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Pain perception and modulation in acute and chronic pain states

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Chapter 3

The influence of offset analgesia on the onset and offset of pain in patients with fibromyalgia

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INTRODUCTION

Fibromyalgia is a chronic pain syndrome characterized by widespread pain, often accompanied by fatigue, sleep disturbances, cognitive dysfunction, and episodes of clinical depression^{1,2}. The etiology of fibromyalgia has not been completely clarified. Currently, the most accepted hypothesis is that fibromyalgia is a central pain syndrome in which the central nervous system is the origin of the pain state or is involved in the pathological amplification of nociceptive input. Evidence supporting this hypothesis includes the observation of increased neuronal activation in brain regions involved in pain processing during nonnoxious stimulation and the presence of a dysfunctional endogenous pain modulatory system¹⁻⁶.

The endogenous pain modulation system is an important modulator of pain perception. It consists of inhibitory and facilitatory descending pathways originating in the brain and projecting to the dorsal horn of the spinal cord, where they inhibit or enhance the passage of nociceptive input to central sites⁷. An imbalance between facilitatory and inhibitory properties of the descending pathways has been associated with chronic central pain states, including fibromyalgia, as measured by a decrease in diffuse noxious inhibitory control (currently known as conditioned pain modulation)^{4,5,8,9}. A relatively new experimental paradigm that is used to evaluate the function of the endogenous pain modulation system is offset analgesia (OA). Offset analgesia is characterized by the perception of profound analgesia upon a small decrease in temperature during noxious thermal stimulation, which is more pronounced than would be expected from the rate of the temperature decrease^{10,11}.

In this study, the presence of OA in patients with fibromyalgia was investigated. We hypothesized that patients with fibromyalgia would have a decreased OA response compared with control subjects. Furthermore, the effect of several variations to the OA paradigm was evaluated to understand the role of OA (or its lack) in the development of pain in control subjects and patients with fibromyalgia. To assess whether the magnitude of OA could be enhanced, repetition of the OA paradigm and additional downward 1°C temperature steps (downward steps test) were applied. To assess whether OA affects onset of pain, we applied OA steps at increasing temperatures (upward OA steps test).

METHODS

Subjects

Sixty-eight individuals participated in 1 or more pain tests, 34 patients with fibromyalgia and 34 age-matched and sex-matched healthy control subjects (Table 1 for the number of subjects who participated in each of the tests). Recruitment began after approval of

the protocol by the local medical ethics committee (Commissie Medische Ethiek LUMC, Leiden, the Netherlands), and the study was registered in the Netherlands trial register under number NTR4023 (www.trialregister.nl). All participants gave written informed consent and underwent a physical examination before enrollment in the study. Patients with fibromyalgia were included if they had a pain score ≥ 5 (on a scale of 0-10) for most of the day and met the 2010 American College of Rheumatology diagnostic criteria¹². These criteria included a widespread pain index (WPI; 0-18 points) that defined the number of body areas in which a patient experienced pain during the last week, and a symptom severity score (SyS-score; 0-12 points), which indicated the level of other core symptoms of fibromyalgia such as fatigue, unrefreshing sleep and cognitive symptoms. Inclusion criteria were a WPI ≥ 7 with a SyS-score ≥ 5 or a WPI of 3 to 6 with a SyS-score ≥ 9 . Exclusion criteria for control subjects and patients included age < 18 or > 75 years, an inability to give written informed consent, a medical disease such as cardiac, liver, renal, or vascular disease that could influence pain perception according to the investigator, and a history of psychiatric disease, pregnancy, and obesity (body mass index > 35). Patients were allowed to continue the use of their pain medication as long as the dose used was constant for the 8 weeks before the study day.

Table 1. Subject characteristics and number of subjects per test

	Control subjects	Patients with fibromyalgia	P
Sex (M/F)	8/26	8/26	
Age (y)	36.5 [23.8 – 47.3]	38.0 [24.8 – 46.3]	0.753
Height (cm)	175.7 \pm 20.0	171.5 \pm 6.4	0.151
Weight (kg)	68.8 \pm 21.6	77.0 \pm 18.0	0.150
BMI (kg/cm ²)	22.1 \pm 2.9	26.1 \pm 5.0	0.016
NRS	0	6.7 \pm 1.2	
Disease duration (y)		14.0 \pm 12.8	
WPI		13.9 \pm 2.9	
SyS-score		8.1 \pm 2.3	
Number of subjects in each test			
Test 1: 1-step OA	34	34	
Test 2: repeated OA	12	28	
Test 3: downward step test	12	12	
Test 4: constant stimulus test	12	28	
Test 5: upward OA step test	12	12	
Test 6: Ramp test	12	12	

Values are presented as numbers, means \pm SD or medians (interquartile range). BMI, body mass index; NRS, numerical rating scale, with 0 indicating “no pain” and 10 indicating “worst pain imaginable”; OA, offset analgesia; SyS-score, symptom severity score; WPI, widespread pain index.

Pain measurements

Noxious thermal stimulation was applied on the skin of the volar side of the non-dominant arm using the 3 × 3 cm thermal probe of the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). The system was tested and calibrated according to the specifications of the manufacturer using a surface thermometer (K-Thermocouple thermometer, Hanna Instruments, Woonsocket, RI). To prevent sensitization or adaptation, the thermode was sequentially moved among 3 different locations on the skin of the forearm¹³. There were at least 15 minutes between the various heat tests. During the induction of pain, the visual analog score (VAS) was measured using a slider on a computerized potentiometer that ranged from 0 mm (no pain) to 100 mm (worst pain imaginable). This allowed for the continuous quantification of the intensity of the noxious stimulus.

Study design

At the start of the study session, the temperature that induced a VAS score of 50 mm was determined. To that end, a series of heat stimuli were applied in the range of 42°C to 49°C for 10 seconds. The temperature that evoked a VAS of 50 mm was used during the remainder of the study and defined as the “test” temperature. Next, 6 different heat pain tests were performed in random order; each pain test was performed 3 times and all tests were performed on 1 day.

Tests 1, 2, and 3 were designed to characterize OA (test 1) and evaluate whether repeated OA steps (test 2) or OA followed by downward steps (test 3) could enhance the magnitude of the OA response. Test 4, the constant stimulus test, served as a control test and enabled measurement of response adaptation in patients with fibromyalgia. In contrast to tests 1 to 3, tests 5 (repeated OA at increasing temperatures) and 6 (ramp test) were designed to assess whether OA affects the onset of a pain response.

Pain test 1: one-step offset analgesia

A regular 1-step OA test was induced using the 3-temperature paradigm as previously described^{14,15}. In short, the temperature of the heat probe was increased by 1.5°C/s from a baseline temperature of 32°C to the individual’s test temperature and kept constant for 5 seconds. Next, the temperature was raised by 1°C for 5 seconds after which it returned back to the individual test temperature (*i.e.*, a decrease by 1°C). This temperature was kept constant for 20 seconds followed by a quick return at 6°C/s toward the baseline temperature (Fig. 1A). We define the 1°C increase which is kept constant for 5 seconds and subsequent 1°C decrease as the OA paradigm.

Pain test 2: repeated offset analgesia

During the repeated OA test, the OA paradigm (1°C increase followed after 5 seconds by a 1°C decrease) was repeated 4 times with an interval of 10 seconds between the 1°C temperature variations (Fig. 1B).

Pain test 3: downward steps test

This is one OA test followed by a stepwise 1°C temperature decreases at 5-second intervals until the baseline temperature was reached (Fig. 1C).

Pain test 4: constant stimulus test

For this test, constant heat stimulation was applied. The heat probe was ramped with 1.5°C/s to the individual test temperature and kept constant for 80 seconds. Next, the temperature returned to baseline (temperature decrease rate = 6°C/s; Fig. 1D).

Pain test 5: upward offset analgesia steps test

This is a repeated OA test at increasing temperatures. During this test, the heat probe temperature was increased in steps of 2°C followed after 3 seconds by a 1°C temperature decrease. After another 3 seconds, the sequence was repeated. The sequence was initiated at 32°C (first step from 32 to 34°C followed by a decrease to 33°C) and continued until the VAS reached a value of 80 mm. At this point, the test was terminated and the temperature quickly returned (at 6°C/s) to 32°C (Fig. 2A). The safe fail temperature was set at 51°C.

Pain test 6: ramp test

A ramp heat stimulus was induced by increasing the temperature of the thermode by 0.5°C/s from baseline (32°C) until the VAS reached a score of 80 mm. At that point, the stimulus was ended and the temperature returned at a rate of 6°C/s to the baseline temperature (Fig. 2B). The safe fail temperature was 51°C.

Data and statistical analyses

Sample size calculation based on data from Ref. ¹⁵ indicated that 12 controls and 12 patients with fibromyalgia would be sufficient to detect a significant difference in OA response. However, the groups were expanded based on the availability of subjects.

Tests 1, 2, and 3

Offset analgesia responses were quantified as previously described ^{14,15}. In short, for each OA paradigm, the decrease in VAS from the peak VAS value to the VAS nadir was measured (Δ VAS) within a 10-second time frame after the 1°C decrease in temperature.

This value was next corrected for the value of the peak VAS: ($\Delta\text{VAS}/[\text{peak VAS}] \times 100\%$) and defined as ΔVAS corrected or ΔVASc .

Test 4

To quantify the adaptation response, area-under-the-curve values were calculated for each test.

Tests 5 and 6

The temperature at which the VAS reached 80 mm was determined and compared between populations and between tests.

Statistical significance between controls and patients was tested using an unpaired 2-tailed Student *t* test for normal distributed data and a Mann–Whitney *U* test for non-normal distributed data. Statistical significance between different tests within a population was tested using a paired 2-tailed student *t* test. The OA responses in test 2 were analyzed by repeated measures analysis of variance with a Dunnett's test for comparisons vs. the first OA response. The analyses were performed using GraphPad Prism version 6.0 for Mac (GraphPad Software Inc, La Jolla, CA).

Data are presented as mean \pm SD or 95% confidence interval unless otherwise stated; *P* values <0.05 are considered significant.

RESULTS

Subject characteristics are shown in Table 1. Patients and control subjects were comparable in age and sex distribution. A 15% higher body mass index was observed for the patients with fibromyalgia. All patients fitted the diagnostic criteria for fibromyalgia according to the 2010 criteria as set by the American College of Rheumatology¹². The following pain medication was continued during the study: acetaminophen, NSAIDs, tramadol, amitriptyline, paroxetine, venlafaxine, sertraline, and duloxetine. The average individual test temperature for control subjects was $46.9 \pm 2.3^\circ\text{C}$ (mean \pm SD) vs. $44.5 \pm 2.3^\circ\text{C}$ for patients with fibromyalgia ($P = 0.004$). No difference was observed in the corresponding VAS scores, which were 51.5 ± 14.5 mm vs. 51.4 ± 9.2 mm, respectively ($P = 0.97$). This indicates that a pain score of 50/100 mm was obtained at a 2.4°C lower temperature in patients with fibromyalgia compared with control subjects, an indication of hyperalgesia in the fibromyalgia population.

Pain test 1: one-step offset analgesia

Thirty-four control subjects and 34 patients with fibromyalgia participated in test 1. Compared with the control group, patients with fibromyalgia had a 32.0% reduced OA

response: Δ VASc scores = $97.8 \pm 4.7\%$ (control subjects) vs. $65.3 \pm 26.2\%$ (patients with fibromyalgia, $P < 0.001$; Fig. 1A). No differences in peak VAS scores were present: 60.1 ± 17.9 mm (control subjects) vs. 64.1 ± 15.7 mm (patients with fibromyalgia, $P = 0.30$).

Pain test 2: repeated offset analgesia

Twelve control subjects and 28 patients with fibromyalgia participated in test 2. In both populations, the second to fourth peak VAS scores decreased significantly from the first one (main effect $P < 0.001$; Fig. 1B). Consecutive peak VAS scores for fibromyalgia patients were 61.7 ± 12.4 mm, 45.6 ± 12.8 mm ($P < 0.001$), 45.7 ± 14.5 mm ($P < 0.001$), and 44.4 ± 13.5 mm ($P < 0.001$). For the controls, these scores were 63.1 ± 18.5 mm, 48.1 ± 15.3 mm ($P < 0.001$), 47.0 ± 22.2 mm ($P < 0.001$), and 32.9 ± 33.8 mm ($P < 0.001$). No differences in peak VAS scores were observed between control subjects and patients with fibromyalgia (main effect $P = 0.16$). In control subjects, the consecutive Δ VASc scores were of similar magnitude (main effect $P = 0.58$): $95.3 \pm 5.9\%$, $94.9 \pm 7.8\%$, $94.6 \pm 10.9\%$, and $98.0 \pm 6.8\%$. Also in patients with fibromyalgia, consecutive Δ VASc scores

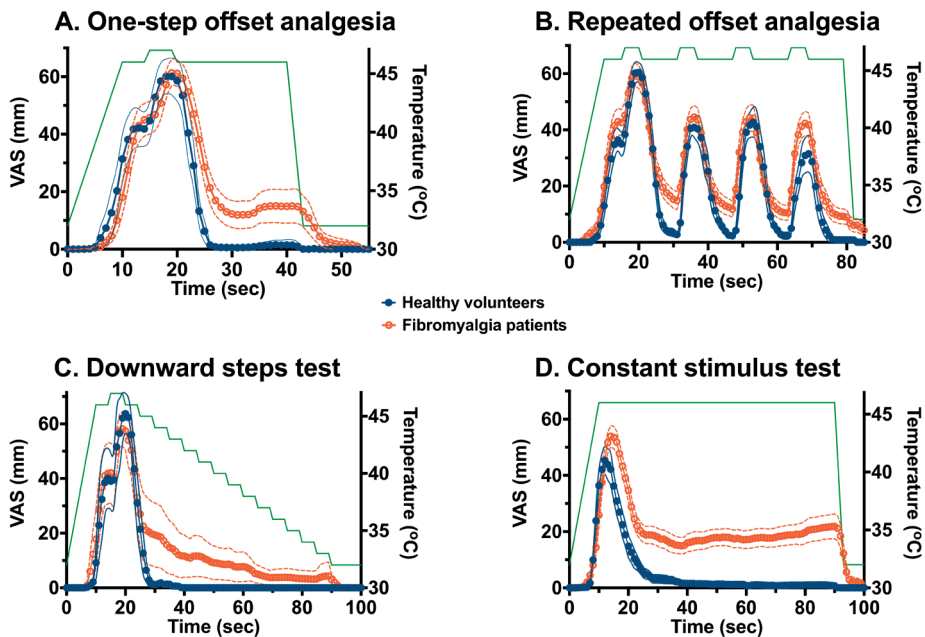


Figure 1. Visual analog scores in response to (A) the 1-step OA paradigm in 34 controls and 34 patients with fibromyalgia, (B) the repeated OA paradigm in 12 controls and 28 patients with fibromyalgia, (C) the downward steps test in 12 controls and 12 patients with fibromyalgia, and (D) the constant stimulus test in 12 control subjects and 28 patients with fibromyalgia. The continuous green lines reflect examples of the temperature paradigms applied. Blue symbols are the data from control subjects; orange symbols are the data from patients with fibromyalgia. The data are mean (circles) \pm 95% CI (thin continuous or broken lines). CI, confidence interval; OA, offset analgesia; VAS, visual analog score.

were similar: $75.0 \pm 23.4\%$, $77.7 \pm 25.5\%$, $78.9 \pm 26.5\%$, and $79.8 \pm 27.0\%$ (main effect $P = 0.46$). The OA responses in patients with fibromyalgia were reduced compared with the control subjects by about 21.3% ($P = 0.03$).

Pain test 3: downward steps test

Twelve control subjects and 12 patients with fibromyalgia participated in test 3. No differences were observed in the peak VAS scores between populations: 64.4 ± 10.5 mm (control subjects) vs. 60.8 ± 8.8 mm (patients with fibromyalgia, $P = 0.38$). The first 1°C temperature step-down resulted in an OA response that was larger in control subjects than in patients with fibromyalgia: $\Delta\text{VAS}_c = 97.5 \pm 3.7\%$ (control subjects) vs. $66.9 \pm 33.7\%$ (patients with fibromyalgia, $P = 0.006$; Fig. 1C). As OA was not or incompletely engaged in patients with fibromyalgia, we hypothesized that another 1°C temperature decrease (after the initial OA paradigm) might complete (or at least in part) the OA response. However, after the initial OA response, no additional OA was produced in patients with fibromyalgia (Fig. 1C).

Pain test 4: constant stimulus test

Twelve control subjects and 28 patients with fibromyalgia performed this test. No difference was observed in peak VAS scores between populations (control subjects: 51.5 ± 11.6 mm vs. patients with fibromyalgia: 59.1 ± 15.4 mm, $P = 0.15$; Fig. 1D). Patients with fibromyalgia displayed a significant decreased adaptation response compared with the controls during the constant heat stimulation test. Average area-under-the-curve scores were 538 ± 99 mm·s for the control subjects vs. 1875 ± 220 mm·s for the patients with fibromyalgia ($P < 0.001$).

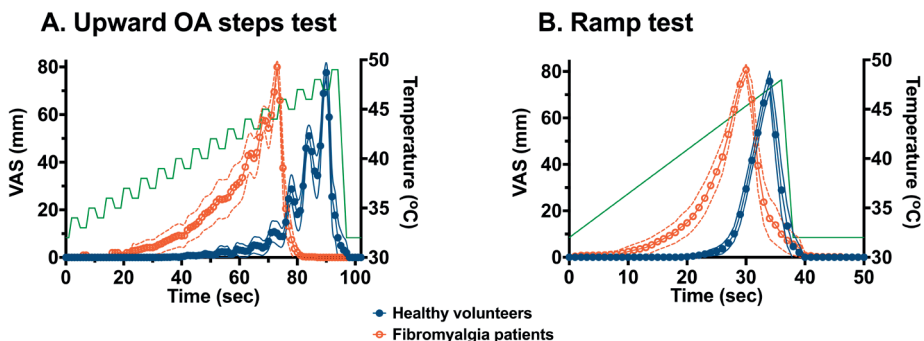


Figure 2. Visual analog scores in response to (A) the upward OA steps test (cutoff is a VAS of 80 mm) in 12 control subjects and 12 patients with fibromyalgia, and (B) the ramp test (cutoff is a VAS of 80 mm) in 12 control subjects and 12 patients with fibromyalgia. The continuous green lines reflect examples of the temperature paradigms applied. Blue symbols are the data from control subjects; orange symbols are the data from patients with fibromyalgia. The data are mean (circles) \pm 95% CI (thin continuous or broken lines). CI, confidence interval; OA, offset analgesia; VAS, visual analog score.

Pain test 5: upward OA steps test

Twelve control subjects and 12 patients with fibromyalgia participated in test 5. The average temperature reached at the cutoff (VAS 80 mm) was $48.8 \pm 0.7^\circ\text{C}$ in control subjects vs. $46.5 \pm 1.4^\circ\text{C}$ in patients with fibromyalgia ($P < 0.001$) with corresponding VAS scores within 3% of the cutoff VAS (controls: 77.9 ± 7.1 mm and patients with fibromyalgia: 81.9 ± 1.4 mm, $P = 0.24$). None of the subjects reached the safe fail temperature of 51°C before they reached the cutoff VAS. Offset analgesia was observed with every decrease in temperature in the control subjects but not in the patients with fibromyalgia (Fig. 2A).

Pain test 6: ramp test

Twelve control subjects and 12 patients with fibromyalgia participated in this test. In this ramp test, the average temperature that was reached at the cutoff (VAS 80 mm) was $48.1 \pm 5.8^\circ\text{C}$ in control subjects vs. $46.2 \pm 1.4^\circ\text{C}$ in patients with fibromyalgia ($P < 0.001$). None of the subjects reached the safe fail temperature of 51°C before they reached the cutoff VAS. Cutoff VAS scores were within 3% of target (controls: 76.8 ± 7.5 mm and patients with fibromyalgia, 82.2 ± 4.1 mm, $P = 0.08$). This indicates that the same pain intensity was reached at a 1.9°C lower temperature in patients with fibromyalgia (Fig. 2B).

Pain test 5 vs. pain test 6

A significant higher temperature was reached at the cutoff VAS value during the upward OA step test (test 5) compared with the ramp test (test 6) in the control subjects ($48.8 \pm 0.7^\circ\text{C}$ [test 5] vs. $48.1 \pm 5.8^\circ\text{C}$ [test 6]; $P < 0.001$) but not in the patients with fibromyalgia ($46.5 \pm 1.4^\circ\text{C}$ [test 5] vs. $46.2 \pm 1.4^\circ\text{C}$ [test 6]; $P = 0.24$). Cut-off VAS-scores were similar though: control subjects 77.9 ± 7.1 mm (test 5) versus 76.8 ± 7.5 mm (test 6; $p = 0.56$); fibromyalgia patients: 81.9 ± 1.4 mm (test 5) versus 82.2 ± 4.2 mm (test 6; $p = 0.76$). This indicates that effective OA engagement (test 5) results in a difference in onset of pain (ie, more pain is tolerated) compared with a condition in which no OA was generated (test 6) in the control subjects. In contrast, in patients with fibromyalgia, reduced OA responses (in test 5) lead to the absence of a difference in the temperature at VAS 80 mm between the 2 tests, hence there was no difference in the onset of pain.

DISCUSSION

In this study, the presence of OA was investigated in patients who experienced chronic pain diagnosed with fibromyalgia and compared with sex-matched and age-matched healthy controls. We observed that compared with control subjects, patients with fibromyalgia show significantly reduced OA and adaptation responses, with an inability to enhance or restore the decreased OA responses by repeating the OA paradigm or

initiating multiple consecutive 1°C temperature decreases. Additionally, we showed that patients with reduced engagement of OA experience their first perception of pain and pain tolerance at lower stimulus intensities compared with controls with more effective OA activation (Fig. 2).

Offset analgesia

Grill and Coghill¹⁰ first described OA in 2002 as a phenomenon that engages temporal filtering in pain processing. The mechanism is activated when a small decrease (1°C-2°C) in temperature during noxious stimulation evokes a disproportionately large reduction in pain perception. Offset analgesia is generally considered a part of the central pain modulation system as activation of the mechanism coincides with activation of brain regions involved in descending pain inhibition^{16,17}. Offset analgesia is different from the spatial contrast enhancement mechanism conditioned pain modulation (CPM; formerly known as diffuse noxious inhibitory control), which is likewise used to evaluate descending inhibition of pain. In CPM, central inhibition of a focal stimulus is induced by the administration of a noxious stimulus at a remote area (ie, spatial filtering)^{9,14,18}. Recently, Nahman-Averbuch *et al.*¹⁸ showed in a functional magnetic resonance imaging study that temporal and spatial filtering of nociceptive information engage different inhibitory processes in the central nervous system. Within the same individual, OA and CPM activated distinctive brain regions, and magnitudes of OA and CPM were not correlated, indicative of 2 separate forms of endogenous inhibition of pain.

The site at which OA originates remains currently unknown. Functional imaging studies showed that OA activation coincides with activation of brain regions involved in descending pain inhibition¹⁶⁻¹⁸. A peripheral origin of OA is supported by evidence from neurophysiological research in monkeys where discharge of heat-sensitive nerve fibers innervating the skin was nearly completely suppressed during a 1°C cooling pulse¹⁹. Furthermore, central acting drugs (opioids, opioid antagonists, and NMDA receptor antagonists) are unable to modify OA responses^{9,14,15,20}. This latter observation stands in sharp contrast to CPM, which is readily affected by central acting drugs such as ketamine and tapentadol^{8,9,14}. These data indicate that OA may be initiated by dynamic responses in primary afferents or spinal processes. Whether the reduced OA responses observed in our cohort of patients with fibromyalgia are related to small fiber pathology remains unknown. However, since there is a marked resemblance between the responses observed in patients with painful peripheral neuropathy and fibromyalgia, it may well be that the abnormal OA responses are related to a similar underlying pathophysiological mechanism of peripheral origin (see also below).

We previously measured OA responses in a large population of volunteers without pain in an age range of 6 to 88 years¹⁵. Irrespective of age and sex, the observed OA responses were all of similar magnitude with Δ VASc values ranging between 92% and

99%. In contrast, a recent study by Naugle *et al.*²¹ observed a (small) reduction in OA responses in an elderly population (60 years and above). Since in our study, the age range of both study populations was 24 to 47 years, we do not expect that age was a confounding factor.

Fibromyalgia and reduced pain inhibition

Just 2 studies evaluated OA responses in patients who experienced chronic pain^{9,15}. Both studies involved patients diagnosed with painful peripheral neuropathy and reduced OA responses were observed comparable with the observation made in this study in patients with fibromyalgia. In painful peripheral neuropathy a Δ VASc cutoff of 88% discriminated between health and disease with 90% sensitivity and 91% specificity¹⁵. According to this criterion, the population patients with fibromyalgia in this study, with an average Δ VASc score of 65%, demonstrate a nonhealthy OA response. This is the first observation of a reduced temporal pain inhibition in fibromyalgia. Since previous findings show that patients with fibromyalgia also lack the ability to induce CPM (and hence have a reduced spatial pain inhibition), fibromyalgia seems characterized by a general inability to activate descending inhibitory pain mechanisms. There is an ongoing debate on the causative mechanism of fibromyalgia. Although a central cause underlying the pathophysiological mechanism of fibromyalgia has long been considered as most important², recent evidence suggests the involvement of peripheral factors. For example, several studies confirmed the presence of small fiber pathology using quantitative sensory testing, confocal cornea microscopy, and skin biopsies²²⁻²⁴. Furthermore, Serra *et al.*²⁵ showed abnormal C-fiber nociceptor activity with signs of hyperexcitability similar to observations in small fiber neuropathy.

Patients with fibromyalgia are known to be more responsive (hyperexcitable) to several sensory stimuli, such as heat, cold, pressure, and electrical pain stimulation²⁶. Compared with healthy controls, a hyperalgesic response was observed for both moderate (VAS 50 mm) and intense (VAS 80 mm) heat pain stimuli in patients with fibromyalgia (probe temperature in patients with fibromyalgia \sim 2.5°C lower at VAS 50 and 80 mm). To the best of our knowledge, fibromyalgia is the first pain syndrome in which observations are made that hyperexcitability to painful stimuli coincides with reduced endogenous pain inhibition of both spatial (CPM) and temporal (OA) nature. Whether the hyperexcitability is a direct cause of altered pain inhibition or a secondary phenomenon remains unknown. Irrespective, we argue that multiple neurophysiological mechanisms underlie fibromyalgia-related pain. Whether these are peripheral factors, central factors or both needs further research. Our data suggest a role for the loss of proper OA engagement in the hyperexcitability to heat pain.

Variations to the offset analgesia paradigm

As OA in patients with fibromyalgia was reduced or incomplete, we hypothesized that repeating the OA paradigm or initiating additional 1°C temperature decreases (after the initial OA test) would improve or complete the OA response. However, both variations to the OA paradigm (test 2 and 3) did not improve the magnitude of the OA response in patients. In test 3 (downward step test, Fig. 1C), we observed no additional OA in patients with fibromyalgia. Instead, the reduction in pain scores showed an almost linear relation to the decline in temperature (Fig. 1C). This may be disease specific but could additionally be related to the test paradigm. Possibly, OA can only be initiated when the temperature decline that initiates the offset response is preceded by a heat stimulus intensity increase²⁷.

Of interest is that OA was able to influence the onset of pain. During the upward OA step test (test 5, Fig. 2A), an OA response was observed with every step decrease in temperature in controls and of lesser magnitude in patients with fibromyalgia. Owing to the presence of these repeated and larger OA responses, control subjects were able to tolerate higher temperatures at a VAS score of 80 mm compared with the ramp test (test 6) where no OA was generated. Owing to the inability to properly engage OA, this was not observed in patients with fibromyalgia who tolerated similar temperatures in tests 5 and 6. These data suggest that OA is an important phenomenon that may influence the onset of pain perception.

Adaptation and habituation

We observed reduced adaptation responses in patients with fibromyalgia (Fig. 1D). The underlying mechanism of heat stimulus adaptation is not completely clarified. Neurophysiological studies suggest that moderate temperatures initiate an adapting discharge pattern in heat nociceptors and in a subgroup of C-fibers^{28,29}. This would indicate that small fibers are involved in the process of adaptation. Offset analgesia is considered to be different from pain adaptation due to the larger and more rapid reduction of pain perception during OA. To compare the offset response initiated by the 1-step OA paradigm (test 1) with the constant stimulation test (test 4), the time interval between peak VAS and VAS nadir was calculated in control subjects. The time interval for the OA response was 4.8 ± 3.5 seconds vs. 16.8 ± 20.3 seconds for the adaptation response. This indicates that the offset response initiated by the OA paradigm was indeed a much faster response than the slow pain adaptation response observed during continuous heat stimulation and implies that OA and pain adaptation have a different underlying physiological mechanism. Irrespective of their mechanisms, both systems are dysfunctional in fibromyalgia. Peak pain responses during the repeated OA paradigm similarly decreased over time for both control subjects and patients (Fig. 1B), which suggest that the process of pain habituation was not affected in patients with fibromyalgia. Pain

habituation differs from pain adaptation; pain habituation is characterized by sensory fatigue on repeated stimulation and pain adaptation is a time-related reduction in pain perception in response to continuous heat stimulation^{29,30}.

In conclusion, we showed that patients with fibromyalgia have reduced OA and adaptation responses that influenced both the onset and offset of pain.

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