain with NF [28].

There are studies that suggest psychological factors influence the results of neural tests [29–31]. Beneciuk et al. [29] reported that asymptomatic subjects with more pain catastrophizing experience a more intense pain when undergoing the Upper Limb Neural Test 1 (ULNT1), while the elbow´s range of motion did not show any correlation. This test is often used as a diagnostic tool in patients with neurogenic symptoms in the upper limb [32], allowing us to assess the median nerve and the brachial plexus mechanosensitivity [33,34]. Therefore, our hypothesis is that chronic nonspecific neck pain patients with NF will present greater mechanosensitivity than those with No-NF when the neural test is applied.

Thus, the aim of our study was to assess differences present in patients with chronic nonspecific neck pain regarding neural mechanosensitivity of the upper limb and

cervical region comparing those with NF and those with No-NF. In addition, the authors expected to observe associations in these two types of chronic nonspecific neck pain between neurodynamic test outcomes and psychosocial factors.

METHODS

Study Design and Raters

A cross-sectional study was conducted to assess differences in the neural mechanosensitivity of patients with chronic nonspecific neck pain with NF compared to patients with chronic nonspecific neck pain with No-NF. The investigation was developed according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement at the beginning of November 2011, being finished in March 2014.

The research team was composed of 4 clinical examiners (6, 6, 8 and 10 years post qualification experience) with over 5 years of experience in manual therapy. Two half-hour training sessions were scheduled to perform the neurodynamic test in a like manner before commencing the actual study; in order to ensure this objective, all examiners performed the tests several times and followed a standardized sequence for each neurodynamic test (See “Mechanosensitivity of the Median Nerve and the Cervical Region” section). This procedure was continued until all examiners performed both test the same way. Additionally, they were responsible for collecting all outcome data, so it was an unblinded study.

Subjects

198 A total of 147 subjects were recruited for the study. The control group (CG) consisted
199 of 33 females and 15 males (mean ± SD age, 43.64 ± 11.09) recruited from the Center
200 for Advanced Studies University La Salle (Madrid, Spain) by print advertisements
201 placed around the campus. All of the subjects in this group were between 18-65 years
202 old and received a physical assessment to confirm their pain-free state. The CG
203 exclusion criteria were as follows: 1) history of cervical, upper limb, orofacial, or
204 upper thoracic pain in the previous 12 months; 2) previous cervical surgery and/or
205 whiplash trauma; and 3) taking any medication during the last 3 months.
206
207 Patients with chronic nonspecific neck pain were consecutively recruited by referral
208 from the primary care center of Coslada (Madrid) and the physiotherapy outpatient
209 department of University Hospital La Paz (Madrid). These patients were classified by
210 the S-LANSS. The final sample was constituted of 49 patients (41 females y 8 males;
211 42.38 ± 14.26) with NF (NF; S-LANSS ≥ 12), and 50 patients (37 females y 13
212 males; 44.76 ± 14.66) with No-NF (No-NF; S-LANSS < 12). The symptomatic
213 subjects were selected if they fulfilled the following inclusion criteria: age between
214 18-65 years; neck/shoulder pain for at least 3 months with symptoms provoked by
215 neck postures, neck movement, or palpation of the cervical musculature; clinical
216 diagnosis of nonspecific neck pain by a medical specialist; and the ability to read and
217 speak Spanish. Patients were also excluded if they presented rheumatologic diseases
218 or any type of cancer, cervical surgery in the past, cervical radiculopathy,
219 myelopathy, whiplash trauma, or if they had received some type of pain treatment,
220 including medication and physical therapy, during the last 3 months.
221

After checking that each of the subjects met the inclusion/exclusion criteria, all participants were asked to read and sign informed consent approved by the local Ethics Committee for Clinical Research of the Hospital La Paz (registration number: PI-1241).

Dependent Outcome.

The S-LANSS was used to identify pain with NF. The application of this scale is comprised of two phases. The first consisted of 5 questions that the patient should answer "yes" if they are related to the pain that they suffered during the last week. The second phase contained two questions for which patients had to examine themselves to determine the presence of allodynia and altered sensation. These items are marked as present or absent with appropriate scale scores. The assessor is then asked to sum the scale scores and compare them with the cut-off values ("if score ≥ 12, then neuropathic mechanisms are likely to contribute to the patient's pain") [35]. The S-LANSS is a modified version of the LANSS scale. The LANSS scale consists of 7 similar questions, two of which include clinical examination by a physician to determine the presence of allodynia and altered pinprick threshold. Thus, the difference between these two scales is that the S-LANSS is a self-administered questionnaire, whereas the LANSS requires physician examination. The original S-LANSS scale has proven to be a reliable and valid instrument for the differential diagnosis of pain with NF [28]. In the absence of a Spanish version of the S-LANSS, we translated the original scale using a translation/back-translation process, following the classic procedure [36]. As a measure of the internal consistency, we used Cronbach's alpha, which was determined to be 0.72.

Primary Measurements

Mechanosensitivity of the Median Nerve and the Cervical Region

These outcomes were assessed using the following neurodynamic tests: ULNT1 and Modified Passive Neck Flexion Test (MPNFT) (Figure 1). Below, the authors briefly describe what each test consisted of and its purpose:

ULNT1

This test was used to assess the mechanosensitivity of the median nerve. To perform the test, all subjects were asked to lie supine. The examiner then placed one of the heads of an ACUMAR digital dual inclinometer (Model ACU 002 from Lafayette Instrument Company; Lafayette, Indiana) at the midpoint of the dominant arm and the other in the distal third of the forearm. Both heads were fixed by means of Velcro strips. According to manufacturer's specifications, this digital inclinometer is capable of measuring -180° to +180º with an accuracy of ± 1. The sequence used for ULNT1 was the following: depression of the shoulder girdle, shoulder abduction 90°, forearm supination, wrist and finger extension, then shoulder external rotation. At this time, the examiner reset the marker on the digital inclinometer. Finally, the examiner proceeded to perform elbow extension. When the participant's symptoms started the physiotherapist recorded the inclinometer´s values (elbow extension range of motion). Following this, the assessor continued to increase elbow extension until reaching the submaximal pain of the subject (the greatest level of pain which the subject was prepared to tolerate) and then asked the participant to indicate the amount of pain perceived using the Visual Analogue Scale (VAS). The examiner performed 3 consecutive repetitions of the ULNT1 with 30 seconds between them. Due to the parameters of shoulder depression and shoulder abduction, the ULNT-1 increases

strain throughout the brachial plexus [34]. Hence, the patient´s symptoms must be reproduced by the test due to its mechanical provocation in the cervical roots and median nerve [37,38]. Hypersensitive responses to this test have been established in chronic neck pain [39,40]. In addition, the ULNT1 is a reliable measure of median nerve mechanosensitivity [Intraclass Correlation Coefficient (ICC) = 0.80; Standard Error of Measurement (SEM) = 3.83º; Minimal Detectable Change (MDC) = 10.58º] [41,42], and can be a valid tool to determine certain diseases such as cervical radiculopathy [43,44].

MPNFT

The passive neck flexion test is used to diagnose possible spinal disorders, headaches, and arm and leg pain with a cervical origin. It was used a modified version of this test in which the subject was placed in the supine position with arms along the body, and the simple digital inclinometer was attached to the frontal bone with Velcro strips. The assessor performed two grasps: 1) on the occipital bone and 2) on the upper jaw (just below the nose of the participant). Subsequently, the examiner made a double chin movement (increasing the tension in the cranio-cervical area), followed by neck flexion. At this point, the procedure used was the same as for the ULNT1; the physiotherapist recorded the range of motion of appearance of symptoms, and the pain intensity perceived by the subject on the VAS. The examiner performed 3 consecutive repetitions of the MPNFT with 30 seconds between them. In the absence of reliability studies of the MPNFT, we used the 3 measurements obtained to assess the reliability of the test (ICC = 0.81-0.91; SEM = 2.18-4.13º; MDC = 5.10-9.64º].

Secondary Measurements

297 Pain intensity was measured via the VAS. It was a 100-mm horizontal line with pain
298 descriptors marked “no pain” at the left side and “the worst pain imaginable” at the
299 right side. The patient was asked what their pain intensity was at the time by marking
300 the VAS with a perpendicular line. The VAS has been found to be a reliable and valid
301 measure of pain [45,46]. A difference of 11.1-mm in the VAS is considered the MDC
302 in patients with a chronic pain of moderate intensity (40-mm < VAS score < 70-mm)
303 [47].
304
305 Disability was assessed using the Neck Disability Index (NDI). It is a 10-item
306 questionnaire, with 6 possible answers that represent 6 levels of functional capacity,
307 ranging from 0 (no disability) to 5 (complete disability). Higher scores indicate more
308 disability (maximum score, 50 points). The NDI has sufficient support in the literature
309 to be the most commonly used method to report neck pain [48,49]. A validated
310 Spanish version of the NDI was used [50]. The MDC for the NDI is reported to be
311 approximately 5 points [48].
312
313 The abbreviated version of the Tampa Scale for Kinesiophobia-11 (TSK-11) was used
314 to assess fear of movement and injury. The validated Spanish version has shown good
315 reliability and validity [51]. The 11 items are scored 1-4, with total scores ranging
316 from 11 to 44. The addition of all the points obtained from each of the items results in
317 the level of kinesiophobia, with higher scores indicating greater perceived
318 kinesiophobia. The SEM and MDC for the TSK-11 were 2.41 and 5.6 points,
319 respectively [52].
320

To evaluate the participant's propensity to catastrophize about pain, it was used the Pain Catastrophizing Scale (PCS). This tool is a 13-item questionnaire designed to measure the three components of pain-related catastrophizing: rumination, magnification, and helplessness, resulting in a unique score. Each item is responded to on a 5-point scale (0 = not at all, 4 = all the time) relating the degree to which the individual experiences a thought or feeling of a painful situation. The Spanish version also showed appropriate psychometric properties [53].

Sample Size

The sample size was calculated by G*Power© 3.1.7 software (University of Düsseldorf, Germany) [54] and was considered as a power calculation to detect between-group differences in the primary outcome measures (Mechanosensitivity of the Median Nerve and the Cervical Region). To obtain 90% statistical power (1-β error probability) with an α error level probability of 0.05, a one-way fixed-effects analysis of variance model and a medium-large effect-size of 0.3 were used; this effect-size was established using a theoretical model based on a previous study [20]. It was estimated that at least 144 subjects would be required (48 per group).

Data Analysis

The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 20.0.[f] (SPSS 21, SPSS Inc., Chicago, IL USA). For all of the analyses, statistical significance was set at $P < 0.05$. The descriptive statistics used to summarize the data for the continuous variables are presented as the means ± standard deviation (SD) and the 95% confidence interval (CI), whereas the categorical variables are presented as an absolute number or relative frequency

346 percentage. For all of the variables, the Z-score was assumed to follow a normal
347 distribution based on the central limit theorem because all of the groups had more
348 than 30 subjects [55,56].
349
350 A chi-square test with residual analysis was used to compare the categorical variables.
351 One-way analysis of variance (ANOVA) was used to analyze the continuous
352 parametric data; the group factor was analyzed for primary and secondary
353 measurements (mechanosensitivity variables of the median nerve and the cervical
354 region; VAS; NDI; TSK-11; PCS). A post hoc analysis with Bonferroni corrections
355 was performed in the case of significant ANOVA findings for multiple comparisons
356 between variables. To test the relationship between neurodynamic test outcomes and
357 psychosocial variables, Pearson's correlations were calculated separately for pain
358 with NF, pain with No-NF and CG.
359
360 Multiple linear regression analysis was performed to estimate the strength of the
361 associations between the results of the mechanosensitivity outcomes of the median
362 nerve and the cervical region (criterion variables) in the two chronic nonspecific neck
363 pain groups (NF and No-NF). The psychological and pain-related variables (TSK-11,
364 PCS, VAS, and NDI) were used as predictor variables.
365
366 The variance inflation factors (VIFs) were calculated to determine whether there were
367 any multi-collinearity issues in any of the three models. The strength of association
368 was examined using regression coefficients (B), P values, and adjusted R^2. The
369 standardized beta coefficients (β) were reported for each predictor variable included
370 in the final reduced models to allow for direct comparison between the predictor

variables in the regression model and the criterion variable being studied. For the regression analysis, the rule of 10 cases per variable was applied to obtain reasonably stable estimates of the regression coefficients [57].

RESULTS

A total of 154 chronic nonspecific neck pain patients were screened, of whom 147 (95.5 %) were eligible and agreed to enter the study. The mean age of the sample was 43.63 ± 13.41 years and most of them were female (75.5%). Regarding the duration of neck pain, the NF group reported an average of 83.8 ± 66.16 months (range, 6-300; 95%CI, 64.79 to 102.8), while the No-NF group reported 84.08 ± 89.53 months (range, 4-360; 95% CI, 58.9 to 109.26). No differences were found between the 3 groups for the demographic characteristics; thus, the groups were similar and comparables. Further descriptive characteristics of the participants are shown in Table 1.

The results of the ANOVA revealed a significant effect for the Group factor [onset of symptoms of ULNT1 ($F = 24.188$; $P < 0.001$); submaximal pain intensity reported in ULNT1 ($F = 22.346$; $P < 0.001$); onset of symptoms of MPNFT ($F = 31.311$; $P < 0.001$); submaximal pain intensity reported in MPNFT ($F = 126.136$; $P < 0.001$); VAS ($F = 428.717$ $P < 0.001$); NDI ($F = 187.755$; $P < 0.001$); TSK-11 ($F = 31.492$; $P < 0.001$); PCS ($F = 28.200$ $P < 0.001$)]. Statistically significant differences between the NF group and No-NF group were found with respect to the onset of symptoms of ULNT1 and MPNFT, as well as the outcomes of the VAS and NDI. Both chronic nonspecific neck pain groups showed statistically significant differences compared with the CG for all outcomes assessed except the onset of symptoms in the ULNT1

for the No-NF group. Table 2 shows the values as mean±SD of each group and mean differences (95% Confidence Interval) between groups.

The authors examined the association (Pearson correlation coefficients) among the mechanosensitivity variables of the median nerve and the cervical region, VAS, NDI, TSK-11, and PCS against themselves for each group (Table 3). The largest association observed in the NF group ($r = -0.733$; $P < 0.001$) and the CG ($r = -0.617$; $P < 0.001$), was between the onset of symptoms of ULNT1 and submaximal pain intensity reported in the same neural test, while in the No-NF group was between submaximal pain intensities reported in both neural tests ($r = 0.601$; $P < 0.001$).

The regression models for criterion variables (mechanosensitivity of the median nerve and the cervical region) are presented in Tables 4 and 5**.** The regression model for the NF group showed that only TSK-11 was a significant predictor of the onset of symptoms of ULNT1 (19% of variance), while VAS was a significant predictor of the onset of symptoms of MPNFT (28% of variance). For this same group, the significant predictor variables of submaximal pain intensity reported in ULNT1 and MPNFT were PCS (25.9% of variance) and NDI (9.8% of variance), respectively. In the No-NF group, the regression model showed that PCS was the only significant predictor variable for the onset of symptoms of ULNT1 (7.1% of variance). The No-NF group obtained the same significant predictor variables as NF group, using submaximal pain intensity reported in ULNT1 (PCS explained 12.8% of variance) and MPNFT (NDI explained 9.8% of variance) as independent variables. No predictor variables were found for any criterion variables in CG, nor for onset of symptoms of MPNFT in the No-NF group.

DISCUSSION

The results of this study demonstrated that chronic nonspecific neck pain patients with NF showed greater neural mechanosensitivity during neurodynamic testing than those with No-NF. Patients with NF also reported greater pain intensity and greater disability when compared to those with No-NF, but these differences were within the limits of the MDC and could thus be explained by measurement error. Furthermore, statistically significant differences were observed between the two groups with chronic nonspecific neck pain versus CG in all variables, except when the No-NF group was compared with CG for onset of symptoms of ULNT1.

Our results are consistent with two previous studies showing a complex presentation of higher levels of pain, disability and hypersensitivity when NF is present in chronic neck pain [13,22]. Our findings are consistent with our hypothesis that patients with chronic nonspecific neck pain and NF will develop symptoms much earlier than patients in the No-NF group in tests focused on increasing neural tension, indicating greater mechanosensitivity in the NF group.

To our knowledge, no previous studies in the literature have evaluated differences in the mechanosensitivity of the cervical region and median nerve of chronic nonspecific neck pain patients with NF and those with No-NF; however, differences in mechanosensitivity as determined by the ULNT1 have been observed between patients with acute whiplash with and without NF [21]. In addition, a study conducted by Beith et al. [58] reported increased mechanosensitivity in low back pain patients

445 with possible neuropathic origin when they received a passive straight leg raise test,
446 compared to patients whose back pain was of possible nociceptive origin.
447
448 Our study agrees with numerous reports that pain with NF is more intense and
449 produces greater disability than pain with No-NF; however, our outcomes did not
450 exceed the MCD and therefore should be taken with caution [58–62]. Nonetheless, no
451 differences were found between both types of pain for kinesiophobia and pain
452 catastrophizing. The evidence concerning psychosocial factors is contradictory. In
453 agreement with our results, some studies have demonstrated that patients with
454 neuropathic orofacial pain have similar levels of catastrophizing, anxiety, and
455 depression as those with non-neuropathic orofacial pain [63,64]. However, studies in
456 subjects with low back pain have found that anxiety and depression, both related to
457 pain catastrophizing [65,66], are significantly higher in patients with NF than in those
458 with No-NF [58,62]. These differences between regions are beyond our knowledge.
459 Reinforcing our results, numerous studies have reported that psychosocial adverse
460 effects caused by chronic pain are independent of their origin [64,67–69].
461
462 Statistically significant differences were observed when either the NF or No-NF
463 group was compared with the CG for all of the variables except the ULNT1 results
464 when the No-NF and CG groups were compared.
465
466 As mentioned previously, no significant difference was found in the range of motion
467 that triggered the onset of symptoms in the ULNT1 between patients with No-NF and
468 the healthy controls, although we observed an important trend toward significance. As
469 far as the authors know, there are no studies available to discuss this result. Other

authors have found differences in the ULNT1 results between patients with chronic whiplash and healthy subjects [22]; thus, our observed lack of differences between the No-NF group and CG could be explained by the fact that chronic whiplash condition presents with NF [12,18]. Heightened neural mechanosensitivity in NF group at sites outside and remote to the symptomatic site (neck region), could be suggestive of central sensitization since there is large evidence that supports the presence of generalized hypersensitivity of the somatosensory system in this condition [11,39,70–72]. In addition, an increased response to the ULNT1 has been proposed as a sign of central sensitization [73,74]. Thus, these findings suggest that the pain with NF might be associated with central sensitization, whereas pain with No-NF might be only peripheral sensitization. Consistent with this theory, other authors have demonstrated higher probability of having signs of central sensitization in patients with pain with NF [12,20,39,71,72,75].

In general, we must emphasize that the contribution of regression models as potential predictors was small. Regression models showed that, for onset of symptoms of ULNT1, a negative predictor in the NF group was kinesiophobia, whereas in the No-NF group it was pain catastrophizing. Increased psychosocial factors are associated with larger outcomes in pain and disability [76–79], which could explain this early onset of symptoms. Regarding the onset of symptoms of MPNFT, only pain intensity was a negative predictor for the NF group, and no predictor was found for the No-NF group. Concerning the submaximal pain intensity reported by performing neurodynamic tests, our findings showed that pain catastrophizing was a positive predictor for ULNT1 in both groups, while for MPNFT the positive predictor was NDI. Again, these results are supported by wide evidence that exhibits an important

link between psychosocial factors, disability, and pain [76–78,80]. It is important to note that in CG, no correlations were found between physical-psychological variables and those related to the neurodynamic tests, and therefore the CG had no predictor variables. However, Beneciuk et al. [29] found that an increase in pain catastrophizing was a predictor of an increased pain intensity perception when ULNT1 was performed. Perhaps the difference between our results and those of Beneciuk lies in that their sample had a much lower average age and was constituted of more males, but really the authors do not know the exact reason for these differences.

Study limitations

This cross-sectional study had some limitations. Firstly, the assessor was unblinded to the results, potentially compromising the validity of them. Thus, these findings should be interpreted with caution. Secondly, it was a cross-sectional study so the results cannot be used with predictive value [81]. Future studies with longitudinal designs to check the trend of these associations are needed. Thirdly, the LANSS scale has been validated to Spanish [82], but not S-LANSS. The unique difference between these two scales is that the latter two items are performed by an examiner in the LANSS scale, while in S-LANSS are performed by the patients themselves. In our opinion, this fact should be considered, although we do not believe that was crucial for our results. Another limitation was that although the S-LANSS scale is validated as a screening tool for pain with NF [28], currently there is no “gold standard,” and this is considered a potential risk for error [28,83].

Clinical Implications

519 Having the tools to identify clinical differences in patients with chronic nonspecific
520 neck pain will allow us to select the most effective interventions for each patient. Our
521 findings reflect a greater sensitization and a greater involvement of negative
522 psychosocial factors in chronic nonspecific neck pain patients with NF versus chronic
523 nonspecific neck pain patients with No-NF.
524

525 **CONCLUSIONS**

526 This study suggests that chronic nonspecific neck pain patients with NF have greater
527 neural mechanosensitivity, pain intensity, and neck disability than those with No-NF;
528 however, the differences for pain intensity and neck disability did not exceed the
529 MDC. Both chronic nonspecific neck pain groups showed statistically significant
530 differences when compared with CG for all outcomes, except between No-NF group
531 and CG for onset of symptoms of ULNT1. Future studies are needed to evaluate the
532 differences in the physical and psychological characteristics between pain with and
533 without NF to support these results.
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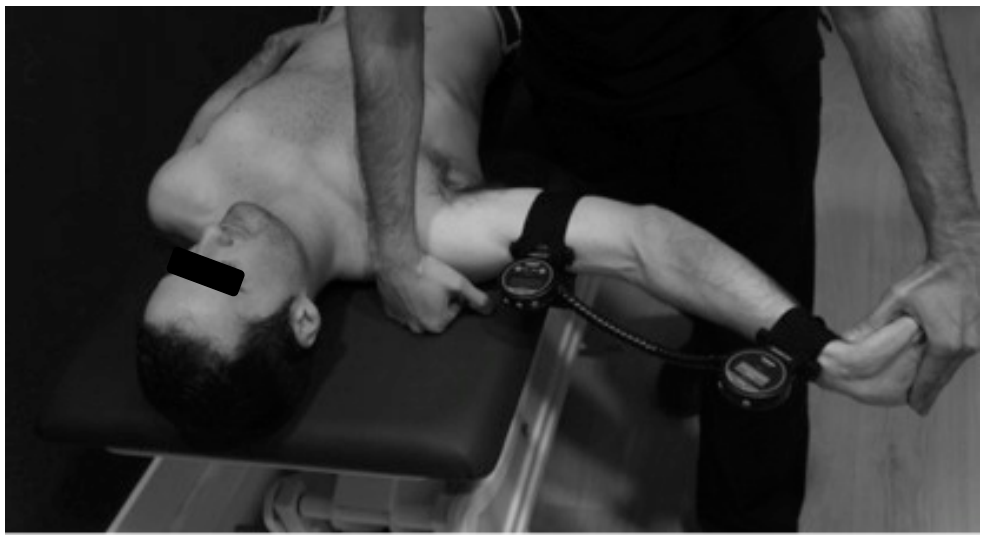
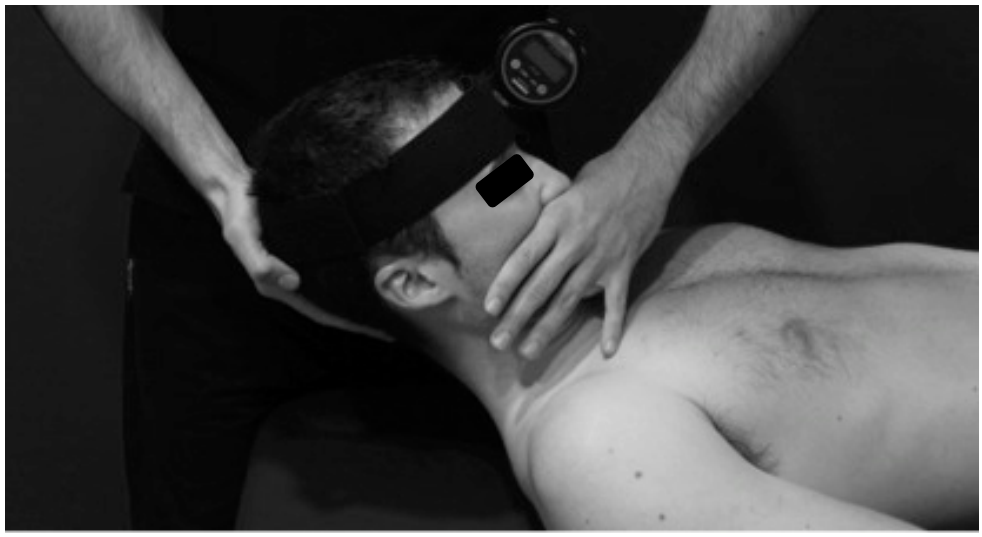
Figure 1. Neurodynamic tests.

NEURODYNAMIC TESTS



a. Upper Limb Neural Test 1.



b. Modified Passive Neck Flexion Test.

Table 1. Demographic characteristics and neck pain duration of participants. Values are mean ± SD and n (%).

	NF (n = 49)	No-NF (n = 50)	CG (n = 48)	P value of independent samples ANOVA or χ^2 test
Age years	42.38 ± 14.26	44.76 ± 14.66	43.64 ± 11.09	0.683*
Gender (female)	41 (83.7)	37 (74)	33 (68.8)	0,222†
Height (cm)	164.65 ± 8.51	164.82 ± 9.34	168.5 ± 8.75	0.061*
Weight (kg)	65.73 ± 11.79	65.57 ± 12.5	65.57 ± 12.98	0.997*
Neck pain duration				
3 to 6mo	3 (6.1)	8 (15.7)	-	0.461†
7 to 12mo	3 (6.1)	5 (9.8)	-	0.161†
13 and 36mo	11 (22.5)	8 (15.7)	-	0.172†
More than 36mo	32 (65.3)	30 (58.8)	-	0.153†

Abbreviations: NF, Pain with Neuropathic Features; No-NF, Pain without Neuropathic Features; CG, Control Group; ANOVA, Analysis Of Variance.
* Independent-samples ANOVA.
† χ^2 tests.

Table 2. Between group comparisons.

	Mean ± SD			Mean difference (95% CI);
	NF	**No-NF**	**CG**	**a) NF vs. No-NF** **b) NF vs. CG** **c) No-NF vs. CG**
OS-ULNT1	62.74 ± 23.14	77.84 ± 15.05	86 ± 8.06	**a)** -15.11 (-23.19 to -7.03) † **b)** -23.27 (-31.51 to -15.02) † **c)** -8.16 (-16.32 to 0.01)
SP-ULNT1	46 ± 22.95	37.18 ± 28.13	14.81 ± 17.94	**a)** 8.82 (-2.57 to 20.22) **b)** 31.19 (19.56 to 42.82) † **c)** 22.38 (10.85 to 33.89) †
OS-MPNFT	53.78 ± 11.83	60.35 ± 9.8	70.04 ± 7.24	**a)** -6.58 (-11.54 to -1.62) † **b)** -16.28 (-21.32 to -11.22) † **c)** -9.69 (-14.44 to -4.94) †
SP-MPNFT	45.53 ± 15.31	48.35 ± 18.98	4.13 ± 8.84	**a)** -2.83 (-10.55 to 4.9) **b)** 41.4 (33.53 to 49.27) † **c)** 44.23 (36.83 to 51.62) †
VAS	59.96 ± 11.93	52.84 ± 14.44	-	**a)** 7.12 (1.81 to 12.42) † **b)** - **c)** -
NDI	16.24 ± 4.79	12.53 ± 5.07	0.66 ± 1.01	**a)** 3.72 (1.72 to 5.71) † **b)** 15.56 (13.55 to 17.62) † **c)** 11.87 (9.86 to 13.88) †
TSK-11	30.84 ± 6.09	29.29 ± 7.62	20.66 ± 6.42	**a)** 1.54 (-1.73 to 4.82) **b)** 10.18 (6.83 to 13.52) † **c)** 8.64 (5.32 to 11.95) †
PCS	16.45 ± 9.56	13.57 ± 9.07	4.55 ± 4.43	**a)** 2.88 (-1.04 to 6.8) **b)** 11.9 (7.9 to 15.89) † **c)** 9.02 (5.06 to 12.97) †

Abbreviations: NF, Pain with Neuropathic Features; No-NF, Pain without Neuropathic Features; CG, Control Group; CI, Confidence interval; OS-ULNT1, Onset of Symptoms-Upper Limb Neural Test 1; SP-ULNT1, Submaximal Pain-ULNT1; OS-MPNFT, Onset of Symptoms-Modified Passive Neck Flexion Test-Range Of Motion; SP-MPNFT, Submaximal Pain-Modified Passive Neck Flexion Test; VAS, Visual Analogue Scale; NDI, Neck Disability Index; TSK-11, Tampa Scale of Kinesiophobia-11; PCS, Pain Catastrophizing Scale.
† $P<0.01$.

Table 3. Pearson correlation coefficient for all outcomes in each group.

Group		SP-ULNT1	OS-MPNFT	SP-MPNFT	VAS	NDI	TSK-11	PCS
NF	**OS-ULNT1**	-0.733†	0.586†	-0.278	-0.371†	-0.212	-0.455†	-0.439†
No-NF		-0.545†	0.392†	-0.198	0.129	-0.228	-0.058	-0.299*
CG		-0.617†	-0.153	-0.118	-	0.102	0.082	-0.136
NF	**SP-ULNT1**		-0.404†	0.493†	0.298*	0.191	0.386†	0.524†
No-NF			-0.079	0.601†	0.126	0.356*	0.224	0.382†
CG			-0.017	0.156	-	0.124	0.053	0.097
NF	**OS-MPNFT**			-0.407†	-0.547†	-0.330*	-0.218	-0.157
No-NF				0.125	0.081	0.004	-0.095	-0.272
CG				-0.113	-	0.008	0.103	0.129
NF	**SP-MPNFT**				0.093	0.349*	0.078	0.187
No-NF					0.251	0.341*	0.018	-0.009
CG					-	0.162	-0.054	-0.04
NF	**VAS**					0.176	0.306*	0.387†
No-NF						0.224	0.342*	0.236
CG						-	-	-
NF	**NDI**						0.229	0.455†
No-NF							0.455†	0.425†
CG							0.069	-0.006
NF	**TSK-11**							0.519†
No-NF								0.509†
CG								0.612†

Abbreviations: NF, Pain with Neuropathic Features; No-NF, Pain without Neuropathic Features; CG, Control Group; OS-ULNT1, Onset of Symptoms-Upper Limb Neural Test 1; SP-ULNT1, Submaximal Pain-Upper Limb Neural Test 1; OS-MPNFT, Onset of Symptoms-Modified Passive Neck Flexion Test; SP-MPNFT, Submaximal Pain-Modified Passive Neck Flexion Test; VAS, Visual Analogue Scale; NDI, Neck Disability Index; TSK-11, Tampa Scale of Kinesiophobia-11; PCS, Pain Catastrophizing Scale.
* $P<0.05$.
† $P<0.01$.

Table 4. Regression model for onset of symptoms of both neurodynamic tests in each chronic neck pain group.

Criterion variable: OS-ULNT1					
Group					
NF	**Overall model** $R^2 = 0.207$ **Adjusted** $R^2 = 0.190$ **F** = 12.247				
	Predictor variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	TSK-11	-1.727	-0.455	0.001	1.00
	Excluded variables				
	VAS	-	-0.256	0.059	1.103
	NDI	-	-0.113	0.401	1.056
	PCS	-	-0.278	0.067	1.368
No-NF	**Overall model** $R^2 = 0.089$ **Adjusted** $R^2 = 0.071$ **F** = 4.811				
	Predictor variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	PCS	-0.496	-0.299	0.033	1.00
	Excluded variables				
	VAS	-	0,212	0.133	1.059
	NDI	-	-0.123	0.418	1.221
	TSK-11	-	0.127	0.428	1.350
Criterion variable: OS-MPNFT					
Group					
NF	**Overall model** $R^2 = 0.299$ **Adjusted** $R^2 = 0.280$ **F** = 16.191				
	Predictor Variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	VAS	-5.485	-0.547	<0.001	1.00
	Excluded Variables				
	NDI	-	-0.223	0.109	1.048
	TSK-11	-	-0.040	0.784	1.124
	PCS	-	0.131	0.401	1.289

Abbreviations: VIF, variance inflation factor; NF, Pain with Neuropathic Features; No-NF, Pain without Neuropathic Features; OS-ULNT1, Onset of Symptoms-Upper Limb Neural Test 1; OS-MPNFT, Onset of Symptoms-Modified Passive Neck Flexion Test-Range Of Motion; VAS, Visual Analogue Scale; NDI, Neck Disability Index; TSK-11, Tampa Scale of Kinesiophobia-11; PCS, Pain Catastrophizing Scale.

Table 5. Regression model for submaximal pain intensity reported in both neurodynamic tests in each chronic neck pain group.

Criterion variable: SP-ULNT1					
Group					
NF	**Overall model**				
	R^2 = 0.274	**Adjusted R^2** = 0.259	**F** = 17.757		
	Predictor variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	PCS	0.126	0.524	<0.001	1.00
	Excluded variables				
	VAS	-	0.112	0.413	1.176
	NDI	-	-0.060	0.671	1.261
	TSK-11	-	0.157	0.284	1.368
No-NF	**Overall model**				
	R^2 = 0.146	**Adjusted R^2** = 0.128	**F** = 8.366		
	Predictor Variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	PCS	0.118	0.382	0.006	1.00
	Excluded variables				
	VAS	-	0.038	0.781	1.059
	NDI	-	0.236	0.106	1.221
	TSK-11	-	0.040	0.796	1.350
Criterion variable: SP-MPNFT					
Group					
NF	**Overall model**				
	R^2 = 0.122	**Adjusted R^2** = 0.098	**F** = 5.256		
	Variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	NDI	0.104	0.349	0.027	1.00
	Excluded variables				
	VAS	-	0.020	0.900	1.048
	TSK-11	-	-0.004	0.978	1.059
	PCS	-	0.014	0.937	1.344
No-NF	**Overall model**				
	R^2 = 0.116	**Adjusted R^2** = 0.098	**F** = 6.461		
	Variables	**Regression coefficient (B)**	**Standardized coefficient (β)**	**P value**	**VIF**
	NDI	0.128	0.341	0.014	1.00
	Excluded variables				
	VAS	-	0.184	0.185	1.053
	TSK-11	-	-0.172	0.257	1.260
	PCS	-	-0.188	0.209	1.221

Abbreviations: VIF, variance inflation factor; NF, Pain with Neuropathic Features; No-NF, Pain without Neuropathic Features; SP-ULNT1, Submaximal Pain-Upper Limb Neural Test 1; SP-MPNFT, Submaximal Pain-Modified Passive Neck Flexion Test; VAS, Visual Analogue Scale; NDI, Neck Disability Index; TSK-11, Tampa Scale of Kinesiop