Pain Inhibition Is Deficient in Chronic Widespread Pain but Normal in Major Depressive Disorder

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Background: Given the complex relationships between fibromyalgia and major depressive disorder (MDD), it has been suggested that fibromyalgia is a "masked" MDD. In experimental settings, fibromyalgia is associated with lowered pain thresholds (hyperalgesia) and deficient pain inhibition. Similarly, it has been recently proposed that the proneness of patients with MDD to develop chronic pain results from a deficit in pain inhibition. This cross-sectional study measured experimentally induced pain perception and inhibition in patients with MDD and patients with fibromyalgia.

Method: Participants were 29 patients with fibromyalgia (American College of Rheumatology criteria), 26 patients with MDD (*DSM-IV* criteria), and 40 healthy controls who did not differ in age, sex, or the presence or absence of a menstrual cycle. Data were collected between June 2007 and May 2008. Thermal stimuli were used to measure pain thresholds. Pain inhibition was elicited using a tonic thermal test (Peltier thermode) administered before and after activation of the diffuse noxious inhibitory controls (DNIC) by means of a cold pressor test.

Results: Thermal pain thresholds were higher in healthy controls compared to patients with MDD and patients with fibromyalgia. Pain ratings during the cold pressor test were lower in healthy controls and patients with MDD relative to patients with fibromyalgia. Finally, DNIC efficacy was stronger in healthy controls compared to patients with fibromyalgia, while no significant differences were found between healthy controls and patients with MDD.

Conclusions: Our results suggest that (1) fibromyalgia and MDD are both associated with signs of hyperalgesia, (2) hyperalgesia is more pronounced in fibromyalgia, and (3) the deficit of pain inhibition is specific to fibromyalgia. As such, these results suggest that there is an overlap between fibromyalgia and MDD, but that fibromyalgia can be distinguished from MDD in terms of DNIC efficacy.

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Fibromyalgia syndrome is characterized by chronic widespread pain, muscle stiffness, persisting fatigue, and sleep disturbances.[1] Given the absence of a clinically demonstrable peripheral nociceptive cause in fibromyalgia, and given that this syndrome is frequently associated with psychiatric disorders such as major depressive disorder (MDD), some authors have argued that fibromyalgia may be secondary to MDD.[2,3] That is, fibromyalgia may represent a "masked" MDD. Contributing to the plausibility of this assumption, it is a well-known clinical fact that patients with MDD report various pain complaints, including back pain, visceral pain, headaches, and muscular pain.[4,5] In addition, there is reliable clinical evidence that MDD is a significant risk factor for the development of chronic pain and, conversely, that chronic pain patients are more prone to suffer from MDD than the general population.[6,7]

The precise role of depressive symptoms in fibromyalgia is a controversial one. On empirical grounds, there are evidence-based findings demonstrating that fibromyalgia is associated with a 2- to 7-fold increase in the likelihood of suffering from comorbid MDD,[8,9] as recently confirmed by a meta-analysis.[10] Clinically, comorbid depressive symptoms exert significant influences on fibromyalgia. Available evidence suggests that depressive symptoms in fibromyalgia are associated with increased disability and poorer quality of life[11] and more persistent fibromyalgia symptoms.[12]

From a methodological perspective, the use of psychophysical and electrophysiologic procedures may provide valuable clues to the understanding of the precise role of MDD in fibromyalgia and, consequently, to the classification of fibromyalgia as a neurologic, rheumatologic, and/or psychiatric disorder. In the last decade, the use of psychophysical and electrophysiologic procedures has produced evidence suggesting an implication of the central nervous system in fibromyalgia. Using thermal, mechanical, and electrical stimuli, numerous studies showed diminished pain thresholds in patients with fibromyalgia relative to controls, indicative of hyperalgesia/allodynia.[13] Experimental studies also highlighted the involvement of endogenous pain modulation systems in the pathophysiology of fibromyalgia. Pain is a dynamic phenomenon resulting from the activity of both endogenous pain excitatory and inhibitory systems. The diffuse noxious inhibitory controls (DNIC) are one of the principal endogenous pain inhibition systems. According to the DNIC theory, a nociceptive stimulation will "cancel out" another nociceptive stimulation (eg, "pain inhibits pain" phenomenon) if it occurs on a body surface distanced from the pain surface.[14,15] The recruitment of DNIC causes a diffuse

diminution of pain perception throughout the body. Using the cold pressor test (CPT),[16] Julien et al[17] found a deficit in DNIC in patients with fibromyalgia but not in low back pain patients, suggesting a pathology-specific deficit.

In MDD, numerous studies measured experimentally induced pain perception using electrical, mechanical, ischemic, and thermal stimuli. So far, these studies have produced inconsistent and contradictory findings. While most groups described increased pain thresholds/tolerance (hypoalgesia) in MDD,[18–20] some groups reported no between-group differences,[21,22] and others showed that patients with MDD have decreased pain thresholds/tolerance (hyperalgesia) relative to healthy controls.[23–25]

The study of pain threshold/tolerance has not produced a satisfactory explanation for the presence of somatic symptoms associated with the disorder. Alternatively, some authors proposed that the proneness to experience pain in MDD may result from a deficit in pain inhibition,[5,18] as serotonin (5-HT) and norepinephrine (NE) are involved in pain inhibition as well in the MDD pathophysiology. Indeed, in animals, numerous studies have shown that the DNIC recruit endogenous opioids in the periaqueductal gray matter (mesencephalon), which trigger the release of 5-HT from neurons localized in the raphe nuclei (medulla), which dampens nociceptive afferents at the dorsal horn of the spinal cord.[26] Noradrenergic projections from the locus ceruleus also produce similar effects.[27] Interestingly, there is substantial evidence of altered 5-HT and NE neurotransmission in MDD, arising from decades of animal research, pharmacologic studies using 5-HT and/or NE reuptake inhibitors, and genetic and brain imaging studies of the 5-HT/NE receptors/transporters.[28–31] Unfortunately, only 1 study has assessed pain inhibition in MDD so far,[18] and it used a procedure—the opening jaw reflex—whose validity as a measure of pain inhibition remains debated.[32,33]

This cross-sectional study sought to investigate the potential similarities and differences in experimentally induced pain perception and pain inhibition between patients with MDD and patients with fibromyalgia. Succeeding in showing that there is a deficit in pain inhibition in patients with MDD would not only provide an explanation for their proneness to experience pain, but it would also lend support to the notion that fibromyalgia is a disorder very similar to MDD. Failure to show a deficit in pain inhibition in MDD would suggest that fibromyalgia is distinguishable from MDD on a core feature of the syndrome.

METHOD

Twenty-nine patients suffering from fibromyalgia, 26 patients with MDD, and 40 healthy controls participated in this study. Data were collected between June 2007 and May 2008. Patients were diagnosed with fibromyalgia using American College of Rheumatology criteria[1] by neurosurgeons, rheumatologists, or physicians on the ward that specialized in the treatment of chronic pain. Patients with fibromyalgia were recruited through newspaper ads, fibromyalgia associations, and referrals from physicians (neurosurgeons, rheumatologists, or general practitioners). None of the patients with fibromyalgia were referred by psychiatrists. None of the patients with fibromyalgia suffered from schizophrenia, psychosis, or bipolar disorder (*DSM-IV* criteria), and none received antipsychotics or mood stabilizers. Patients with MDD were diagnosed using *DSM-IV* criteria and were referred by a psychiatrist (J.F.C.). Patients with MDD did not suffer from any known chronic pain conditions. Participants (patients with MDD and fibromyalgia and controls) who were pregnant or breastfeeding; who had diabetes, lupus, or rheumatoid arthritis; or who were suffering from a cardiac pathology were excluded from the study. The Human Ethics Committees of the Université du Québec en Abitibi-Témiscamingue and Université de Sherbrooke approved the research protocol, and all participants gave their written informed consent.

Patients with fibromyalgia, patients with MDD, and controls did not differ in terms of age (mean ± SD years = healthy controls: 45.2 ± 6.0; patients with MDD: 46.5 ± 9.0; patients with fibromyalgia: 48.6 ± 7.1; $F_{2,92} = 1.865$; $P = .161$), sex ratio (healthy controls = 24 women, 16 men; patients with MDD = 16 women, 10 men; patients with fibromyalgia = 22 women, 7 men; $\chi^2 = 2.085$; $P = .353$), and the presence or absence of a regular menstrual cycle (healthy controls = 24 absence, 16 presence; patients with MDD = 20 absence, 6 presence; patients with fibromyalgia = 23 absence, 16 presence; $\chi^2 = 3.720$; $P = .156$). Patients in the MDD group received 1 or more of the following types of antidepressants: (1) atypical antidepressants (6 patients); (2) selective serotonin reuptake inhibitors (17 patients); and (3) norepinephrine and selective serotonin reuptake inhibitors (6 patients). Patients in the fibromyalgia group received 1 or more of the following types of antidepressants: (1) selective serotonin reuptake inhibitors (8 patients); (2) norepinephrine and selective serotonin reuptake inhibitors (4 patients); and (3) tricyclic antidepressants (5 patients). Healthy controls receiving antidepressant medications were excluded from the study.

Clinical Assessments

The components of health (including anxiety and depression) most affected by fibromyalgia were measured using the French version of the Fibromyalgia Impact Questionnaire.[34,35] Mood symptoms in patients with MDD were measured with the French version of the Beck Depression Inventory.[36,37]

Thermal Pain Thresholds

Thermal pain thresholds (TPTs) were measured by applying a thermode on the left forearm of participants. The Peltier thermode used (TSA II, Medoc Advanced Medical Systems, Durham, North Carolina) was a heating plate connected to a computer that allowed a precise setting of experimental temperature. Experimental temperature was initially set at 32°C and was gradually increased by a rate of 0.3°C per second. Subjects were instructed to verbally report when their sensations changed from heat to pain. For each subject, the procedure was repeated 3 times to ensure the stability of TPT measurement.

Table 1. Experimentally Induced Pain Perception and Inhibition in Patients With Major Depressive Disorder, Patients With Fibromyalgia, and Healthy Controls

Measure	Healthy Controls, Mean (SD)	Major Depressive Disorder, Mean (SD)	Fibromyalgia, Mean (SD)	Statistics	Multiple Comparisons*
Thermal pain thresholds, °C	43.0 (3.6)	39.6 (4.2)	37.6 (4.2)	$F_{2,92} = 16.370$; $P = .0001$	Healthy controls > major depressive disorder; healthy controls > fibromyalgia
Experimental temperature required to induce moderate pain, °C	46.8 (0.8)	46.3 (1.7)	43.7 (2.6)	$F_{2,92} = 27.305$; $P = .0001$	Healthy controls > fibromyalgia; major depressive disorder > fibromyalgia
COVAS pre–cold pressor test,[a] %	60.4 (18.6)	61.8 (15.3)	49.8 (14.3)		
COVAS post–cold pressor test,[a] %	46.5 (22.7)	52.0 (23.0)	49.9 (26.0)		
DNIC efficacy, %	20.9 (34.4)	17.0 (28.9)	−3.0 (49.7)	$F_{2,92} = 3.429$; $P = .037$	Healthy controls > fibromyalgia
NPRS cold pressor test rating (0–100)[b]	57.4 (22.2)	51.0 (28.6)	77.9 (19.6)	$F_{2,92} = 10.337$; $P = .0001$	Healthy controls < fibromyalgia; major depressive disorder < fibromyalgia

[a]Tonic heat pain ratings (0% = no pain to 100% = most intense pain imaginable) during a 120-second COVAS. [b]Pain intensity (0 = no pain to 100 = most intense pain imaginable) as rated verbally every 15 seconds during a 2-minute cold pressor test.
*$P < .017$ (Bonferroni correction).
Abbreviations: COVAS = computerized visual analog scale, DNIC = diffuse noxious inhibitory controls, NPRS = Numerical Pain Rating Scale.

Temporal Summation

The temporal summation test was completed after the pretest and consisted of a continuous heat pulse administered with a thermode for 2 minutes on the left forearm of participants. Experimental temperature reached a predetermined fixed value and remained constant during the 2-minute testing period (time 0 to time 120). It was set at a value corresponding to a temperature individually predetermined to induce a 50% pain rating during the pretest. Participants were not told that the temperature remained constant throughout testing. During thermal stimulation, pain intensity was measured each second using a computerized visual analog scale (COVAS) that ranged from 0% (no pain) to 100% (most intense pain imaginable). Temporal summation is usually elicited using phasic (repetitive) pain stimuli to induce temporal summation, but some groups have also shown that tonic stimuli reliably produce the effect.[38–41] More importantly, a recent study by Granot et al[42] directly compared both procedures and found that phasic and tonic stimuli produce similar temporal summation effects. Research in our laboratory has shown that pain perception scores increase progressively through the 2 minutes of testing even if the thermode temperature remains constant,[43,44] suggesting a temporal summation effect.

Diffuse Noxious Inhibitory Controls

To capture the effects of DNIC, we administered the temporal summation procedure twice and conducted a CPT between administrations.[43] The CPT consisted in the immersion of the opposite (right) arm (up to the shoulder) for 2 minutes in a bath of cold water. Temperature of the water was set at 12°C to ensure that the CPT was sufficiently painful to elicit DNIC while tolerable for 2 minutes. During the test, subjects rated verbally their pain intensity every 15 seconds using the Numerical Pain Rating Scale, also ranging from 0 to 100. The CPT recruits the DNIC because it is a strong nociceptive stimulation that takes place during a lengthy time span[45] and is applied over a large body surface area.[16] By comparing the pain evaluation during the temporal summation test (thermode) acquired before and after the CPT, we were able to measure the inhibitory effect of the DNIC response.

Statistical Analyses

For statistical purposes, we used various dependent variables, namely (1) TPTs, (2) experimental temperature (as determined during the pretest), (3) efficacy of DNIC (percentage of change between post-DNIC and pre-DNIC mean COVAS scores [time 0 to time 120]), and (4) mean pain intensity during the CPT.

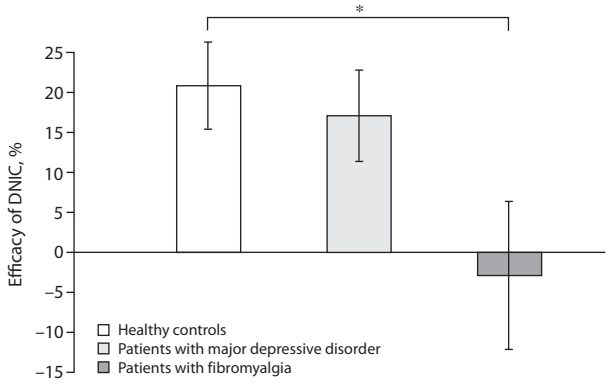
A multivariate analysis of variance was conducted to explore the potential differences between patients with fibromyalgia and healthy volunteers. The Wilks λ criterion was used to determine if the combined set of dependent variables was affected by group analysis (patients with fibromyalgia versus controls). The level of significance was set at $P > .05$. If the multivariate analysis was significant, univariate analyses of variance were conducted on each dependent variable. Multiple comparisons were subsequently performed after applying Bonferroni correction. Pearson correlation analyses between mood symptoms and thermal pain measures were also performed.

RESULTS

Results from the multivariate analysis of variance revealed that the values recorded for the combined set of experimental variables (TPTs, experimental temperature, DNIC efficacy, and CPT) were significantly different between patients with fibromyalgia and healthy controls ($F = 9.503$; $P = .0001$).

For each dependent variable, analyses of variance were subsequently performed and revealed significant between-group differences for (1) TPTs, (2) experimental temperature, (3) DNIC efficacy, and (4) pain ratings during the CPT (Table 1; Figure 1). Multiple comparisons were performed, and we found that TPTs were higher in healthy controls compared to patients with MDD and to patients with fibromyalgia. In addition, we found that experimental temperature was

Figure 1. Efficacy of DNIC in Patients With Major Depressive Disorder, Patients With Fibromyalgia, and Healthy Controls[a,b]



[a]Data are presented as mean ± SD. [b]Patients with fibromyalgia presented a significant DNIC deficiency when compared to healthy controls ($F_{2,92} = 3.429$; $P = .037$).
*$P < .05$.
Abbreviation: DNIC = diffuse noxious inhibitory controls.

higher in healthy controls and patients with MDD compared to patients with fibromyalgia. Pain rating during the CPT was lower in healthy controls and patients with MDD relative to patients with fibromyalgia. Finally, DNIC efficacy was stronger in healthy controls compared to patients with fibromyalgia.

Multiple comparisons did not reveal significant differences in DNIC efficacy between patients with MDD and patients with fibromyalgia, despite the fact that the DNIC efficacy was of 17% in patients with MDD and of –3% in patients with fibromyalgia. Therefore, we compared pre-DNIC and post-DNIC tonic heat pain ratings ($COVAS_{0–120}$) in each group using paired sample *t* tests, and we applied Bonferroni correction ($P < .05/3$ groups → $P < .017$). These post hoc analyses highlighted significant pain inhibition in healthy controls ($t = 4.304$; $P = .0001$) and in patients with MDD ($t = 2.877$; $P = .008$) but not in patients with fibromyalgia ($t = –0.016$; $P = .987$). Notably, there were no significant differences in DNIC efficacy between patients with fibromyalgia receiving antidepressants and those who did not (mean ± SD DNIC efficacy = fibromyalgia with antidepressants: –12.4% ± 51.9; fibromyalgia without antidepressants: 6.1% ± 47.5; $F = 0.995$; $P = .327$).

Finally, mood symptoms did not correlate with any thermal pain measures in the fibromyalgia or the MDD group (all *P*s > .05).

DISCUSSION

Given the complex relationships between fibromyalgia and MDD, this study sought to identify the similarities and differences in experimentally induced pain perception and modulation between these 2 groups of patients and healthy controls. Using tonic thermal stimuli, we found that TPTs were higher in healthy controls compared to patients with MDD and patients with fibromyalgia. In addition, we found that the experimental temperature required to induce moderate pain (50%) was higher in healthy controls and patients with MDD relative to patients with fibromyalgia. In the same vein, pain ratings during the CPT were higher in patients with fibromyalgia relative to patients with MDD and healthy controls. Importantly, the study also measured DNIC efficacy in the 3 groups and revealed a deficit in DNIC in patients with fibromyalgia relative to healthy controls. Regarding DNIC efficacy, the difference between patients with fibromyalgia and patients with MDD did not emerge as significant. However, when we performed paired sample *t* tests, we observed significant pain inhibition in healthy controls and in patients with MDD but not in patients with fibromyalgia.

The most important finding of this study is the fact that we detected a deficit in DNIC efficacy in fibromyalgia only. A lack of pain inhibition in fibromyalgia has been described repeatedly in the literature,[17,46,47] and it has been raised as a potential mechanistic explanation for the increased pain sensitivity observed in MDD.[5,18] Here, we found that DNIC were efficient in patients with MDD, and as such, this result shows that fibromyalgia can be distinguished from MDD on a core feature of the syndrome. Decades of clinical research show that MDD is associated with disturbances in 5-HT and NE functioning,[28,31] and preclinical studies highlight a key role for these neurotransmitters in descending pain pathways.[26,27] Nevertheless, disturbances in 5-HT and NE in MDD do not seem to translate into a deficit in pain inhibition. To our knowledge, only 1 study previously measured pain inhibition in MDD,[18] and it used a paradigm (ie, opening jaw reflex) whose validity has been questioned.[32,33] Given the current state of knowledge, it does not seem that MDD is associated with a deficit in pain inhibition, as is the case with fibromyalgia. However, further studies are required before ruling out this hypothesis. Indeed, patients with MDD involved in our study did not suffer from comorbid chronic pain. Thus, we can only infer that patients with MDD without comorbid chronic pain do not seem to have deficient DNIC. It remains to be determined whether DNIC efficacy in patients with MDD with comorbid chronic pain is normal or deficient. Another concern is related to the fact that patients with MDD were receiving antidepressant treatment at the moment of testing. Antidepressants block the uptake of 5-HT and/or NE, and increase the availability of these transmitters in the synaptic cleft. The use of antidepressants may have restored normal 5-HT and NE functioning in patients with MDD and, consequently, normalized the efficacy of their DNIC, given the role of 5-HT and NE in descending pain pathways. Thus, antidepressants may have masked an effect that would have emerged in drug-free patients. However, we performed a subanalysis of patients with fibromyalgia receiving antidepressants and those who did not, and we observed that antidepressants do not influence DNIC efficacy in patients with fibromyalgia, as DNIC efficacy was similar in both subgroups.

Our results showed that patients with MDD and patients with fibromyalgia have lowered TPTs relative to healthy controls, suggestive of hyperalgesia. This result highlights

an important similarity between patients with fibromyalgia and patients with MDD in terms of experimentally induced pain perception, and it is consistent with the fact that fibromyalgia and MDD also present symptomatic similarities (eg, anxiety, sadness, fatigue, headaches, gastrointestinal disorders). Despite this similarity, it must be mentioned that hyperalgesia was more pronounced in fibromyalgia relative to MDD, as experimental temperature was lower and pain ratings during the CPT were higher in fibromyalgia relative to both healthy controls and patients with MDD. As mentioned in the introduction, lowered pain thresholds in fibromyalgia have regularly been described in the literature, irrespective of the type of stimuli used to elicit pain.[48–51] As for the lowered TPTs observed in patients with MDD, this result deserves further discussion, as both increased and decreased pain thresholds have been reported in experimental studies involving patients with MDD.[18–20,23–25] The reasons for these discrepant results remain elusive and may be related to sex differences, severity/chronicity of depressive symptoms, types of experimental stimuli, and antidepressants. Here, 62% of patients with MDD were females, a ratio typical of what is commonly observed in the disorder. The fact that patients were taking antidepressants is unlikely to be the explanatory factor because increased and decreased pain thresholds have been reported in drug-free as well as medicated patients.[18–20,23–25] As for the type of stimuli, it is also unlikely to explain our results because hyperalgesic responses in MDD have been described mostly when using ischemic painful stimuli.[23,52] On the other hand, severity of depressive symptoms may have contributed to our results. Indeed, it has paradoxically been observed that pain complaints are more frequent when the depressive symptoms are less severe.[53] In the same vein, experimental studies involving patients with less severe depressive symptoms have produced the most reliable hyperalgesic responses (lowered pain thresholds).[52,54] In our sample, it must be noted that only 2 patients with MDD out of 26 had been hospitalized (once each) for their symptoms. However, we performed correlation analyses and found no relationships between mood symptoms and thermal pain measures in patients with MDD (this was also true for the group of patients with fibromyalgia).

Hyperalgesia (lowered pain thresholds) in fibromyalgia have been attributed to deficient pain inhibition and spinal hyperexcitability.[17,55] In MDD, it remains to be determined which subgroup of patients presents hypoalgesic and hyperalgesic responses. The mechanisms underlying lowered pain thresholds in MDD also need to be identified, as they may provide explanations for the increased proneness of these patients to develop chronic pain conditions. For the moment, the results from the current study do not support the hypothesis that hyperalgesia in MDD is related to deficient pain inhibition.

To our knowledge, this is the first study to directly compare patients with fibromyalgia and patients with MDD in their respective responses to thermal nociceptive stimuli. The results from this study suggest that (1) fibromyalgia and MDD are both associated with signs of hyperalgesia, that (2) hyperalgesia is more pronounced in fibromyalgia, and that (3) the deficit of pain inhibition is specific to fibromyalgia. As such, these results suggest that the clinical overlap between fibromyalgia and MDD translates into similar thermal hyperalgesia. However, our results also suggest that fibromyalgia can be distinguished from MDD on a core feature of the syndrome, namely deficient DNIC. Further head-to-head comparisons are required to determine the similarities and differences of patients with fibromyalgia and patients with MDD regarding experimentally induced pain perception and modulation. The study of DNIC efficacy in drug-free patients with MDD is also warranted.

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