Distraction Analgesia in Chronic Pain Patients

The Impact of Catastrophizing

Kristin L. Schreiber, M.D., Ph.D., Claudia Campbell, Ph.D., Marc O. Martel, Ph.D., Seth Greenbaum, B.A., Ajay D. Wasan, M.D., M.Sc., David Borsook, M.D., Ph.D., Robert N. Jamison, Ph.D., Robert R. Edwards, Ph.D.

ABSTRACT

Background: Diverting attention away from noxious stimulation (*i.e.*, distraction) is a common pain-coping strategy. Its effects are variable across individuals, however, and the authors hypothesized that chronic pain patients who reported higher levels of pain catastrophizing would derive less pain-reducing benefit from distraction.

Methods: Chronic pain patients (n = 149) underwent psychometric and quantitative sensory testing, including assessment of the temporal summation of pain in the presence and absence of a distracting motor task.

Results: A simple distraction task decreased temporal summation of pain overall, but, surprisingly, a greater distraction analgesia was observed in high catastrophizers. This enhanced distraction analgesia in high catastrophizers was not altered when controlling for current pain scores, depression, anxiety, or opioid use (analysis of covariance [ANCOVA]: F = 8.7, P < 0.005). Interestingly, the magnitude of distraction analgesia was inversely correlated with conditioned pain modulation (Pearson R = -0.23, P = 0.005).

Conclusion: Distraction produced greater analgesia among chronic pain patients with higher catastrophizing, suggesting that catastrophizing's pain-amplifying effects may be due in part to greater attention to pain, and these patients may benefit from distraction-based pain management approaches. Furthermore, these data suggest that distraction analgesia and conditioned pain modulation may involve separate underlying mechanisms. **(ANESTHESIOLOGY 2014; 121:1292-301)**

HE biopsychosocial model of pain acknowledges many wide-ranging influences on the human pain experience, including coping mechanisms such as distraction.¹⁻³ Interindividual differences in the perception of pain are shaped by variations in physiology, psychological functioning, and the use of specific pain-related coping techniques. Moreover, interactions between these factors may impact the degree of pain which each individual experiences, and how effective particular analgesic strategies may be. Distraction, which is widely used in pediatrics as a nonpharmacologic pain-reducing strategy, has also been shown to be analgesic in adults in clinical studies,4 laboratory-based psychophysical studies,^{5–7} and functional neuroimaging studies.⁸ Importantly, the effectiveness of distraction in reducing pain is associated with variation in biopsychosocial processes such as catastrophizing,⁷ attentional capacity,⁹ and the presence of chronic pain. 10 Collectively, chronic pain patients appear to have an attentional bias toward painful stimuli¹¹ and higher pain sensitivity on formal testing, 12-18 which may be exacerbated by negative cognitive processes (e.g., catastrophizing). What is less well understood is whether this association varies among individual chronic pain patients. If so, this could impact the efficacy of coping strategies such as distraction.

What We Already Know about This Topic

- Experimental pain experience can be amplified by rapid repetition of the stimulus (temporal summation) and can be reduced by pain elsewhere (conditioned pain modulation) and by distraction
- Catastrophizing, often associated with chronic pain, might reduce the analgesic effects of distraction

What This Article Tells Us That Is New

- In 149 chronic pain patients, pain reporting during temporal summation was decreased by distraction to a greater extent in those with high catastrophizing
- Analgesia from conditioned pain modulation was inversely related to that from distraction, suggesting these rely on different mechanisms

While there is some evidence that catastrophizing is associated with less effective, or more delayed, distraction analgesia, 7.9,19,20 it is also plausible that effective external distraction could diminish the negative consequences of catastrophizing, as catastrophizing may involve difficulty with internally distracting oneself from pain. Importantly, previous research investigating the relationship between catastrophizing and distraction analgesia has been conducted in healthy controls,

Presented in part at the American Pain Society Meeting, New Orleans, Louisiana, May 8, 2013.

Submitted for publication March 28, 2014. Accepted for publication August 28, 2014. From the Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts (K.L.S., S.G., R.N.J., R.R.E.); Department of Psychiatry and Behavioral Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (C.C., A.D.W.); Department of Anesthesiology and Psychiatry, University of Pittsburgh Medical Center (C.C., A.D.W.); Department of Psychiatry, Brigham and Women's Hospital (M.O.M., R.N.J., R.R.E.); and Center for Pain and the Brain, P.A.I.N. Group, Boston Children's Hospital, Boston, Massachusetts (D.B.).

Copyright © 2014, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2014; 121:1292-301

rather than in patients with chronic pain. The salience of pain-related information is likely to be heightened in individuals with chronic pain, 21 and chronic opioid use. 22-24 Moreover, the impact of catastrophizing, which is *quantitatively* less in healthy controls than chronic pain patients, may also be *qualitatively* different between these two populations.

Temporal Summation of Pain (TSP), which measures the increase in pain sensation during a train of stimuli, is a quantitative sensory test (QST) which assays central sensitization. TSP is variable among normal individuals²⁵ and groups (gender,²⁶ age²⁷), and may also indicate an individual's endogenous analgesic response,²⁸ predict postsurgical pain^{29–34} and clinical outcomes,^{35,36} distinguish differences between lowand high-opioid users,²³ and risk for opiate misuse.³⁷ Patients with fibromyalgia,^{12,13} temporomandibular disorders,¹⁴ persistent postoperative pain,^{15–17} and functional abdominal pain,¹⁸ have demonstrated increased TSP relative to pain-free controls. TSP has been associated with catastrophizing in pain patients,³ and is relatively portable and easy to perform.

In the current study, we investigated the effect of a brief, simple distraction task on TSP in 149 patients with chronic pain. We hypothesized that distraction would reduce TSP, but to a variable extent among individuals. On the basis of previous studies in normal volunteers, we hypothesized that catastrophizing would be associated with that variability, with higher levels of catastrophizing predicting less distraction analgesia. Finally, as there is evidence that distraction analgesia may work through a mechanism distinct from that underlying descending endogenous analgesia in healthy volunteers, we also investigated the relationship between distraction analgesia and conditioned pain modulation (CPM) in these chronic pain patients.

Materials and Methods

Study Design and Participants

This was a cross-sectional cohort study of 149 patients with persistent spine pain performed in a single, large, urban, university-based pain management center. Participants were recruited by posters advertising the study in and around the Pain Management Center at Brigham and Women's Hospital. Pain site was primarily low back, but included upper back and neck as well. Patients were eligible if they had experienced persistent spinal pain for more than 6 months, and were able to speak, read, and write in English. Patients were excluded if they had a diagnosis of cancer or other malignant disease, cognitive limitations that precluded providing selfreport data, or a history of myocardial infarction. Recruitment was conducted via local posting of electronic and print advertisements. Interested participants called in, and underwent a telephone-based screening before coming in for an initial study visit. Participants received \$50 as compensation for their participation. The study was conducted with Institutional Review Board approval (Partners Institutional

Review Board at Brigham and Women's Hospital) and within the Helsinki guidelines for pain research in human subjects.* All patients underwent an informed consent process before participation in the study.

Questionnaires

Standard demographic information was collected by self-report, including current opioid use. Questionnaires administered included: (1) the *Brief Pain Inventory*, ³⁸ which is frequently recommended as a measure of pain severity and pain interference for patients with chronic malignant or non-malignant pain, ³⁹ (2) the *Beck Depression Inventory* (BDI), a well-validated, commonly used, general measure of depressive symptomatology, ⁴⁰ (3) the *Pain Catastrophizing Scale* (PCS), a well-validated, widely used, self-report measure of catastrophic thinking associated with pain, ⁴¹ with good psychometric properties in pain patients and controls, ⁴² and (4) Assessment of pain-related anxiety, consisting of the *Pain Anxiety Symptoms Scale* (PASS), ⁴³ a verbal anxiety rating (on a 0–100 scale, with "no anxiety" and "severe anxiety" as the respective anchors).

Session Protocol

Study subjects provided informed consent. Many of these procedures have been described in our previous studies. ^{37,44,45} Ratings of current clinical pain intensity (on a 0–10 scale, 0 = "no pain", 100 = "the most intense pain imaginable") were obtained before the psychophysical testing session. During the session, subjects were seated comfortably in a reclining chair. First, resting blood pressure and heart rate were assessed, after which participants underwent the psychophysical testing procedures described below, with the order of testing: mechanical temporal summation task, distraction task, thermal threshold and tolerance testing, pressure threshold and tolerance testing, cuff pressure testing, followed by CPM. One tester did all the QST assessments.

Mechanical Temporal Summation Task

Participants first underwent an assessment of mechanical temporal summation using weighted punctate probes, as in a previous study.³⁷ The lowest-force stimulator that produced a sensation of discomfort (128 or 256 mN for most subjects) was used to apply a train of 10 stimuli to the skin of the dorsum of the hand, on the middle phalange of the middle finger at the rate of 1 per second. Participants rated the painfulness of the first, fifth, and tenth stimulus, and also rated any ongoing pain after-sensations 15 s after the final stimulus. There were two total temporal summation runs. The first temporal summation run was in the absence and the second in the presence of the distracting stimulus. These were separated in time by a task to determine the subject's 20% grip force strength (two trials of maximum grip strength—see below).

Distraction Task

We developed a brief active distraction task involving performance of sustained handgrip of a targeted grip force.

^{*} Available at: http://www.wma.net. Accessed May, 30, 2011.

Numerous studies in adults⁸ and children⁴⁶ have documented the effectiveness of similar distraction techniques in reducing pain perception, while generating a broad distribution of individual differences in the magnitude of distraction analgesia. In the current study, we used a simple active physical task that could be completed quickly. After the initial temporal summation run, participants twice squeezed a handgrip dynamometer (Vakind Technology Co., Shenzen, China) to assess maximum grip strength in their dominant hand. These two trials were averaged, after which the experimenter calculated 20% of the maximum handgrip force and marked this level on the dynamometer. Next, the experimenter informed subjects that the task involving temporal summation of mechanical probe pain would be performed on the nondominant hand while the subject was asked to "concentrate on trying to maintain 20% handgrip strength as uniformly as possible" using the dominant hand. Participants were again asked to rate the pain intensity of the first, fifth, and tenth probe stimulus, as well as after-sensations, while maintaining 20% grip strength until the final rating. Distraction analgesia was calculated as the difference in temporal summation of mechanical pain between the "distracted" and "nondistracted" conditions.

Other OST measures

In addition to the temporal summation task in the absence and presence of distraction, subjects underwent several QSTs. Contact heat stimuli were delivered using a contact thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel). A 9 cm2 thermode was applied to the volar forearm, and followed an ascending method of limits paradigm with a rate of rise of 0.5°C/s. Thermal assessment included sampling of warmth and cool thresholds, followed by heat pain thresholds and cold pain threshold, followed by heat pain tolerance all tested on the ventral forearm.^{37,47} Mechanical pain thresholds were assessed using a digital pressure algometer (Somedic, Sollentuna, Sweden). Pressure pain thresholds (PPTh) were determined twice, bilaterally at the trapezius muscle and the metacarpophalangeal joint of the thumb. At each site, mechanical force was applied using a 0.5-cm² probe covered with polypropylene pressure-transducing material; pressure was increased at a steady rate of 30 kPA/s until the subject indicated that the pressure was "first perceived as painful." Reaction to prolonged pressure pain was ascertained using a pneumatic tourniquet cuff over the gastrocnemius muscle, which was inflated to and maintained at a particular pressure to produce a pain intensity rating of 40/100 (tailored to each individual), maintained for 2 min, and rated each 30 s.48 Responses to noxious cold were evaluated upon immersion of the right hand in a circulating cold water bath maintained at 4°C, which was also used to assess CPM, a noninvasive test of endogenous paininhibitory systems using a heterotopic noxious conditioning stimulation paradigm. 49,50 In the current protocol, during each cold pressor test, PPTh was assessed on the contralateral

trapezius. CPM was quantified as percent change in PPTh during the cold pressor tasks relative to baseline PPTh, with an increase in PPTh being expected. A final cold pressor test was used to derive an index of cold pain tolerance, with cold pain intensity ratings (0–100) also obtained at 30 s intervals during and following cold pressor test.

While no formal *a priori* power analysis was performed, sample size was based on previous literature^{51,52} investigating the impact of catastrophizing on pain processing, which had fewer patients than the current work. We therefore considered that the number of patients in the current study were sufficient to detect the effects we were investigating.

Statistics

All analyses were performed using SPSS (V 19, Chicago, IL). Patients were classified as high or low catastrophizers based on a median split of PCS scores (PCS median = 22). Descriptive data for continuous variables were presented as means and SDs, whereas descriptive data for categorical variables were presented as percentages, and differences between low and high catastrophizers among these variables were analyzed using t test and Fisher's exact test, respectively. A temporal summation score was computed by subtracting a patient's first pinprick pain rating from their tenth pinprick pain rating in a train of 10.

To examine whether pinprick pain ratings varied as a function of catastrophizing and the distraction task, a threeway (catastrophizing × distraction task × pinprick stimulus number) mixed analysis of variance (ANOVA) was conducted. Furthermore, to examine whether temporal summation score varied as a function of patients' catastrophizing, opioid status, or the distraction task, a three-way (catastrophizing × opioid status × distraction task) mixed ANOVA was used, with TSP scores (ratings of tenth stimulus - ratings of first stimulus) as the dependent variable. Significant interactions between these factors were investigated. A follow-up (catastrophizing × distraction task) ANCOVA with BDI and PASS included as a covariate was conducted to investigate the potentially confounding impact of depression on this relationship. To investigate the interrelationships among QST outcomes (and determine whether any significant associations were accounted for by catastrophizing), both raw Pearson correlation coefficients and partial correlations (controlling for PCS scores) were calculated between QST measures, and between PCS and depression and anxiety scores. To account for the multiple QSTs used, we adjusted the P value considered significant using a Bonferroni correction for each modality tested. Specifically, when comparing groups of patients (high and low catastrophizing, opioid- and nonopioid users) on 10 psychosocial and demographic variables, we adjusted the significance level to P < 0.005 (table 1). Five Mechanical QSTs (cuff, pressure) were employed, and therefore we adjusted the significance level to P < 0.01 (table 2). Three heat QSTs and three cold pain QSTs were used, and therefore we adjusted the

significance level to P < 0.02 (table 2). Four pinprick measures were included in the temporal summation task, and therefore we adjusted the significance level to P < 0.0125 (table 3). Eight comparisons were made between opioid and nonopioid-treated patients, and therefore we adjusted the significance level to P < 0.00625 (table 4). In considering correlations between QSTs, we performed a total of 11 correlations, and therefore we adjusted the significance level to P < 0.005 (table 5).

Results

Study Population

Slightly more than half (55%) of the 149 participants were women, and mean age was 47.8 ± 10.5 years. Subjects reported an average current pain score of $5.0\pm2.4/10$. Roughly half (48%) of patients reported taking opioids chronically. Of note, men and women pain patients did not differ on any of the QSTs or psychosocial measures examined, with the exception of PPTh at the trapezius, with women patients having a lower PPTh (t (147) = -2.95, P = 0.004).

Catastrophizing about pain was assessed using the PCS, which yielded a mean score of 22.2±11.9 (range 0–48). No differences in age, gender, baseline or posttesting vitals were observed between low and high catastrophizers. However, consistent with other studies, pain scores (present pain, worst pain, least pain) were significantly higher among high catastrophizers. Similarly, anxiety (PASS) and depressive symptoms (BDI) were significantly greater in high catastrophizers (table 1).

Relationship of Catastrophizing to QST Outcomes and Measures of Negative Affect

To characterize the relationship between catastrophizing and pain sensitivity in this chronic pain cohort, we compared scores on several standard QST measures between high and

low catastrophizers. High catastrophizers had higher cuff pressure sensitivity (table 2). Conversely, other QST measures (e.g., pressure, heat, and cold pain threshold and tolerance) were not significantly different between high and low catastrophizing groups (table 2). Repeated pinprick stimuli did evoke a greater degree of temporal summation of mechanical pain in high catatrophizers (table 3, fig. 1). Conversely, CPM, a measure of descending inhibition, was not different between high and low catastrophizers in this sample of pain patients (table 3).

To investigate the relationship of catastrophizing to measures of negative affect, a Pearson correlation was performed. Consistent with previous studies, results of these correlational analyses indicated that catastrophizing was associated with significantly higher scores on the BDI (r = 0.47, P < 0.0001) and on the PASS (r = 0.66, P < 0.0001).

Influence of Catastrophizing and Distraction on Pinprick Pain Ratings

To investigate the relationship of catastrophizing and distraction and stimulus order, a three-way (catastrophizing × distraction × pinprick stimulus number) mixed ANOVA was conducted to examine whether pinprick pain ratings and temporal summation varied as a function of catastrophizing and the distraction task. Results of this ANOVA revealed a significant main effect for catastrophizing (F [1, 143] = 7.2, P < 0.008), such that average pinprick pain ratings were significantly higher in high catastrophizers (m = 27.2, SD = 2.2) than low catastrophizers (m = 18.3, SD = 2.4). There was also a significant main effect for distraction (F [1,143] = 26.6, P < 0.0001), such that pinprick rating were lower in the presence of the distraction task. As expected, a significant main effect was observed for stimulus number (F [2,286] = 83.9, P < 0.0001), revealing that temporal summation of mechanical pain did occur across the 10 stimuli.

These main effects were qualified by a significant catastrophizing × pinprick stimulus number interaction effect

Table 1. Subject Demographics and Pain Characteristics: Differences between Patients with Low and High Catastrophizing

	All Subjects	Low Catastrophizing (n = 69)	High Catastrophizing (n = 76)	
Demographics and Pain Characteristics	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	P Value
Age	47.8 ± 10.5	49.1 ± 11.2	46.7±9.8	0.19
Female gender	56%	51%	58%	0.41
Opioid use	48%	51%	55%	0.62
BPI: current pain*	5.1 ± 2.6	4.0 ± 2.5	6.1 ± 1.8	< 0.0001
BPI: least pain*	3.8 ± 2.5	2.7 ± 2.3	4.7 ± 2.3	< 0.0001
BPI: worst pain*	6.5 ± 2.6	5.4 ± 2.6	7.4 ± 2.2	< 0.0001
Pain-related anxiety*	40.2 ± 19.1	30.0 ± 14.8	50.0 ± 17.5	< 0.0001
BDI*		10.4 ± 7.5	16.5±8.8	< 0.0001
PCS*	22.2 ± 11.8	12.2 ± 6.4	31.3 ± 7.5	< 0.0001

Missing values for PCS, BDI, and Pain-related Anxiety Score on four subjects; statistical tests were t test for continuous variables, Fisher's exact test for discrete variables.

^{*}After Bonferroni adjustment for multiple comparisons, significance set as P < 0.005.

BDI = Beck's Depression Inventory; BPI = Brief Pain Inventory; PCS = Pain Catastrophizing Scale.

Table 2. Comparison of Low and High Catastrophizing Chronic Pain Patients on Quantitative Sensory Testing Measures

	Low Catastrophizing	High Catastrophizing	_
Quantitative Sensory Testing Measure	Mean ± SD	Mean ± SD	P Value
Cuff pressure (mmHg) at 40/100 pain intensity* (n = 69/76)	155±44	129±56	0.002
Pain rating at end of 2 min cuff test (out of 100) (n = 69/75)	43 ± 20	46 ± 23	0.368
Pain rating 15 s after cessation of cuff test (n = 69/75)	4 ± 10	9±17	0.021
Pressure pain threshold trapezius (n = 69/76)	336 ± 169	281 ± 142	0.038
Pressure pain threshold thumb (n = 69/76)	390 ± 168	342 ± 188	0.112
Warmth detection threshold (°C) (n = 55/65)	33.7 ± 5.0	34.1 ± 4.7	0.665
Heat pain threshold (°C) (n = 55/65)	41.1 ± 6.8	40.0 ± 6.3	0.393
Cold pain threshold (°C) (n = 55/64)	12.4±11.0	15.9 ± 9.9	0.080
Heat pain tolerance (°C) (n = 55/64)	45.1 ± 7.0	44.1 ± 6.6	0.427
Cold pain tolerance (s) (n = 66/74)	54.1 ± 50.0	39.2 ± 40.0	0.053
Max cold pain rating (n = 66/74)	84.0 ± 14.2	89.0±15.2	0.044

Statistics used were t tests for continuous variables.

(F [2,286] = 6.4, P = 0.002), with higher catastrophizers showing more dramatically increasing pain scores in the train of stimuli. There was also a significant distraction \times stimulus number interaction effect (F [2,286] = 6.0, P = 0.003), which was driven by a reduction of temporal summation in the distraction condition. Finally, there was also a significant three-way interaction between catastrophizing \times stimulus number \times distraction (F [2,286] = 4.7, P = 0.010). As depicted in figure 1, this three-way interaction was characterized by a prominent reduction in temporal summation within the high catastrophizing group during the distraction task, such that high and low catastrophizers did not differ significantly in temporal summation during the distraction condition, t (143) = -1.46, P = 0.147.

Influence of Catastrophizing, Opioid Status, and Distraction on Temporal Summation

A three-way (catastrophizing × opioid status × distraction task) mixed ANOVA was used to examine whether temporal summation varied as a function of patients' catastrophizing, opioid status, or the distraction task. Results of this analysis

again revealed a significant main effect for catastrophizing (F [1,141] = 6.8 P = 0.01), such that scores on the temporal summation index were significantly greater in high catastrophizers (m = 17.1, SD = 1.9) than low catastrophizers (m = 9.8, SD = 2.0). There was also a significant main effect for distraction on temporal summation (F [1,141] = 8.6, P = 0.004), with lower temporal summation during the distraction task than the control task. These main effects were qualified by a significant catastrophizing × distraction interaction effect (F [1,141] = 6.6, P = 0.011), as high catatrophizers showed a greater diminution of temporal summation during conditions of distraction ("distraction analgesia") than did low catastrophizers (fig. 1, C). There was not a clear main effect of opioid use on temporal summation and also no significant two- or three-way interactions with opioid status.

Given the significant positive correlation between catastrophizing and higher depressive and anxiety symptoms, a follow-up ANCOVA was conducted to examine whether the PCS × distraction interaction effect on temporal summation remained significant even after controlling for BDI and PASS scores. Results of this ANCOVA revealed that the

Table 3. Measures of Pain Modulation in Low and High Catastrophizing

	Low Catastrophizing (n = 69)	High Catastrophizing (n = 76)	
Quantitative Sensory Testing Measure	Mean ± SD or %	Mean ± SD or %	P Value
Pinprick 1 pain rating	15.0±15.2	18.6±17.9	0.186
Pinprick 5 pain rating*	20.7 ± 19.4	31.1 ± 25.3	0.007
Pinprick 10 pain rating*	25.0 ± 22.2	39.1 ± 30.5	0.002
Post 15 s pain rating	2.1 ± 6.3	5.1 ± 13.0	0.080
Temporal summation score (Difference tenth to first)*	10.0 ± 15.0	20.4 ± 21.8	0.001
CPM index (pain threshold with/without conditioning stimulus × 100)	130±33	122±33	0.127

Statistics used were t tests for continuous variables.

CPM = Conditioned Pain Modulation.

^{*} After Bonferroni adjustment for multiple comparisons, significance set as P < 0.01 for pressure-related QSTs and P < 0.02 for heat and cold pain-related QSTs.

QST = Quantitative sensory test.

^{*}After Bonferroni adjustment for multiple comparisons, significance set as P < 0.0125.

Table 4. Comparison of Opioid and Nonopioid Users

	Nonopioid	Opioid	
Factor	Mean ± SD or %	Mean ± SD or %	P Value
Age (n = 77/72)	48.6±10.7	47.0±10.3	0.364
Female gender (n = 77/72)	58%	53%	0.513
BPI:current pain* (n = 77/68)	4.4 ± 2.7	5.8 ± 1.7	0.002
BPI: least pain* (n = 77/68)	3.2 ± 2.6	4.5 ± 2.2	0.001
BPI: worst pain* (n = 77/68)	5.8 ± 2.8	7.2 ± 2.3	0.001
Pain-related anxiety (n = 77/68)	39.7 ± 22.7	40.6 ± 14.0	0.767
PCS (n = 77/68)	22.1 ± 12.7	22.3±10.9	0.910
BDI (n = 77/68)	12.1 ± 8.9	15.2 ± 8.4	0.036

Missing values for PCS, BDI, and Pain-related Anxiety Score on 4 subjects; statistical tests were t test for continuous variables, Fisher's exact test for discrete variables.

main effect of catastrophizing (F [1,142] = 4.7, P = 0.030) and distraction (F [1,142] = 7.8, P = 0.005), as well as the interaction between these two factors (F [1,142] = 10.7, P = 0.001) remained significant even when including BDI and PASS scores as covariates. We further explored the nature of this interaction using partial correlations (controlling for BDI and PASS scores), which allowed us to examine PCS scores as a continuous, rather than a categorical, variable. Partial correlations revealed a significant association between PCS scores and temporal summation in the nondistracted condition (r = 0.23, P = 0.006), but the partial correlation between PCS scores and temporal summation in the distraction condition was not significant (r = 0.02, P = 0.823).

Table 5. Correlation between Distraction Analgesia and Nociceptive Sensitivity on Quantitative Sensory Testing

	Correlation with Distraction Analgesia Index	_
Quantitative Sensory Testing Measure	Pearson Correlation Coefficient	P Value
Cuff pressure (mmHg) at 40/100 pain intensity	-0.055	0.506
Pain rating at end of 2 min cuff test	-0.012	0.882
Pain rating 15 s after cessation of cuff test	-0.004	0.961
Pressure pain threshold trapezius	-0.04	0.628
Pressure pain threshold thumb	-0.136	0.097
Warmth detection threshold (°C)	-0.209	0.02
Heat pain threshold (°C)*	-0.279	0.002
Cold pain threshold (°C)	-0.014	0.882
Heat pain tolerance	-0.236	0.009
Max cold pain rating	0.228	0.006
Conditioned Pain Modulation index*	-0.231	0.005

Pearson correlation coefficients were calculated between Quantitative Sensory Testing measures.

A follow-up Steiger's Z-test revealed that the magnitude of these correlation coefficients was significantly different (Z = 3.16, P < 0.01), indicating that the use of distraction eliminates the initially significant association between catastrophizing and temporal summation of pain.

In this cohort, there was an equal distribution of patients taking opioids chronically (n = 72) and nonopioid users (n = 77), allowing an investigation of the impact of chronic opioid use on distraction analgesia and its relation to catastrophizing. Opioid users reported significantly higher pain scores on the Brief Pain Inventory (table 4). However, no difference in age, gender, pain-related anxiety, depression, stress, or catastrophizing was observed between opioid users and nonusers (table 4). Similarly, there was no evidence for baseline psychophysical differences between opioid users and nonopioid users, as measured by all QST measures, with the exception of the cold pain rating at 30 s (data not shown).

Relationship of Distraction Analgesia to Pain Sensitivity and Conditioned Pain Modulation

Distraction analgesia was variable among patients. To understand the relationship of distraction analgesia to general pain sensitivity, and to CPM, we conducted a correlational analysis of distraction analgesia with other QSTs. Among this group of chronic pain patients, greater distraction analgesia correlated with lower heat pain threshold (table 5), suggesting that more heat pain sensitive patients displayed larger analgesic effect of distraction. However, no such correlation was observed for measures of pressure, heat or cold pain (table 5). Interestingly, distraction analgesia magnitude was inversely correlated with CPM R = -0.23, P = 0.005), such that those with the lowest degree of pain inhibition showed relatively greater distraction analgesia. The pattern of association between distraction analgesia and other QST responses was not altered when controlling for baseline levels of temporal summation.

Discussion

This study investigated individual differences in pain processing among a group of chronic spine pain patients, including

^{*}After Bonferroni adjustment for multiple comparisons, significance set as P < 0.00625

BDI = Beck's Depression Inventory; BPI = Brief Pain Inventory; PCS = Pain Catastrophizing Scale.

^{*}After Bonferroni adjustment for multiple comparisons, significance set as P < 0.005.

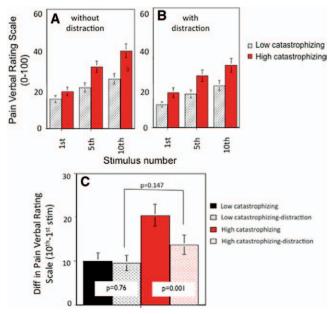


Fig. 1. The impact of distraction on temporal summation of pain in high and low catastrophizers was assessed. Using the lowest-force weighted pinprick stimulator that produced a sensation of discomfort, a train of 10 stimuli (frequency 1 Hz) was applied to the skin of the dorsum the middle phalange of the middle finger. Temporal summation of pain was more pronounced in chronic pain patients with high catastrophizing (A). A distracting handgrip task decreased pinprick scores in both groups (B). However, the distraction task reduced temporal summation in patients with high catastrophizing to a greater degree (C), essentially reducing their temporal summation score to the level of patients with low catastrophizing. ANOVA showed a significant interaction between distraction analgesia and catastrophizing, and follow-up t test indicated that high and low catastrophizers did not differ significantly in temporal summation during the distraction condition, t (143) = -1.46, P = 0.147, while in the nondistracted condition, they did, t (143) = -3.34, t < 0.001.

distraction analgesia, with a specific focus on the influence of catastrophizing. The current findings support the conclusions of previous research demonstrating enhanced TSP among patients high in catastrophizing.³ In addition, as expected, even a brief and simple distracting motor task was able to reduce pain. While the pain-relieving and hyperalgesia-reducing effects of distraction have been well-documented in clinical and QST studies, this is the first report of distraction's capacity to reduce TSP in a clinical cohort. It is noteworthy that a simple, brief, cognitive mechanical task was able to substantially reduce an endogenous pain-facilitatory process such as TSP. Interestingly, despite the overall effectiveness of distraction to reduce TSP, there was a variable effect among this group of chronic pain patients, with the most pronounced analgesia occurring in patients who reported the highest levels of catastrophizing. Given that previous studies in healthy volunteers have found less effective distraction analgesia among higher catastrophizers, this was somewhat surprising and contrary to our initial hypothesis. It may suggest that nociceptive processing among chronic pain patients is altered in comparison to individuals without chronic pain. In addition, there may be important differences between individual chronic pain patients, which may predict their differential response to various distraction-based treatments for pain.

Distraction Analgesia and Catastrophizing

Consistent with previous studies of individuals without chronic pain, higher catastrophizing was associated with amplified TSP. However, high catastrophizers also appeared to benefit most from the analgesic effects of distraction, such that their degree of TSP was essentially decreased to the level of low catastrophizers in the presence of the distracting stimulus (fig. 1, C). This seems especially remarkable because catastrophizing is generally associated with reduced analgesic effectiveness in a variety of contexts,³ and would appear to be at odds with some previous work showing higher catastrophizing to be associated with reduced distraction analgesia.^{5,7} Importantly, these previous reports differ from current study in multiple respects: subject samples (healthy participants in previous studies vs. chronic pain patients in current study), pain induction methods (capsaicin or cold pressor pain vs. a brief mechanical temporal summation task), time course of pain responses studied, and type of distraction task, all of which potentially account for the differing results.

Several putative mechanisms could explain the finding that chronic pain patients with higher catastrophizing in this study exhibited greater distraction analgesia on the TSP assay. First, the TSP assay may be particularly well-suited to detect these interactions. The sustained attention that is required to give repeated pain ratings during this test may allow a greater degree of pain catastrophizing to develop, and as such, make it more sensitive to detect the interaction of catastrophizing with attentional state. Second, chronic pain patients exhibit an overall higher level of catastrophizing compared with volunteers with no chronic pain, and it is possible that

a qualitatively different relationship of catastrophizing and attention occurs at this level. Third, there may be increased relevance of attentional states to the experience of pain in chronic pain patients.^{11,21} The long-term stress of living with chronic pain may itself alter the psychological, physiological, and cognitive processing,⁵³ and negatively impact the ability to effectively modulate attention, and self-initiate coping mechanisms such as distraction. As catastrophizing exerts its impact in part by the individual involuntarily focusing attention or ruminating on pain, high catastrophizers may be more susceptible to effective external distraction and a subsequent greater reduction of the pain response. Deliberate diversion of attention away from this painful stimulus may in fact buffer some of the pain-amplifying effects of negative affective and cognitive processes involved in catastrophizing.

Collectively, the current findings suggest that the association between catastrophizing and distraction analgesia is complex, and additional research is needed to elucidate all the potentially interacting factors that contribute to individual differences in the pain-relieving effects of distraction. However, future treatment studies in those with high catastrophizing may benefit from the inclusion of distraction training for this patient group, which is otherwise generally considered to be treatment-resistant.

Relationship of Distraction Analgesia to Pain Sensitivity and Endogenous Pain Modulation

Chronic pain patients show structural, functional, and neurochemical brain changes compared with healthy controls⁸ and the success of any given analgesic strategy may vary widely across individuals with any given chronic pain diagnosis. The current findings suggest that a tendency toward catastrophic thinking about pain may actually favor distraction as an analgesic strategy. That is, some of the pain-amplifying impact of catastrophizing may be effectively neutralized during the deliberate diversion of attention away from noxious stimulation. To better characterize the individuals who had greater distraction analgesia, we also investigated the correlation of distraction analgesia with other QST responses. Interestingly, those with low levels of endogenous pain inhibition measured as CPM had higher (more effective) distraction analgesia scores. This is perhaps not surprising, as TSP is generally considered to be a measure of pain facilitation, whereas CPM seems to be a measure of pain inhibition.^{54,55} The inverse correlation between distraction analgesia and CPM observed in this study endorses the idea that these pain modulatory processes may involve different underlying neurobiological mechanisms, allowing the possibility for synergistic combination of these analgesic approaches (e.g., combining a CPM paradigm with a distraction task may enhance its pain-reducing qualities). Indeed, one previous study found that distraction analgesia and CPM were separable and additive when applying both approaches simultaneously.6 Similarly, another study found additive effects of combining distraction with CPM, culminating in inhibition

of thermal temporal summation, in a chronic pain cohort (fibromyalgia patients).⁵⁶

The current sample of patients was roughly evenly split into those using opioids and those using exclusively nonopioid medications. In both animal and human studies, chronic opioid use is associated with both opioid tolerance and opioid-induced hyperalgesia.⁵⁷ Given that distraction analgesia may involve endogenous opioid neurotransmission,²² and chronic opioid use may alter pain-modulatory processes²³ and modulate the effect of emotional states on pain,²⁴ we speculated that chronic opioid use might negatively impact its efficacy. However, we did not observe a difference in distraction analgesia in the temporal summation assay between those patients on chronic opioid therapy compared to those patients not currently using opioids. Similarly, there was no significant interaction between opioid use and catastrophizing. An important consideration is that opioid use was not randomized in this study, and indeed patients taking opioids chronically reported greater pain and depression, potentially confounding any definitive conclusion in this regard.

Limitations

Inclusion in the study was voluntary, which allows for selection bias among participants. We did not randomize the order of distracted and nondistracted temporal summation tasks, which increases the possibility of order effects (e.g., habituation). However, previous studies of temporal summation have reported no systematic changes across trials, 58,59 and previous work has suggested that individuals high in catastrophizing exhibit less habituation than low catastrophizers.⁵⁴ We used only a single pain modality (noxious mechanical punctate stimulation) in the assay of distraction analgesia. In general, QST-assessed indices of pain sensitivity and pain modulation tend to be moderately intercorrelated, but further assessment of the pain-reducing effects of distraction on other pain modalities (e.g., heat pain, cold pain, electrical pain, etc.) could reveal the generalizability of distraction's analgesic effects that were observed in this study. In addition, pinprick pain is a relatively moderate pain stimulus, and possibly with a more intense pain stimulus, low catastrophizing patients would exhibit higher distraction analgesia, similar to that exhibited by high catastrophizing patients. We did not include a "control" condition, and thus cannot exclude the possibility that the observed effects were attributable to a process other than distraction (e.g., motor activity-dependent inhibition of pain, or a form of exerciseinduced analgesia). We are doubtful that such processes played a major contributory role in this study, as analgesic effects derived from physical activity typically require much longer and more intense activity than the brief, mild, handgrip task used here, and as patients with chronic pain do not generally demonstrate robust exercise-induced analgesia. 60 Finally, because of the nature of the distraction task data, we treated PCS scores as dichotomous rather than continuous. In response to peer review, we also performed additional

analyses treating PCS as continuous variable, which did not alter any of the significant findings.

Conclusions

The current study confirms previous reports of enhanced temporal summation of pain in subjects high in catastrophizing, and is the first to document the capacity of distraction to reduce temporal summation of pain in pain patients, with this effect being most pronounced among those highest in catastrophizing. In addition, we observed a modest but significant inverse relationship between distraction analgesia and CPM, suggesting that these pain-modulatory processes may occupy distinct neurobiological pathways and contribute independently to each individual's pain experience. The results of this study would suggest that patients high in catastrophizing, who may be less likely to benefit from CPM, may, in fact, derive sizable benefits from distraction-based pain-management approaches.

Acknowledgments:

The authors gratefully acknowledge all the patients who agreed to take part in the study, without whose participation and cooperation this work would not have been possible.

This study is supported by National Institutes of Health, Bethesda, Maryland, grants R01AG034982 (to Dr. Edwards) and R21AR057920 (to Dr. Edwards).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Schreiber: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. klschreiber@partners.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

- Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC: The biopsychosocial approach to chronic pain: Scientific advances and future directions. Psychol Bull 2007; 133:581–624
- Kerns RD, Sellinger J, Goodin BR: Psychological treatment of chronic pain. Annu Rev Clin Psychol 2011; 7:411–34
- Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA: Pain, catastrophizing and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216–24
- Morris LD, Louw QA, Grimmer-Somers K: The effectiveness of virtual reality on reducing pain and anxiety in burn injury patients: A systematic review. Clin J Pain 2009; 25:815–26
- Verhoeven K, Van Damme S, Eccleston C, Van Ryckeghem DM, Legrain V, Crombez G: Distraction from pain and executive functioning: An experimental investigation of the role of inhibition, task switching and working memory. Eur J Pain 2011; 15:866–73
- Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D: 'Pain inhibits pain' mechanisms: Is pain modulation simply due to distraction? Pain 2010; 150:113–20
- Campbell CM, Witmer K, Simango M, Carteret A, Loggia ML, Campbell JN, Haythornthwaite JA, Edwards RR:

- Catastrophizing delays the analgesic effect of distraction. Pain 2010; 149:202-7
- 8. Jensen KB, Berna C, Loggia ML, Wasan AD, Edwards RR, Gollub RL: The use of functional neuroimaging to evaluate psychological and other non-pharmacological treatments for clinical pain. Neurosci Lett 2012; 520:156–64
- 9. Van Ryckeghem DM, Crombez G, Van Hulle L, Van Damme S: Attentional bias towards pain-related information diminishes the efficacy of distraction. Pain 2012; 153:2345–51
- Snijders TJ, Ramsey NF, Koerselman F, van Gijn J: Attentional modulation fails to attenuate the subjective pain experience in chronic, unexplained pain. Eur J Pain 2010; 14:282.e1–10
- Sharpe L, Dear BF, Schrieber L: Attentional biases in chronic pain associated with rheumatoid arthritis: Hypervigilance or difficulties disengaging? J Pain 2009; 10:329–35
- 12. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ Jr: Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003; 102:87–95
- Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD: Brain activity related to temporal summation of C-fiber evoked pain. Pain 2007; 129:130–42
- 14. Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S: Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. Pain 1998; 76:71–81
- Edwards RR, Mensing G, Cahalan C, Greenbaum S, Narang S, Belfer I, Schreiber KL, Campbell C, Wasan AD, Jamison RN: Alteration in pain modulation in women with persistent pain after lumpectomy: Influence of catastrophizing. J Pain Symptom Manage 2013; 46:30–42
- 16. Schreiber KL, Martel MO, Shnol H, Shaffer JR, Greco C, Viray N, Taylor LN, McLaughlin M, Brufsky A, Ahrendt G, Bovbjerg D, Edwards RR, Belfer I: Persistent pain in postmastectomy patients: Comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain 2013; 154:660–8
- Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, Englert D, Greco C, Brufsky A, Ahrendt G, Kehlet H, Edwards RR, Bovbjerg DH: Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain 2013; 14:1185–95
- 18. Dengler-Crish CM, Bruehl S, Walker LS: Increased wind-up to heat pain in women with a childhood history of functional abdominal pain. Pain 2011; 152:802–8
- Van Damme S, Crombez G, Eccleston C: Disengagement from pain: The role of catastrophic thinking about pain. Pain 2004; 107:70–6
- 20. Verhoeven K, Goubert L, Jaaniste T, Van Ryckeghem DM, Crombez G: Pain catastrophizing influences the use and the effectiveness of distraction in schoolchildren. Eur J Pain 2012; 16:256–67
- Borsook D, Edwards R, Elman I, Becerra L, Levine J: Pain and analgesia: The value of salience circuits. Prog Neurobiol 2013; 104:93–105
- 22. Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C: Attention modulates spinal cord responses to pain. Curr Biol 2012; 22:1019–22
- 23. Ram KC, Eisenberg E, Haddad M, Pud D: Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain new perspective of opioid-induced hyperalgesia. Pain 2008; 139:431–8
- Burns JW, Bruehl S: Anger management style, opioid analgesic use, and chronic pain severity: A test of the opioid-deficit hypothesis. J Behav Med 2005; 28:555–63
- Anderson RJ, Craggs JG, Bialosky JE, Bishop MD, George SZ, Staud R, Robinson ME: Temporal summation of second pain: Variability in responses to a fixed protocol. Eur J Pain 2013; 17:67–74

- 26. Fillingim RB, Maixner W, Kincaid S, Silva S: Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998; 75:121–7
- Harkins SW, Davis MD, Bush FM, Kasberger J: Suppression of first pain and slow temporal summation of second pain in relation to age. J Gerontol A Biol Sci Med Sci 1996; 51:M260-5
- 28. Eisenberg E, Midbari A, Haddad M, Pud D: Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects. Pain 2010; 151:104–9
- Bisgaard T, Klarskov B, Rosenberg J, Kehlet H: Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 2001; 90:261–9
- Granot M, Lowenstein L, Yarnitsky D, Tamir A, Zimmer EZ: Postcesarean section pain prediction by preoperative experimental pain assessment. Anesthesiology 2003; 98:1422–6
- 31. Hsu YW, Somma J, Hung YC, Tsai PS, Yang CH, Chen CC: Predicting postoperative pain by preoperative pressure pain assessment. ANESTHESIOLOGY 2005; 103:613–8
- 32. Werner MU, Mjöbo HN, Nielsen PR, Rudin A: Prediction of postoperative pain: A systematic review of predictive experimental pain studies. Anesthesiology 2010; 112:1494–502
- Werner MU, Duun P, Kehlet H: Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. Anesthesiology 2004; 100:115–9
- 34. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M: Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 2008; 138:22–8
- Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA: Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage 2013; 21:1236–42
- Aasvang EK, Brandsborg B, Christensen B, Jensen TS, Kehlet H: Neurophysiological characterization of postherniotomy pain. Pain 2008; 137:173–81
- 37. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN: Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. J Pain 2011; 12:953–63
- 38. Tan G, Jensen MP, Thornby JI, Shanti BF: Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004; 5:133–7
- 39. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113:9–19
- Beck AT, Steer RA, Garbin MG: Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev 1988; 8:77–100
- Sullivan MJ, Bishop SR, Pivik J: The Pain Catastrophizing Scale: Development and validation. Psychol Assess 1995; 7:524–32
- 42. Van Damme S, Crombez G, Bijttebier P, Goubert L, Van Houdenhove B: A confirmatory factor analysis of the Pain Catastrophizing Scale: Invariant factor structure across clinical and non-clinical populations. Pain 2002; 96:319–24

- 43. McCracken LM, Zayfert C, Gross RT: The Pain Anxiety Symptoms Scale: Development and validation of a scale to measure fear of pain. Pain 1992; 50:67–73
- Edwards RR, Kronfli T, Haythornthwaite JA, Smith MT, McGuire L, Page GG: Association of catastrophizing with interleukin-6 responses to acute pain. Pain 2008; 140:135–44
- 45. Edwards RR, Wasan AD, Bingham CO 3rd, Bathon J, Haythornthwaite JA, Smith MT, Page GG: Enhanced reactivity to pain in patients with rheumatoid arthritis. Arthritis Res Ther 2009; 11:R61
- 46. Koller D, Goldman RD: Distraction techniques for children undergoing procedures: A critical review of pediatric research. J Pediatr Nurs 2012; 27:652–81
- 47. Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB: Catastrophizing as a mediator of sex differences in pain: Differential effects for daily pain *versus* laboratory-induced pain. Pain 2004; 111:335–41
- 48. Graven-Nielsen T, Arendt-Nielsen L: Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010; 6:599–606
- 49. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O: Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain 2010; 14:339
- 50. Yarnitsky D: Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010; 23:611–5
- 51. George SZ, Wittmer VT, Fillingim RB, Robinson ME: Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. J Pain 2007; 8:2–10
- 52. Edwards RR, Smith MT, Stonerock G, Haythornthwaite JA: Pain-related catastrophizing in healthy women is associated with greater temporal summation of and reduced habituation to thermal pain. Clin J Pain 2006; 22:730–7
- 53. Simons LE, Elman I, Borsook D: Psychological processing in chronic pain: A neural systems approach. Neurosci Biobehav Rev 2014; 39:61–78
- 54. Price DD, Hayes RL, Ruda M, Dubner R: Neural representation of cutaneous aftersensations by spinothalamic tract neurons. Fed Proc 1978; 37:2237–9
- Pud D, Granovsky Y, Yarnitsky D: The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain 2009; 144:16–9
- 56. Staud R, Robinson ME, Vierck CJ Jr, Price DD: Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003; 101:167–74
- 57. Chu LF, Angst MS, Clark D: Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. Clin J Pain 2008; 24:479–96
- Kong JT, Johnson KA, Balise RR, Mackey S: Test-retest reliability of thermal temporal summation using an individualized protocol. J Pain 2013; 14:79–88
- Cathcart S, Winefield AH, Rolan P, Lushington K: Reliability of temporal summation and diffuse noxious inhibitory control. Pain Res Manag 2009; 14:433–8
- 60. Nijs J, Kosek E, Van Oosterwijck J, Meeus M: Dysfunctional endogenous analgesia during exercise in patients with chronic pain: To exercise or not to exercise? Pain Physician 2012; 15:ES205–13