Irritable Bowel Syndrome: Methods, Mechanisms, and Pathophysiology.

Methods to assess visceral hypersensitivity in irritable bowel syndrome

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Keszthelyi D, Troost FJ, Masclee AA. Methods to assess visceral hypersensitivity in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 303: G141–G154, 2012. First published May 17, 2012; doi:10.1152/ajpgi.00060.2012.—Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, characterized by recurrent abdominal pain or discomfort in combination with disturbed bowel habits in the absence of identifiable organic cause. Visceral hypersensitivity has emerged as a key hypothesis in explaining the painful symptoms in IBS and has been proposed as a “biological hallmark” for the condition. Current techniques of assessing visceral perception include the computerized barostat using rectal distensions, registering responses induced by sensory stimuli including the flexor reflex and cerebral evoked potentials, as well as brain imaging modalities such as functional magnetic resonance imaging and positron emission tomography. These methods have provided further insight into alterations in pain processing in IBS, although the most optimal method and condition remain to be established. In an attempt to give an overview of these methods, a literature search in the electronic databases PubMed and MEDLINE was executed using the search terms “assessment of visceral pain/visceral nociception/visceral hypersensitivity” and “irritable bowel syndrome.” Both original articles and review articles were considered for data extraction. This review aims to discuss currently used modalities in assessing visceral perception, along with advantages and limitations, and aims also to define future directions for methodological aspects in visceral pain research. Although novel paradigms such as brain imaging and neurophysiological recordings have been introduced in the study of visceral pain, confirmative studies are warranted to establish their robustness and clinical relevance. Therefore, subjective verbal reporting following rectal distension currently remains the best-validated technique in assessing visceral perception in IBS.

visceral nociception; rectal distension; brain imaging

IRRITABLE BOWEL SYNDROME (IBS) is a common gastrointestinal (GI) disorder, affecting 10–15% of the population in developed countries. Referred to as a functional GI disorder, it is characterized by lower abdominal discomfort or pain with disturbed defecation in the absence of apparent structural or biochemical abnormalities that might explain the symptoms (38). Despite being very common, the pathophysiology of IBS is incompletely understood, which poses problems in the search for effective therapeutic approaches. Nonetheless, it is now widely accepted that an altered visceral sensitivity through abnormal endogenous pain processing plays an important role in the pathogenesis of IBS (74). Both central and peripheral mechanisms have been suggested to be involved in the development of pain symptoms (56). Several studies have provided evidence that IBS is associated with a dysregulation of the brain-gut axis, with peripheral sensory alterations dominating in some patients and disturbed central processing dominating in others (7). Because the treatment and management strategies deployed to ameliorate these different aberrant mechanisms are distinct (i.e., pharmacological vs. psychological therapy), identifying the predominant underlying pathology remains an important clinical and therapeutic objective. Several tests have been developed over the past decades to assess and quantify visceral perception in IBS. The majority of current knowledge about visceral perception, however, is largely dependent on studies using subjective perception threshold determination and identifying altered cortical activity by use of neuroimaging, with far less rigorous and validated experimental paradigms than used in the area of somatic research. This review aims to give an overview of these methods, highlighting the advantages and limitations, and to define future directions for visceral pain research.

Altered Visceral Pain Processing in IBS: Where Does It Go Wrong? A Theoretic Overview

Peripheral afferent pathways. Innervation of the GI tract from the esophagus through the transverse colon is provided by vagal afferents originating from the nodose ganglia and projecting centrally to the nucleus of the solitary tract. Vagal afferents are therefore important in the sensory innervation of the upper GI tract, in particular the esophagus and stomach (13), and are believed to mediate nonnoxious physiological sensations, such as satiety and nausea (5). Vagal innervation decreases down the length of the GI tract and is sparse in the distal colon. The more distal parts of the lower bowel are innervated by pelvic nerve afferents, originating from the sacral dorsal root ganglia and projecting to the sacral spinal cord. Besides, afferent innervation is provided throughout the entire GI tract by the splanchnic nerves projecting to T5–L2 segments of the spinal cord. More specifically, colonic afferents fibers project both to pelvic and splanchnic nerves. Pelvic afferents innervate the rectum, whereas splanchnic afferents innervate the distal colon and extend more proximally (18, 80). In general, the pelvic pathway is a predominantly low-threshold pathway (18, 39), responding to low intensity of mechanical stimulation, whereas the splanchnic pathway is predominantly a high-threshold pathway (18). Recently, Kyloh et al. (59) demonstrated that the sensory innervation of the distal colon and rectum is significantly greater than the midproximal colon, probably due to additional afferent nerve pathways recruited for the defecation reflex.

Both the pelvic and splanchnic systems carry afferents, which can be functionally divided into different subclasses:
Mucosal afferents respond exclusively to fine tactile stimuli on the luminal surface. The majority of these afferents are also chemosensitive (69) but have not been demonstrated to exhibit sensitization to chemical stimuli. Muscular afferents respond to distension at physiological levels (<20 mmHg) and provide input for the perception of distension or contraction. Muscular-mucosal afferents respond to both tactile and distension stimuli (both noxious and physiological). These afferents predominate in the pelvic pathway (18).

Serosal and mesenteric afferents respond to noxious levels of distension (>30 mmHg). They detect overdistension and high-amplitude contractions (52). These afferents are most commonly found in the splanchnic pathway.

Mechanically insensitive afferents have the ability to acquire mechanosensitivity in inflammatory conditions and generate spontaneous activity in the noxious range (40). On average, ~25% of pelvic and splanchnic afferents are mechanosensitive (40). It is also important to acknowledge, however, that not all mechanosensitive afferents are able to respond to mechanical stimuli (17, 19).

Sensitization of these distal peripheral afferents has been identified as an important mechanism in visceral hypersensitivity in IBS (4). The important question arises which afferents can in fact potentially contribute to altered visceral perception. Hughes et al. (52) demonstrated that high-threshold mesenteric and serosal afferents of the splanchnic pathway show sustained sensitization following mild transient inflammation. These afferents also exhibit chemosensitivity to a various number of mediators, including bradykinin and ATP (17), providing evidence for a role of these afferents in postinflammatory hyper-sensitivity conditions.

On the other hand, a significant proportion of mechanosensitive afferents in colorectal pelvic and lumbar splanchnic pathways in mice have been demonstrated to acquire mechanosensitivity, albeit short lasting (~20 min), under brief inflammatory conditions. Also, following treatment with zymosan resulting in long-lasting visceral hypersensitivity, a switch from mechanosensitive to mechanosensitive phenotype was seen in a significant number of pelvic afferents (41). In fact, mechanosensitive afferents in the pelvic nerve are more likely to acquire such mechanosensitivity than their splanchnic counterparts (40). This suggests a superior role for these “silent” afferents, in particular in the pelvic nerve, in conditions of visceral hypersensitivity, which is supported by the observation that visceromotor responses to noxious colorectal distension are absent after transection of the pelvic pathway but remain unaffected after transection of the splanchnic pathway (59). However, other studies were unable to find an increase in the total number of afferents showing firing activity following inflammation (52), which would indicate recruitment of these otherwise mechanosensitive afferents. This suggests that postinflammatory hypersensitivity is probably explained based on the existing population of afferents. Therefore, the role of “silent” afferents in sustained visceral hypersensitivity remains to be further elucidated.

Overall, the selective sensitization of a single nociceptive pathway seems unlikely in IBS. First, IBS patients often complain of bloating, cramps, urgency, and discomfort in addition to experiencing pain, suggesting the involvement of multiple or multimodal afferent pathways. Second, IBS patients experience pain for long periods of time, which cannot be related to ongoing luminal distension at noxious levels. Third, nociceptor activation alone may not be sufficient to cause chronic pain or discomfort, suggesting the importance of other, in particular central, modulatory factors.

Spinal cord. Visceral afferents constitute less than 10% of all spinal afferent input (2). Upon entering the spinal cord, visceral afferents terminate in spinal cord laminae I, II, V, and X (104) and converge onto spinal neurons in the lumbarosacral and thoracolumbar segments.

In the spinal cord, two major ascending pathways have been proposed to be involved in visceral nociception: the anterolateral and the dorsal column pathways (see Fig. 1). Ascending pathways of the anterolateral quadrant, most importantly the spinothalamic tract, have been proposed to conduct nociceptive information of visceral origin, besides transmission of signals evoked by noxious cutaneous stimuli. Spinothalamic projections are largely to the ventral posterior lateral and ventral posterior inferior nuclei of the thalamus, which in turn project to primary and secondary somatosensory cortices. These pathways transmit information regarding the intensity, duration, and location of noxious stimuli. However, unlike somatic sensation, which has strong homuncular representation in the primary somatosensory cortex, visceral representation is more diffuse. This could be the explanation for visceral sensation being poorly localized compared with somatic sensation.

Apart from projection to ventral posterior thalamic nuclei, spinothalamic afferents have been shown to connect with the medial thalamus at the level of the nucleus submedius (3). This region has been consistently shown to be activated in brain imaging studies (106). From these nuclei, ascending pain signals spread bilaterally to the prefrontal cortex, including the anterior cingulate cortex (ACC) (2). In addition, there are projections to the periaqueductal gray matter (PAG), which has reciprocal connections with the medial thalamic nuclei and receives a direct input from the ACC. Neural terminations arising from medial thalamic nuclei are ideal for providing motivational and affective qualities associated with noxious stimulation, which should be activated by visceral stimuli that have a dominant affective component.

The spinoreticular tract, another constituent of the anterolateral system, conducts sensory information from the spinal cord to the reticular formation in the brain stem (see Fig. 1). The reticular formation is mainly involved in the reflexive, affective, and motivational properties of such stimulation (23). Third-order reticulothalamic tract neurons project from the dorsal and caudal medullary reticular formation to the medial and intralaminar nuclei of the thalamus. The spinomesencephalic tract, yet another component of the anterolateral system, ascends the spinal cord with fibers to various regions in the brain stem, including the PAG, locus coeruleus, and dorsal reticular nucleus in the medulla (117).

Early studies have demonstrated that sensation of visceral distension was retained following extensive anterolateral chor-dotomy (113), lesioning the anterolateral afferent system, suggesting the existence of an alternative spinal ascending nociceptive pathway. Although the dorsal column system has traditionally been viewed as a pathway responsible for the discriminative aspects of tactile sensations and for kinesthesia, more recent studies have in fact identified the dorsal column as being of superior importance in visceral nociception compared...
with spinothalamic and spinoreticular tracts (116). A dorsal column lesion in monkeys has been demonstrated to reduce the response of ventral posterior lateral neurons previously excited by colorectal distension (26). Furthermore, subpopulations of neurons within the dorsal horn have also been demonstrated to project to the lateral parabranchial nucleus and the PAG (116), supporting their role in nociceptive processes. Whichever spinal pathway is used to transport afferent input, from the thalamus, information is conveyed to cortical areas involved in sensory processing or those involved in processing emotional or affective information (84).

Cortical pain processing. Because pain is a complex, multifactorial subjective and conscious experience, a large distributed brain network is accessed during nociceptive processing. A variety of regions identified as the “homeostatic afferent network” (previously referred to as the “central pain matrix”), consisting mainly of the posterior insula (primary interoceptive cortex), the anterior midcingulate cortex (aMCC), and the thalamus, have been found to be consistently activated in response to visceral stimuli (35, 94). This network is primarily responsible for pain processing but also mediates affective, motivational, and motor aspects of a certain noxious stimulus. The single most consistent activation in brain imaging studies investigating visceral pain was found in the insular cortex, which is involved in integration of somatic and visceral information (posterior insula) and its affective component (anterior insula). Furthermore, lower GI stimulation has been consistently shown to activate the anterior portions of the MCC, having direct connections with limbic and brain stem structures (106).

Besides the homeostatic afferent network, brain imaging studies have also demonstrated a greater activation of the emotional arousal network following painful visceral stimuli, including the locus coeruleus complex, amygdala, hypothalamus, parahippocampal gyrus, perigenual anterior cingulate cortex (pACC), anterior insula, and orbitofrontal cortex (106). This arousal network is engaged in the emotional processes modulating visceral responses, such as anticipatory anxiety or fear. The greater engagement of the emotional arousal network may also play a role in central pain amplification and is consistent with a model of IBS characterized by increased stress, anxiety, vigilance, and altered autonomic responses.

More specifically, anterior activation of MCC extending into the superior portion of the pACC has been reported in studies of nonnociceptive pain, e.g., anticipated, imagined, or empathy-related pain (81). The pACC is considered to be the primary cortical region in the descending pain inhibition system, with a high concentration of opioid receptors (112) and
connections to the PAG (12). IBS patients demonstrating hypersensitivity to rectal distension in fact showed reduced deactivation in this region compared with normosensitive IBS patients and healthy controls, suggesting alterations in descending modulatory nociceptive control (61). Also, Berman et al. (11) showed that, in IBS patients, alterations during cued expectation of an averse rectal stimulus correlated with subsequent brain responses to the delivered stimulus in the pACC. IBS patients have been shown to engage the anterior insula (11) and the thalamus (71) to a greater extent during pain expectation. The greater activation of these regions is consistent with inappropriate engagement of descending pain facilitatory mechanisms triggered by the prediction of an averse stimulus, and this has been interpreted as a possible prediction bias related to the expected pain intensity (11).

**Descending control of pain perception.** Neural circuits have been described originating from supraspinal sites that influence nociceptive activity in the spinal cord and primary afferents. The function of this supraspinal pain control is to either amplify or subordinate noxious or potentially noxious stimuli in coordination with the individual’s homeostatic needs (70). A key component of this descending system is the PAG. Stimulation of this area leads to selective repression of pain, leaving other sensory modalities intact, an effect that appears to be mediated via both the presynaptic inhibition of primary afferent input into the dorsal horn and the inhibition of dorsal horn projection neurons (8). The PAG receives input from collaterals of ascending fibers as well as from higher cortical centers such as the frontal neocortex, the pACC, the central nucleus of the amygdala, the hippocampus, and the hypothalamus. Output of the PAG is to the rostroventral medulla and the dorsolateral pontine tegmentum. These two regions project to spinal cord dorsolateral funiculus and selectively target the dorsal horn laminae that accommodate nociceptive relay neurons. This circuit can therefore selectively modulate nociceptive transmission by acting on primary afferent nociceptive terminals and dorsal horn neurons responsive to nociceptive stimulation (93).

Some neurons of the dorsal horn of the spinal cord are strongly inhibited when a noxious stimulus is applied to any part of the body, distinct from their excitatory receptive fields. This phenomenon is termed “diffuse noxious inhibitory control” (DNIC) (62). Accordingly, acute aversive heterotopic stimulation provides a temporary relief on chronic and recurrent pain. DNIC paradigms, such as the RIII reflex (see below), typically involve measurement of the nociceptive threshold for a “test” stimulus before, during, and after application of a second noxious “conditioning” stimulus to an anatomically remote area of the body. DNIC have been proposed to be triggered by ascending spinothalamic fibers, with the medullary reticular formation playing a crucial role in the subsequent descending modulation of spinal nociception (32).

More recently, it has become evident that descending pathways not only suppress but can also facilitate nociception (43, 114). Overall, studies of visceral perception have demonstrated that nociceptive and antinociceptive information is processed in parallel. This is particularly true for supraspinal sites, where evidence of nociceptive-specific neurons is rare and evidence of supraspinal nociceptive-specific nuclei is nonexistent (44). Furthermore, current studies have not been able to delineate distinct inhibitory and facilitatory pathways, but rather indicate that the modulatory nociceptive balance appears to be distributed over the same functional circuits (114).

**Assessment of Visceral Nociception in IBS**

**General principles.** The complexity of visceral nociceptive processes, as illustrated above, has imposed a challenge in assessing visceral perception in IBS. Traditionally, visceral perception has been tested by delivering a certain controlled sensory stimulus and measuring the nociceptive response evoked by it (see Fig. 2). The GI tract contains afferents that encode a wide range of intensities and modalities of stimulation including electrical, mechanical, thermal, and chemical (including nutrient) stimuli. Choosing the correct stimulation method or interpreting differential responses to multiple stimuli may be of superior relevance in delineating pathological mechanisms. For instance, electrical stimulation is often thought of as nonphysiological and therefore of limited use in assessing GI sensation. Furthermore, manipulation of the environment in which a sensory stimulus is given, before and after nutrient infusion or heterotopic stimulation, for instance, can yield important physiological and pathophysiological information above and beyond that gained purely from quantitative sensory testing alone. With respect to the assessment of visceral perception, perhaps the most important aspect is the objectivity and robustness of the measuring the magnitude of the pain response, used as primary end point for the experiment. Measurement of the pain response using verbal scores and scales to assess perceptive intensity and thresholds of nociception is largely influenced by subjective components, making it prone to reporting bias. Brain imaging and neurophysiological measurements, on the other hand, theoretically offer a more objective assessment of nociceptive responses. However, as will be illustrated later, these outcome measures are also greatly affected by cognitive-affective mechanisms, posing a challenge to the search for a surrogate marker of altered visceral perception in IBS.

**Mechanical stimuli: rectal distension.** Until recently, employing gut distensions has most widely been used to test visceral perception in IBS. Previous studies indicate that 35–60% IBS patients exhibit increased visceral sensitivity to rectal balloon distension and that this hypersensitivity could be a biological marker of IBS (15, 33, 68a, 74, 82). The distal colon has also been used as an anatomic location to assess visceral perception. Both rectal and sigmoid distensions have been employed, although the overwhelming majority of studies have applied rectal distensions. It appears that when phasic distensions are applied, only minor differences can be observed with regard to the visceroperceptual responses between rectal and sigmoid distensions (37, 64). Since rectal distension has emerged as an attractive and more easily reachable alternative, we will aim further to focus on the discussion of this technique. The recent observation that the rectum also contains more afferents makes the rectum indeed an ideal target in assessing visceral nociception (59).

Rectal visceral sensitivity can be tested by using polyethylene bags in conjunction with a barostat (108). The barostat is a device that maintains a constant pressure within an air-filled polyethylene bag and can measure variations in rectal tone by recording changes in the intrarectal pressure and volume. Rectal distension can be done according to a certain protocol,
during which different pressures are applied to the rectal wall. During this procedure, the intensity and quality of perception can be measured by means of rating scales.

Several different distention protocols have been applied to assess visceral perception in IBS. The lowered sensory thresholds seen in IBS have been shown to be elicited by rapid rates of rectal distension, whereas in the majority of patients the perception threshold during slow rectal distension pressure is not different from that in normal control subjects. It has also been postulated earlier that rapid phasic distensions preferentially stimulate serosal afferents (63). These afferents are particularly chemosensitive to inflammatory and enteroendocrine mediators such as serotonin (5-HT), which suggests a role for nociception in conditions in which sensitization of visceral afferents is involved (52). Accepting that these afferents are at least in part responsible for the development of visceral hypersensitivity in IBS, rapid rectal distensions theoretically offer an ideal tool to assess perceptional status in these patients. Furthermore, complex distension protocols with non-random presentation of stimuli such as double random staircase distension reduce psychological response bias by making the stimulus unpredictable to the subject (72), which is desirable considering that IBS patients may be particularly prone to such bias due to anticipatory anxiety. However, these complex protocols usually require more distension levels and increasing the number of interrogations about sensations may introduce bias or errors in a fatigued and stressed or disinterested participant.

Measurement of perception magnitude. During rectal distension, several parameters of visceral sensitivity can be collected to assess perceptional status. These include perceived intensity of the stimulus, extent of the viscerosomatic referral area and the threshold at which different sensations (pain, discomfort, urge) appear during the distension protocol (83). These components of visceral perception are not uniformly used by various groups, making comparison of study results troublesome. Standardization of testing procedures is therefore highly desirable, such as application of similar distension protocols and definitions in visceroperception assessment.

As for the intensity of perception, different scales including numeric rating scales, verbal rating scales, verbal descriptor scales, magnitude estimation, and visual analog scales are employed. Visual analog scales have emerged as having psychometric properties that are superior to the other pain scaling methods because they fulfill multiple criteria for ideal pain measurement and assessment (86). These criteria include ratio scale properties, high test-retest reliability and repeatability, the capacity to detect small differences, internally consistent measures of clinical and experimental pain, sensitivity to variables that increase or decrease pain, detection of individual differences in pain sensitivity, and ease of use (85).
The majority of the research groups investigating visceral perception using the barostat techniques have focused on identifying the thresholds for perception in IBS patients because these have been shown to be lowered compared with healthy volunteers. However, threshold measurements of pain perception are limited since they fail to assess alterations in pain intensity that may occur over a wide range of noxious intensities. On the other hand, investigation of the perceived intensity of the given stimulus as well as recording the viscerosomatic referral area can give extra information on processing of visceral stimuli (74, 83). In addition to lowered thresholds to visceral stimuli, marked alterations in somatic referral patterns in response to balloon distension of the colon have been described in patients with IBS (57). Atypical referral of internal sensation is a strong indication for altered spinal processing of visceral sensory information and is a manifestation of central sensitization. Therefore, assessment of viscerosomatic referral may have added value in determining the perceptual status in IBS.

Currently, distension paradigms differ in duration and type of inflation (tonic vs. phasic), level of bias (ascending vs. randomized distension), and measurement of response magnitude (perceptual threshold or rating). Despite the fact that not all patients exhibit hypersensitivity to rectal distensions, the barostat procedure appears to be a reliable and valid approach to assess visceral nociception. The barostat has been shown by several studies to be reproducible in a single subject for at least two test occasions (45, 46, 103), with the best reproducibility seen in higher pressure ranges (36–48 mmHg; Ref. 31). This is underlined by the fact that the barostat has also shown robust changes following administration of a narcotic analgesic even in small crossover samples, further supporting the measure’s validity for assessing pain perception (34, 65). It is also important to note that these perceptual alterations were independent of changes in compliance or tone (16). Evidence from crossover studies points to considerable reliability and validity for rectal distensions to testing visceral perception, reviewed extensively by Mayer et al. (72). Furthermore, the barostat method in conjunction with verbal reporting has shown to have high sensitivity and specificity for detecting visceral hypersensitivity in IBS patients (95.5 and 71.8%, respectively) (15).

However, given their subjective nature, rectal distensions in combination with verbal reporting can only be an indirect measure of the underlying neurophysiological processes. Because of the influence of cognitive and emotional factors, the relationship between visceral afferent sensitivity and conscious pain perception is highly nonlinear. This could also account for the fact that numerous studies have found poor correlation between sensitivity testing by barostat procedure and IBS symptom severity (55, 58, 72, 83, 111).

Augmentation of the sensory response: postprandial visceral perception. Visceral sensitivity studies are generally performed in the fasted state. However, bowel symptoms in IBS patients often exacerbate after food consumption (98). There is ample evidence that GI nutrient content may either be the source of or contribute to abnormal, painful, or uncomfortable visceral perception in IBS (87). Several groups have reported on the effect of nutrients on visceral sensitivity in IBS patients. Rectal and colon perception thresholds in IBS patients have been shown to be lowered following intraduodenal infusion of fat (21, 96). Furthermore, a liquid meal was shown to enhance rectal sensitivity in IBS (68, 97, 109), with a fatty meal producing more pronounced effect compared with a carbohydrate meal (97). These results could represent normal nutrient sensing, with which rectal distensions interact abnormally, resulting in an augmented perceptual response. On the other hand, they may also suggest a malfunction in intestinal nutrient sensing resulting in increased visceral perception following a meal. It has been postulated that enterendocrine cells in the intestinal mucosa respond to changes in luminal contents by releasing mediators such as cholecytokinin and 5-HT, which in turn activate specific receptors on primary afferent nerve terminals. Cholecystokinin, a peptide released in response to intake of fat, has been postulated to sensitize mechanoreceptors because it has been demonstrated to increase rectal nociception in healthy volunteers (90). 5-HT, on the other hand, could also be a mediator of meal-induced nociception as higher postprandial levels of 5-HT have been reported in IBS patients (9). Furthermore, Simrén et al. (99) demonstrated that antagonizing 5-HT3 receptors reduces lipid-induced colonic hypersensitivity. Therefore, testing of visceral sensitivity in IBS patients in a postprandial state can also have an added value in assessing visceral perceptual status.

Nonmechanical stimuli: electrical stimulation. Besides mechanical stimulation, a number of other stimulation modalities have been used to assess visceral sensitivity. Transmucosal electrical nerve stimulation, for instance, induces perception by nonspecific stimulation of afferent pathways without the involvement of a specific receptive unit. Transmucosal electrical stimulation of the jejunum in healthy controls and IBS patients resulted in subjective sensations similar to those elicited by jejunal balloon distension. However, whereas IBS patients had lower sensory thresholds to mechanical stimulation of the small intestine compared with controls, thresholds to electrical intestinal stimulation were similar in IBS patients and controls. On the other hand, altered viscerosomatic referral areas were seen in response to both types of jejunal stimulation (1). A decrease in sensory thresholds in IBS has also been demonstrated to electrical stimulation of the rectum (88). A disadvantage of using electrical stimulation is the nonspecific activation of nerve endings, resulting in neural discharge from nerves, which might not otherwise be activated during nociceptive processes.

Thermal stimuli. Thermal stimulation of the gut can be provided via intraluminal bags by recirculating water at adjusted temperatures. Thermal stimuli are also potentially applicable in conjunction with mechanical and electrical stimuli for the evaluation of visceronociceptive responses. It has been demonstrated that, similarly to mechanical stimuli, IBS patients also demonstrate lower thresholds to thermal stimulation of the rectum (66).

Chemical stimuli. Chemical stimuli have been used widely to study pain mechanisms. Capsaicin is commonly applied as a sensitizing stimulus in studies of somatic pain. Hammer et al. (45a) demonstrated that intestinal capsaicin infusion resulted in a sensation of warmth and burning, in addition to the generation of cramps. This cramping sensation was independent of changes in bowel motility or biomechanics and the authors concluded that capsaicin was acting directly on mechanosensitive afferents. In addition to capsaicin producing these unique sensory characteristics, it was also noted that the time to first sensation of a second capsaicin infusion was significantly
reduced, suggesting the induction of peripheral sensitization of capsaicin-sensitive afferents (45a). Capsaicin has therefore also been successfully used to evaluate chemical hypersensitivity in functional dyspepsia (42). On the other hand, drawbacks of chemical stimuli include relative long latency time to onset of effects, compared with other stimulation modalities, and the fact that these effects are often not reproducible (79). Therefore, validation of results using chemical stimulation in IBS is still warranted.

**Brain Imaging**

In the past decade, accumulating evidence on visceral nociceptive processes has emerged from results of brain imaging studies. Brain imaging techniques rely on the principle that increased neuronal activity within the brain is associated with increased metabolism and regional cerebral blood flow (rCBF). Comparison of images recorded during resting and active periods following administration of a nociceptive stimulus, for instance rectal distension, reveals regions of increased cortical activity, and these measures have been used to increase understanding of the functional properties of the brain.

**fMRI.** The most commonly used brain imaging entity, functional magnetic resonance imaging (fMRI), is based on the difference in the magnetic properties of oxygenated and deoxygenated blood, specifically the difference in decay time of the magnetic resonance signal from oxyhemoglobin and deoxyhemoglobin, referred to as the blood oxygenation level-dependent technique. This difference in signal characteristics allows for the localized detection of rCBF. These regional changes in blood flow, volume, and oxygenation of hemoglobin derive from changes in neuronal activity and, thus, regions of activation may be identified by subtracting rCBF during a control condition from blood flow during a stimulus condition or by correlating regional blood flow with the intensity or time course of a stimulus or its perception (107). A major advantage of fMRI is that it is noninvasive and noncumulative, allowing subjects to be studied repetitively. fMRI has an excellent spatial resolution (2–5 mm), especially in the more superficial layers. Limitations are seen in the deeper structures, such as the brain stem and thalamus, owing to pulsation artifacts. The temporal resolution is poor (1–3 s), and therefore fMRI is not a specific tool for investigating the neuronal activity directly related to the painful stimuli. Since the exogenous brain activity takes place within the first 150 ms poststimulus, the response may miss the fast-occurring activity and model, instead, the endogenous activity rather than brain responses due to pain.

**PET.** Positron emission tomography (PET) scanning utilizes biological molecules synthesized with radiolabeled isotopes, such as 15O-labeled water to monitor regional changes in cerebral blood flow. The most commonly used in visceral pain research is H215O. In the normal brain, rCBF is closely coupled to regional cellular metabolism; therefore 15O-labeled water serves as a reliable monitor of cerebral interneuronal activity (47). Alterations in rCBF can then be mapped to specific intracerebral structures and foci, using either MRI or a computerized stereotactical method. PET has excellent spatial resolution (2–5 mm) and allows the operator to tag important biological molecules that bind to targeted receptor groups or glucose metabolism in active neuronal tissue. PET is superior in imaging radiopharmaceuticals and/or other ligands because it offers the ability to study receptor distribution and explore the site of action. This also allows an insight into the organization of functional networks in the brain, which cannot be achieved merely morphological investigations or regional blood flow analysis. However, the temporal resolution of PET is poor (minutes), and since the subject receives a considerable dose of radiation, group analyses are needed for meaningful results, interpreting endogenous brain activity following pain rather than exogenous brain activity following painful stimulation. Another major disadvantage is the expense and limited availability of a PET scanner.

**Brain imaging techniques: validity remains to be confirmed.** Several brain imaging studies have demonstrated altered activation patterns in IBS following rectal distension compared with healthy controls (94, 106). Following initial excitement, given the relative novelty of the technique in studying visceral pain, a number of questions remain regarding the validity of these testing modalities. These modalities rely on observing between-scan or between-session differences that are attributed to changes in the experimental paradigm, for example measurements at baseline, during rectal distension, or during anticipation of such stimulus. However, changes occurring in brain activity between sessions can be attributed to many other factors including nonsystematic variations in the scanner’s acquisition characteristics, variations in head orientation, movement, and psychophysiological effects such as the level of arousal that can vary from session to session (27). In fact, Coen et al. (27) demonstrated a decrease in perceived stimulus intensity due to habituation over three different sessions in healthy volunteers using esophageal stimulation by fMRI. Another study by Naliboff et al. (77) examined perceptual and brain activity responses to rectal distensions in IBS and healthy controls using H215O PET six times over a 12-mo period. Interestingly, it was found that perceptual rating normalized over the 12 mo of the study, whereas IBS symptom severity did not, indicating decreased vigilance. In response to rectal distention, stable activation of regions of the homeostatic afferent network (including thalamus and insula) was observed over the 12-mo period, while activity in the emotional arousal network decreased. These findings indicate a differential habituation response to repeated rectal distensions during this testing procedure over these distinct functional networks.

A limited number of studies have evaluated brain activation responses to different treatments in IBS. Morgan et al. (76) reported on the effect of low-dose amitriptyline on rectal distension-induced brain activation combined with a psychological stressor in 19 women with painful IBS using fMRI. Although decreased activation was demonstrated in the pACC when applying the psychological stressor, no effect of amitriptyline was found on symptoms or distension alone. Berman et al. (10) reported on the effects of a 3-wk alosetron treatment in 49 nonconstipated IBS patients using H215O PET. Treatment was associated with reduced blood flow in the amygdala, the prefrontal cortex, and the pontine region, but not in the homeostatic afferent network. Furthermore, these changes were only observed at baseline and during expectation, not during rectal distension, suggesting an effect on the arousal network, rather than those associated with primary processing of sensory input. A small study by Lackner et al. (60) using H215O PET investigated the effect of cognitive behavioral therapy in six IBS patients. Reductions of regional flow in the pACC and the...
parahippocampal gyrus were observed, accompanied by improvement in GI symptoms and psychological functioning. A recent study demonstrated that treatment with neurokinin-1 antagonist resulted in reduced activation in the emotional arousal network, which was paralleled by an improvement in mood and pain rating (105). Similarly, normalizations between key regions of the emotional-arousal circuit in patients were shown following treatment with a corticotropin-releasing factor-1 antagonist during expectation of abdominal pain, in particular in patients with high level of anxiety (51). Although studies using classical analgesics are still lacking, it appears that brain imaging is more sensitive in detecting changes in the emotional-arousal network, responsible for modulatory effects of pain sensation, rather than in the homeostatic afferent network. However, additional studies will be necessary to confirm the robustness of measuring brain activation patterns to assess therapeutic efficacy in IBS, especially in patients with comorbid anxiety.

Another limitation of brain imaging studies is their poor correlation with symptoms. A recent fMRI study found significant alterations in brain activity patterns comparing normosensitive and hypersensitive IBS patients, even though no significant differences were observed between the two groups in terms of GI symptoms (61). This questions the fact whether changes in brain activity, as reflected by imaging studies, show any correlation with symptom severity.

**Neurophysiological Recordings To Assess Visceral Nociception**

**CEP.** Cerebral evoked potentials (CEPs) are the electrical manifestation of the brain’s response to an external stimulus. This technique involves the brief presentation of a sensory stimulus, which is time and phase locked to the recording of the electroencephalogram (EEG) via surface electrodes placed on the scalp. Stimulus-specific CEPs occur at a fixed time after each stimulus, whereas other brain activity occurs randomly. CEP amplitudes are typically lower than the amplitudes of spontaneous EEG; but the CEP amplitudes become higher during the averaging process, and most of the background noise cancels out. To extract the CEPs with a good signal-to-noise ratio, a number of stimulations are presented at a certain frequency, and these stimulation trials are then cleaned for artifacts and averaged. The main CEP peak components are termed P1, N1, P2, and N2. Neurophysiological convention describes negative potentials as upward deflections (N1 and N2) and positive potentials as downward deflections (P1 and P2). Each peak in the CEP represents a synaptic event associated with the synchronous transmission of afferent information from one group of neurons to another. Latency refers to time (in ms) from the stimulus trigger to the peak component. Amplitude is defined as the voltage difference between consecutive CEP peaks. Early recorded CEP complex (~100 ms) represents stimulus-specific activation of the primary or secondary somatosensory cortex and insula and depends on transmitted afferent signal strength intensity. P1 latency represents the time interval between stimulus and activation of these regions. In healthy subjects, as the perceived stimulus intensity increases, there is a concurrent reduction in latency and an increase in amplitude of the CEP components (50). Cortical activity of ~250 ms or more after visceral stimulation reflects brain endogenous processing of the afferent information and represents a more general “arousal”-type response. Hobson et al. (49) established the following relationship between CEP morphology and pain thresholds: 1) Afferent hypersensitivity refers to pain perception at relatively low stimulus intensity with a normal-latency P1 component. 2) Hypervigilance refers to pain perception at low stimulation intensity, but with prolonged-latency P1 responses (indicating that afferent signaling pathways are not sensitized; instead, patients were “amplifying” normal-intensity stimuli once the stimulus reached the brain). 3) Hyposensitivity refers to maximum stimulus application (limited by the stimulator and safety reasons) without eliciting a normal CEP response. On this basis, it has been proposed that CEP can neurophysiologically distinguish noncardiac chest pain patients using esophageal stimulation into altered afferent transmission and increased secondary processing (49). More recently, IBS patients were also characterized according to their neurophysiological profile by recording CEPs following rectal stimulation. An overwhelming majority (49%) had normal pain threshold and normal afferent sensory transmission. Only a minority (24%) of the patients afferent hypersensitivity, 12% were hypervigilant, and 15% were even hypoesthetic to rectal electrical stimuli (6). This study, however, did not assess the relationship of CEP responses to IBS symptom severity.

Other groups (24, 100, 118) have observed shorter latencies in IBS patients compared with healthy controls. This was further shortened following meal intake (24) or thermal stress (drinking cold water) (118) in IBS patients, whereas no effect was observed in healthy controls. This decreased latency was suggested to be caused by an increase in the number of rectal afferents recruited and their higher conduction. However, no evidence exists that the conductance velocity of these otherwise silent afferents would differ from the preexistent population of afferent nerves. These silent afferents could rather account for the larger amplitude of the evoked potentials observed in IBS (100).

It is also to be noted that there are considerable discrepancies between the studies that have employed CEP, which makes comparison somewhat troublesome. This is probably due to methodological differences. Both electrical and mechanical stimuli have been used to generate neural responses. Electrical stimulations have the advantage that they allow precise latency measurements; in case of balloon distension, the responses are preceded by a variable latency of 50 ms due to balloon inflation. On the other hand, electrical stimuli can provoke contractile activity during and after stimulation, which causes increased variability in the responses recorded.

Overall, CEP is an intriguing method to assess visceral perception because it has excellent temporal resolution and potentially allows discrimination between peripheral and central components of nociception. Furthermore, CEPs recorded following rectal distension are perfectly reproducible in the same subject (30, 67). Although surrogate measurements of visceral pain can be obtained from other visceral function studies, such as barostat or metabolic imaging techniques, evaluation of pain by use of these tools has several limitations, including anticipation, habituation, and lack of non-stimulus-specific activity. CEP, on the other hand, potentially provides an objective measurement of the pain response and does have the required temporal resolution, with early potentials indica-
tive of peripheral afferent input and later potentials of central processing, thereby allowing discrimination of the origin of underlying pathology. However, knowledge on CEP responses in IBS is still limited. It remains to be established, furthermore, which parameter of CEP recordings (e.g., peak latency or amplitude) are of clinical relevance, in particular in terms of detecting visceral hypersensitivity and defining response to a certain therapy (25). Validation of the technique is warranted to legitimize its role in assessing visceral perception, such as definition of the relation of the CEP response to symptom severity. Currently, research involving registration of CEP is being practiced in only a few laboratories, and further research is necessary to validate findings and address the observed discrepancies in results.

MEG. Magnetoencephalography (MEG) is a noninvasive neuroimaging modality that allows detection of cortical neuronal magnetic activity arising from postsynaptic current flow in neurons, as opposed to metabolic changes, which are considered secondary markers of neural activity. Visceral stimulation leads to cortical activation that generates minute magnetic fields, which are 1/8 of the magnetic field of the Earth (20). These can be detected with highly sensitive sensors known as SQUIDs (superconducting quantum interference devices), which are contained within a helmetlike apparatus that covers the subject’s head (115). By mathematically modeling the topographic distribution of the magnetic field pattern on the scalp, the three-dimensional location of the neurons generating the signal can be inferred. As well as having comparable spatial resolution to PET and fMRI, MEG has a superior (millisecond) temporal resolution that permits a more dynamic interpretation of brain area activation after visceral stimulation. This latter quality and the technological advances allowing deeper regions of the brain to be studied offer the exciting prospect of providing a second-by-second evaluation of pain pathway activation and patterns of aberrant pain processing.

In CEP, the electrical signal recorded is distorted by the structures that lie between the cortical source and the recording electrode, making the localization of the neural correlates of the response difficult, therefore resulting in poor spatial resolution. Unlike the electrical signal recorded with CEP, in MEG the magnetic field generated by an active group of cortical neurons passes through these structures without attenuation. Because the early MEG responses are stimulus specific, this type of approach has a greater potential for becoming a robust and objective outcome measure to study GI sensory processing. MEG is especially sensitive to the tangential activity in the cortex. A technical limitation of MEG, however, is that it is less able to resolve the radial current, which makes imaging in deeper regions of the brain troublesome. Magnetic fields generated by subcortical neurons are not readily detectable because, unlike cortical neurons, which are arranged in columns, many of the subcortical neurons are arranged in a spherically symmetric manner so that the magnetic fields emitted are mutually cancelled. Currently, MEG is not widely available; systems are only present in specialist centers. Also, a very limited amount of studies have investigated visceral nociception using MEG (101), with no studies published to date in IBS.

Recording spinal reflex responses: the RIII reflex. Apart from registering changes in neural activity using either brain imaging or EEG/MEG, assessment of reflex responses to noxious stimulation also offers an objective marker of spinal nociceptive processes, in particular. The flexion reflex, also known as the nociceptive withdrawal reflex and described first by Sherrington (95), is a polysynaptic and multisegmental spinal reflex that induces a complex flexion synergy of the ipsilateral limb following a cutaneous stimulus. The mechanical response is a rapid withdrawal movement that constitutes a protective mechanism against possible limb damage. The flexion reflex can be elicited experimentally by the electrical stimulation of a cutaneous sensory nerve (most often the sural nerve) and consists of the activation of an ipsilateral flexor muscle (usually the biceps femoris), which is recorded using standard electromyographic equipment. Hugon (53) distinguished two excitatory components of this reflex having latencies of 40–60 ms (RII) and 85–120 ms (RIII) and explained these as due to activation of different cutaneous group A-fiber afferents (Aβ and Aδ, respectively). The RII reflex is a less stable and poorly investigated response, elicited at low nociceptive stimulation intensity. Therefore, the threshold of the RII is significantly below the pain threshold and is not seen in all subjects (53). On the contrary, the RIII reflex, a widely investigated and ever-present response, is considered to correspond to the intensity of the stimulus (six- to sevenfold the detection threshold) (75). Evidence exists that the threshold of the RIII reflex, defined as the average minimal current that elicited the reflex response, corresponds to the pain threshold and that the size of the reflex is related to the level of pain perception (91). Therefore, the RIII reflex has been proposed to be a useful tool in assessing nociception, free of the subjective nature of verbal reporting and subsequent report bias.

Several studies have investigated the influence of rectal distension on the RIII reflex in humans, offering further scope for studying the spinal projections from viscera afferents and their correlations with the nociceptive pathways. Bouhassira et al. (14) showed that rapid rectal distensions facilitated the RIII reflex recorded from the lower limb, but at the highest distension level (i.e., 40 mmHg) facilitation was followed by inhibition. In contrast, slow-ramp distensions induced gradual inhibition of the RIII reflex that correlated with both the distension volume and the visceral sensation. It has been proposed that reflex inhibitions were probably related to the activation of spinal and/or supraspinal pain modulation systems, possibly through a DNIC-like mechanism. One plausible explanation for the facilitatory effects following rectal distension, which were not observed when the reflex was recorded at the upper limb, was that they were caused by the convergence of rectal and RIII afferents at the same levels of the spinal cord. Furthermore, the authors suggested that the opposite effects of rapid- and slow-ramp distensions on the RIII reflex could be due to the selective activation of different populations of rectal mecanoreceptors.

In a later study employing the same methodology in IBS patients, it was demonstrated that the RIII reflex was significantly facilitated during slow-ramp distension (as opposed to the inhibition seen in healthy controls). Inhibitions induced by rapid distensions were significantly reduced compared with healthy controls (28). These results suggest a failure of descending antinociceptive control, leading to hyperexcitability of spinal nociceptive neurons in IBS. However, factors such as sustained attention, anticipation of pain, sustained muscle contraction, the type of which may occur when contracting the
Measurement of Autonomic Dysfunction in IBS

Experimental data indicate that increased sympathetic activity magnifies perception of gut stimuli (54). In humans, cardiac sensitivity to the baroreflex [CSB, afferent limb of the autonomic nervous system (ANS)] and cardiac vagal tone (efferent limb of the ANS) have been used to measure responses related to ANS, reviewed recently by Mazurak et al. (73). A study by van der Veek et al. revealed that IBS patients exhibited increased baseline CSB relative to healthy controls (110). CSB was also measured following visceral afferent stimulation by use of mild and intense rectal distension. During intense stimulation, the CSB increase observed following mild stimulation persisted in controls, whereas it declined to baseline in IBS. The authors suggested that this difference was due to altered information processing in the brain stem, more specifically in the nucleus of the solitary tract. More recently, Spaziani et al. (102) were not able to reproduce the findings, showing lower CSB in IBS compared with controls. This can be explained by the fact either that changes in ANS function are not uniformly present in IBS or that the techniques to record these alterations are still suboptimal. A clear disadvantage of this approach, for instance, is that it requires offline analysis of data acquired over a 60- to 90-s period, which limits the investigation of an otherwise dynamic regulatory process. This poorer temporal resolution masking fluctuations may result in a false impression of a solitary rise or drop in the ANS measure of interest. New advances in technology may give us the opportunity to expand on these experiments in a degree of detail not previously possible.

Measuring Visceral Pain in IBS: Where Do We Stand Now? Opportunities and Pitfalls

Currently, a considerable number of methods are employed to assess visceral perception in IBS (see Tables 1 and 2 for comparison of the different techniques). Over the past decades, rectal distensions in combination with verbal reporting have emerged as a robust, valid, practically applicable, and widely accepted method to test visceral perception in IBS. Increased sensitivity to rectal distension has been suggested to represent a biological marker for IBS (74). Also, several additional approaches have been applied to increase the diagnostic sensitivity of the barostat, including meal stimuli (68). However, not all IBS patients represent this hypersensitivity to rectal distension. Furthermore, the invasive nature of this barostat method has somewhat withheld the widespread application of rectal distensions in clinical practice. Moreover, a number of recent observations have implicated that subjective reporting during rectal distension can largely be influenced by psychological factors, such as vigilance and anxiety. IBS patients have in fact been shown to have a psychological tendency to report urge and pain rather than increased neurosensory sensitivity.

| Table 1. Comparison of methods used to record responses to rectal distension in irritable bowel syndrome |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Test-Retest Reproducibility** | **Specificity/Sensitivity in Detecting Visceral Hypersensitivity** | **Correlation with Symptoms** | **Responsiveness to Treatment** |
| Verbal reporting (e.g., VAS) | Highly consistent (31, 45) | 95.5% sensitivity, 71.8% specificity at 40 mmHg of distension (15) | Moderate (opioid analgesics: 34, 65) |
| Brain imaging | Habituation (decreased hypervigilence) following repeated testing (27, 77) | ND | Moderate (No classical analgesics examined) |
| CEP | Excellent (30, 67) Coefficient of variation <0.1% for N1 and P1 following esophageal stimulation (50) | ND | Moderate (No classical analgesics examined) |
| RIII reflex | Excellent Coefficient of variation 16% for pain threshold following electrocutaneous stimulation (75) | ND | Moderate (No classical analgesics examined) |
| MEG responses | ND | ND (Lack of definition of proper readout) | ND |
| ANS responses | Poor (inconsistent results) (73) | ND | ND |

ND, not determined; VAS, visual analogue scale; CEP, cerebral evoked response; MEG, magnetoencephalography; ANS, autonomic nervous system; CRF-1, corticotropin releasing factor-1; IBS, irritable bowel syndrome; BOLD, blood oxygen level-dependent. References are shown in parentheses.
(36). This makes the identification of patients who have true visceral hypersensitivity, without the interference of subjective reporting, especially challenging. This is considerably true in a patient group with a high incidence (50–80%) of psychological disorders such as heightened anxiety, depression, somatization, dysthymia, and panic disorders have been reported (38).

As for rectal distension and verbal reporting, almost 40 years have passed since its first introduction by Ritchie (87a), allowing extensive characterization of the method. The use of brain imaging techniques in the study of visceral pain, on the other hand, is a relative novelty. Although these techniques represent an unparalleled opportunity to observe cortical processes during nociception, up to now results of brain imaging studies in IBS have varied considerably or have been contradictory. This imposes a burden in establishing alterations in brain activity as an objective and reliable measure of visceral perception. In fact, these techniques potentially raise more questions than answers. Reaching a consensus about observed changes has proven to be difficult to the variety of experimental paradigms (including subliminal, percept related, and stimulus related), analytic techniques, reporting practices, and heterogeneous study populations (including patients with and without visceral hypersensitivity). Furthermore, it has become apparent that responses observed during brain imaging are also largely influenced by psychological factors. This questions the idea that responses observed during brain imaging are also largely influenced by psychological factors, with a higher tendency of patients with functional gut disorders to report pain.

Much of this difficulty lies in the complex nature and intrinsic heterogeneity of the condition. Brain imaging studies have also showed extensive activation in the arousal network, even in the absence of the actual stimulus. Therefore, it can be assumed that unless specific study paradigms are designed to differentiate brain responses to anticipation from the actual stimulus, brain responses during distension would also largely be influenced by the anticipation response. This distinction is especially difficult as these processes are functionally distributed in the same neural circuits.

Second, delineation between different mechanisms involved in pain generation in individual patients is necessary to determine therapeutic strategies. Following initial excitement of the clear demonstration of altered activation patterns in brain imaging studies, it remains unclear whether abnormal central activation patterns seen in brain imaging studies are related to 1) enhanced selective attentional processes (hypervigilance), 2) compromised endogenous pain inhibition system or facilitation of central pain processing at spinal or supraspinal level, or 3) normal processing of pathological visceral input from the periphery due to peripheral sensitization. Recent advances in electrophysiological recordings have provided very intriguing results with respect to the identification of these different mechanisms in this heterogeneous population of patients; however, these results still await validation and characterization. Future research will have to establish whether these neurophysiological responses can become legitimate and objective measures for visceral hypersensitivity in IBS. Because pain is a conscious feeling, the ultimate goal in pain imaging will be to follow the pain stimulus throughout the neuraxis and to identify the locations of altered nociceptive processing, which is a prerequisite for adequate therapeutic correction.

Third, a further challenge in visceral sensitivity testing is that currently used methods only poorly correlate with symptoms. Poor correlation has been found between perception thresholds to rectal stimulus and symptom severity (83, 111), as

### Table 2. Comparison of brain imaging and neurophysiological techniques

<table>
<thead>
<tr>
<th>Method</th>
<th>Temporal Resolution</th>
<th>Spatial Resolution</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMRI</td>
<td>1–3 s</td>
<td>2–5 mm</td>
<td>Safe (no radiation)</td>
<td>Artifacts produced by pulsation, interference of endogenous brain activity</td>
</tr>
<tr>
<td>PET</td>
<td>40–60 s</td>
<td>2–5 mm</td>
<td>Allows receptor studies</td>
<td>Radiation, costs, limited information on anatomy, interference of endogenous brain activity</td>
</tr>
<tr>
<td>CEP</td>
<td>100 ms</td>
<td>poor</td>
<td>Safe and inexpensive</td>
<td>Time-consuming, limited availability, lacking validation, Considerable signal distortion</td>
</tr>
<tr>
<td>MEG</td>
<td>100 ms</td>
<td>2–5 mm</td>
<td>Allows dynamic interpretation of brain area activation after visceral stimulation</td>
<td>Limited availability, very limited knowledge on visceral pain testing, poor signals from deeper brain regions</td>
</tr>
<tr>
<td>RIII reflex</td>
<td>85–120 ms</td>
<td>poor</td>
<td>Safe and inexpensive</td>
<td>Lacking validation</td>
</tr>
</tbody>
</table>

fMRI, functional magnetic resonance imaging; PET, positron emission tomography; CEP, cerebral evoked potential; MEG, magnetoencephalography.
as well as between changes in brain responses to rectal stimulation during repeated stimulation and associated changes in symptom severity (78). This implies that changes observed during sensory testing using administration of an acute stimulus might not even relate to the generation of chronic pain symptoms. Therefore, a further provision for exploring novel therapeutic entities will be providing proof that symptoms are attributed to altered sensitivities, which can be tested clinically, and that therapies aimed at the correction of hypersensitivity result in clinical benefit (22). Because visceral hypersensitivity remains a paramount clinical phenomenon observed in IBS, methods to assess visceral perception, including the barostat approach and novel imaging techniques, have prompted further interest to unravel mechanisms of altered pain processing in IBS. Addressing the methodological shortcomings will potentially result in the identification of a robust objective clinical marker. Multimodal approaches, using the combination of verbal reporting as well as hemodynamic and electrophysiological responses for instance, have the potential to compensate for the shortcomings of the individuals’ methods. This will allow us to further elucidate visceral pain mechanisms and indeed open new horizons in the treatment of chronic pain in IBS.

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