J Rehabil Med 2014; 46: 553–560

ORIGINAL REPORT

NECK PAIN INTENSITY DOES NOT PREDICT PRESSURE PAIN HYPERALGESIA: RE-ANALYSIS OF SEVEN RANDOMIZED CONTROLLED TRIALS

Romy Lauche, PhD[1], Holger Cramer, PhD[1], Jost Langhorst, MD[1], Gustav Dobos, MD[1] and Björn Gerdle, MD, PhD[2]

From the [1]Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany, [2]Rehabilitation Medicine, Department of Medicine and Health Sciences, Linköping University and Pain and Rehabilitation Centre, UHL, County Council of Östergötland, Linköping, Sweden

Objectives: **To determine factors, including pain intensity, associated with pressure pain sensitivity in chronic non-specific neck pain and with changes after therapeutic interventions.**

Methods: **This re-analysis used pooled data from 7 randomized controlled clinical trials. Pressure pain thresholds were assessed at the hand and at the site of maximal pain in the neck region before and after different non-pharmacological interventions. Age, gender, neck pain intensity and duration, mental health, expectancy and time interval between measurements were used to determine factors influencing pressure pain thresholds as well as pressure pain threshold changes.**

Results: **A total of 346 patients (77 males, 269 females, mean age 52.6 years (standard deviation 12.0 years)) were included in study, 306 of whom provided a complete data-set for analysis. Pressure pain thresholds at the neck area or the hand did not correlate with pain intensity. Changes in pressure pain thresholds correlated with time between measurements, indicating time-sensitive changes.**

Discussion: **No coherent correlations between pressure pain thresholds and pain intensity were found. Further research is needed to evaluate the relationship between pain intensity and pressure pain thresholds before its use as a valid substitute of pain rating can be supported. Until then, the results of trials with respect to using pressure pain thresholds as an outcome variable must be interpreted with care.**

Key words: neck pain; chronic pain; pressure pain sensitivity; hyperalgesia.

J Rehabil Med 2014; 46: 553–560

Correspondence address: Romy Lauche, Kliniken Essen-Mitte, Klinik für Naturheilkunde und Integrative Medizin, Am Deimelsberg 34a, DE-45276 Essen, Germany. E-mail: r.lauche@kliniken-essen-mitte.de

Accepted Feb 4, 2014; Epub ahead of print Apr 8, 2014

INTRODUCTION

Neck pain is a major public health problem with a mean lifetime prevalence of 50% (1). It is associated with more than 10% of work absenteeism, and disabling neck pain is reported by approximately 5% of adults (2).

Many studies of neck pain have been published in the past decade (3–11). Most studies have utilized self-reported outcomes, namely pain intensity on visual analogue or numeric rating scales, together with outcomes reflecting function and quality of life. Such self-reported outcomes have been criticized, as insufficient blinding might increase the risk of bias (12).

There are numerous physiological measures that are considered a valuable addition, as process variables or even alternatives to self-reported outcomes. A measure proposed in the context of chronic neck pain is the pressure pain threshold (PPT), i.e. the threshold distinguishing the feeling of mechanical pressure from that of painful pressure. Pressure pain sensitivity has been used to quantify hyperalgesia to mechanical stimuli in clinical settings and in clinical and experimental research. It is considered a valuable diagnostic tool to distinguish patients with different underlying aetiology or to predict treatment responses. For example, elevated responses to pressure pain in the acute stage of whiplash-associated disorders (WAD) have demonstrated predictive value to identify patients likely to have poor functional recovery (13); however, other studies suggest no or only limited predictive value (14).

The relationship between subjective pain reports and PPT, however, has not yet been established; results from previous studies indicate that such correlation might exist. For example, studies have found prominent differences in PPT in patients with neck pain compared with healthy controls. Patients with chronic WAD not only showed lower PPT (15–17), but also lower heat and cold pain thresholds at the neck area (16). Increased pressure pain sensitivity at remote areas, such as the tibialis muscle (15–17), also indicated alterations in central pain processing (17). Neck pain intensity was negatively correlated with cervical PPT in acute (18) or chronic WAD (17). Since the responses to pressure pain were predictive for functional recovery, the use of PPT was recommended for acute WAD (13). No significant associations between psychological factors and PPT have been found for chronic WAD (17).

For chronic non-specific neck pain without traumatic onset, PPT was lower in patients than in controls at the neck (15, 19, 20), and over the median and ulnar nerves (19); and on the tibialis muscle using an experimentally induced pain paradigm

 doi: 10.2340/16501977-1815

 ISSN 1650-1977

(21). PPT at the masseter muscles showed some correlation with pain intensity and duration (20), and a low correlation between cervical PPT and pain-related disability has also been observed (15). Contrary to WAD, anxiety and depression seem to influence PPT in patients with non-specific neck pain (21).

Changes in PPT have further been used to indicate treatment effects. Increased PPT was observed after exercise (11, 22), manual therapy (23) or thrust manipulation (24); however, only one study found a direct correlation between changes in pain intensity and PPT of the painful area (11).

Based on the above referred literature, there are hints that pain intensity and PPT are correlated. This re-analysis of 7 randomized controlled trials (RCT) aimed to determine factors, including pain intensity, associated with PPT in patients with chronic non-specific neck pain.

METHODS

Design

This re-analysis used pooled data from 7 RCTs conducted at the Department of Complementary and Integrative Medicine, Faculty of Medicine, University of Duisburg-Essen in Essen, Germany (3–9). All studies had been approved by the local ethics committee prior to patient recruitment and all patients had given written informed consent prior to inclusion in the study.

Patients

Inclusion criteria were: chronic non-specific neck pain for at least 5 days/week for at least 3 consecutive months; mean pain intensity of 40–45 mm on a 100-mm visual analogue scale (VAS). Exclusion criteria were: presence of neck pain caused by traumatic, inflammatory, rheumatological or malignant diseases; serious physical or mental disorders (cancer, polyneuropathy, diabetes mellitus, psychosis, severe depression, etc.). Patients were further allowed non-steroidal pain medication and physiotherapeutic interventions, if the treatment regimen had not been altered for 4 weeks prior to the trials and were continued unaltered during the trials. However, patients who had had invasive treatments, such as injections or acupuncture within 4 weeks or surgery within 12 months prior to the trial, were excluded. More information on additional inclusion criteria can be found in the original reports (3–9).

Interventions and control groups

The following therapies were evaluated in the included trials: heat pad application (3), yoga (5), and different types of cupping therapy, namely wet cupping (7), dry cupping (6), cupping massage (8, 9) and pulsating cupping (4). Therapies included 1 (7), or multiple treatments (3–6, 8, 9), therapeutic interventions at the clinic (4–7, 9) or home-based application (3, 8). Time between measurements ranged from 4 (7) to 84 days (8). Control groups received usual care (3, 4, 6, 7, 9), progressive muscle relaxation (8) or home-based exercise (5).

Outcomes

PPT were measured using a digital algometer (Somedic AB, Hörby, Sweden) with a 1 cm^2 probe. Pressure was ramped up by 40 kPa/s (5, 8) or 50 kPa/s (3, 4, 6, 7, 9) until the patient indicated a perception of pain in addition to pressure alone by using the push-button connected to the algometer. The algometer allowed monitoring of the applied ramp on the display by giving the assessor a visual feedback to adjust the increase in pressure. When the patient used the push-button, the display froze and showed the exact results. PPT was determined 3 times in a row at intervals of approximately 30 s at the individual site of maximal pain in the neck and trapezius region and near the primary pain area within the same dermatome, as well as at the patient's right thenar eminence (i.e. the C6 dermatome) at pre- (PPT_neck_pre, PPT_hand_pre) and post-intervention (PPT_neck_post, PPT_hand_post). If patients had bilateral pain, the side with the higher pain levels was chosen for measurement. The means of 3 measurements for each location were used for analysis. For determination of treatment-induced changes the difference between pre- and post-intervention measure was calculated for each patient (PPT_neck_diff, PPT_hand_diff).

PPT measurements were conducted by different assessors across the studies; however, initial and repeated measurements were always conducted by the same researcher. All assessors had been trained and supervised by the same investigators (RL, HC). Previous studies suggested that inter-rater reliability of PPT is very good with intraclass correlations from 0.75 to 0.91 (25, 26).

Age (years), gender (0 – male, 1 – female) and pain duration (years) were registered in all patients at pre-intervention.

Current neck pain intensity was measured on a 100-mm VAS, with 100 mm being "the worst pain imaginable" (27) pre- (VAS_pre) and post-intervention (VAS_post). Also, difference scores were calculated by subtracting the pre- from the post-score (VAS_diff). A negative difference between pre- and post-intervention indicates improvement, with larger difference scores indicating larger improvements. VAS and PPT are inversely related, i.e. lower VAS and higher PPT at post-intervention indicate changes in the same direction.

Expectation was measured on a 100-mm VAS, with 100 mm being the "highest expectation in treatment efficacy" at pre-intervention (Expectation). Although the VAS for expectation has not been strictly validated in research studies, it is often used in clinical trials.

Mental health was measured using the Mental Health Index (MHI) at pre- (MHE_pre) and post-intervention (MHI_post). The MHI is a subscale of the 36-item Short Form health survey (SF-36) (28) and consists of 5 items that measure mental health status (range 0–100). It is seen as a valid measurement of major depression (29) with a cut-off of 59/60 points. In this re-analysis the baseline (MHI_pre) and the difference score (MHI_diff) were used as indicators of mental health (29).

Finally, the time between measurements, i.e. the number of days between pre- and post-intervention measurements, was also determined.

Statistical analysis

The following analyses were conducted:

1. Cross-sectional analyses: the association between baseline data (age, gender, pain duration, expectation, VAS_pre, MHI_pre) and PPT_neck_pre and PPT_hand_pre was regressed.
2. Longitudinal analyses: the association between baseline data (age, gender, pain duration, expectation, VAS_pre, MHI_pre) and PPT_neck_post and PPT_hand_post was regressed for all patients and for patients in the intervention group alone.
3. Longitudinal analyses: the association between baseline data (age, gender, pain duration, expectation, VAS_pre, MHI_pre) and time between measurements, and PPT_neck_diff and PPT_hand_diff was regressed for all patients and for patients in the intervention group alone.
4. The multivariate correlation pattern based on differences in PPT, VAS, MHI together with age, pain duration, gender and expectation was investigated.
5. Differences in variables that separated the 2 groups (intervention vs control group) were regressed.

All statistical analyses were performed using SPSS software (version 20.0; IBM Inc., New York, USA) and SIMCA-P+ (Version 13.0; Umetrics Inc., Umeå, Sweden); a probability of < 0.05 (2-tailed) was considered significant in all tests. In tables and the text, mean values and 1 standard deviation ($\pm$ 1 SD) are given.

For cross-sectional analysis of baseline scores data of all patients were included, but for longitudinal analyses only data from patients with complete baseline and post-intervention scores were included.

For investigating the multivariate correlation patterns principal component analysis (PCA) and partial least squares or projection to latent structures (PLS-OPLS/O2PLS) were applied using SIMCA-P+. For a more detailed discussion concerning the relevance of these methods in the context of human pain sensitivity see our previous studies of chronic WAD and chronic neck pain (17, 21). Briefly, PCA can be viewed as a multivariate correlation analyses. The PCA implemented in SIMCA-P+ (in contrast to the simpler form in SPSS) includes cross-validation in order to secure stable results and a special algorithm (NIPALS) for handling missing data. Classical methods assume variable independence among the regressors when interpreting the results of regression analyses, e.g. multiple linear regression (MLR). PLS, in contrast to MLR, can handle and take advantage of multi-collinearity (i.e. high correlations) among the X-variables, which was expected in the present study.

PCA using SIMCA-P+ was used to extract and display systematic variation in a data matrix. If necessary, variables were log transformed before statistical analysis. A cross-validation technique was used to identify non-trivial components. Variable loading on the same component are positively correlated, and variables with high loadings but with different signs are negatively correlated. Variables with high loadings that had a 95% confidence interval not exceeding zero were considered significant. Hence, the most important of these were those with high absolute loadings. Significant variables with high loadings (positive or negative) are more important for the component under consideration than variables with lower absolute loadings. The obtained components are, by definition, not correlated and are arranged in decreasing order with respect to explained variation (R^2). R^2 describes the goodness of fit; the fraction of sum of squares of all the variables explained by a principal component. Q^2 describes the goodness of prediction; the fraction of the total variation of the variables that can be predicted by a principal component using cross-validation methods. In the present study PCA was carried out in order to investigate the presence of multivariate outliers and multivariate correlation patterns. Outliers were identified using the 2 powerful methods available in SIMCA-P+: score plots in combination with Hotelling's T2 (identifies strong outliers) and distance to model in X-space (identifies moderate outliers). Strong outliers were excluded from the subsequent analyses.

Partial least square regression (PLS) (i.e. PLS-OPLS/O2PLS) was used for the multivariate regression analysis. The importance of the variables is measured as a variable influence on projection (VIP) value. This indicates the relevance of each X-variable pooled over all dimensions and Y-variables; the group of variables that best explain Y. VIP ≥ 1.0 was considered significant. VIP values between 0.80 and 1.0 were considered as borderline significant. Coefficients (PLS scaled and centred regression coefficients) were used to note the direction of the relationship (positive or negative).

MLR could have been an alternative method, but this assumes that the regressor (X) variables are independent. If multi-collinearity (i.e. high correlations) occurs among the X-variables, the regression coefficients become unstable and their interpretability breaks down. MLR also assumes that a high subject-to-variables ratio is present (e.g. >5), which is not required for PLS. In fact PLS can handle subject-to-variables ratios <1.

RESULTS

Sample description

The sample in this cross-sectional analysis consisted of 346 patients; 77 males and 269 females. The intervention group consisted of 171 patients; the corresponding figure for the control group was 175 (Table I). Longitudinal analyses were based on 306 patients; the other 40 patients (11.6%) were lost to follow-up, with the majority reporting scheduling problems or lost interest. A few patients also dropped out due to symptom worsening or gave no reason. Detailed information can be found in the original study reports (3–9). The mean age was 52.6 years (SD 12.0 years), age range 19–81 years. Pain intensity at the time of the measurement visit ranged from 0.0 to 97.0 mm VAS, with a mean of 46.0 mm. The fact that current pain intensity was below the inclusion criteria was probably a result of separated screening and measurement visits (3). Pain duration ranged from 3 months to 45 years, with a mean of 7.6 years (SD 7.5 years), expectation of treatment efficacy was high with a mean of 73.0 mm (SD 22.7 mm) VAS. The MHI score was a mean of 66.4 (SD 17.0). PPT scores were lower at the neck (277.2 kPa [SD 135.2 kPa]) than the hand (355.6 kPa [SD 138.6 kPa]).

Regression analyses

Identification of outliers. Using PCA, 4 outliers (# 701, 706, 707, 936) were identified and excluded from subsequent analyses.

Cross-sectional regressions. We started by analysing whether the 2 PPT variables could be regressed using the baseline data. A significant model, but with low explained variation ($R^2 = 0.06$), was obtained when regressing the 2 PPT variables simultaneously (i.e. 2 Y-variables) (Table II). Hence, high PPTs at baseline (PPT_neck_pre and PPT_hand_pre) were associated with being male, short pain duration and high age.

No significant model was obtained for PPT_neck_pre alone. For PPT_hand_pre higher values were associated with being a man, short pain duration and high age ($R^2 = 0.07$) (Table II).

Table I. *Sociodemographic and clinical characteristics (mean ± 1 SD) at baseline. Right-hand column shows the result of statistical evaluations (χ^2 or* t*-test), reported as* p*-values*

Variable	Total sample ($n=346$)	Intervention group ($n=171$)	Control group ($n=175$)	*p*-value
Gender, female/male, *n*	269/77	134/37	135/40	0.44
Age, years, mean (SD)	52.6 (12.0)	51.9 (12.3)	53.3 (11.6)	0.27
Pain duration, years, mean (SD)	7.6 (7.5)	7.2 (7.4)	8.1 (7.5)	0.24
Pain intensity, mm VAS, mean (SD)	4.6 (2.0)	4.9 (2.0)	4.4 (1.9)	0.02*
MHI_pre, mean (SD)	66.4 (17.0)	66.0 (16.7)	66.8 (17.3)	0.66
PPT_neck_pre, mean (SD)	277.2 (135.2)	277.3 (125.8)	277.1 (144.2)	0.99
PPT_hand_pre, mean (SD)	355.6 (138.6)	364.4 (140.0)	347.0 (137.0)	0.25
Expectation, mm VAS, mean (SD)	72.9 (22.7)	78.2 (19.7)	67.9 (24.7)	<0.01*

*$p<0.05$.

SD: standard deviation; VAS: visual analogue scale; MHI: Mental Health Index; PPT: pressure pain threshold.

Table II. *Partial least square regressions of pressure pain thresholds (PPT) variables prior to the interventions using gender, age, pain intensity and duration, expectation and MHI as regressors; results from the cross-sectional analyses. For each X-variable and regression the variable importance in projection (VIP) and the direction of correlation are reported. A variable is significant if VIP > 1.0 (bold)*

Model	Variable	VIP	Direction of correlation	Model fit R^2
PPT_neck_pre and PPT_hand_pre (2Y-variables) (n=342)	Gender	**1.63**	Being male resulted in higher PPT	0.06
	Pain duration	**1.26**	Patients with shorter pain duration have higher PPT	
	Age	**1.07**	Older patients have higher PPT	
	VAS_pre	0.63		
	Expectation	0.32		
	MHI_pre	0.29		
PPT_neck_pre (n=342)	No significant model was obtained			
PPT_hand_pre (n=341)	Gender	**1.74**	Being male resulted in higher PPT	0.07
	Pain duration	**1.26**	Patients with shorter pain duration have higher PPT	
	Age	**1.04**	Older patients have higher PPT	
	VAS_pre	0.45		
	Expectation	0.22		
	MHI_pre	0.21		

VAS: visual analogue scale; MHI: Mental Health Index.

Table III. *Partial least square regressions of pressure pain thresholds (PPT) variables after the intervention (longitudinal analyses) using gender, age, PPT, pain intensity and MHI at baseline, pain duration, time between the measurements and expectation as regressors. For each X-variable and regression the variable importance in projection (VIP) and the direction of correlation are reported. A variable is significant if VIP > 1.0 (bold)*

Model	Variable	VIP	Direction of correlation	Model fit R^2
PPT_neck_post in all patients (n=303)	PPT_neck_pre	**2.74**	Higher baseline PPT resulted in higher post-intervention PPT	0.60
	Gender	0.52		
	Pain duration	0.33		
	Age	0.15		
	Time between measurements	0.16		
	VAS_pre	0.10		
	Expectation	0.28		
	MHI_pre	0.01		
PPT_neck_post in intervention group only (n=143)	PPT_neck_pre	**2.60**	Higher baseline PPT resulted in higher post-intervention PPT	0.64
	Gender	0.81		
	Pain duration	0.60		
	VAS_pre	0.31		
	MHI_pre	0.30		
	Expectation	0.16		
	Time between measurements	0.07		
	Age	0.01		
PPT_hand_post in all patients (n=302)	PPT_hand_pre	**2.54**	Higher baseline PPT resulted in higher post-intervention PPT	0.48
	Gender	**1.04**	Being male resulted in higher post-intervention PPT	
	Pain duration	0.47		
	Age	0.36		
	Expectation	0.31		
	MHI_pre	0.08		
	Time between measurements	0.06		
	VAS_pre	0.01		
PPT_hand_post in intervention group only (n=143)	PPT_hand_pre	**2.43**	Higher baseline PPT resulted in higher post-intervention PPT	0.59
	Gender	**1.15**	Being male resulted in higher post-intervention PPT	
	MHI_pre	0.58		
	Pain duration	0.53		
	Age	0.29		
	VAS_pre	0.21		
	Expectation	0.15		
	Time between measurements	0.06		

VAS: visual analogue scale; MHI: Mental Health Index.

Longitudinal analyses

Longitudinal analyses for post-intervention PPTs. In PLS regressions with all subjects, as well as with subjects from the intervention group, the only variable that intercorrelated with PPT_neck_post was the respective baseline score (Table III; $R^2 = 0.60–0.64$).

In a PLS regression with all subjects only the respective baseline score was intercorrelated with PPT_hand_post (Table III; $R^2 = 0.48$). For the intervention group it was further associated with male gender and higher PPT scores (Table III; $R^2 = 0.59$).

Longitudinal analyses for the difference in PPTs. The regression for PPT_neck_diff revealed VAS_diff, MHI_diff, age and time between measurements as significant factors; the significant model had a low R^2 (Table IV; $R^2 = 0.06$). In the intervention group the factors associated with an increase in PPT were: longer time between measurements, male gender, younger age and lower expectation (Table IV; $R^2 = 0.13$).

Table IV. *Partial least square regressions of pressure pain thresholds (PPT) difference scores (post – pre) (longitudinal analyses) using gender, age, pain intensity and MHI at baseline and differences, pain duration, expectation and time between measurements as regressors. For each X-variable and regression the variable importance in projection (VIP) and the direction of correlation are reported. A variable is significant if VIP > 1.0 (bold)*

Model	Variable	VIP	Direction of correlation	Model fit R^2
PPT_neck diff in all patients ($n = 302$)	VAS_diff	**1.94**	A larger pain reduction resulted in larger increase in PPT difference score	0.06
	MHI_diff	**1.31**	A larger increase in mental health resulted in larger increase in PPT difference score	
	Age	**1.26**	Being younger resulted in larger increase in PPT	
	Time between measurements	**1.01**	Longer time between measurements resulted in larger increase in PPT difference score	
	VAS_pre	0.71		
	Expectation	0.39		
	Gender	0.37		
	MHI_pre	0.26		
	Pain duration	0.26		
PPT_neck_diff in intervention group only ($n = 143$)	Time between measurements	**1.72**	Longer time between measurements resulted in larger increase in PPT difference score	0.13
	Gender	**1.57**	Being male resulted in larger increase in PPT	
	Age	**1.11**	Being younger resulted in larger increase in PPT difference score	
	Expectation	**1.06**	Having lower expectation resulted in larger increase in PPT difference score	
	VAS_pre	0.87		
	MHI_pre	0.42		
	VAS_diff	0.37		
	MHI_diff	0.30		
	Pain duration	0.23		
PPT_hand diff in all patients ($n = 302$)	Time between measurements	**2.52**	Longer time between measurements resulted in larger increase in PPT difference score	0.05
	Gender	**1.29**	Being male resulted in larger increase in PPT difference score	
	VAS_diff	0.42		
	MHI_diff	0.06		
	Pain duration	0.64		
	Age	0.38		
	VAS_pre	0.36		
	Expectation	0.31		
	MHI_pre	0.10		
PPT_hand_diff in intervention group only ($n = 143$)	Time between measurements	**2.04**	Longer time between measurements resulted in larger increase in PPT difference score	0.11
	Age	**1.35**	Being younger resulted in larger increase in PPT difference score	
	Gender	1.05	Being male resulted in larger increase in PPT difference score	
	Expectation	0.76		
	MHI_pre	0.76		
	MHI_diff	0.54		
	Pain duration	0.54		
	VAS_pre	0.38		
	VAS_diff	0.02		

SD: standard deviation; VAS: visual analogue scale; MHI: Mental Health Index.

The regression for PPT_hand_diff revealed time between measurements and gender as significant factors; the significant model had a low R^2 (Table IV; $R^2 = 0.05$). For the analysis of the intervention group an increase in PPT_hand was associated with longer time between measurements, male gender and younger age (Table IV; $R^2 = 0.11$).

PCA of differences in PPT, VAS, MHI together with age, pain duration, gender and expectation. No significant model was obtained.

Which of the differences in variables separate the 2 groups (intervention vs control). The significant PLS regression ($R^2 = 0.21$) identified the following variables as important in descending order (VIP > 1.0 are significant; for the significant variables are given the sign of the correlation after the VIP value): VAS_diff (VIP = 1.50(–)), PPT_neck_diff (VIP = 1.04(+)), MHI_diff (VIP = 0.76) and PPT_hand_diff (VIP = 0.27). Hence, belonging to the intervention group was associated with improvements in pain intensity (VAS) and in PPT_neck.

DISCUSSION

General findings

The simple assumption, that high pain intensity equals high pressure pain sensitivity could not be supported by the present results. Despite a large sample of subjects we were not able to establish a coherent correlation pattern between PPT and pain intensity, either in the cross-sectional or the longitudinal analyses. Even though both variables include subjective aspects (i.e. perception of pain), there are important differences that may explain the lack of significant correlations and lack of consensus in the literature concerning their relationships (correlations). Hence, the pain intensity variables describe more or less an on-going habitual chronic situation, while PPT measurements concern the recognition of a new nociceptive stimulus (pressure) in painful or pain-free tissues. Another difference is that PPT is measured within a very limited area/volume of tissue, while habitual pain intensity can be perceived to originate from large anatomical areas. Moreover, these 2 variables may differ with respect to what extent they are sensitive to psychological and contextual factors. Even though no direct correlation was found mediating links, e.g. psychological factors may exist between the 2 variables. Another explanation may be that the relationship between pain intensity and PPT is not linear due to presence/degree of central sensitization (including structural reorganization of pain-matrix in CNS and altered descending control of nociception). Our results are in contrast to studies reporting significant correlations between pain intensity and PPT in patients with low-back pain (30, 31) and those with non-traumatic neck pain (16, 18). In patients with chronic WAD no consistent pattern is obvious in the available literature (14, 16, 18).

Pre-intervention pressure pain thresholds

Pre-intervention scores of PPT at the hand were higher in males, in patients with high age and with shorter pain duration (Table II).

Our results concerning gender, with females exhibiting lower thresholds, are in agreement with other studies (25). However, there is no clear explanation for this gender difference. Binderup et al. (32) suggested, in a brief review of the literature, that the gender difference is multifactorial and that physiological (subcutaneous fat, muscle size, degree of temporal summation), hormonal, cultural and psychological factors might contribute to the gender effect.

The results for age are inconclusive: while some studies found increased thresholds, others found decreased (33) or no difference in thresholds with higher age (34). Those studies, however, are of very different sample sizes and the positive correlation between PPT and age is in line with those from the larger study (35).

Interestingly, lower PPT at the hand was also associated with longer pain duration, which is in agreement with other studies (36) possibly reflecting a loss of endogeneous inhibition with higher age. Effects of pain on PPT at segmentally connected areas have been reported previously; for example, studies have found decreased thresholds for measurements over the median and ulnar nerves (19) or the orofacial region (20) in patients with neck disorders, which are indicative of segmental sensitization. In the present study higher pressure pain sensitivity at the hand was associated with longer pain duration supporting the connection between pain perception and segmental pain processing. Contrary to this interpretation it can be argued that it was not possible to establish a significant regression for the most painful area, i.e. the neck area (Table II). Such a relationship, however, would have been reasonable in this context. The significantly lower PPT of the neck than in the hand might indicate a floor effect for PPT of the neck, which, in turn, may explain the lack of significant regression.

Post-intervention pressure pain thresholds

Post-intervention scores of PPT were mainly correlated with the respective baseline scores (Table III). This may reflect steady intrapersonal pressure pain sensitivity. However, some of the above-mentioned factors related to gender, e.g. thickness of subcutaneous fat, muscle size, hormonal, and ethnic/cultural, together with genetic factors mediating anxiety and depression may also contribute to the importance of baseline scores (32). The fact that gender was not a significant regressor of PPT of the neck cannot be explained based on current knowledge (Table III).

Changes in pressure pain thresholds

Changes in PPT_hand and PPT_neck (Table IV) in all subjects and in the intervention group consistently revealed time between measurements and age/gender as significant regressors. For PPT_neck there were also significant influences of VAS_diff and MHI_diff, but these factors were not confirmed in the corresponding analysis in the intervention group alone. Moreover, this regression had a low explained variation (Table IV). Together with time between measurements as the most important factor for changes in PPT, this leaves an inconsistent picture.

In the case of time between measurements in the regressions using all subjects, it could be assumed that such a factor

reflects a treatment-independent time effect. Such changes in PPT have been observed before; and while a repetition within a short time-frame leads to a decrease in thresholds (37, 38), repetitions after a longer interval lead to substantial increase in PPT (39). However, time between measurements was also a significant regressor in the intervention group only, which challenges our suggestion of a treatment-independent time effect. In the intervention group this variable can include an effect of the actual time between measurements. In conclusion, time between measurements was the most important factor influencing changes in PPT; however, only a small amount of variance can be explained according to the regressions presented in Table IV. Other significant factors, such as gender and age, in these regressions may simply reflect gender- and age-specific plasticity of the pain processing system.

Differences between groups

Belonging to the intervention group was associated with changes in pain intensity and PPT. Thus, indicating treatment effects in the intervention group and an overall smaller amount of pain and pressure pain sensitivity. Even though both these pain aspects changed in the intervention group, we found no coherent correlation between them.

Strengths

Despite its limitations this represents one of the largest studies evaluating the relationship between pain intensity and pressure pain sensitivity. Since all trials had been conducted at the same department, it might also be assumed that the methods to determine pain intensity and PPTs were applied in a comparable manner. Another strength is the use of appropriate and potent multivariate statistical methods to explore patterns between PPT and pain intensity and other variables, which limits the risk of biased results. Finally, reliability of the PPT can be considered good to very good (40).

Limitations

This analysis is limited by several factors, such as the studies' context and the patient sample. All studies were conducted at the department for internal and integrative medicine, with a focus on complementary and alternative therapies. Most patients were recruited via advertisements and therefore explicitly interested in complementary and alternative therapies. Results might therefore be influenced by self-selection.

Results may further be limited by the fact, that mechanical neck pain might not constitute a very homogeneous patient sample *per se*; even after exclusion of traumatic, inflammatory and secondary causes there might still be substantial differences in activated pain mechanisms including central alterations across the subjects of the investigated patient cohort. However, since no valid classification is available to date, this could not be considered in the analysis.

Another limitation was created by the choice of the measurement location for the PPT. PPT had been measured at the most painful site, which, in most cases, was the trapezius muscle. However, studies have shown that measurements at different locations on the body are mostly comparable (21). It may further be limited by the use of different observers, but all assessors have been trained and supervised by the same investigators, which should have reduced inter-observer differences.

Finally, studies with rather heterogeneous therapies with different proposed modes of actions were included in this analysis, and none of those therapies has been recommended by in treatment guidelines for chronic neck pain. Since time between measurements was included in the analysis possible bias in that regard should have been at least partially reduced.

Conclusions

Pressure pain sensitivity at the neck area or the hand did not correlate with pain intensity. Changes in PPT correlated with time between measurements indicating time-sensitive changes. More studies are necessary to evaluate the relationship between pain intensity and PPT before its use as a valid supplement to subjective pain ratings can be supported. Results of trials with respect to using PPT as an outcome variable must be interpreted with care until the complexity of the relationship has been resolved.

ACKNOWLEDGEMENTS

The original trials were supported by a grant from the Karl and Veronica Carstens-Foundation, Essen, Germany. The Karl and Veronica Carstens-Foundation had no role in the design, data collection, analysis and interpretation of data, in preparation of the manuscript or the decision to submit the manuscript for publication. The authors would like to thank the researchers involved in the trials as well as the study participants.

REFERENCES

1. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J 2006; 15: 834–848.
2. Cote P, van der Velde G, Cassidy JD, Carroll LJ, Hogg-Johnson S, Holm LW, et al. The burden and determinants of neck pain in workers: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976) 2008; 33: S60–S74.
3. Cramer H, Baumgarten C, Choi KE, Lauche R, Saha F, Musial F, et al. Thermotherapy self-treatment for neck pain relief – a randomized controlled trial. Eur J Integr Med 2012; 4: e371–e378.
4. Cramer H, Lauche R, Hohmann C, Choi KE, Rampp T, Musial F, et al. Randomized controlled trial of pulsating cupping (pneumatic pulsation therapy) for chronic neck pain. Forsch Komplementmed 2011; 18: 327–334.
5. Cramer H, Lauche R, Hohmann C, Lüdtke R, Haller H, Michalsen A, et al. Randomized-controlled trial comparing yoga and home-based exercise for chronic neck pain. Clin J Pain 2013; 29: 216–223.
6. Lauche R, Cramer H, Choi KE, Rampp T, Saha FJ, Dobos GJ, et al. The influence of a series of five dry cupping treatments on pain and mechanical thresholds in patients with chronic non-specific neck pain – a randomised controlled pilot study. BMC Complement Altern Med 2011; 11: 63.
7. Lauche R, Cramer H, Hohmann C, Choi KE, Rampp T, Saha FJ, et al. The effect of traditional cupping on pain and mechanical

thresholds in patients with chronic nonspecific neck pain: a randomised controlled pilot study. Evid Based Complement Alternat Med 2012; 2012: 429718.
8. Lauche R, Materdey S, Cramer H, Haller H, Stange R, Dobos G, et al. Effectiveness of home-based cupping massage compared to progressive muscle relaxation in patients with chronic neck pain – a randomized controlled trial. PLOS ONE 2013; 8: e65378.
9. Schumann S, Lauche R, Irmisch G, Hohmann C, Rolke R, Saha F, et al. The effects of 5 sessions of cupping massage on chronic non-specific neck pain: a randomized controlled pilot study. BMC Complement Altern Med 2012; 12: 80.
10. Ylinen J, Kautiainen H, Wiren K, Hakkinen A. Stretching exercises vs manual therapy in treatment of chronic neck pain: a randomized, controlled cross-over trial. J Rehabil Med 2007; 39: 126–132.
11. Ylinen J, Takala EP, Kautiainen H, Nykanen M, Hakkinen A, Pohjolainen T, et al. Effect of long-term neck muscle training on pressure pain threshold: a randomized controlled trial. Eur J Pain 2005; 9: 673–681.
12. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008; 336: 601–605.
13. Walton DM, Macdermid JC, Nielson W, Teasell RW, Reese H, Levesque L. Pressure pain threshold testing demonstrates predictive ability in people with acute whiplash. J Orthop Sports Phys Ther 2011; 41: 658–665.
14. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. Pain 2005; 114: 141–148.
15. Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. Clin J Pain 2005; 21: 175–181.
16. Stone AM, Vicenzino B, Lim EC, Sterling M. Measures of central hyperexcitability in chronic whiplash associated disorder – a systematic review and meta-analysis. Man Ther 2013; 18: 111–117.
17. Wallin M, Liedberg G, Borsbo B, Gerdle B. Thermal detection and pain thresholds but not pressure pain thresholds are correlated with psychological factors in women with chronic whiplash-associated pain. Clin J Pain 2012; 28: 211–221.
18. Kamper SJ, Maher CG, Hush JM, Pedler A, Sterling M. Relationship between pressure pain thresholds and pain ratings in patients with whiplash-associated disorders. Clin J Pain 2011; 27: 495–501.
19. Javanshir K, Ortega-Santiago R, Mohseni-Bandpei MA, Miangolarra-Page JC, Fernandez-de-Las-Penas C. Exploration of somatosensory impairments in subjects with mechanical idiopathic neck pain: a preliminary study. J Manipulative Physiol Ther 2010; 33: 493–499.
20. La Touche R, Fernandez-de-Las-Penas C, Fernandez-Carnero J, Diaz-Parreno S, Paris-Alemany A, Arendt-Nielsen L. Bilateral mechanical-pain sensitivity over the trigeminal region in patients with chronic mechanical neck pain. J Pain 2010; 11: 256–263.
21. Sjors A, Larsson B, Persson AL, Gerdle B. An increased response to experimental muscle pain is related to psychological status in women with chronic non-traumatic neck-shoulder pain. BMC Musculoskelet Disord 2011; 12: 230.
22. O'Leary S, Falla D, Hodges PW, Jull G, Vicenzino B. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. J Pain 2007; 8: 832–839.
23. de Camargo VM, Alburquerque-Sendin F, Berzin F, Stefanelli VC, de Souza DP, Fernandez-de-las-Penas C. Immediate effects on electromyographic activity and pressure pain thresholds after a cervical manipulation in mechanical neck pain: a randomized controlled trial. J Manipulative Physiol Ther 2011; 34: 211–220.
24. Mansilla-Ferragut P, Fernandez-de-Las Penas C, Alburquerque-Sendin F, Cleland JA, Bosca-Gandia JJ. Immediate effects of atlanto-occipital joint manipulation on active mouth opening and pressure pain sensitivity in women with mechanical neck pain. J Manipulative Physiol Ther 2009; 32: 101–106.
25. Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain 2007; 23: 760–766.
26. Geber C, Klein T, Azad S, Birklein F, Gierthmuhlen J, Huge V, et al. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. Pain 2011; 152: 548–556.
27. Tiplady B, Jackson SH, Maskrey VM, Swift CG. Validity and sensitivity of visual analogue scales in young and older healthy subjects. Age Ageing 1998; 27: 63–66.
28. Bullinger M, Kirchberger I. SF-36. Fragebogen zum Gesundheitszustand. Handanweisung. Göttingen: Hogrefe; 1998.
29. Friedman B, Heisel M, Delavan R. Validity of the SF-36 five-item Mental Health Index for major depression in functionally impaired, community-dwelling elderly patients. J Am Geriatr Soc 2005; 53: 1978–1985.
30. Fishbain DA, Lewis JE, Gao J. Is There significant correlation between self-reported low back pain visual analogue scores and low back pain scores determined by pressure pain induction matching? Pain Pract 2012; 13: 358–363.
31. Giesbrecht RJ, Battie MC. A comparison of pressure pain detection thresholds in people with chronic low back pain and volunteers without pain. Phys Ther 2005; 85: 1085–1092.
32. Binderup AT, Arendt-Nielsen L, Madeleine P. Pressure pain sensitivity maps of the neck-shoulder and the low back regions in men and women. BMC Musculoskelet Disord 2010; 11: 234.
33. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 2005; 115: 410–418.
34. Edwards RR, Fillingim RB. Age-associated differences in responses to noxious stimuli. J Gerontol A Biol Sci Med Sci 2001; 56: M180–M185.
35. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006; 123: 231–243.
36. Leffler AS, Kosek E, Hansson P. The influence of pain intensity on somatosensory perception in patients suffering from subacute/chronic lateral epicondylalgia. Eur J Pain 2000; 4: 57–71.
37. Jones DH, Kilgour RD, Comtois AS. Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. J Pain 2007; 8: 650–656.
38. Ylinen J, Nykanen M, Kautiainen H, Hakkinen A. Evaluation of repeatability of pressure algometry on the neck muscles for clinical use. Man Ther 2007; 12: 192–197.
39. Persson AL, Brogardh C, Sjolund BH. Tender or not tender: test-retest repeatability of pressure pain thresholds in the trapezius and deltoid muscles of healthy women. J Rehabil Med 2004; 36: 17–27.
40. Sterling M, Jull G, Carlsson Y, Crommert L. Are cervical physical outcome measures influenced by the presence of symptomatology? Physiother Res Int 2002; 7: 113–121.