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 only in a subgroup of patients who have a neurologic lesion, this attempt to mimic 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.

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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, although not in every individual. In addition to the main causal factors such as morphological damage, further factors need to trigger its development. Among these, psychological factors have been highlighted. They contribute to interindividual differences in the sensitivity to pain and its chronification. For instance, pain anxiety and catastrophizing contribute negatively to neuropathic pain and its treatment. Pain vigilance, ie, a tendency to focus on pain-related bodily sensations, was also related to the development of chronic pain. Moreover, general positive psychological attitudes such as dispositional optimism have been linked to lower pain intensity and better coping with pain. By contrast, negative affectivity and distress, comprising mood, somatization, and anxiety, have been positively linked to the development of chronic pain.

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. 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.

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 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. To this end, the psychological phenotypes of the participants of that study 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. 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), 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. 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 cm² skin area and covering it with plaster for 30 minutes before testing. 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 was assessed using a standardized clinical test battery for neuropathic pain (QST), developed by the German Research Network on Neuropathic Pain. 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. Detection and pain thresholds to thermal cold and warm stimuli were assessed on a 9-cm² skin area using a thermode at a baseline temperature of 32°C and increasing or decreasing the temperature by 1°Cs (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 cm²). 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 malleus 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 Algo-meter; 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 sensitivity (MPS), dynamic mechanical allostdry (ALL/DMMA), 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, as reported elsewhere.

The z-transformed QST parameter values obtained at the test site were compared with corresponding values published from 1,236 patients with neuropathic pain 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. A neuropathy-like QST pattern was ascribed to the person’s level of optimism.

The present 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) 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 German version). 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 always expect good things to happen to me”) is regarded as an optimism score, and the sum of the 3 negatively framed items (ie, “I hardly ever expect good 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], 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), 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), 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) was applied. This scale comprises 13 items, which can be split into the subscales ruminative, 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; German version). 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,
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 previously40 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 $\alpha$ 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: $z = -1.746$, $P = .893$) and sex distribution (2 $\times$ 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...
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)

<table>
<thead>
<tr>
<th></th>
<th>PCS</th>
<th>PASS</th>
<th>PVAQ</th>
<th>ADS</th>
<th>STAI</th>
<th>LOT</th>
<th>SOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>1</td>
<td>.67*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASS</td>
<td>.67</td>
<td>1</td>
<td>.36*</td>
<td>.48*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVAQ</td>
<td>.36</td>
<td>.36</td>
<td>1</td>
<td>.70</td>
<td>.24</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>ADS</td>
<td>.31</td>
<td>.31</td>
<td>.70</td>
<td>1</td>
<td>.59</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>STAI</td>
<td>.22</td>
<td>.22</td>
<td>.59</td>
<td>.37</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOT</td>
<td>.15</td>
<td>.15</td>
<td>.37</td>
<td>.37</td>
<td>.59</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SOMS</td>
<td>.29</td>
<td>.29</td>
<td>.58</td>
<td>.58</td>
<td>.54</td>
<td>.54</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** Significance levels of correlations of variables with themselves are omitted.

*Correlation is significant at the .001 level (2-tailed).

\( \ddagger P < .05.\)

\( \ddagger P < .01.\)

\( \ddagger P = .0808.\)

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

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

**NOTE.** The upper part of the table shows the original PCA results; in the lower part, the PCA after varimax 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 1. Distribution of psychological parameters. The beanplots 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. *\( P < .05.\)
The hypothesis that participants showing a neuropathy-like pattern of pain inducible by topical capsaicin application 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 contributed the largest part, compared with the other psychological variables, to the variance in psychological factors, differed significantly among the groups defined with respect to neuropathy inducibility, and emerged again as the main criterion by which these participants can be identified among a random sample of healthy volunteers.

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. 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 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%.

Discussion

The hypothesis that participants showing a neuropathy-like pattern of pain inducible by topical capsaicin application 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 contributed the largest part, compared with the other psychological variables, to the variance in psychological factors. Differed significantly among the groups defined with respect to neuropathy inducibility, and 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. 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, and also during chronic pain. Moreover, dispositional optimism, together with positive affect and low emotional distress, was a protective factor against the development of neuropathic pain after breast surgery. Thus, the present finding resembles an important protective relationship between higher levels of optimism and chronic pain identified in clinical settings. Therefore, our results support the hypothesis that healthy participants in whom a neuropathy-like pain phenotype can be experimen tally 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.

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, 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. 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 as well as general cognitive attitudes, such as optimism, 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. Evidence also suggests that the influence of dispositional optimism on pain perception is mediated by lower levels of pain catastrophizing. 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. 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. 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, 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, 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.

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