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A More Pessimistic Life Orientation Is Associated With Experimental Inducibility of a Neuropathy-like Pain Pattern in Healthy Individuals

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Abstract: **The clinical pattern of neuropathic pain, diagnosed using the quantitative sensory testing (QST) battery (German Research Network on Neuropathic Pain), could be partly mimicked in healthy volunteers after topical capsaicin application. However, similar to clinical neuropathic pain that develops in only a subgroup of patients who have a neurologic lesion, this attempt to mimick a neuropathic pain pattern succeeded only in a small fraction (18%) of healthy individuals. In the present assessment, we pursued the hypothesis that the inducible subgroup differed from the other healthy participants with respect to their psychological phenotype. Therefore, in an observational study, participants were assessed using a comprehensive set of psychological variables comprising general psychological and pain-related cognitive-emotional mechanisms. The sum scores of the questionnaires were significantly linearly correlated with each other. Principal component analysis indicated that a major source of variance (46%) could be attributed to dispositional optimism examined via the Life Orientation Test (LOT). The LOT score significantly differed between the groups of participants, either those in whom a neuropathy-like pattern of pain assessed via QST could be partly (50–60% of the 11 QST parameters) induced (n = 20) or not (n = 90; *P* = .0375). It emerged again as the main selection criterion in a classification and regression tree predicting a participant's group assignment (inducible neuropathy-like QST pattern versus noninducible neuropathy-like QST pattern) at a cross-validated accuracy of 95.5 ± 2.1%. Thus, the few participants in a random sample of healthy volunteers who, after topical capsaicin application, partly resemble (to a degree of about 60%) the clinical pattern of neuropathic pain in the QST test battery, are preselectable on the basis of psychological factors, with a particular emphasis on pessimistic life attitudes.**

Perspective: ***In a small fraction of 18% of healthy volunteers, topical capsaicin application resulted in a neuropathy-like pattern in 50 to 60% of the components of a clinical test battery. These individuals displayed a more pessimistic life attitude as assessed by means of the LOT.***

Key words: *Dispositional optimism, quantitative sensory testing, catastrophizing, experimental pain, healthy individuals.*

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Neuropathic pain develops as a result of lesions of the peripheral or central somatosensory nervous system,[1] although not in every individual. In addition to the main causal factors such as morphological damage, further factors need to trigger its development.[69] Among these, psychological factors have been highlighted. They contribute to interindividual differences in the sensitivity[15,22,25] to pain and its chronification.[34,37,48,52] For instance, pain anxiety and catastrophizing contribute negatively to neuropathic pain and its treatment.[43,51,59,61,65] Pain vigilance, ie, a tendency to focus on pain-related bodily sensations, was also related to the development of chronic pain.[35,36] Moreover, general positive psychological attitudes such as dispositional optimism have been linked to lower pain intensity and better coping with pain.[6,18,19,21,34] By contrast, negative affectivity and distress, comprising mood, somatization, and anxiety, have been positively linked to the development of chronic pain.[10,13,62,64]

We have recently shown that the clinical pattern resembling neuropathic pain can be partly mimicked (60–70% of 11 standardly measured quantitative sensory testing [QST] parameters) in a few healthy volunteers after topical capsaicin application.[40] However, similar to clinical neuropathic pain, in this previous study, only a few of the participants, 18%, displayed neuropathy-like symptoms. Identifying those individuals in whom neuropathic pain will develop after a triggering incident is an active research topic and has already led to the association of various factors with this clinical course.[5] Considering the contribution of psychological factors to the development of neuropathic pain, in the present analysis, we tested the hypothesis that healthy individuals in whom a pattern of neuropathic pain can be experimentally induced differ with respect to psychological factors from those in whom this was not possible. To this end, the psychological phenotypes of the participants of that study[40] were described using a set of psychological variables comprising catastrophizing, pain anxiety and pain vigilance, dispositional optimism, mood, somatization, and state anxiety. These psychological factors have been selected to include a comprehensive set of risk factors as well as dispositional optimism representing a resilience factor that were evidently related to chronic pain.

Methods

Participants, Study Design, and Pain Data

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the Medical Faculty of the Goethe University, Frankfurt am Main, Germany. Informed written consent was obtained from each participant. The present assessment is a secondary analysis of a recently published study.[40] The assessments were performed in the same random sample of healthy individuals of Caucasian ethnicity by self-assignment (N = 110, aged 18–36 years, 46 men),[40] mostly medical students in the local faculty. The ethics vote included coverage of the present psychological assessments. The participants' health was ascertained by medical history and physical examination, including vital signs.

This report focuses on psychological factors that had been acquired as an add-on during a previous investigation and had not been reported before.[40] In this previous study, we assessed the degree to which a pattern of neuropathic pain can be induced in healthy volunteers in reaction to experimentally induced pain. In this study, experimental hyperalgesia was obtained by applying 150 mg capsaicin cream (.2%, manufactured by the local hospital pharmacy) onto a 3 × 3 cm^2 skin area and covering it with plaster for 30 minutes before testing.[49] The body area to be tested was randomly assigned to the participants; possible sites were the dorsal sides of the hand in the dermatome of the nervus radialis (n = 61) or of the foot in the dermatome of the nervus fibularis profundus (n = 49). The resemblance of clinical neuropathic pain after application of the well-established experimental pain model of capsaicin sensitization[49] was assessed using a standardized clinical test battery[56] for neuropathic pain (QST), developed by the German Research Network on Neuropathic Pain.[56,57] QST uses the administration of thermal and mechanical stimuli grouped into 7 tests that result in 13 different parameters of sensory perception and pain. The detailed methodology was reported in the previous study.[40] Detection and pain thresholds to thermal cold and warm stimuli were assessed on a 9-cm^2 skin area using a thermode at a baseline temperature of 32°C and increasing or decreasing the temperature by 1°C/s (TSA 2001-II; Medoc, Ramat Yishai, Israel). The thermal sensory limen (TSL) was assessed using alternating applications of cold and warmth. If during this procedure the participant indicated a sensation of warmth or heat pain during administration of a cooling temperature, a paradoxical heat sensation was noted. The mechanical detection threshold was assessed by applying 10 punctate stimuli using von Frey hairs at strengths of .25 to 512 mN (Optihair2-set; Marstock Nervtest, Schriesheim, Germany). The mechanical pain threshold was measured using 10 pinprick stimuli at 8 to 512 mN (The Pin-Prick; MRC Systems, Heidelberg, Germany). The mechanical pain sensitivity and dynamic mechanical allodynia were determined using pinprick stimulus intensities of 8 to 512 mN applied concomitantly with stimuli of light touch. The participant rated how painful each stimulus was on a numerical rating scale ranging from 0 ("no pain") to 100 ("strongest pain imaginable"). The wind-up ratio was measured in 5 runs, starting with a single stimulus of 256 mN followed by series of 10 stimuli of the same intensity (application frequency 1 Hz, skin area of application 1 cm^2). The vibration detection threshold was obtained by applying a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) on the processus styloideus radii for the hand area or the malleolus medialis for the foot area. The pressure pain threshold was assessed by applying blunt pressure stimuli at the musculus thenar or the musculus abductor hallucis (Commander Algometer; JTECH Medical, Midvale, UT). The QST tests were

administered standardly twice in each participant, once on untreated skin defined as the control side, and again contralaterally on the same but hypersensitized body area, defined as the test side. The order of administration was as follows: cold and warm detection thresholds (CDT/WDT), TSL, cold and heat pain thresholds (CPT/HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (ALL/DMA), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT). The room temperature was kept at 20–25°C while testing. Measurements were taken by trained investigators (V.D., B.G.O., H.H.) fully adhering to the published instructions,[50,56,57] as reported elsewhere.[40]

The z-transformed QST parameter values obtained at the test site were compared with corresponding values published from 1,236 patients with neuropathic pain [42] using Bayesian statistics. Bayesian decision rules enabled assignment of QST parameter values obtained at the test side to either normal or neuropathic. This provided a quantitative criterion for the agreement with the expected QST pattern of neuropathic pain for each individual as a neuropathy inducibility score (NIS), calculated as $\mathrm{NIS} = \sum(\mathrm{QST} \in \mathrm{Neuropathy})$.[40] The analysis was possible for the 11 z-transformed QST values given in Maier et al,[42] whereas 2 further QST parameters, ie, the paradoxical heat sensations and the dynamic mechanical allodynia, were not provided in that study[42] in a suitable form for the present analysis. Participants were then grouped for the resemblance of their QST pattern to neuropathic pain. This previous analysis showed that several QST parameters acquired at the capsaicin-sensitized site deviated from normal. These deviations resembled in up to 7 QST parameters (of a total of 11[56]) the QST profiles of sensory disturbances observed in patients with neuropathic pain. Higher degrees (50–60%) of resemblance to neuropathic QST pattern were obtained in 20 (18%) of the participants. This previous result was the basis for grouping the participants in the present analysis into group 1, comprising clusters of participants in whom a neuropathy-like QST pattern could be induced by means of topical capsaicin application, and group 2, comprising clusters of participants in whom the hypersensitization did not result in a neuropathy-like QST pattern. In the present secondary analysis, we aimed at testing differences in clinically relevant psychological factors between these 2 groups.

Assessment of Psychological Factors

A set of psychological factors has been selected to include 1) dispositional optimisms indicating a general attitude toward life events, 2) general psychological factors such as mood, somatization, and state anxiety indicating negative affectivity and distress, and 3) pain-related cognitive-emotional mechanisms such as pain catastrophizing, pain anxiety, and vigilance. The overall sum score of each questionnaire was used for analysis to describe the level of the psychological variable measured by the respective questionnaire. As the present assessment was an exploratory one, we restricted the analysis of psychological factors to the overall level of the psychological variable represented by the sum score of each questionnaire.

Assessment of General Life Attitude in Terms of Dispositional Optimism

Dispositional optimism was assessed using the German version of the revised Life Orientation Test (LOT-R,[58] German version[17]). This examines the general expectancy of positive or negative outcome across life situations. It consists of 10 items (3 positive, 3 negative, and 4 filler items) rated on a 5-point scale ranging from 1 ("strongly agree") to 5 ("strongly disagree"). The sum of the 3 positively framed items (ie, "I am always optimistic about my future") is regarded as an optimism score, and the sum of the 3 negatively framed items (ie, "I hardly ever expect things to go my way") provides a pessimism score. An overall sum score defines a continuously rated level of optimism (from low to high levels of optimism). In line with the exploratory character of the present study, we used the sum score but not the subscales to represent the person's level of optimism.

Assessment of Negative Affectivity and Distress

Emotional, somatic, and cognitive symptoms of depressive mood in the preceding week were assessed using the German version of the Center for Epidemiologic Studies Depression Scale (CES-D and Allgemeine Depressionsskala [ADS],[24] the German version of the CES-D). Its 20 items were rated on a 4-point Likert scale, providing CES-D total scores of 0 to 60. Somatoform symptoms were assessed by means of the Screening for Somatoform Symptoms scale (SOMS, German version[55]), which queries 53 physical symptoms not explicable by organic causes. Participants were instructed to rate the intensity of each symptom during the last 7 days on a 5-point Likert scale. State anxiety comprising the subjective feelings apprehension, tension, and worry were assessed using the respective subscale of the State-Trait Anxiety Inventory (STAI-X1, German version[38]), which consists of 20 items rated on a 5-point rating scale.

Assessment of Pain-Related Cognitive-Emotional Processing

As a measure of pain-related catastrophizing, the Pain Catastrophizing Scale (PCS[63]) was applied. This scale comprises 13 items, which can be split into the subscales rumination, magnification, and helplessness. Each item is rated on a 5-point scale, providing possible total scores of 0 to 52. Pain-related anxiety across cognitive, behavioral, and physiological domains was assessed using the Pain Anxiety Symptoms Scale (PASS[45]; German version[70]). This scale comprises 4 subscales, ie, cognitive anxiety, escape/avoidance, fearful appraisal, and physiological anxiety. Its items are rated on a 6-point scale, providing total PASS scores between 0 and 240. Although pain anxiety and catastrophizing share overlapping constructs,

ie, in terms of a negative anticipation of the threat value of pain,[64,67] catastrophizing represents a cognitive attitude, whereas pain anxiety represents an emotional attitude toward pain experiences.[64] For this reason, they are analyzed in the present assessment as separate variables. Pain vigilance was assessed using the Pain Vigilance and Awareness Questionnaire (PVAQ[44]) as a comprehensive measure validated in chronic pain and nonclinical samples. It consists of 16 items rated on a 6-point scale, assessing awareness, vigilance, preoccupation, and observation of pain. The possible PVAQ total score ranges from 0 to 80. For the present study, German versions of the PCS and PVAQ were used, which had been successfully applied previously in several experimental and clinical pain studies.[3,11,29,35,37]

Data Analysis

The present analysis addressed the question whether participants in whom a neuropathy-like QST pattern was inducible after topical capsaicin application displayed psychological differences from the other participants. Regarding the inducibility of a neuropathy-like sensory pattern, the participants had been grouped into a total of 7 clusters. Those participants in whom the neuropathy-like QST pattern was inducible were assigned to 2 distinct clusters (ie, clusters 2 and 6 identified previously[40] and provided in Supplementary Table 1). The present analysis focused therefore on these 20 participants, who formed group 1, showing a neuropathy-like QST pattern after topical capsaicin application. All other participants were combined to group 2, ie, comprising 90 participants in whom hypersensitization did not result in a neuropathy-like QST pattern. Statistical analysis was performed using Stata (version 13.1 for Linux; StataCorp, College Station, TX) and MATLAB (version 8.3.0.532 for Linux; MathWorks, Natick, MA); the α level was set at 5%.

Data analysis first addressed the sources of variance in the psychological factors and the association of those factors that account for the largest proportion of the variance with the participants' group assignment. Considering the conceptual vicinity of some of the psychological factors (eg, pain catastrophizing and pain anxiety), (linear) intercorrelation between the questionnaires can be expected. For a dimensionality reduction without losing too much information and a conversion of the possibly correlated variables into a set of values of linearly uncorrelated variables, a principal component analysis (PCA)[47] was performed. For a PCA, the eigenvalues of the covariance matrix are regarded, ie, the larger the eigenvalues, the larger the variance of the data that are captured by the corresponding factor. For the selection of the set of largest eigenvalues, the Kaiser-Guttman criterion (eigenvalue >1)[20,32] was applied. PCA was followed by a varimax rotation,[31] which enabled the assignment of single principal components to particular psychological factors, thereby facilitating the interpretation of the results. Psychological factors that contributed high loadings to principal components, ie, accounting for a large proportion of the total variability among the participants' psychological phenotypes, were assessed for group differences by means of Wilcoxon rank-sum tests.[71] Age and sex differences between the groups were tested by means of Wilcoxon rank-sum tests and cross-tabulation statistics, respectively.

Subsequent analysis focused on establishing classification rules based on the psychological factors to provide additional psychological characteristics for selecting participants who displayed a neuropathy-like QST pattern after capsaicin sensitization. To this end, the group membership (see above) was submitted to classification and regression tree (CART) analysis.[7] CART analysis was more suitable for providing simple test-based selection criterion using stepwise algorithm-based preselection than multiple linear regression analysis, which would have provided combinations of linear equations. As candidate factors for CART analysis, the sum scores of the 7 psychological variables and the participant's age and sex were used. The resulting model was cross-validated using a leave-*k*-out approach (for more details about cross-validation, see, for example, http://en.wikipedia.org/wiki/Cross-validation_%28statistics%29); the data were partitioned into 10 randomly chosen subsamples with equal size. The choice of the subsamples was stratified, ie, had the same class proportions. For each subsample, CART analysis was constructed on the remaining data and used to predict the subsample. This was repeated 10 times, and the prediction performance of the models built on these reduced data sets was tested on the respective remaining data. The average accuracy of these models in the validation sample was reported as the cross-validated model accuracy.

Results

The distribution and key descriptive statistics (median, range) of the psychological variables are shown in Fig 1, separately for group 1, comprising 20 participants showing a neuropathy-like QST pattern after topical capsaicin application, and group 2, comprising 90 participants without neuropathy-like signs of hypersensitization. There was a distinguishable variability in the questionnaire scores between the 2 groups (Fig 1). Significant explanation of group differences could be shown for the LOT score (displayed in intense color in Fig 1). No significant differences existed between the groups concerning age (Wilcoxon rank-sum tests: $z = -.137$, $P = .893$) and sex distribution (2×2 cross-tabulation: $\chi^2 = 1.746$, $P = .216$).

The sum scores of most of the questionnaires were significantly linearly correlated with each other, with the exception of the scores of STAI and PCS and of STAI and PVAQ (Table 1). After PCA, the sources of variance of psychological factors were found to comprise 7 variance components (Table 2). Two principal components of the intercorrelation matrix passed application of the Kaiser-Guttman criterion,[20] ie, emerged with eigenvalues >1 (Table 2). The first component explained 45% of the total variance among all psychological

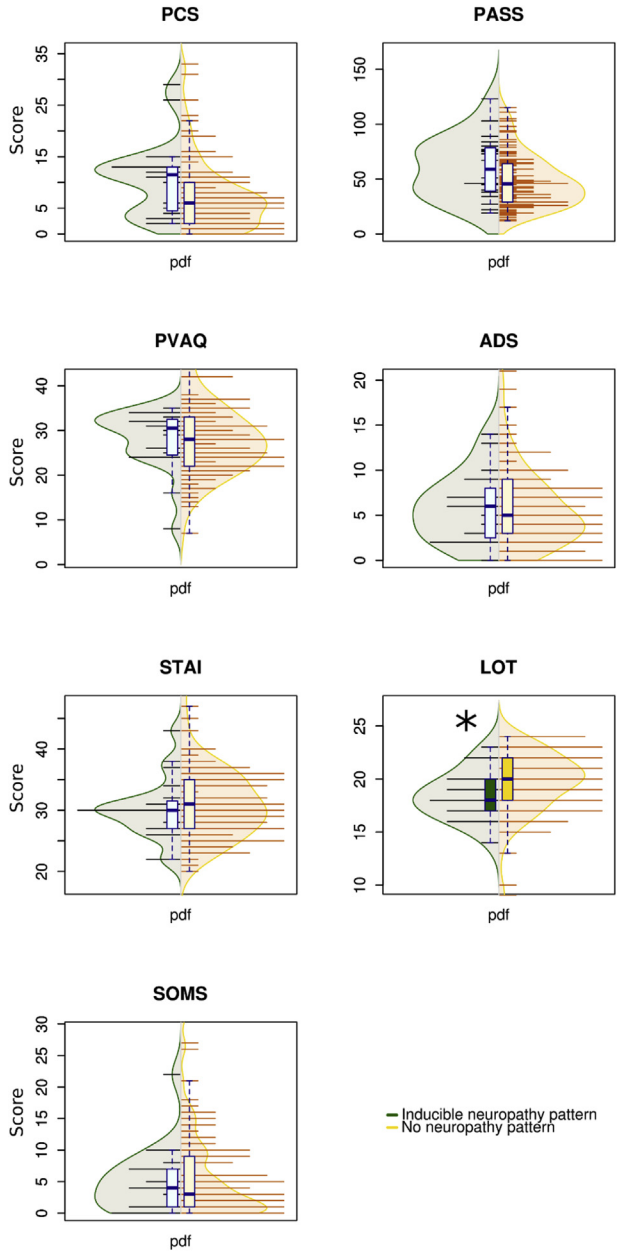

Figure 1. Distribution of psychological parameters. The beanplots[33] show the individual observations as small lines in a one-dimensional scatter plot, surrounded by the probability density function (pdf) of the distributions. The plots are split in 2 halves, showing on the left, the data obtained in group 1 (green), comprising n = 20 participants displaying a neuropathy-like QST pattern after topical capsaicin application, and on the right, the data obtained in group 2 (gold), comprising n = 90 participants without neuropathy-like signs of hypersensitization. Single ratings are shown as lines in one-dimensional scatter plot surrounded by a Gaussian density plot of the distributions (colored areas). Box and whisker plots of the same data are overlaid on the beanplots. They have been constructed using the minimum, quartiles, median (solid black red line within the box), and maximum. The main group difference was found with the LOT score, which is therefore shown in more intense colors. *$P < .05$ for group differences.

variables. After varimax rotation, it was identified to carry high loadings from the LOT sum score (Table 2, lower half). This variable significantly differed between groups 1 and 2 (Wilcoxon rank-sum tests: z = 2.08, $P = .0375$). Specifically, participants in whom a neuropathy-like QST pattern could be induced after topical capsaicin application displayed a lower LOT score (group 1: median = 18, interquartile range = 17–20) than the other participants (group 2: median = 20, interquartile range = 18–22; Fig 1). The second component, explaining a further 19% of the total variance, received its main loading from the ADS sum score. However, this second factor did not significantly differ between groups (Wilcoxon rank-sum tests, z = .260, $P = .7945$).

In agreement with PCA, CART analysis provided the following result: The LOT score was identified by

Table 1. Pearson Correlation Matrix Among 7 Psychological Factors (N = 110)

	PCS	PASS	PVAQ	ADS	STAI	LOT	SOMS
PCS	1						
PASS	.67*	1					
PVAQ	.36*	.48*	1				
ADS	.2†	.31*	.22†	1			
STAI	.09	.32*	.05	.53*	1		
LOT	−.44*	−.47*	−.24†	−.59*	−.37*	1	
SOMS	.22†	.29‡	.29‡	.5*	.17§	−.43*	1

NOTE. Significance levels of correlations of variables with themselves are omitted.
*Correlation is significant at the .001 level (2-tailed).
†$P < .05$.
‡$P < .01$.
§$P = .0808$.

Table 2. Component Loadings (1–7) for the PCA Performed on the Correlation Matrix Among 7 Psychological Factors (N = 110)

	Component Loading						
Factor	1	2	3	4	5	6	7
Original PCA							
PCS	.37	.47	−.26	−.39	.12	.38	.51
PASS	.44	.34	−.29	.07	.30	−.13	−.70
PVAQ	.31	.41	.33	.70	−.30	−.06	.21
ADS	.41	−.45	.12	.06	−.26	.70	−.25
STAI	.30	−.49	−.51	.40	.30	−.20	.36
LOT	−.45	.15	.04	.40	.58	.53	−.03
SOMS	.35	−.17	.69	−.19	.55	−.17	.11
Eigenvalues	3.12	1.30	.87	.68	.45	.32	.25
Variance explained (%)	44.6	18.6	12.5	9.7	6.4	4.6	3.6
Varimax rotated PCA							
PCS	0	0	0	0	0	1	0
PASS	0	0	0	0	0	0	1
PVAQ	0	0	0	0	1	0	0
ADS	0	1	0	0	0	0	0
STAI	0	0	1	0	0	0	0
LOT	1	0	0	0	0	0	0
SOMS	0	0	0	1	0	0	0

NOTE. The upper part of the table shows the original PCA results; in the lower part, the PCA after varimax[31] rotation is shown enhancing the association of single psychological factors with the principal components of the variance. The percent fraction of the variance explained by the single components is also given.

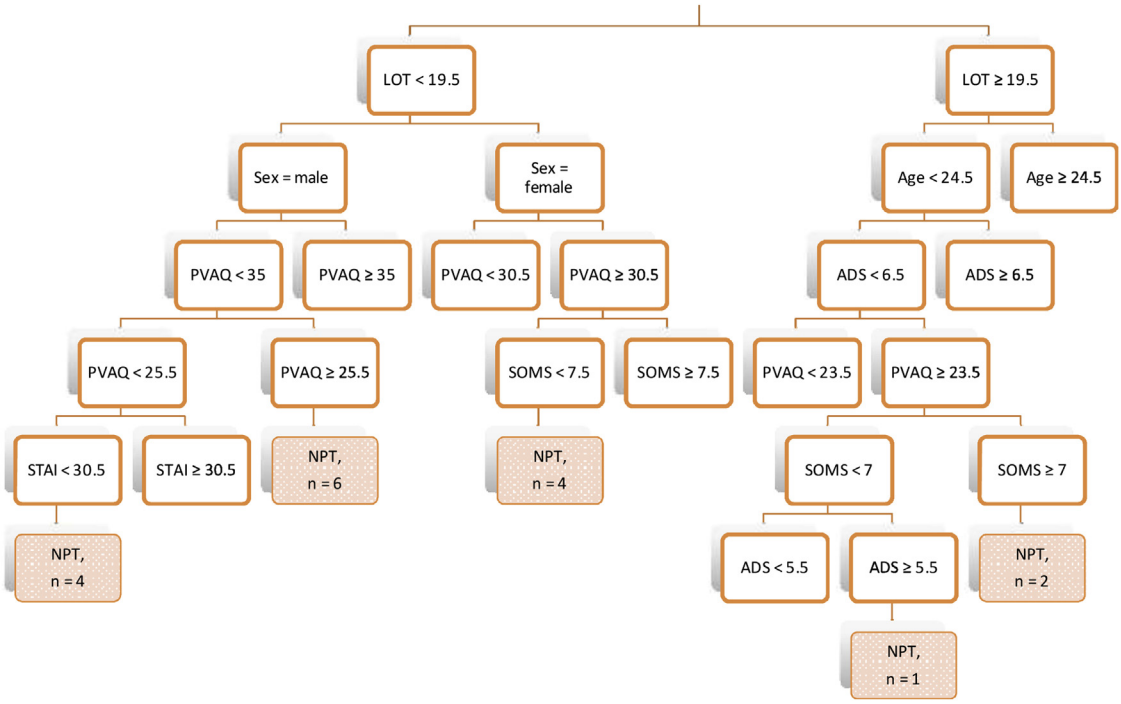

Figure 2. CART analysis visualizing the decision algorithm for assignment of participants to group 1, ie, to the group in whom a neuropathy (NPT)-like QST pattern could be induced by topical capsaicin application as elaborated elsewhere.[40] CART analysis identified LOT, PVAQ, STAI, SOMS, and ADS as a basis for group assignment. When the condition noted at each decision node applies, the tree is followed down the respective path. At the end of the path, the number of participants belonging to group 1 is indicated. For example, the assignment to group 1 can be expected under the following conditions: A participant will react with a neuropathy-like QST pattern to topical capsaicin application if he is a man, has an LOT score of <19.5, and has a PVAQ score between 25.5 and 35. This leads to the end of the second path in the figure, where NPT = 6 means that 6 participants of group 1 had been classified because they fulfilled the criteria requested by the respective path (rule). The complete model provided an assignment to either group 1 or group 2, with an overall cross-validated accuracy of 95.5 ± 2.1%.

CART analysis as particularly important in the present context, ie, it was the first classification criterion for participants' assignment to either group 1 or group 2 (Fig 2). CART analysis further associated additional psychological factors and the participants' age and sex with the inducibility of a neuropathy-like pain pattern (group 1) as diagnosed using the QST test battery (Fig 2). This was compiled into algorithms comprising several rules that, when adhered to, indicated the association of a participant to group 1 with an accuracy of 85% (for details, see Supplementary Table 2). For example, according to one of these rules, a participant can be expected to react to topical capsaicin application by showing a neuropathy-like pattern in the QST test battery if he is of male sex, has a LOT score of <19.5, and has a PVAQ score between 25.5 and 35 (Fig 2). Most of the rules required a LOT score lower than 19.5, which agrees with the direction of the results obtained with PCA. Exception from this rule, ie, membership of group 1 with LOT >19.5, was only rarely observed and associated when particular further conditions applied such as comparatively younger age (<24.5 years), which was lower than the median age of 25 years in this cohort, and an ADS score lower than 6.5. The complete CART model (Fig 2) provided an overall cross-validated correct identification of group membership, either group 1 or group 2, at an accuracy of 95.5 ± 2.1%.

Discussion

The hypothesis that participants showing a neuropathy-like pattern of pain inducible by topical capsaicin application[40] differ with respect to psychological phenotype from those participants not showing a neuropathy-like QST pattern after sensitization could be verified by the present analysis. The results clearly converged toward a more pessimistic life attitude as the main characteristic of participants who react to capsaicin application by developing a transient neuropathy-like pain pattern. The score obtained in the LOT 1) contributed the largest part, compared with the other psychological variables, to the variance in psychological factors, 2) differed significantly among the groups defined with respect to neuropathy inducibility, and 3) emerged again as the main criterion by which these participants can be identified among a random sample of healthy volunteers.

Dispositional optimism describes a person's generalized attitude toward an expectation of positive outcomes in different life situations.[18] Of the 7 psychological variables, the LOT score was best associated with the difference between the subgroup of healthy participants developing a neuropathy-like QST pattern after topical capsaicin sensitization and the subgroup without such clinically relevant changes in their somatosensory perception. Dispositional optimism has been shown to be a positive predictor of health status under different

clinical conditions,[4,16,66] after psychological trauma,[30,60] and also during chronic pain.[9,27,54] Moreover, dispositional optimism, together with positive affect and low emotional distress, was a protective factor against the development of neuropathic pain after breast surgery.[8] Thus, the present finding resembles an important protective relationship between higher levels of optimism and chronic pain identified in clinical settings.[4,27,48,53] Therefore, our results support the hypothesis that healthy participants in whom a neuropathy-like pain phenotype can be experimentally induced share psychological characteristics with patients with neuropathic pain. Thus, the similarity of our results with psychological findings in patients with pain suggests dispositional optimism as an additional psychological factor for selection of healthy volunteers in analgesic drug studies. This may enhance the predictivity for clinical analgesia by resembling patients not only in their pain pattern but also with respect to the underlying psychological background.

Complete similarity between the psychological phenotype of the healthy volunteers displaying a neuropathy-like QST pattern after topical capsaicin application and that reported from patients with chronic (neuropathic) pain was not expected. The small fraction of 18% of a random sample of healthy volunteers exhibited the neuropathy-like pattern in only 50 to 60% of the QST parameters, which is an incomplete resemblance of symptoms in patients with neuropathic pain. On these grounds, a complete resemblance of those patients in the psychological dimension could not be expected. The similarity was mainly limited to optimism, and further psychological factors reported as characterizing patients with pain were not relevant in the context of the present cohort. Already the second important source of variance, the ADS score accounting for 19% of the total variance, and assessing depressive mood in the preceding week did not significantly differ between the 2 groups of participants. Moreover, the present finding emphasized significant similarities between the healthy participants in whom a neuropathy-like QST pattern can be induced and patients with neuropathic pain in a general psychological factor.[8] However, more specifically pain-related cognitive-emotional mechanisms, such as pain catastrophizing, pain anxiety, and vigilance, also known to play a role in neuropathic pain,[51,59,61] did not play a distinct role in the present context. In the fear avoidance model of chronic pain, a reciprocal relationship between such pain-related psychological factors and pain is proposed.[67,68] Although under persistent pain conditions, patients may exhibit increased levels of pain catastrophizing, anxiety, and hypervigilance, the levels of these in healthy individuals may not play a meaningful role, specifically when investigating the degree to which experimental pain manipulation can provoke clinically comparable neuropathic pain signs in healthy volunteers.

However, pain-related cognitive mechanisms[39] as well as general cognitive attitudes, such as optimism,[14,21] have been previously associated with individuals' behaviors in experimentally induced pain. Healthy participants seemed to react less sensitively to experimental pain, eg, the cold pressor test, when reporting higher levels of optimism.[14] Evidence also suggests that the influence of dispositional optimism on pain perception is mediated by lower levels of pain catastrophizing.[21,26] Catastrophic thinking is one of several cognitive mechanisms (eg, hope, pain acceptance, approaching coping with stressors) currently discussed as mediators of the optimism–pain relationship.[18] However, the present assessment was obtained from a small group of 20 participants. The absolute group differences in the LOT score were modest, and an interpretation of further, more complex psychological phenotypes from the present study lacks a robustly powered data basis.

A more comprehensive inclusion of further psychological factors emerged only in the algorithm to select the participants with neuropathy-like pattern inducibility that was derived after the CART analysis. The CART analysis (Fig 2) allowed these participants to be characterized to a limited extent. That is, one of the psychological phenotypes was characterized by lower levels of optimism, male sex, and lower levels of pain vigilance. In contrast, for a few women, lower scores in dispositional optimism, a lower somatization score, and higher levels of pain vigilance seemed to be predictive for the inducibility of a neuropathy-like QST pattern. Systematic reviews of sex/gender differences in pain suggest greater pain sensitivity in women than in men.[2,12] This might be related among other factors to different cognitive-emotional coping styles[2] in terms of greater psychological sensitivity in women,[23] ie, fear of pain.[28] Whether such gender-related coping styles involve both general and pain-specific psychological factors, and whether differences comprise dispositional and situational psychological factors in the same way, remains to be clarified. The present CART analysis did not hint any particular assumptions. Moreover, although CART analysis has no lower limit of sample size, the sample nevertheless strongly advises caution in interpreting the results. This has been exercised mainly by interpreting the primary result of the CART analysis, ie, the LOT score that stood at the tree root, where the number of participants was still larger. In contrast, downward in the tree, the node sizes became smaller, which eluded valid interpretation except for detecting some plausible features. Therefore, the present algorithm might rather support a selection of participants who, as reported in the previous study,[40] can be selected with almost similar accuracy (80%) by testing the QST parameters mechanical pain sensitivity, wind-up ratio, and TSL after topical capsaicin administration. Thus, the present psychological factor–based algorithm might be best used as an add-on to strengthen the selection of participants for enrollment in analgesic drug studies that use highly selected cohorts to enhance predictivity for clinical analgesia. Importantly, to apply it as a selection criterion, the full tree with the derived rules needs to be applied. For this purpose, validation in a larger sample is clearly desirable.

The present analysis has its limitations, mainly because the study was not designed as a psychological experiment; rather, its main focus was to analyze whether and to what extent a clinical established pattern of neuropathic pain can be induced in healthy participants. Because this resulted in an overall positive result, the present analysis questioned whether those few participants in whom clinically comparable sensory signs can be obtained differ in psychological factors from the average. The present analysis therefore was limited in its sample size, which was given by the main analysis. Apart from the main finding of a more pessimistic life orientation, further psychological conclusions about this subgroup of participants can be drawn only with great caution. The result nevertheless emphasizes the usefulness of psychological testing in a pharmacological environment of experimental pain models, in which it is still not standard for enrollment of participants. Furthermore, as discussed earlier, the CART algorithm of psychological factor–based selection rules requires prospective validation and adaptions in a larger sample size. This similarly applies to the suitability of participants for predictive analgesic studies, which requires proof in a pharmacological study in healthy volunteers. Thus, although the present work may be considered as a methodological step toward even better experimental drug studies in human volunteers,[41,46] establishment in drug development still needs several further experiments.

The induction of a clinically relevant neuropathy-like QST pattern after topical capsaicin application seems to be easier in participants who tend toward a more pessimistic life orientation. Dispositional optimism appears as an eligible psychological factor for additional preselection of participants tending to show clinically comparable signs of neuropathic pain after experimental sensitization. These findings agree, at least partially, with psychological findings in patients with chronic pain.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jpain.2015.05.004.

References

1. Baron R, Binder A, Wasner G: Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 9:807-819, 2010

2. Bartley EJ, Fillingim RB: Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth 111: 52-58, 2013

3. Baum C, Huber C, Schneider R, Lautenbacher S: Prediction of experimental pain sensitivity by attention to pain-related stimuli in healthy individuals. Percept Mot Skills 112: 926-946, 2011

4. Beitel M, Savant JD, Cutter CJ, Peters S, Belisle N, Barry DT: Psychopathology and pain correlates of dispositional optimism in methadone-maintained patients. Am J Addict 21(Suppl 1):S56-S62, 2012

5. Boogaard S, De Vet HC, Faber CG, Zuurmond WW, Perez RS: An overview of predictors for persistent neuropathic pain. Expert Rev Neurother 13:505-513, 2013

6. Boselie JJ, Vancleef LM, Smeets T, Peters ML: Increasing optimism abolishes pain-induced impairments in executive task performance. Pain 155:334-340, 2014

7. Breimann L, Friedman JH, Olshen RA, Stone CJ: Classification and Regression Trees. Boca Raton, Chapman and Hall, 1993

8. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD, Thompson AM, Cairns Smith W, Chambers WA, Scott NW, Recovery Study G: Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. Pain 155: 232-243, 2014

9. Cruz-Almeida Y, King CD, Goodin BR, Sibille KT, Glover TL, Riley JL, Sotolongo A, Herbert MS, Schmidt J, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB: Psychological profiles and pain characteristics of older adults with knee osteoarthritis. Arthritis Care Res (Hoboken) 65:1786-1794, 2013

10. Diatchenko L, Fillingim RB, Smith SB, Maixner W: The phenotypic and genetic signatures of common musculoskeletal pain conditions. Nat Rev Rheumatol 9:340-350, 2013

11. Dimova V, Horn C, Parthum A, Kunz M, Schöfer D, Carbon R, Griessinger N, Sittl R, Lautenbacher S: Does severe acute pain provoke lasting changes in attentional and emotional mechanisms of pain-related processing? A longitudinal study. Pain 154:2737-2744, 2013

12. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd: Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 10: 447-485, 2009

13. Finan PH, Quartana PJ, Smith MT: Positive and negative affect dimensions in chronic knee osteoarthritis: effects on clinical and laboratory pain. Psychosom Med 75:463-470, 2013

14. Geers AL, Wellman JA, Helfer SG, Fowler SL, France CR: Dispositional optimism and thoughts of well-being determine sensitivity to an experimental pain task. Ann Behav Med 36:304-313, 2008

15. George SZ, Hirsh AT: Psychologic influence on experimental pain sensitivity and clinical pain intensity for patients with shoulder pain. J Pain 10:293-299, 2009

16. Gison A, Dall'Armi V, Donati V, Rizza F, Giaquinto S: Dispositional optimism, depression, disability and quality of life in Parkinson's disease. Funct Neurol 29:113-119, 2014

17. Glaesmer H, Hoyer J, Klotsche J, Herzberg PY: Die Deutsche Version des Life-Orientation-Tests (LOT-R) zum dispositionellen Optimismus und Pessimismus. Zeitschrift für Gesundheitspsychologie 16:26-31, 2008

18. Goodin BR, Bulls HW: Optimism and the experience of pain: benefits of seeing the glass as half full. Curr Pain Headache Rep 17:329, 2013

19. Goodin BR, Glover TL, Sotolongo A, King CD, Sibille KT, Herbert MS, Cruz-Almeida Y, Sanden SH, Staud R, Redden DT, Bradley LA, Fillingim RB: The association of greater dispositional optimism with less endogenous pain

facilitation is indirectly transmitted through lower levels of pain catastrophizing. J Pain 14:126-135, 2013

20. Guttman L: Some necessary conditions for common factor analysis. Psychometrika 19:149-161, 1954

21. Hanssen MM, Peters ML, Vlaeyen JW, Meevissen YM, Vancleef LM: Optimism lowers pain: evidence of the causal status and underlying mechanisms. Pain 154:53-58, 2013

22. Hanssen MM, Vancleef LM, Vlaeyen JW, Peters ML: More optimism, less pain! The influence of generalized and pain-specific expectations on experienced cold-pressor pain. J Behav Med 37:47-58, 2014

23. Hashmi JA, Davis KD: Deconstructing sex differences in pain sensitivity. Pain 155:10-13, 2014

24. Hautzinger M, Bailer M: Allgemeine Depressionsskala ADS. Weinheim, Beltz, 1992 [in German]

25. Hirsh AT, George SZ, Bialosky JE, Robinson ME: Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. J Pain 9:806-812, 2008

26. Hood A, Pulvers K, Carrillo J, Merchant G, Thomas M: Positive traits linked to less pain through lower pain catastrophizing. Pers Individ Dif 52:401-405, 2012

27. Hoofwijk DM, Fiddelers AA, Peters ML, Stessel B, Kessels AG, Joosten EA, Gramke HF, Marcus MA: Prevalence and predictive factors of chronic postsurgical pain and poor global recovery one year after outpatient surgery. Clin J Pain, http://dx.doi.org/10.1097/AJP.0000000000000207. Epub before print.

28. Horn ME, Alappattu MJ, Gay CW, Bishop M: Fear of severe pain mediates sex differences in pain sensitivity responses to thermal stimuli. Pain Res Treat 2014:897953, 2014

29. Huber C, Kunz M, Artelt C, Lautenbacher S: Attentional and emotional mechanisms of pain processing and their related factors: a structural equations approach. Pain Res Manag 15:229-237, 2010

30. Iacoviello BM, Charney DS: Psychosocial facets of resilience: implications for preventing posttrauma psychopathology, treating trauma survivors, and enhancing community resilience. Eur J Psychotraumatol 5:23970, 2014

31. Kaiser HF: The varimax criterion for analytic rotation in factor analysis. Psychometrika 23:187-200, 1958

32. Kaiser HF, Dickman K: Analytic determination of common factors. Am Psychol 14:425, 1959

33. Kampstra P: Beanplot: A boxplot alternative for visual comparison of distributions. J Stat Software, Code Snippet 28:1-9, 2008

34. Keogh E, Book K, Thomas J, Giddins G, Eccleston C: Predicting pain and disability in patients with hand fractures: comparing pain anxiety, anxiety sensitivity and pain catastrophizing. Eur J Pain 14:446-451, 2010

35. Lautenbacher S, Huber C, Baum C, Rossaint R, Hochrein S, Heesen M: Attentional avoidance of negative experiences as predictor of postoperative pain ratings and consumption of analgesics: comparison with other psychological predictors. Pain Med 12:645-653, 2011

36. Lautenbacher S, Huber C, Kunz M, Parthum A, Weber PG, Griessinger N, Sittl R: Hypervigilance as predictor of postoperative acute pain: its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. Clin J Pain 25:92-100, 2009

37. Lautenbacher S, Huber C, Schofer D, Kunz M, Parthum A, Weber PG, Roman C, Griessinger N, Sittl R: Attentional and emotional mechanisms related to pain as predictors of chronic postoperative pain: a comparison with other psychological and physiological predictors. Pain 151:722-731, 2010

38. Laux L, Glanzmann P, Schaffner P, Spielberger C: Das State-Trait-Angstinventar (Testmappe mit Handanweisungen, Fragebogen STAI-G Form X 1 und Fragebogen STAI-G Form X 2). Weinheim, Beltz, 1981 [in German]

39. Lee JE, Watson D, Frey-Law LA: Psychological factors predict local and referred experimental muscle pain: a cluster analysis in healthy adults. Eur J Pain 17:903-915, 2013

40. Lötsch J, Dimova V, Hermens H, Zimmermann M, Geisslinger G, Oertel BG, Ultsch A: Pattern of neuropathic pain induced by topical capsaicin application in healthy subjects. Pain 156:405-414, 2015

41. Lötsch J, Oertel BG, Ultsch A: Human models of pain for the prediction of clinical analgesia. Pain 155:2014-2021, 2014

42. Maier C, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, Gierthmühlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihöfner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uçeyler N, Valet M, Wasner G, Treede R-D: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 150:439-450, 2010

43. Mankovsky T, Lynch M, Clark A, Sawynok J, Sullivan MJ: Pain catastrophizing predicts poor response to topical analgesics in patients with neuropathic pain. Pain Res Manag 17: 10-14, 2012

44. McCracken L: "Attention" to pain in persons with chronic pain: a behavioural approach. Behav Res Ther 28: 271-284, 1997

45. McCracken LM, Zayfert C, Gross RT: The Pain Anxiety Symptoms Scale: development and validation of a scale to measure fear of pain. Pain 50:67-73, 1992

46. Oertel BG, Lötsch J: Clinical pharmacology of analgesics assessed with human experimental pain models: bridging basic and clinical research. Br J Pharmacol 168:534-553, 2013

47. Pearson K: On lines and planes of closest fit to a system of points in space. Philosophical Magazine 6:559-772, 1901

48. Peters ML, Sommer M, van Kleef M, Marcus MA: Predictors of physical and emotional recovery 6 and 12 months after surgery. Br J Surg 97:1518-1527, 2010

49. Petersen KL, Rowbotham MC: A new human experimental pain model: the heat/capsaicin sensitization model. Neuroreport 10:1511-1516, 1999

50. Pfau D, Klein T, Blunk JA, Geber C, Krumova E, Limbeck C, Magerl W, Maier C, Westermann A, Schuh-Hofer S, Tiede W, Treede RD: QST Quantitative sensorische Testung, Handanweisung für den Untersucher, Eine standardisierte Testbatterie für die Quantitative Sensorische Testung nach den Regeln des Deutschen Forschungsverbundes Neuropathischer Schmerz (DFNS). Rolke R, Andrews A, Magerl W, Treede RD (eds.): Lehrstuhl für Neurophysiologie, Universitätsmedizin Mannheim, 2010. [in German]

51. Phillips TJ, Brown M, Ramirez JD, Perkins J, Woldeamanuel YW, Williams AC, Orengo C, Bennett DL, Bodi I, Cox S, Maier C, Krumova EK, Rice AS: Sensory, psychological, and metabolic dysfunction in HIV-associated

peripheral neuropathy: a cross-sectional deep profiling study. Pain 155:1846-1860, 2014

52. Pincus T, Burton AK, Vogel S, Field AP: A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine 27:E109-E120, 2002

53. Powell R, Johnston M, Smith WC, King PM, Chambers WA, Krukowski Z, McKee L, Bruce J: Psychological risk factors for chronic post-surgical pain after inguinal hernia repair surgery: a prospective cohort study. Eur J Pain 16: 600-610, 2012

54. Ramirez-Maestre C, Esteve R: Disposition and adjustment to chronic pain. Curr Pain Headache Rep 17:312, 2013

55. Rief W, Hiller W, Heuser J: SOMS–Das Screening für Somatoforme Störungen (Manual zum Fragebogen). Bern, Huber, 1997

56. Rolke R, Baron R, Maier C, Tölle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123: 231-243, 2006

57. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD: Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 10:77-88, 2006

58. Scheier MF, Carver CS, Bridges MW: Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 67:1063-1078, 1994

59. Schlereth T, Heiland A, Breimhorst M, Fechir M, Kern U, Magerl W, Birklein F: Association between pain, central sensitization and anxiety in postherpetic neuralgia. Eur J Pain 19:193-201, 2014

60. Segovia F, Moore JL, Linnville SE, Hoyt RE, Hain RE: Optimism predicts resilience in repatriated prisoners of war: a 37-year longitudinal study. J Trauma Stress 25:330-336, 2012

61. Selvarajah D, Cash T, Sankar A, Thomas L, Davies J, Cachia E, Gandhi R, Wilkinson ID, Wilkinson N, Emery CJ, Tesfaye S: The contributors of emotional distress in painful diabetic neuropathy. Diab Vasc Dis Res 11:218-225, 2014

62. Shedden Mora M, Weber D, Borkowski S, Rief W: Nocturnal masseter muscle activity is related to symptoms and somatization in temporomandibular disorders. J Psychosom Res 73:307-312, 2012

63. Sullivan M, Bishop S, Pivik J: The pain catastrophizing scale: development and validation. Psychol Assess 7: 524-532, 1995

64. Sullivan MJ, Thorn B, Rodgers W, Ward LC: Path model of psychological antecedents to pain experience: experimental and clinical findings. Clin J Pain 20:164-173, 2004

65. Toth C, Brady S, Hatfield M: The importance of catastrophizing for successful pharmacological treatment of peripheral neuropathic pain. J Pain Res 7:327-338, 2014

66. Vassend O, Quale AJ, Roise O, Schanke AK: Predicting the long-term impact of acquired severe injuries on functional health status: the role of optimism, emotional distress and pain. Spinal Cord 49:1193-1197, 2011

67. Vlaeyen JW, Linton SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 85:317-332, 2000

68. Vlaeyen JW, Linton SJ: Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain 153:1144-1147, 2012

69. von Hehn CA, Baron R, Woolf CJ: Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 73:638-652, 2012

70. Walter B, Hampe D, Wild J, Vaitl D: Die Erfassung der Angst vor Schmerzen: eine modifizierte deutsche Version der Pain Anxiety Symptom Scale (PASS-D) (Assessment of pain-related anxiety: A revised German version of the Pain Anxiety Symptoms Scale). Der Schmerz 15:83 [German]

71. Wilcoxon F: Individual comparisons by ranking methods. Biometrics 1:80-83, 1945