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SPECIAL REPORTS AND REVIEWS

Is Rectal Pain Sensitivity a Biological Marker for Irritable Bowel Syndrome: Psychological Influences on Pain Perception

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Background & Aims: Rectal pain sensitivity has been called a biological marker for irritable bowel syndrome, but this conclusion may be premature. This article is a critical review of the evidence for psychological influences on perception. *Methods:* The world literature accessible through *Index Medicus* from 1973 to 1997 was systematically reviewed. *Results:* Evidence favoring a biological basis for pain sensitivity is that two thirds of patients report pain at abnormally low thresholds of rectal distention despite normal somatic pain thresholds. Pain thresholds are not correlated with anxiety or depression. Evidence favoring psychological influences on perception is that patients with the irritable bowel syndrome rate even sham distentions as more painful, and when perception tests that minimize psychological influences are used, they have normal sensory thresholds. Also, stress alters sensory thresholds. Sensitization by repeated distention has been cited as evidence of a biological basis for hyperalgesia, but it is not unique to patients with irritable bowel. Brain imaging shows that different regions are activated by painful distention in patients with irritable bowel syndrome, but this is consistent with psychological influences on perception. *Conclusions:* Psychological factors influence pain thresholds in patients with the irritable bowel syndrome. Two cognitive traits, selective attention to gastrointestinal sensations and disease attribution, may account for increased pain sensitivity.

Abdominal pain is one of the cardinal symptoms of irritable bowel syndrome (IBS). The diagnostic criteria for this disorder emphasize pain that is relieved by defecation or that is associated with a change in the frequency or consistency of stools,[1–4] and physicians rate the severity of IBS[5] primarily on the basis of pain reports. Pain is the symptom that patients with IBS list as their most distressing,[6] and it is a major factor in whether they consult a physician.[7,8]

Ritchie[9] was the first to show that IBS patients report pain at a lower volume when a balloon is inflated in the lumen of the bowel, and his observations have been replicated by more than 20 subsequent studies. It is widely assumed that a lowered threshold to report pain from intraluminal distention determines the frequency and severity of clinical pain in IBS, and this assumption is supported by significant correlations between pain thresholds and the severity of clinical pain.[10,11] However, these correlations are relatively small ($r = 0.30–0.40$), showing that other factors than pain threshold contribute to the severity of clinical pain.[11]

The consistency with which patients with IBS are found to have lower pain thresholds led Mertz et al.[10] to speculate that rectal pain sensitivity is a biological marker for IBS, and that this biological marker reflects alterations in stretch receptors or spinal pathways for pain.[12,13] If confirmed, this would have great importance for our understanding of the pathophysiology of IBS and for its treatment; in fact, pharmaceutical companies are developing new drugs intended to decrease visceral sensitivity on the assumption that this is the pathophysiological mechanism for IBS. Our hypothesis is that the lower pain thresholds of patients with IBS could be caused, at least in part, by psychological influences on perception, that is, perceptual response bias. As a first attempt to address this hypothesis, we performed a literature review of the interactions between psychological influences and pain perception. Our review has led us to propose a hypothetical model of how psychological influences may interact with physiological factors to determine pain thresholds and perhaps the manifestation and presentation of symptoms in patients with IBS.

Abbreviations used in this paper: AML, ascending method of limits; IBS, irritable bowel syndrome.

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Methodological Considerations

This article is based on a review of the world literature that is indexed in *Index Medicus* for the years 1973–1997. Only articles relating to pain thresholds in patients with IBS were included; the literature on pain perception in functional dyspepsia and functional esophageal disorders was not surveyed. Search terms were irritable bowel, pain, barostat, and the names of selected authors known to have contributed to this literature. No non-English language articles that reported original data on this topic were identified.

Discomfort and pain have been used interchangeably by most investigators in this field, and this practice has been continued in this review.

The review spanned a 24-year period during which the diagnostic criteria for IBS were evolving. However, there were no apparent differences in the proportion of IBS patients judged to have low pain thresholds between early publications and publications occurring after the development of the Rome criteria for IBS.[2] Therefore, the diagnostic criteria for IBS were not considered in this review.

Patients with IBS are sometimes grouped into diarrhea-predominant and constipation-predominant subtypes. One study[14] suggested that patients with diarrhea-predominant disease may have lower pain thresholds than those with constipation-predominant disease, but no other studies of rectal pain sensitivity have subclassified their patients in this way. Therefore, this subclassification was not considered further in the review.

Methods of Studying Visceral Perception

Perceptual Response Bias

Nonperceptual factors, such as prior learning and the anticipated consequences of reporting pain, can affect the threshold at which pain is reported. For example, some subjects may report pain at a low intensity of stimulation to insure that they do not experience harm, whereas other subjects may deny pain even at levels of stimulation that cause tissue damage because they want to appear strong or stoical. When measuring perceptual sensitivity, the investigator normally tries to minimize these nonperceptual influences on perception, which are collectively called perceptual response bias. Methods of accomplishing this goal are summarized below and are described in greater detail in other articles.[15,16] Our review of the literature (see below) suggests that the method used to assess pain perception strongly influences the outcome of the study and the conclusions drawn regarding pain sensitivity in IBS.

Ascending Method of Limits

The method most commonly used to study perception of intraluminal distention in the gastrointestinal tract is the ascending method of limits (AML). This involves presenting progressively larger distentions until the subject reports pain or discomfort. The AML is susceptible to psychological influences on pain perception because the stimuli are predictable, and the subject is aware that the distentions will terminate when he or she reports pain.[15,16]

Tracking

In theory, one could make distentions unpredictable by presenting them in a random or a quasi-random sequence.[10,17,18] However, in pain research it is not practical or ethical to use truly random sequences of distentions because this will involve presenting some distentions that are significantly higher than the pain thresholds of many subjects. The tracking technique and the double random staircase technique[15] were developed to circumvent this problem; they both require that successive distentions be adjusted up or down based on the subject's responses to avoid presenting distentions that are well above the pain threshold, but these adjustments are done in a way which makes them unpredictable. The tracking technique achieves this by always either increasing the amount of distention or keeping it the same after each trial on which the subject does not report pain, and either decreasing the amount of distention or keeping it the same after each trial on which the subject does report pain. Whether the next distention changes or stays the same is determined by a random process.

Double Random Staircase

In double random staircase, the sequence of distentions is made unpredictable to the subject by using a computer to randomly alternate between two distention sequences (staircases). On each staircase, the distentions always increase after each trial on which the subject does not report pain, and they always decrease after each trial on which the subject does report pain.

Signal Detection

The signal detection technique[15,19] defines perceptual sensitivity, not as the minimum amount of distention that is perceived as painful but as the ability to discriminate between two (or more) similar intensities of distention that are painful. The assumption is that subjects who have greater perceptual sensitivity will be more accurate in discriminating between the two intensi-

ties of distention. This technique eliminates perceptual response bias more effectively than techniques based on the concept of a threshold, as shown by experiments in which the threshold for reporting a sensory event was manipulated by changing the consequences of different responses (e.g., paying an incentive for correctly detecting a sensory event or penalizing the subject for false alarms) and showing that these manipulations of response threshold did not alter the index of discriminability between the stimuli.[20]

Intensity Ratings

Some investigators[10,21] use the subject's rating of the intensity of pain in response to standard volumes or pressures as the measure of perceptual sensitivity. This has the advantage that only a few distentions may suffice. However, intensity ratings, like sensory thresholds, may be influenced by psychological factors such as the need to validate the presence and severity of a disease state or, conversely, by a desire to appear stoical.

Somatic Referral of Pain

The dorsal horn neurons in the spinal cord that receive input from stretch receptors in the bowel wall also receive input from nociceptors in the skin, and pain from intraluminal distention is often referred to (i.e., felt) in these cutaneous dermatomes.[22] Atypical areas of somatic referral[10,23,24] or enlarged areas of referral[10,18,25] have been interpreted as evidence of increased or abnormal pain sensitivity in patients with IBS.

Distinction Between Hyperalgesia and Allodynia

In neurophysiological studies in which one can identify and record from separate populations of receptors, some of which are identified as pain receptors and others as receptors that do not normally participate in pain perception, a useful distinction can be made between hyperalgesia and allodynia: hyperalgesia refers to a lower threshold for activation of pain receptors and allodynia refers to the possibility that, under some circumstances, non–pain pathways may give rise to pain.[26] Attempts have been made to apply this distinction to human pain perception studies by labeling it as hyperalgesia when patients rate a given amount of distention as more intensely painful than controls, and by labeling it as allodynia when patients report pain at a lower threshold of distention compared with controls.[13] However, this distinction seems illogical in situations in which it is not possible to distinguish between different receptor subtypes and in which the stimulus-response curves for patients and controls are more or less parallel: a difference in the intensity of sensation, when measured over an appropriate range of stimulus intensities, may translate into a difference in the threshold for first report of pain.

Reproducibility of Pain/Discomfort Thresholds

When the conditions of testing are kept constant, thresholds for distention-related sensations for gas, urgency, and discomfort as measured by the AML show adequate reproducibility across weeks.[14] However, sensory thresholds change in response to eating a meal,[27] stress and relaxation,[21,28,29] and attention or distraction.[30]

Different Approaches to Measuring Pain Yield Different Outcomes

Twenty-seven studies of distention-related pain or discomfort were reviewed, some of which used more than one method of assessing sensory thresholds. When the balloon was inflated in a continuous or cumulative manner until the first report of pain or discomfort (AML method), 11 studies[14,17,31–39] found lower thresholds in patients with IBS than in healthy controls and 5 studies[10,18,40–42] found no difference. When phasic distentions were presented in an ascending series until the first report of discomfort/pain (also the AML), 11 studies[10,18,37,42–49] found IBS patients to be more sensitive and 3 studies[41,50,51] did not. The tracking technique was used in 4 studies[25,40,43,44]; only 1 study[43] showed IBS patients to be more sensitive. Naliboff et al.[44] compared the AML to tracking in the same subjects and reported that there were differences between patients with IBS and controls when using the AML but no differences when using tracking. Naliboff and Mayer[16] reviewed this topic and drew similar conclusions. Moreover, when the signal detection technique was used, which provides the maximum discrimination of perceptual sensitivity from response bias, there were no differences in sensitivity between IBS patients and controls for rectal distention[43] or esophageal distention.[50]

Blank trials (simulated distentions) provide a method for examining purely psychological influences on perception. Silverman et al.[52] used sham distentions of the rectum to investigate which parts of the brain are activated by painful distentions; they reported that sham distentions were perceived similarly to actual distentions and the sham distentions activated the same areas of the brain as the real distentions. The changes in cerebral blood flow to sham distentions appear to represent "real" responses to the anticipation of painful distention rather than measurement error because the changes were statistically significant. Mertz et al.[53] reported that patients

with functional dyspepsia (not IBS) and healthy controls both reported experiencing discomfort in response to sham distentions of the stomach, and patients with functional dyspepsia were more likely than controls to rate the sham distentions as painful.

Thresholds for Nonpainful Sensations Produced by Distention

If response bias caused by negative emotions such as anxiety influence perception in patients with IBS, one would expect response bias to be strongest for pain, which is a potentially threatening sensation, weakest for nonthreatening sensations such as the lowest detectable distention, and intermediate for urgency to defecate. Conversely, if visceral hypersensitivity is primarily due to biological differences between IBS patients and controls, one might expect patients with IBS to differ from controls for all sensations. Five of 7 studies that tested the threshold for lowest detectable sensation[31,33,43,46,47,54] showed no difference between IBS patients and controls; 4 of 8 studies that tested the threshold for stool sensation[10,14,18,28,41,42,44,45] showed no difference between IBS patients and controls; and in 6 of 8 studies of urgency,[14,28,33,40,41,44,45,54] IBS patients were found to be more sensitive than controls. These studies show mixed outcomes and would be difficult to interpret as supporting either a psychological or a biological interpretation of visceral hypersensitivity.

Pain From the Skin

If increased pain sensitivity in patients with IBS is part of a neurotic tendency to label any aversive stimulus as painful, one would expect IBS patients to have lower thresholds for pain produced by aversive stimuli applied to the skin as well as lower thresholds for gastrointestinal distention. Six studies have tested this hypothesis,[28,34,35,46,51,55] and all 6 found patients with IBS to be either similar to or less sensitive than healthy controls to painful stimulation of the skin. These studies show that increased pain sensitivity is specific to the gastrointestinal tract; in so doing they demonstrate that general psychological traits such as anxiety cannot explain lower thresholds to distention-related pain. These studies have been interpreted as evidence that psychological factors do not influence pain thresholds, but it must be remembered that IBS patients who are worried about having a digestive disease might be fearful of sensations arising from distention of the gastrointestinal tract without being similarly fearful of sensations arising from the skin; their fears might influence their perception and labeling of these sensations as painful. Hence, these data from studies of somatic pain sensation do not really exclude the possibility that psychological traits alter the pain perceptions arising in the bowel.

Experimental Manipulation of Psychological State: Effects on Pain Threshold

If patients with IBS are more sensitive to visceral pain because of psychological bias, interventions that reduce negative emotional states should raise the pain threshold and result in fewer or less severe reports of pain. Consistent with this hypothesis, Prior et al.[28] reported that, in patients with diarrhea-predominant IBS, the thresholds for gas, stool, urge, and discomfort were all significantly increased during hypnosis compared with pretreatment. Ford et al.[21] reported that stress (dichotic listening task) increased the intensity of gas and pain sensations in the sigmoid colon, and relaxation (progressive muscle relaxation training) significantly decreased the intensity of gas sensations in the sigmoid. However, Metivier et al.[29] reported different results: they found that both physical stress (holding a hand in ice water) and psychological stress (dichotic listening) were associated with a significant increase in thresholds (decreased sensitivity) for first sensation, urgency, and pain. The effects of relaxation were not assessed. They speculate that sensory thresholds may have been higher during their experimental stress condition due to distraction.

The role of distraction was directly assessed by Accarino et al.[30] when they compared the rated intensity of sensations produced by jejunal distention under two conditions: while the subject was distracted by performing a cognitive task and while the subject was given an anticipatory signal to indicate when the distention would occur. The rated intensity of the sensation was significantly less with distraction compared with the warning signal condition, suggesting that manipulating the subject's attention to the visceral stimulus affected his or her perception.

These studies suggest that the subject's psychological state and/or attention to the distending stimulus can significantly alter the threshold for perception compared with baseline. The inconsistencies between studies may have occurred because distraction (which may raise sensory thresholds) and stress (which may lower sensory thresholds) were confounded in some studies.

Sensitization by Repeated Distention of the Rectum

Munakata et al.[25] reported that repeated distentions of the rectum at a painful intensity caused sensitiza-

tion (i.e., reduced sensory thresholds) in patients with IBS but not in healthy controls. If sensitization is indeed unique to IBS patients, this would suggest that visceral hypersensitivity in IBS has a biological basis. However, others have observed sensitization phenomena in healthy controls[43,56] and in laboratory rats.[57]

Activation of Different Regions of the Brain by Rectal Distention

Silverman et al.[52] used positron emission tomography (PET scanning) to show that rectal distention caused activation of different regions of the brain in IBS patients compared with controls both during painful distention of the rectum and in response to the anticipation of painful distention (i.e., during blank trials). Distention caused activation of the anterior cingulate gyrus in healthy controls, but caused activation of the left prefrontal cortex in patients with IBS. Thus, there is an anatomic difference in the central pathways mediating visceral pain in IBS. However, Silverman et al. interpreted their findings in a way that is consistent with the influence of psychological processes on perception: they point out that the prefrontal cortex is a part of the brain involved in the interpretation of sensations and suggest that the lack of activation of the anterior cingulate gyrus in IBS patients represents a failure of descending inhibitory pathways linked to the different interpretations given to these sensations by IBS patients.

Correlation of Psychological Traits With Sensory Thresholds

If lower pain thresholds in patients with IBS are a result of psychological influences on perception, one would expect to see a correlation between pain thresholds and psychological test scores. In 8 of 10 studies addressing this question,[10,25,28,34,43–45,47,48,55] these correlations were not statistically significant: traditionally defined psychological traits such as anxiety, depression, and neuroticism are not predictive of pain thresholds. However, somatization as measured by the number of nongastrointestinal and nonpsychiatric symptoms reported on the Cornell Medical Index[58] and by the somatic anxiety scale of the Trauma Symptom Checklist-40[59] do correlate significantly and substantially with pain thresholds.[43] Somatization is defined as a tendency to notice many bodily sensations and to interpret them as symptoms of disease, and somatization has been shown to occur in patients with IBS.[7] This suggests that the psychological mechanism responsible for reduced pain thresholds in IBS may be a selective attention to somatic sensations, especially gastrointestinal sensations.[60–62]

A Model to Account for Perceptual Response Bias

Figure 1 shows a schematic representation of how psychological factors may interact with physiological events to affect pain perception and related health outcomes. The evidence for the components of this hypothetical model is as follows.

Selective Attention and Disease Attribution

The literature reviewed above suggests that perceptual response bias contributes to the decreased threshold to report pain in IBS, but these data also show that perceptual response bias is not caused by a neurotic tendency to label all aversive stimuli as painful because, first, thresholds for aversive stimulation to the skin are not lower in IBS patients and, second, general psychological traits such as neuroticism and anxiety do not correlate with pain thresholds. In Figure 1 we propose that perceptual response bias is caused by two related cognitive traits: a selective focus of attention on gastrointestinal sensations and a tendency to interpret gastrointestinal sensations as symptoms of disease. These cognitive traits are related: people are more likely to pay close attention to gastrointestinal symptoms if they believe that these sensations signify a disease or if they are afraid they may have a disease and, conversely, becoming aware of many gastrointestinal sensations may reinforce the belief that one has a disease. The hypothesis that selective attention and disease attribution influence the perception and reporting of symptoms has precedents in previous cognitive behavioral theories of IBS.[61–63]

Childhood Reinforcement and Modeling of Illness Behavior

We have previously shown[64,65] that reinforcement and modeling of gastrointestinal illness behavior during childhood are significantly correlated with having the diagnosis of IBS as an adult. An important aspect of these studies was the demonstration that childhood learning of illness behavior is relatively specific: if parents reinforced and modeled bowel-related illness behavior during childhood, the child was more likely to have IBS but not necessarily dysmenorrhea as an adult, whereas if the parents reinforced and modeled menstrual-related illness behavior, the (female) child or adolescent was more likely to grow up to report menstrual-related symptoms and to be diagnosed as having dysmenorrhea.[66] The effects of childhood social learning on adult symptom reporting were also independent of stress and neuroticism.[65] We propose in Figure 1 that childhood reinforcement and modeling is the principal determinant of selective atten-

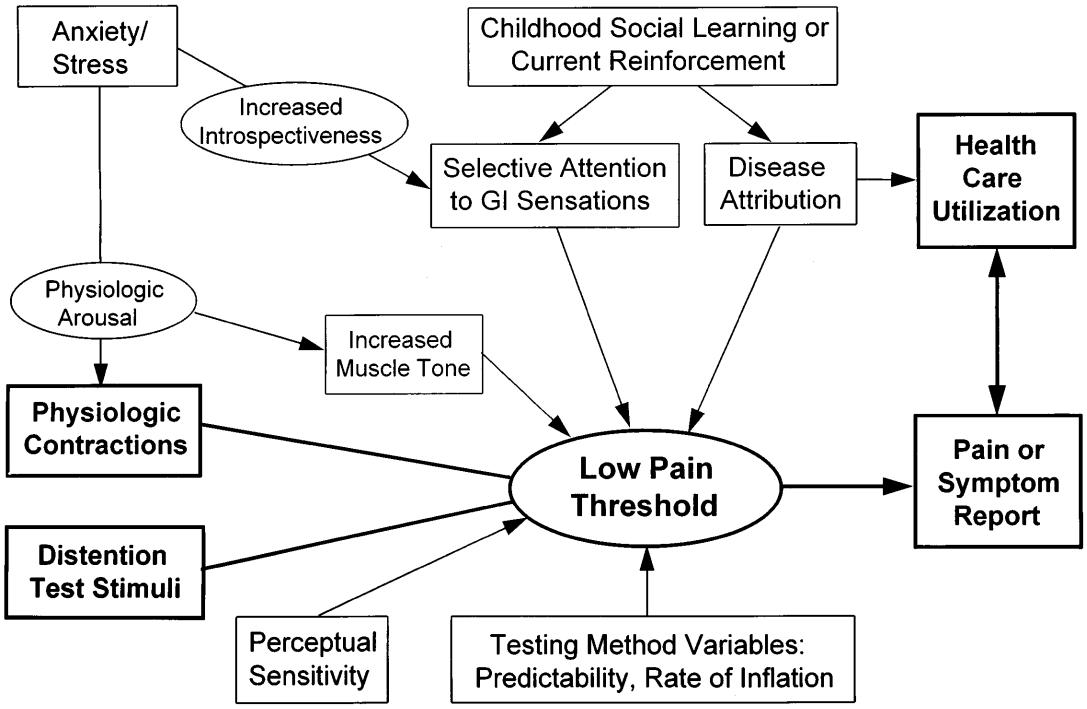

Figure 1. Schematic model showing how cognitive/psychological, physiological, and methodological factors may interact to influence the threshold for pain produced by rectal distention. The model suggests that the threshold for pain influences the frequency and severity of clinical pain and the utilization of health care services by patients with IBS.

tion to gastrointestinal sensations and of disease attribution.

Effects of Psychological Stress on Pain Perception

Psychological stress is associated with an increased number of bowel symptoms in patients with IBS[7,67] and, conversely, stress-reduction techniques[68–71] result in decreased reports of abdominal pain and other bowel symptoms. Figure 1 suggests that stress may influence the frequency of pain complaints by increasing the amount of contractile activity[72,73] even if the pain threshold remains constant.

Independent of its effects on contractile activity, stress seems to influence the threshold amount of distention at which pain is reported.[21,29] This could occur through either of two mechanisms. Stress may increase smooth muscle tone,[74,75] which may decrease the volume of distention required to produce pain.[43,76,77] Alternatively, stress may influence pain perception by increasing selective attention to gastrointestinal sensations. This hypothesized pathway (Figure 1) is based on the theory and data of Mechanic and Hansell[60,78,79] showing that individual differences in exposure to psychosocial stressors are correlated with scores on a general measure of introspectiveness and with reports of somatic symptoms.

Perceptual Sensitivity

Figure 1 also represents the possibility that low pain thresholds in IBS may be due in part to peripheral physiological mechanisms such as sensitization of dorsal horn cells in the spinal cord.[10,12,13,18] These peripheral physiological mechanisms are represented in Figure 1 as being independent of psychological influences on perception.

Method Variables

The bottom portion of Figure 1 shows that the method used to assess perception may influence the measured pain threshold and may therefore affect the conclusions drawn from any experiment about the relationships among other variables in the model. These method variables (e.g., predictability of the stimuli and rate of inflation) are not shown as interacting with other variables in the model because it is proposed that they contribute primarily measurement error to the model, which the investigator should be aware of and should try to minimize.

Health Care Utilization

Figure 1 also shows a pathway linking disease attribution to health care utilization. This relationship is well substantiated by the research of Leventhal et al.,[80,81]

Mechanic and Hansell,[60,79] and Pilowsky et al.,[82] among others. Figure 1 shows a reciprocal relationship between symptom reporting and health care utilization.

Summary and Conclusions

Observations that have been cited as evidence for a biological basis for visceral hyperalgesia are as follows: (1) Approximately two thirds of patients with IBS report pain or discomfort at a lower threshold than healthy controls. (2) Patients with IBS have larger areas and/or atypical areas of somatic referral than healthy controls when the rectum is distended. This has been interpreted as evidence for sensitization of spinal afferents. (3) Pain thresholds are not correlated with anxiety or depression, as might be expected if psychological traits are the principal determinants of pain thresholds. (4) Patients with IBS do not show lower thresholds for painful stimulation of the skin, as might be anticipated if pain thresholds are due to a neurotic tendency to label all aversive sensations as painful.

The findings that favor a psychological rather than a purely biological basis for increased pain sensitivity in IBS are as follows: (1) When techniques such as tracking that minimize psychological influences on perception are used, one is less likely to see a difference between IBS patients and controls. When signal detection analysis, which provides the most stringent control for psychological influences on perception, is used, no differences between IBS patients and controls are observed. (2) Patients with IBS rate even blank distention trials as more painful than control subjects. (3) Manipulation of the subject's attention and changes in arousal level produced by stress and relaxation seem to alter the perceived intensity of distention-related sensations.

Recently reported observations on sensitization by repeated painful distention of the rectum and on brain imaging are not easily interpreted as supporting either biological or psychological influences on perception. One group[25,44] reported that repeated painful distention of the rectum causes lower thresholds and increased size of referral area in patients with IBS but not in healthy controls. If sensitization is unique to IBS, this would argue for a biological basis for hyperalgesia associated with this disorder. However, other investigators[43,56] found no difference in the degree of sensitization between IBS patients and controls. Silverman et al.[52] have shown that rectal distention activates a different part of the brain in patients with IBS compared with controls, but the investigators interpreted this anatomic difference as consistent with psychological differences in the cognitive processing of painful sensations.

Figure 1 presents a hypothetical model that attempts to integrate the various psychosocial, physiological, and methodological variables believed to influence the threshold at which patients with IBS report pain from rectal distention. This model suggests that early childhood learning through the reinforcement and modeling of illness behavior by parents is a principal determinant of selective attention to gastrointestinal sensations and disease attribution, and that these two cognitive traits are in turn the principal determinants of perceptual response bias.

In conclusion, the widely held view of a few years ago that visceral hyperalgesia is a biological marker for IBS[10,12,13,83] needs to be reevaluated in the light of more recent findings. Many of these findings cannot be explained on the basis of hypothesized biological differences between patients with IBS and controls; they suggest that psychological factors play an important role in determining where on the continuum of intensity of sensation IBS patients begin to report pain. By understanding the role of psychological influences on pain perception we may gain new insights into the etiology of this disorder. This may in turn redirect our search for more effective treatments toward central rather than peripheral control of pain pathways and toward psychological interventions.

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