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Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome

Mathieu Piché [a,c,d,e,g,*], Marianne Arsenault [d,e], Pierre Poitras [f], Pierre Rainville [b,c,d,e], Mickael Bouin [f]

[a] Department of Physiology, Université de Montréal, Montreal, Que., Canada H3T 1J4
[b] Department of Stomatology, Université de Montréal, Montreal, Que., Canada H3T 1J4
[c] Groupe de recherche sur le système nerveux central (GRSNC), Université de Montréal, Montreal, Que., Canada H3T 1J4
[d] Centre de recherche en neuropsychologie et cognition (CERNEC), Université de Montréal, Montreal, Que., Canada H3T 1J4
[e] Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM), Université de Montréal, Montreal, Que., Canada H3T 1J4
[f] Service de Gastroentérologie de l'Hôpital Saint-Luc du CHUM, Université de Montréal, Montreal, Que., Canada H3T 1J4
[g] Département de chiropratique, Université du Québec à Trois-Rvières, Que., Canada G9A 5H7

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ABSTRACT

The mechanisms of chronic pain in irritable bowel syndrome (IBS) have been widely investigated but remain unclear. The present study investigated the relation between visceral hypersensitivity, cutaneous thermal sensitivity, and central pain mechanisms. Rectal sensitivity was assessed with a barostat, and forearm and calf sensitivity with a contact thermode. Central mechanisms were assessed by counterirritation using sustained cold-pain to the hand and painful electric shocks to the ankle. Psychological symptoms were also assessed, using questionnaires. Female volunteers with diarrhea-predominant IBS ($n = 27$) and healthy controls ($n = 25$) participated in the study. IBS patients had lower rectal and calf pain thresholds compared to controls (p's < 0.05). IBS patients also reported more pain than controls for rectal distensions, and heat pain on the calf and forearm (all p's < 0.001). Cold-pain inhibited shock-pain in controls but not IBS patients (controls: -13.5 ± 5.3 vs IBS: $+1.9 \pm 10.5$; $p < 0.01$). In addition, visceral hypersensitivity was significantly correlated to cutaneous thermal hypersensitivity and pain inhibition deficits, although effects were only weak and moderate, respectively. Furthermore, covariance analyses indicated that psychological factors accounted for group differences in visceral hypersensitivity and pain inhibition deficits. In conclusion, this study confirms the relation between altered pain inhibition processes and widespread hypersensitivity in IBS. The present results also suggests that psychological symptoms and altered pain processing in IBS patients may reflect at least in part, common underlying mechanisms.

1. Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder including abdominal pain and bowel dysfunction [46]. Several studies have shown that patients with IBS demonstrate increased rectal perception, and central or peripheral sensitization is considered as a plausible physiopathological mechanism in many of these patients [7,21,30,31,33,41]. Somatic hypersensitivity has also been documented in various studies using a variety of pain tests such as foot or hand immersion in hot water [17,32,49], hand immersion in cold water [6], contact heat stimulations (thermode) [42], or electrical stimulation of the skin, subcutis and muscle layers of the abdomen, upper and lower limb [9]. However, contradictory results showing no somatic hypersensitivity in IBS patients have been reported in other studies using electrocutaneous stimulations [13,22], hand immersion in cold water [54,60], transmucosal and transcutaneous electrical stimulation [1] or pressure applied on tender points [11]. These discrepancies could be related to methodological issues but also to heterogeneity of IBS symptomatology and pathophysiology.

Recent studies were designed to investigate the pathophysiology of pain in IBS. Both peripheral and central mechanisms have been suggested to explain hypersensitivity associated with IBS [3,39]. Spinal sensitization has been proposed to explain both visceral hypersensitivity and the secondary hyperalgesia found in lumbosacral dermatomes, consistent with the viscerosomatic convergence on spinal neurons [49]. In support of this hypothesis, intra-rectal application of lidocaine in IBS patients was shown to reduce both rectal and thermal cutaneous hypersensitivity in the lower limb. This also implies a role for peripheral afferents in maintaining hypersensitivity [50].

* Corresponding author. Address: Département de Chiropratique, Université du Québec à Trois-Rivières, 3351 Boul. Des Forges, C.P. 500 Trois-Rivières, Que., Canada G9A 5H7. Tel.: +1 819 376 5011x3998; fax: +1 819 376 5204.
E-mail address: mathieu.piche@uqtr.ca (M. Piché).

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On the other hand, thermal hypersensitivity was also reported in body areas remote from dermatomes in which viscerosomatic convergence might be involved [6,9,17,32,42,49]. This widespread hypersensitivity has been suggested to reflect an alteration of descending pain modulation mechanisms [12,43,56,57]. In these studies, counterirritation was used to activate diffuse noxious inhibitory controls (DNIC) [25]. IBS patients displayed decreased inhibition of pain [43,56,57] and facilitation of spinal nociception [12], suggesting a deficit in cerebro-spinal modulatory mechanism. However, the profile of pain sensitivity reported in the patients participating in the studies mentioned above [43,56,57] did not show unequivocal evidence of visceral hypersensitivity in quantitative sensory tests. Furthermore, the correlation between the deficit in inhibitory processes and both somatic and visceral pain sensitivity was not tested directly such that different patients might independently show deficits in any of those tests. Although visceral hypersensitivity, somatic hypersensitivity and altered pain modulation mechanisms could explain pain symptoms in IBS patients, the relation between these deficits remains unclear.

The aim of the present study was to clarify the putative role of central pain mechanisms in IBS. Visceral sensitivity to rectal distensions, somatic sensitivity to cutaneous heat stimulation and modulation of acute pain by the cold pressor test were examined in diarrhea-predominant IBS patients. Correlation analyses were performed to assess whether visceral hypersensitivity was associated with thermal hypersensitivity and pain modulation deficits. We hypothesized that IBS patients would show visceral and thermal hypersensitivity related to a decrease in pain inhibition, as evidence for an alteration in central pain-regulatory mechanisms.

2. Methods

2.1. Participants

The Research Ethics Board of St-Luc Hospital approved the study. The potential effect of menstrual cycle on pain sensitivity and pain modulation was controlled by testing all participants in the follicular phase. Participants were instructed to eat and drink as usual on the day of the experiment. All participants gave written informed consent acknowledging their right to withdraw from all or some of the experiments without prejudice and received a compensation of 50$ for their time and commitment to the study.

2.1.1. Controls

Twenty-five healthy women (mean age: 29.0 ± 1.5) volunteered to participate in the study. Recruitment was done by advertisement in the hospital and the university campus. Participants were included if they had normal bowel habits and no known GI disease, and were excluded for: (1) taking any medication within 2 weeks prior to the experiment and (2) having a history of GI symptoms, acute or chronic illness or a psychiatric disorder, as reported in a questionnaire on bowel symptoms and general health history.

2.1.2. Patients

Twenty-seven women (mean age: 34 ± 2.1 years) with diarrhea-predominant IBS were recruited in the study by advertisement and from referrals to the gastroenterology unit of Hôpital St-Luc in Montreal (Qc, Canada). All these patients were evaluated by one gastroenterologist (MB) experienced in the evaluation of IBS. Normal physical examination, normal colonoscopy with biopsy, exclusion of organic diseases and symptoms of IBS based on Rome III criteria were required to make the diagnosis of IBS. Patients were excluded if they presented other chronic pain syndromes (e.g. fibromyalgia), psychiatric disorders, or used medication that could alter pain perception and modulation in the 2 weeks prior to the experiment, including anxiolytics, antidepressants and other psychotropic agents.

2.2. Procedure

The study consisted in three quantitative sensory experiments performed on the same day: (1) visceral sensitivity; (2) thermal sensitivity and (3) pain modulation by counterirritation. The total duration of sensitivity testing was approximately 40 min performed in a single 2-h session with pauses of at least 15 min between tests. Experiment 1 was performed in all 27 IBS patients and 19 controls (some controls only volunteered for the cutaneous tests). Experiment 2 included all 27 IBS patients and all 25 controls but the experiment was interrupted in one control participant who could not tolerate the heat stimulation. The paradigm used in Experiment 3 was always performed last to avoid long-lasting after-effects induced by the sustained cold pressor pain. This experiment was also modified after the beginning of the study because many patients did not tolerate this test (possibly as a result of their hypersensitivity). As a result, a subgroup of 15 IBS patients and 22 controls was tested uniformly with the modified paradigm, as described below. Four additional patients and four controls were further excluded from experiment 3 because they could not tolerate the electrical stimulation. Results of Experiment 3 are therefore based on a subset of 11 IBS and 18 controls.

2.2.1. Visceral sensitivity testing

A barostat bag (thin-wall polyethylene) was attached tightly at both ends to a single-lumen silastic tube (external diameter = 18 French). The lumen of the tube was located within the barostat bag, and the open-end of the tube was connected to the output of the bellows chamber. The maximal capacity of the bag was 600 mL with a maximal length of 11 cm, resulting in a spherical bag shape. Before placement in the rectum, the barostat bag was checked for air leaks and maintained at 40 mm Hg of pressure for 10 min. Within the range of volumes used in the study, the barostat bag compliance was considered as infinite.

Distensions were performed with an electronic barostat (J&G electronics, Toronto, Canada) including a built-in computer system programmed to perform automatic distensions with fixed time lags and bag pressure increments. The volume of air inside the bag was determined electronically by the computer from the known excursion of the bellows within the reservoir system. The distension protocol was adapted from previously described procedures for phasic rectal distensions [52]. After the application of Sodium Phosphates Enema (Fleet-enema; Johnson & Johnson, Toronto, Canada) to empty the rectum, the barostat bag was inserted with the distal attachment site close to the anal canal. The tube was then secured in its proper position with a piece of adhesive. Subjects were comfortably reclined in a supine position on a padded table. Instructions about the nature of the distensions protocol and the ratings of sensations were given to the participants and the examiner remained in the room. Participants had no visual or auditory cues to anticipate the intensity of distensions. Distensions were performed automatically by the computer following the ascending method of limit [25] (10–50 mm Hg; successive stimuli at 5 mm Hg increments). The volume of air inside the bag was determined by the computer to reach and maintain the desired pressure. Phasic distensions of 30 s were delivered with an inter-stimulus interval of 30 s, during which the balloon was completely deflated. Each of the nine distension pressures was delivered only once. During the distension sequence, participants indicated the threshold for the first sensation, pain and unpleasantness and they rated the intensity of pain and unpleasantness at the end of each stimulus. When unpleasantness or pain threshold was not attained, a value of 55 mm Hg was assigned as thresh-

old. It was emphasized that participants could ask the experimenter to interrupt the procedure at any time and that the barostat bag could deflate instantaneously at any time.

2.2.2. Somatic sensitivity testing

Somatic sensitivity was assessed with a 9 cm^2 contact thermode (MEDOC TSA-2001) applied on the right forearm and calf using the ascending method of limit (42–50 °C with increments of 0.5 °C). Phasic stimulation of 30 s was delivered with an inter-stimulus interval of 30 s, during which the probe was moved to the other limb (alternating between the anterior aspect of the forearm and the lateral aspect of the calf). Each of the 18 heat stimulation intensity was delivered only once on each limb and the probe was placed alternately on three different spots of skin to avoid sensitization (each area of the forearm or calf was stimulated only six times at the most, including non painful stimuli). The lateral aspect of the calf was chosen to test for hypersensitivity related to viscerosomatic convergence of primary afferents from the rectum and lumbosacral dermatomes. The forearm area was chosen as a site remote from lumbosacral dermatomes to test for diffuse somatic hypersensitivity. Pain threshold was defined as the temperature of the first stimulus producing pain. Pain tolerance was defined as the maximum temperature tolerated by subjects or the temperature inducing a pain rating of 100 (which ever came first).

2.2.3. Counterirritation paradigm

Participants were comfortably seated in a reclining chair with a knee flexion of approximately 120°. Transcutaneous electrical stimulation was delivered with a Grass S48 stimulator (Astro-Med Inc., West Warwick, RI, USA) isolated with a custom made constant current stimulus isolation unit. The stimulation consisted in a 30 ms train of 10 × 1 ms pulse, delivered on degreased skin over the retro-maleolar path of the left sural nerve by means of a pair of custom made surface electrodes (1 cm^2, inter-electrode distance of 2 cm). Electromyographic (EMG) activity of the short head of the biceps femoris was recorded with a pair of surface electrodes (Type EL-508, Biopac systems Inc., Goleta, CA, USA). The EMG signal was amplified 1000 times, band pass filtered (100–500 Hz), sampled at 1000 Hz (MP150, Biopac systems Inc., Goleta, CA, USA) and stored on a personal computer for off-line analyses. The intensity of the electrical stimulation was adjusted individually at 120% of the RIII-reflex threshold using the staircase method [58]. These stimuli were designed to assess the nociceptive flexion reflex (NFR or RIII-reflex). However, because some subjects did not tolerate the stimulus intensity required to reach 120% of the reflex threshold, shock-pain data was obtained using shock intensity corresponding to moderate pain at baseline (i.e. below 120% of the RIII-threshold). Results of this experiment are therefore limited to ratings of shock-pain and cold-pain.

The brief painful electrical stimulation was delivered every 6 s for 8 min. After 3 min, counterirritation was produced for 2 min by immersion of the contralateral hand in cold water adjusted to +4 °C just before immersion (cold pressor test). After counterirritation, the hand was removed from water and the shocks continued for 3 min to assess recovery. Shock-pain was rated at the end of each of the three conditions: (1) before immersion; (2) during immersion and (3) recovery. Cold-pain ratings were collected at the end of the recovery period.

2.3. Pain and unpleasantness ratings

Participants were asked to rate pain intensity and unpleasantness for each visceral distension and cutaneous heat stimulus in Experiments 1 and 2. Unpleasantness was not limited to pain-evoked unpleasantness but also to the non painful discomfort that the stimulus produced. Pain intensity and unpleasantness were evaluated with two separate visual/numerical analogue scales (VAS) comprising numerical anchors for no pain/unpleasantness (0), light pain/unpleasantness (25), moderate pain/unpleasantness (50), strong pain/unpleasantness (75) and extreme pain/unpleasantness (100) [40]. The sequence of ascending intensities was performed up to the limit of the experiment (50 mm Hg or 50 °C) or was discontinued when the participants reached their pain tolerance level. In that case, a VAS score of 100 was given to the subsequent stimulation levels. First, mean pain ratings for all intensities were compared between groups. Then, the group differences were assessed for each intensity level with the Fisher post hoc analysis.

2.4. Psychological assessment

The following three questionnaires were administered before the pain tests to examine their possible modulating effect of pain sensitivity: the pain catastrophizing scale [45], the Beck Depression inventory [5] and the SCL-90 symptom check list for psychological distress [15]. In addition, the St-Luc Gastrointestinal (GI) Index was used to assess severity of GI symptoms [35,36] and patients were asked to report the overall mean intensity of the pain experienced in the last 10 days on a visual analogue scale.

2.5. Data analysis

All results are expressed as means ± SEM. Statistical analyses were done in Statistica v6.0 (Statsoft Inc., Tulsa, OK, U.S.A.) with significance thresholds set to $p < 0.05$. Visceral sensitivity, somatic sensitivity, pain modulation and psychological factors were assessed with *t*-tests, ANOVA, ANCOVA, multiple regressions and Pearson's correlations as needed. For correlation analyses including visceral and thermal hypersensitivity, the ratings at the distension pressure of 50 mm Hg and at a temperature of 44.5 °C were used as the group difference was the most important at those levels.

3. Results

3.1. Groups characteristics

Characteristics of control subjects and IBS patients are reported in Table 1. The groups were not statistically different for age ($p = 0.056$), height ($p = 0.51$) or weight ($p = 0.45$). The mean duration of IBS symptoms was 9.8 ± 1.9 years and the mean pain intensity in the last 10 days (clinical pain) was 47.3 ± 3.6. The global

Table 1
Characteristics of participants.

	Age (y.o.)	Height (m)	Weight (kg)	GI symptoms severity	Duration (years)	Pain (10 days)	PCS	Depression	Distress
IBS ($n = 27$)	34 ± 1.5	1.65 ± 0.01	67.2 ± 2.8	63.6 ± 4.9***	9.8 ± 1.9	47.3 ± 3.6	20.1 ± 2.7*	11.1 ± 1.9*	57.3 ± 1.8***
CTL ($n = 25$)	29 ± 2.1	1.66 ± 0.01	64.5 ± 2.1	8.1 ± 2.4	–	–	11.6 ± 2.0	4.9 ± 1.4	44.1 ± 2.3

GI symptoms severity: St-Luc G1 scale; pain: 0–100 pain intensity rating scale; PCS = pain catastrophizing scale; Depression = Beck depression inventory; distress: symptoms check list (SCL-90).

* $p < 0.05$.

*** $p < 0.001$.

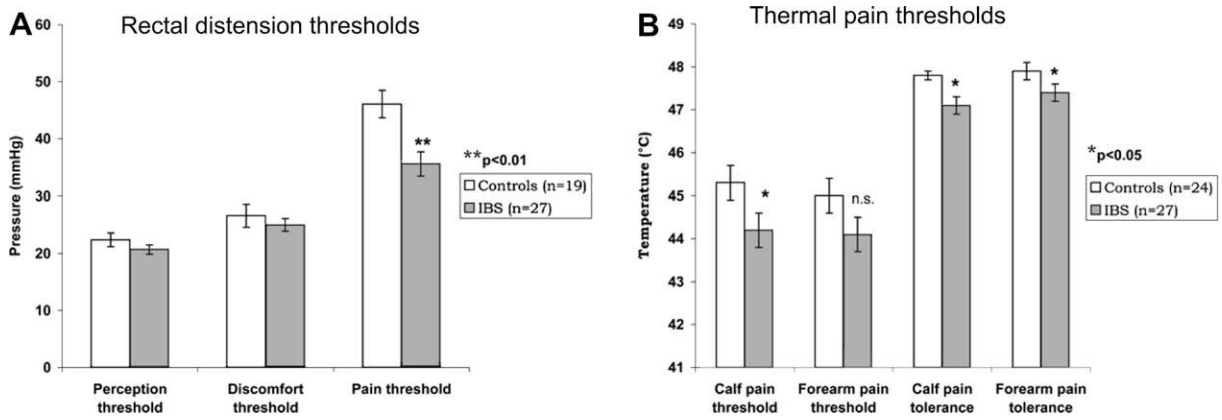

Fig. 1. Visceral and thermal hypersensitivity in IBS patients. (A) Perception and discomfort thresholds were not different between groups but IBS patients showed a lower pain threshold compared to controls. (B) IBS patients showed lower calf pain thresholds and lower calf and forearm pain tolerance for cutaneous heat stimulation. Forearm pain threshold was also lower in IBS patients although the effect was not statistically significant. $^{**}p < 0.01$; $^{*}p < 0.05$; n.s. not significant; $p = 0.085$.

severity of GI symptoms was moderate in IBS patients and significantly higher than in controls ($p < 0.001$). Mean pain intensity in the last 10 days was also significantly correlated to global severity across patients ($r^2 = 0.44$, $p < 0.001$). In addition, IBS patients reported a significantly higher level of pain catastrophizing compared to controls ($p < 0.05$), although this level of catastrophizing is within the normal range [44] (clinical threshold = 30). Moreover, IBS patients reported more symptoms of depression compared to controls ($p < 0.05$), indicative of mild depressive symptoms [5] (mild depression score: 10–16). Furthermore, IBS patients reported more psychological distress compared to controls ($p < 0.001$) although this level of distress is within normal range [28] (clinical threshold = 60).

3.2. Visceral hypersensitivity in IBS patients

Results on rectal distension thresholds are reported in Fig. 1A. There was no significant difference for the first perception threshold between IBS patients and healthy controls (20.7 ± 0.8 vs 22.4 ± 1.2 mm Hg, $p = 0.24$). There was also no significant difference for the discomfort threshold between IBS patients and healthy controls (25.0 ± 1.1 vs 26.6 ± 2.0 mm Hg, $p = 0.46$). In contrast, the pain threshold was significantly lower in IBS patients than in controls (35.6 ± 2.1 vs 46.1 ± 2.4 mm Hg, $p < 0.01$), indicating visceral hypersensitivity.

3.3. Thermal hypersensitivity in IBS patients

Results on somatic pain thresholds and tolerance are reported in Fig. 1B. The analyses of variance testing the group effect across sites confirmed a significant main effect of group for both threshold ($F = 7.32$, $p < 0.01$) and tolerance ($F = 12.0$, $p < 0.001$). Sites did not differ significantly (threshold: $F = 0.36$, $p = 0.55$; tolerance: $F = 1.6$, $p = 0.21$) and the interaction between groups and sites did not approach significance (threshold $F = 0.06$, $p = 0.80$; tolerance: $F = 0.1$, $p = 0.72$). Planned pair-wise contrasts confirmed that calf pain threshold was significantly lower in IBS patients than in controls (44.2 ± 0.4 vs 45.3 ± 0.4 °C, $p < 0.05$). Calf pain tolerance was also significantly lower in IBS patients than in controls (47.1 ± 0.2 vs 47.8 ± 0.1 °C, $p < 0.05$). As for forearm sensitivity, pain tolerance was significantly lower in IBS patients than in controls (47.4 ± 0.2 vs 47.9 ± 0.2 °C, $p < 0.05$) but the difference in pain threshold was marginally significant (IBS patients: 44.1 ± 0.4 °C; controls: 45.0 ± 0.4 °C, $p = 0.085$). However, the absolute group difference in thresholds was similar at the two sites (calf: 1.1 °C; forearm: 0.9 °C) and the factorial ANOVA revealed no interaction between groups and the site of stimulation (see above). We also verified that the group difference in thermal sensitivity was not accounted for by visceral sensitivity testing performed before thermal sensitivity testing in all IBS patients but not all controls. Excluding controls that did not participate to visceral sensitivity testing did not change any of the results described above. Therefore, these results are consistent with robust widespread thermal hypersensitivity in IBS patients.

3.4. Pain and unpleasantness ratings

Pain and unpleasantness ratings for rectal distensions and cutaneous heat stimulations were compared between groups to assess suprathreshold sensitivity. Overall, for all distension pressures taken together, IBS patients reported significantly more pain ($F(1, 387) = 34.3$, $p < 0.001$) and unpleasantness ($F(1, 387) = 25.8$, $p < 0.001$) compared to controls (see Fig. 2A and B). Furthermore, IBS patients significantly reported more pain than controls for distensions of 35 mm Hg (23.5 ± 5.3 vs 7.2 ± 3.8; $p < 0.05$), 40 mm Hg (34.3 ± 6.0 vs 11.8 ± 5.5; $p < 0.001$), 45 mm Hg (43.9 ± 6.8 vs 15.5 ± 6.1; $p < 0.001$), and 50 mm Hg (51.8 ± 7.1 vs 19.7 ± 7.2; $p < 0.001$), as revealed by the Fisher post hoc analysis. These results confirm visceral hypersensitivity in IBS patients. As for cutaneous heat stimulation, for all stimulation intensities taken together, IBS patients reported more calf pain ($F(1, 816) = 45.1$, $p < 0.001$) and unpleasantness ($F(1, 816) = 26.4$, $p < 0.001$) and more forearm pain ($F(1, 816) = 48.9$, $p < 0.001$) and unpleasantness ($F(1, 816) = 36.6$, $p < 0.001$) compared to controls, confirming widespread thermal hypersensitivity in IBS patients (see Fig. 2C–F).

3.5. Pain modulation by counterirritation

The evaluation of pain modulation by counterirritation was performed by comparing shock-pain intensity and unpleasantness before, during and after immersion of the hand in cold water (see Fig. 3A and B). The control group showed a significant inhibition of shock-pain intensity and unpleasantness during counterirritation compared to baseline (intensity: 28.4 ± 4.7 vs 41.9 ± 6.4, $p < 0.001$; unpleasantness VAS: 37.7 ± 5.2 vs 51.7 ± 6.3, $p < 0.001$). In contrast, IBS patients showed no significant modulation of shock-pain intensity and unpleasantness during counterirritation compared to baseline (intensity VAS: 51.9 ± 10.5 vs 50.0 ± 7.5, $p = 0.67$; unpleasantness VAS: 55.1 ± 8.7 vs 59.1 ± 5.5, $p = 0.36$). Furthermore, this modulation of shock-pain intensity and unpleasantness during counterirritation was significantly different between IBS and controls (modulation of intensity VAS: −13.5 ± 5.3

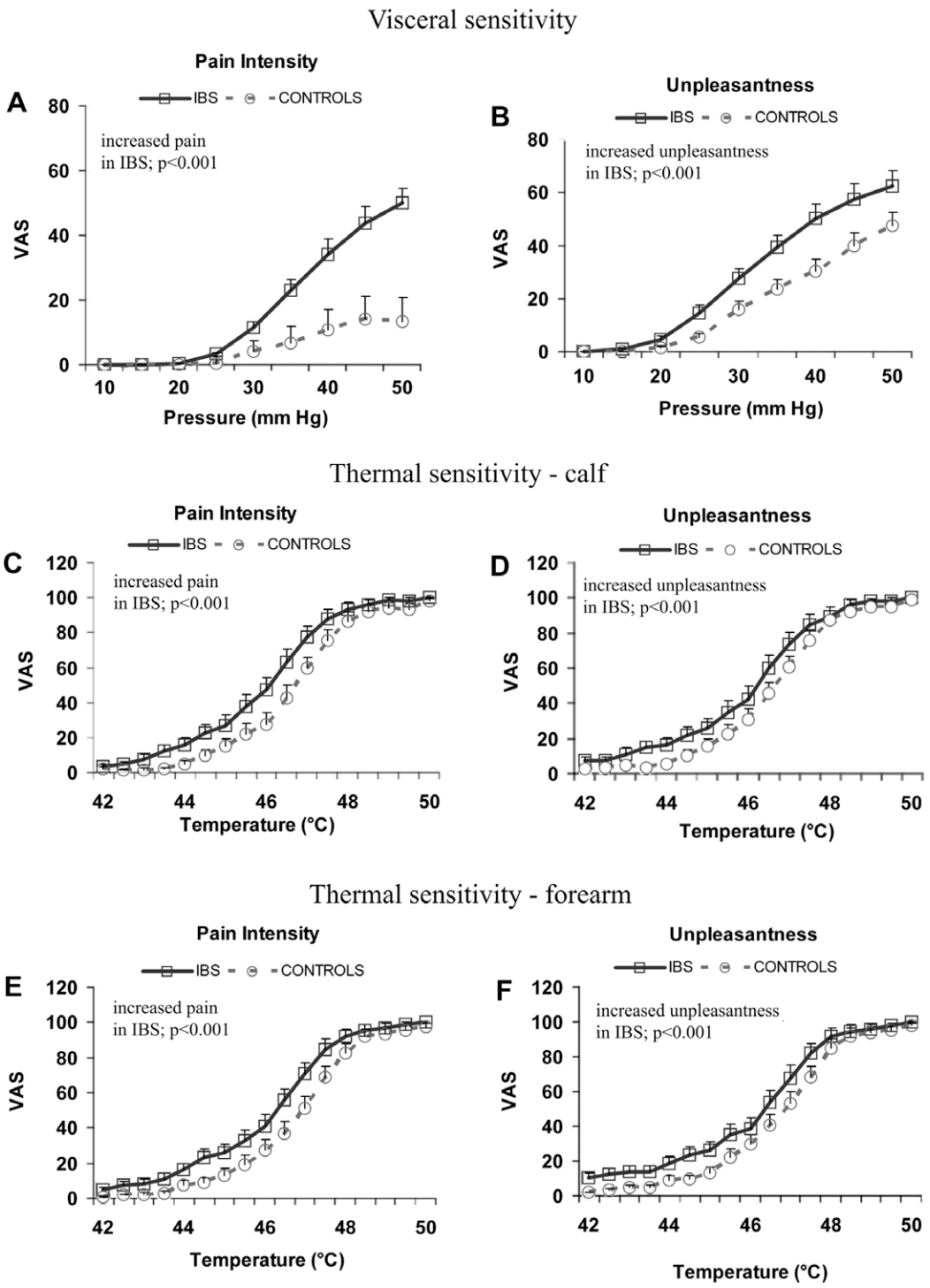

Fig. 2. Stimulus–response curves for visceral and thermal sensitivity. IBS patients showed increased pain intensity and unpleasantness compared to controls for rectal distensions and cutaneous heat stimulation of calf and forearm.

vs +1.9 ± 10.5, $p < 0.01$; unpleasantness VAS: −14.0 ± 5.3 vs −4.0 ± 8.8, $p < 0.05$ (one-tail). This clearly shows that the decrease in pain normally produced by counterirritation is not observed in this group of IBS patients.

Interestingly, the intensity of the pain produced by the counterirritation stimulus predicted the degree of inhibition of shock-pain intensity ($r^2 = 0.27$, $p < 0.05$ and unpleasantness ($r^2 = 0.38$, $p < 0.01$) in controls (see Fig. 3C). Conversely, the intensity of the pain produced by the counterirritation stimulus was associated with a non-significant facilitation of shock-pain intensity ($r^2 = 0.09$, $p = 0.37$) and unpleasantness ($r^2 = 0.14$; $p = 0.26$) in IBS patients (Fig. 3D). This emphasizes the alteration of pain inhibition processes affecting somatic sensitivity in IBS patients.

3.6. Effect of psychological symptoms on pain processing

Table 1 shows that IBS patients scored higher on scales of psychological symptoms. In order to assess the contribution of these

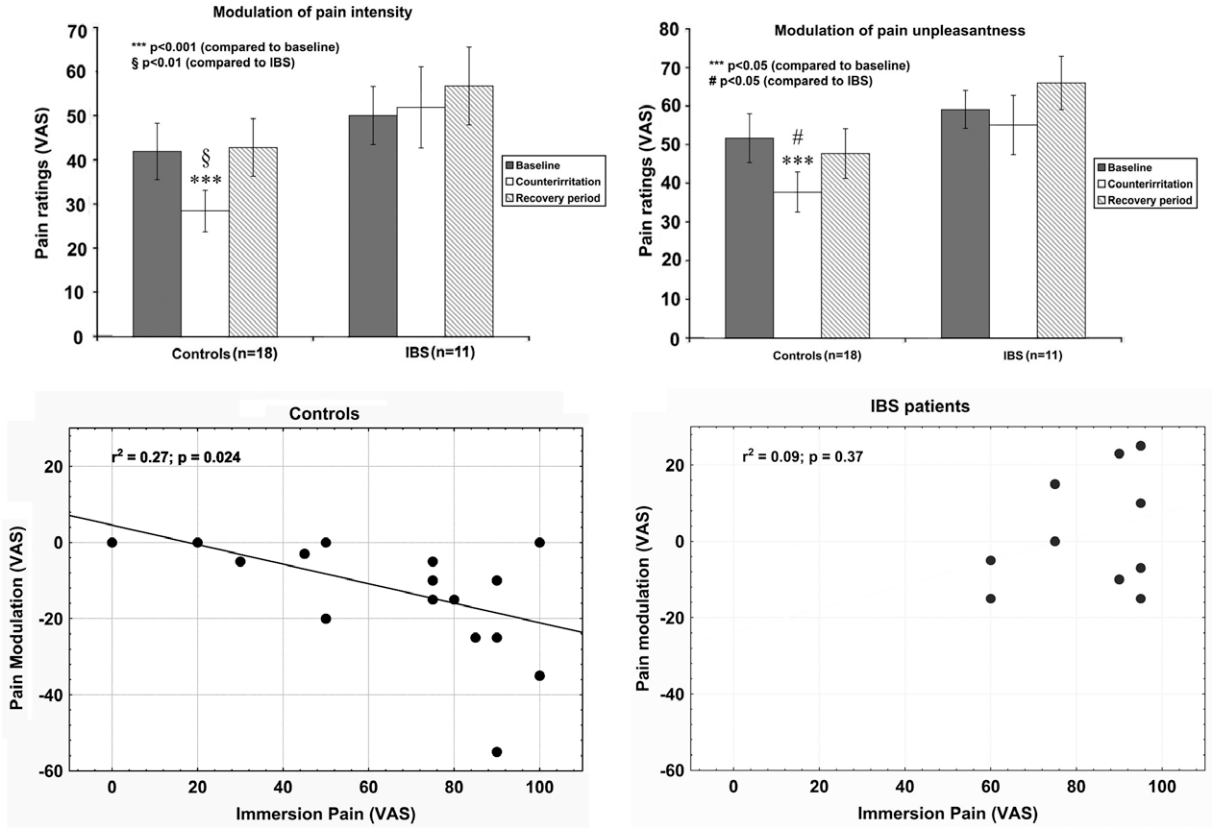

Fig. 3. Altered pain inhibition in IBS patients. Counterirritation produced a profound inhibition of pain intensity and unpleasantness in controls (A and B). In contrast, IBS patients did not show significant inhibition of either pain intensity or unpleasantness during counterirritation (A and B). Stronger immersion pain was related to stronger shock-pain inhibition during the cold pressor test in controls (C). In contrast, IBS patients showed a trend towards facilitation of shock-pain with stronger immersion pain (D). $^{***}p < 0.001$ compared to baseline; $^{\#}p < 0.05$, $^{\S}p < 0.01$ between groups.

psychological factors to pain sensitivity in IBS patients, IBS patients and controls were compared on pain sensitivity measures after accounting for differences in psychological scores (PCS, Beck and SCL-90) using covariance. After controlling for psychological symptoms severity, visceral sensitivity to rectal distensions (threshold and suprathreshold) and pain modulation by counterirritation were not different between groups (p's > 0.05; Table 2). In contrast, thermal sensitivity remained significantly different between groups. This suggests that visceral hypersensitivity and the deficit in pain inhibition shown in IBS patients reflect, at least partly, the effect of psychological factors including catastrophizing, depression and psychological distress on pain processing. To confirm these results, multiple regression models were used to test the correlation between psychological symptoms (catastrophizing, depression and psychological distress) and pain sensitivity. As expected, psychological symptoms were significantly related to visceral pain thresholds ($r^2 = 0.24$; $p < 0.01$), visceral hypersensitivity ($r^2 = 0.24$; $p < 0.01$) and pain inhibition deficits ($r^2 = 0.39$; $p < 0.01$), but not to calf pain thresholds ($r^2 = 0.05$; $p = 0.53$), calf pain tolerance ($r^2 = 0.08$; $p = 0.25$) and forearm pain tolerance ($r^2 = 0.14$; $p = 0.07$). This strengthens the possibility that psychological factors and altered pain processing may reflect common underlying mechanisms in the central nervous system.

3.7. Correlation analyses in the group of IBS patients

Pearson's correlations were further performed separately in the group of IBS patients in order to relate visceral sensitivity to thermal sensitivity, pain inhibition deficits, GI and psychological symptoms. Table 3 and Fig. 4 summarize the results. Overall, decreased visceral pain threshold was associated with decreased thermal pain threshold of calf and forearm, increased cold pressor pain sensitivity and with alteration of unpleasantness inhibition during counterirritation. Increased visceral pain during suprathreshold distensions was associated with these same predictors in addition to depression (Beck) and psychological distress (SCL-90). Also, low-

Table 2
Effect of psychological symptoms on pain processing.

IBS vs controls	Without covariance t (p-value)	With Psy covariance F (p-value)
Visceral pain threshold	3.26 (0.002)	*2.23 (0.14)*
Visceral hyperalgesia	3.23 (0.002)	*3.18 (0.08)*
Calf pain threshold	2.20 (0.03)	4.99 (0.03)
Forearm pain tolerance	2.28 (0.03)	4.45 (0.04)
Calf pain tolerance	2.61 (0.01)	6.73 (0.01)
Pain modulation by counterirritation	2.80 (0.009)	*1.41 (0.25)*

Italicized values: variables for which group difference was not significant after controlling for psychological variables.

Table 3
Correlation analyses of sensitivity disturbance in IBS patients.

Pearson *r*2	Visceral pain threshold	Visceral hyperalgesia
Visceral pain threshold ($n = 27$)	–	0.76***
Forearm pain threshold ($n = 27$)	0.22*	0.16*
Calf pain threshold ($n = 27$)	0.23*	0.19*
Forearm hyperalgesia ($n = 27$)	0.22*	0.27**
Calf hyperalgesia ($n = 27$)	0.19*	0.20*
Cold pressor pain sensitivity ($n = 11$)	0.18*	0.20*
Pain modulation by counterirritation – intensity ($n = 11$)	0.27	0.19
Pain modulation by counterirritation – unpleasantness ($n = 11$)	0.53*	0.37*
IBS symptoms severity ($n = 27$)	0.01	0.01
Clinical pain intensity ($n = 27$)	0.03	0.01
Duration of IBS symptoms ($n = 27$)	0.01	0.01
Pain catastrophising scale ($n = 27$)	0.08	0.08
Beck Depression inventory ($n = 27$)	0.06	0.19*
SCL-90 global severity index ($n = 27$)	0.11	0.23*

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

er visceral pain thresholds were strongly associated with higher suprathreshold pain ratings. These results indicate that thermal hypersensitivity, pain inhibition deficits, depression symptoms and psychological distress are significant predictors of visceral hypersensitivity. In addition, pain inhibition deficits were related to calf pain thresholds ($r^2 = 0.40$; $p = 0.02$) and marginally to forearm pain thresholds ($r^2 = 0.30$; $p = 0.08$), consistent with the hypothesized involvement of descending modulation in somatic hypersensitivity.

Unexpectedly, the global severity of GI symptoms and their duration did not correlate with acute visceral nor thermal sensitivity (all p's > 0.19). Furthermore, mean clinical pain in the last 10 days was not significantly related to acute visceral hypersensitivity ($r^2 = 0.01$; $p = 0.6$), However, contrary to our expectations, patients reporting more clinical pain also displayed *weaker* pain inhibition deficits during counterirritation ($r^2 = 0.39$, $p = 0.04$), and less somatic hyperalgesia (calf pain threshold: $r^2 = 0.20$, $p = 0.02$; forearm pain thresholds: $r^2 = 0.14$, $p = 0.059$). Altogether, these results confirm that acute somatic hypersensitivity, acute visceral hypersensitivity and pain inhibition deficits are related to each other and to psychological symptoms but indicate that these pain disturbances are not associated with more severe global GI symptoms in this group of IBS patients. Moreover, results suggest that increased spontaneous visceral pain may attenuate deficits observed with acute somatic pain tests.

4. Discussion

In the present study, visceral sensitivity was assessed in relation to thermal sensitivity and pain inhibition produced by counterirritation, in a group of female patients with diarrhea-predominent IBS and a group of healthy controls. In addition to visceral and thermal cutaneous hypersensitivity, IBS patients showed a clear deficit of somatic pain inhibition. Importantly, the deficit of pain inhibition was significantly associated with visceral and thermal hypersensitivity. The present results also demonstrate that psychological symptoms and altered pain processing in IBS patients, including visceral hypersensitivity and deficits in pain inhibition, may reflect at least in part, common underlying mechanisms.

4.1. Widespread hypersensitivity

In the present study, IBS patients showed clear visceral hypersensitivity, with threshold and suprathreshold distensions, consistent with several studies [1,3,7,17,31,32,41,49]. In addition, widespread thermal hypersensitivity was demonstrated with cutaneous heat stimulation at threshold and suprathreshold temperatures, consistent with a previous study using similar methods [42]. An important question concerning the mechanisms of hypersensitivity in IBS is whether somatic hypersensitivity depends on viscerosomatic convergence or generalized spinal hyperexcitabil-

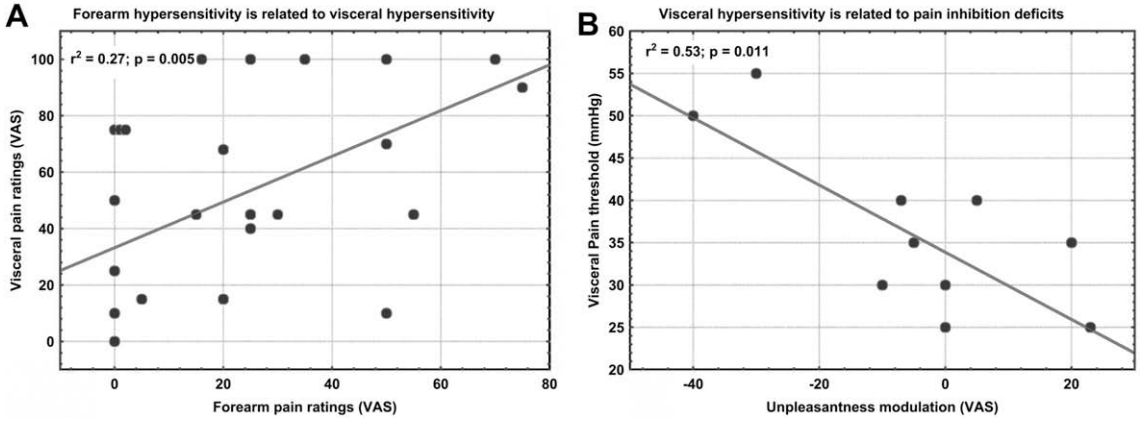

Fig. 4. Thermal hypersensitivity and pain inhibition deficits predict visceral hypersensitivity in IBS patients. (A) Forearm pain ratings: pain intensity reported at 44.5 °C in IBS patients; Visceral pain ratings: pain intensity reported at 50 mm Hg in IBS patients. (B) Unpleasantness modulation: difference of unpleasantness ratings between baseline and during the cold pressor test; Visceral pain thresholds: pressure (mm Hg) of the first stimulus producing pain.

ity. In a study using cutaneous heat stimulation, a group of 9 IBS patients had uniform cutaneous heat hypersensitivity independent of stimulus location or intensity [42]. However, this conclusion was based on suprathreshold ratings only. In this context, the use of suprathreshold pain ratings vs pain thresholds may lead to different conclusions. Accordingly, the present results indicate that suprathreshold stimuli are rated as more painful in IBS patients compared to controls, but the group difference for forearm pain threshold was marginally significant. Although the difference between forearm and calf pain thresholds was not statistically significant in IBS patients, this somewhat weaker hypersensitivity at the forearm is consistent with topographically organized central hyperexcitability, as shown in animal models of persistent pain [27]. It is also consistent with the more pronounced thermal hypersensitivity in lumbosacral dermatomes [49] and skin hypersensitivity to electrical stimulation in areas of pain referral but not in control sites [9]. Taken together, the results of these studies and ours indicate that somatic hypersensitivity in IBS patients involves different regions of the body but may be more readily detected in dermatomes which afferents converge on spinal neurons receiving bowel afferents.

4.2. Deficit of pain inhibition processes

Previous studies have shown that visceral pain inhibition induced by the cold pressor test is altered in IBS patients [43,56,57] and it was suggested that altered pain processing in IBS patients is related to modification of cerebro-spinal modulatory processes [12]. In the present study, control subjects showed a strong inhibition of shock-pain during cold counterirritation. This effect was also stronger for subjects reporting more cold pressor pain. This is consistent with the recruitment of DNIC proportionally to the intensity of the counterirritation stimulus [59]. Conversely, IBS patients showed no significant shock-pain inhibition during the cold pressor test, indicating a clear alteration of pain modulation processes. This is consistent with the studies mentioned above [12,43,56,57] and shows that not only visceral but also somatic pain inhibition is altered in IBS patients.

An important new finding is that this pain inhibition deficit was significantly related to visceral and thermal hypersensitivity. At least three explanations could account for this result. First, in addition to sensitization of convergent dorsal horn neurons by tonic inputs from visceral afferents [39,50,51], visceral and somatic hyperalgesia may also depend on altered descending modulation. This is consistent with the development and maintenance of secondary hyperalgesia induced by descending projections from the rostral ventromediale medulla to the dorsal horn of the spinal cord [47]. Secondly, diffuse processes related to DNIC [24] or spinal heterosegmental modulation [8], which are triggered by counterirritation, may be defective or may be normal but ineffective to inhibit sensitized dorsal horn neurons. Lastly, considering the association of pain inhibition deficits with psychological symptoms, the latter may interfere with descending inhibition or trigger descending facilitatory processes. This possibility will further be discussed in the following section. Together, those three physiological mechanisms may contribute independently or synergistically to widespread hypersensitivity in IBS.

An intriguing finding of the present study is the larger deficit in counterirritation analgesia and the relatively larger somatic hypersensitivity observed in the IBS patients currently reporting *less* clinical pain (see section 3.7 *Correlation analyses in the group of IBS patients*). These unexpected effects are unlikely to be explained by a report bias, whereby acute somatic pain would be under-rated in contrast to the strong clinical pain, because pain regulation (counterirritation analgesia) was assessed using painful shocks adjusted individually to produce moderate pain at baseline in all subjects (see Fig. 3A and B). Besides, chronic pain syndromes characterized by widespread pain such as fibromyalgia have been associated with increased opioid levels in the cerebro-spinal fluid [4] and decreased cerebral binding of exogenous opioids [20], possibly reflecting spontaneous activation of central pain-regulatory processes. Similar activation in IBS patients having experienced more pain recently may partly compensate for their regulatory deficit but this may be insufficient to neutralize the spinal sensitization underlying the overall group hypersensitivity [39]. Previous studies have reported no relation between the clinical presentation of IBS and (1) somatic hypersensitivity [42] or (2) increased spinal nociceptive processing induced by rectal distensions [12], whereas the severity of IBS symptoms was positively correlated to altered rectal perception in other studies [31,38]. In many other reports, the relation between GI symptoms and alteration of pain processing was not specifically examined [9,26,32,43,48,49,56]. The present results raise the possibility that the current clinical pain level might have a moderating role on acute pain-regulatory processes but further research is needed in order to clarify the link between clinical pain and altered pain processing in IBS.

4.3. Contribution of psychological symptoms to altered pain processing

Increased psychological symptoms have been reported in IBS patients [10,14,18,23,35,53] and experimental manipulation of the psychological state was shown to modulate sensory thresholds to visceral distension [2,16,19,37]. Therefore, the relative contribution of these factors has to be taken into account in the interpretation of quantitative pain tests.

The present results show that the large group differences in visceral sensitivity and pain inhibition during the cold pressor test were not significant after controlling for the severity of psychological symptoms. This important finding does not invalidate visceral hypersensitivity and pain inhibition deficits in IBS patients but rather shows that at least part of the group differences may be explained by common processes underlying psychological symptoms. However, it should be emphasized that psychological factors cannot explain all sensory disturbances. As a demonstration of the complexity of the pathophysiological processes, thermal hypersensitivity observed in this study was not significantly related to psychological symptoms. This implies that hypersensitivity may develop at least partly independently from psychological symptoms and that psychological symptoms are insufficient to explain every aspect of altered pain processing in IBS. Furthermore, we have recently observed that descending modulation and psychological factors are two independent factors contributing to pain inhibition deficits in IBS (unpublished observation).

It has been suggested that psychological stress and symptoms may trigger the development of IBS [29,34,55]. However, chronic visceral hypersensitivity in IBS patients may also contribute to the development and/or the reinforcement of psychological symptoms, which in turn may enhance pain. Thus, pain facilitation processes associated with psychological factors may contribute to the hypersensitivity and pain inhibition deficits observed in IBS patients. These hypothetical mechanisms are not necessarily exclusive but may rather add to the other potential mechanisms mentioned above.

4.4. Limitations and future directions

Our sample size is comparable to several previous reports investigating IBS using psychophysical methods; however, this sample should be considered small (especially in the third experiment). Although the difference in counterirritation analgesia between groups is very robust, it is difficult to determine if this pain inhibition deficit is representative of the IBS population as

important individual variations were noted. Our results also apply to female IBS-D patients only, a subgroup of patients that was selected to limit heterogeneity. Previous studies suggest that altered central pain modulation processes may generalize to constipation-predominant and alternating IBS [12,57] but further studies are needed to confirm the generalization of our findings. Furthermore, although we found a relation between pain inhibition deficits, hypersensitivity and psychological symptoms, effects were only weak to moderate. Further investigations with larger samples are needed to confirm these correlations and prospective studies should be conducted to explore the dynamical relation between ongoing clinical symptoms and pain-regulatory deficits within individuals.

4.5. Conclusion

In conclusion, the results of the present study suggest widespread hypersensitivity in IBS patients, affecting visceral as well as thermal cutaneous sensitivity. Importantly, this study demonstrates that this widespread hypersensitivity is related to pain inhibition deficits. In addition, psychological symptoms were shown to contribute to these sensory dysfunctions and may be involved in pain modulation processes that are related to chronic pain. Future studies should clarify the interactions between cerebro-spinal processes involved in pain processing and sensory dysfunctions observed in IBS patients and the potential fluctuations in pain inhibitory deficits associated with clinical symptoms. Understanding these mechanisms may lead to development of better pharmacological and non pharmacological treatments for pain management in IBS patients.

Conflict of interest

The authors have no financial or other relationship that might lead to a conflict of interest.

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