5 Lessons Learned from Visceral Sensory Stimulation: Implications for Treatment of Chronic Abdominal Pain

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Introduction

Abdominal pain is of frequent occurrence, even in the normal population, and it is probably the most prevalent symptom in the gastroenterology clinic. Consequently, characterization of gut pain is fundamental in the diagnosis and assessment of organ dysfunction, and optimal treatments will only be achieved on the basis of a better understanding of underlying pathology and pain mechanisms. In the clinical setting, many patients with chronic abdominal pain suffer from comorbidity such as nausea, narcotic addiction, physical and emotional disability, and malnutrition. Therefore, a detailed characterization of pain symptoms is often difficult to obtain and is often blurred by symptoms from the associated comorbidities as well as medication. This is particularly problematic when underlying pain mechanisms are under investigation. In order to bypass this problem, experimental pain models based on quantitative sensory testing (QST) can be used [1–3]. QST provides information on sensory function at the peripheral and central level of the nervous system by recording subjects' responses (subjective or objective) to different external stimuli of controlled intensity. The primary advantages of QST are that a pain stimulus can be controlled, delivered repeatedly, and modulated, and that the responses can be assessed qualitatively and quantitatively with psychophysical, neurophysiological, or different imaging methods—Fig. 5.1. The methods have proven to be an important instrument to characterize basic physiology as well as mechanisms underlying pathological pain disorders [1–3]. The interest in human *visceral* QST has increased rapidly during the last decade, and also in gastroenterology the focus has been on developing methods for experimental induction and assessment of pain.

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Experimental Visceral Pain Stimuli

The natural origin of visceral pain is not fully understood, although a variety of innate stimuli are clearly associated with pain from the viscera. Naturally occurring visceral stimuli are distention of hollow organs, ischemia, inflammation, spasms, and traction of the gut. Also, thermal stimuli (heat and cold) may provoke pain from the viscera although (apart from the esophagus) this seems not to occur under normal physiological conditions [4].

The ideal experimental stimulus to elicit gut pain in humans should mimic innate visceral stimuli, be minimally invasive, reliable in test–retest experiments, and quantifiable. The response to the stimulus should increase with increasing stimulus intensity and preferably the pain should reflect observations in diseased organs by evoking phenomena such as allodynia and hyperalgesia [5, 6]. The different methods currently available for visceral sensory stimulation are:

- Electrical stimuli
- Mechanical stimuli
- Thermal stimuli
- Chemical stimuli and models evoking visceral hyperalgesia

Ischemic stimuli are difficult to quantify in human and is normally not used as a direct stimulus. In the following sections, the individual pain stimuli most widely used for visceral QST and experimental-evoked hyperalgesia are briefly discussed.

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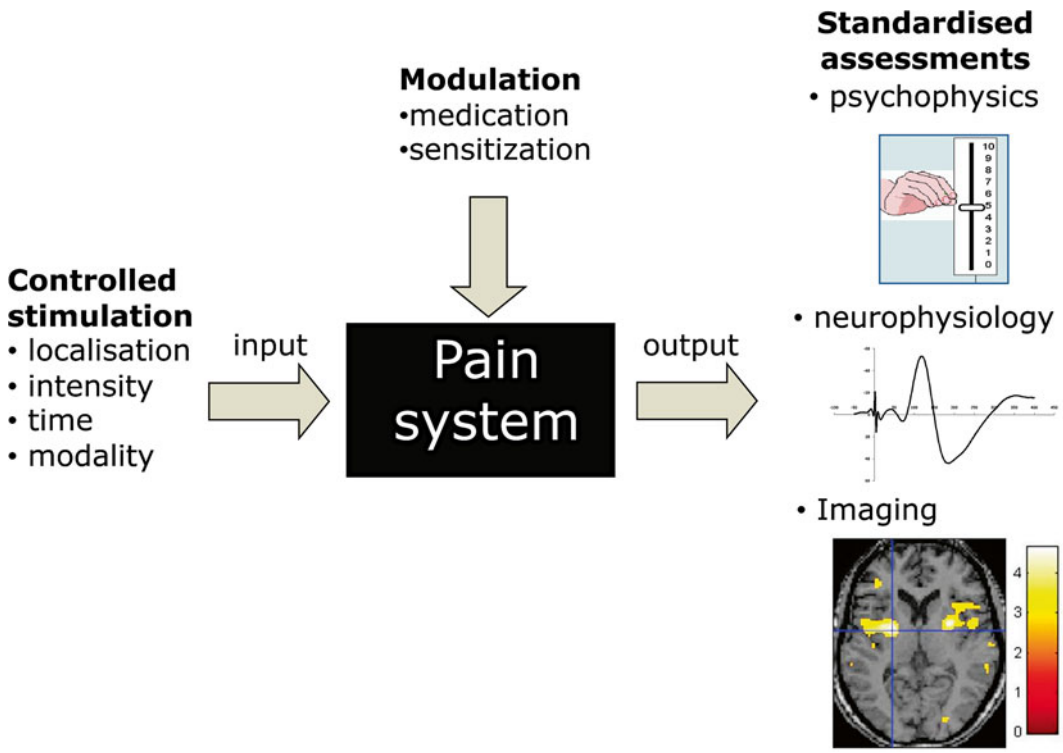

Fig. 5.1 The concept of experimental pain. The pain system can be considered as a "black box" between the experimental stimulation (input) and the response (output). When input and output are reproducible, it is possible to reveal differences in pain processing between, e.g., healthy volunteers and patients. Furthermore, modulation of the pain system is possible through various mechanisms (e.g., medication, modulation, or sensitization) and may provide additional information

Electrical Stimulation

Depolarization of visceral nerve afferents by electrical current has been widely used as an experimental stimulus of the human gut. The electrical stimuli have proved to be safe in all parts of the gastrointestinal (GI) tract and are easily controlled over time. As the stimulus by-pass peripheral receptors in the gut wall, the method is used to characterize afferent transmission and central processing of visceral stimuli [1–3, 7]. A major challenge of visceral electrical stimulation is varying electrode contact with gut mucosa. Integration of the electrical stimulation device and a biopsy forceps of an endoscope provide an elegant solution to this problem and allows application of stimuli in well-defined areas throughout the GI tract with high spatial precision.

Mechanical Stimulation

The mechanical properties of the gut are important for its function as a digestive organ and it contains numerous mechanoreceptors distributed mainly in the muscle layers of the gut [8]. Mechanical stimulation of the gut is typically done by distension of a balloon positioned in the segment under investigation. Widely used methods are computerized systems such as the "Barostat," where balloon pressure and volume can be strictly controlled during distension and thereby transmit a controlled mechanical stimulus [9]. The major advantage of the Barostat system and similar pressure–volume-based methods are the relatively low costs and reliability, making it useful for routine purposes. However, the accuracy of these systems has been questioned mainly due to uncontrolled elongation of the balloon during distension in nonspheric organs such as the rectum. Accordingly, elongation and deformation of the balloon during distention may not reliably reflect mechanoreceptor activation. These problems may be overcome by calculation of the balloon radius and tissue strain using impedance planimetry or imaging-based methods such as ultrasound or magnetic resonance. In accordance with recent studies, strain of the gut is probably the most consistently mechanical parameter relating to mechanoreceptors activation and possibly the subjective sensory response [10]. However, the technical complexity of such systems has so far limited their use to advanced experimental GI research and they are not widely used in the clinical setting.

Thermal Stimulation

Short-lasting thermal stimuli of the human GI tract are believed to activate unmyelinated afferents in the mucosa through the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor. This is opposed to mechanical and electrical stimuli activating afferents in both superficial and deeper layers in the viscera [8]. Although thermal stimuli of the gut have been used to some extent in animal studies, temperature stimuli in the human GI tract have only been used in a limited number of studies. This has mainly been due to difficulties in controlling the temperature rate (being essential for control of nociceptor activation). However, new technologies for thermal stimulation of the GI tract have been developed. These are based on continuously recirculating of water inside a balloon with concomitant measurement of balloon temperature [11]. The model has been used in many studies unraveling pain mechanisms in patients and was recently modified for use in the lower gut (rectosigmoid) [7]. Based on this method, the temperature stimuli show a linear stimulus–response relationship, thus demonstrating validity of the model. However, uncertainty in pain assessments due to fast increase in temperature (2 °C/min) has been demonstrated and recently it was proposed that individual differences in reaction time could affect the accuracy of rating. Consequently, in future studies a slower temperature increase (0.2 °C/min) is recommended [12, 13].

Chemical Stimulation and Models Evoking Visceral Allodynia and Hyperalgesia

Inflammation of the gut generally leads to altered sensations including pain. This has been investigated experimentally in patients with, e.g., esophagitis [4]. Chemical stimulation of the GI tract more closely resembles clinical diseases and is believed to approach the ideal experimental visceral pain stimulus [14]. Most chemical stimuli are assumed to activate unmyelinated C-fibers. Following chemical stimulation, tissue injury generates release of multiple molecules acting synergistically to produce inflammatory responses and hyperalgesia. Acid stimulation is the most common used method to evoke such visceral hyperalgesia, although chemical stimulation with alcohol, bradykinin, glycerol, capsaicin, and hypertonic saline has also been used to induce gut sensitization [1–3]. To mimic the clinical situation experimentally, it may be necessary to use a mixture of chemical substances with diverse tissue effects. An example of such mixed chemical stimulation is seen in the combination of acid and capsaicin working through different cellular interaction sites. Accordingly, acid targets the TRPV1 receptor extracellularly, whereas the capsaicin targets the TRPV1 receptor predominantly intracellularly. The method has been applied in, e.g., the esophagus of healthy volunteers and provides a human model to study visceral hyperalgesia [12, 13]. Most studies on visceral hyperalgesia have demonstrated increased pain to one or more stimulation modalities after experimentally induced sensitization by chemicals. Also, the duration and magnitude of hypersensitivity has been shown to be related to exposure area and dose of the chemicals [15]. Although chemical stimulation and experimental induced hyperalgesia generally posses high reproducibility in test–retest experiments, it has been demonstrated that the hyperalgesic response to acid is variable comparing the first time a subject is exposed to esophageal acid perfusion with the second time [12, 13]. Therefore, it is recommended to have a training session, where the subjects are introduced and exposed to chemical perfusion in order to familiarize them with the stimulus.

Multimodal Visceral Stimulation

The major limitation of the existing human models for visceral pain stimulation is that they may not mimic clinical pain because they are based on single, short-lasting stimuli only partly involving the many mechanisms typically activated during diseases. Therefore, the basic neurobiological mechanisms in clinical pain may be different from those relating to an experimental stimulation and experimental visceral models mimicking more closely the clinical situation are needed. Such a model should be based on multimodal testing regimens in which different receptors and central nervous system mechanisms are activated. Hence, a test battery where different stimuli are used will increase the probability for activation of a range of relevant nervous mechanisms. Especially if the stimulation is relatively long lasting and includes modalities known to evoke peripheral as well as central sensitization of the nervous system, the likelihood that part of the model will mimic clinical pain is high despite the nonharmful nature of the stimulation. To fulfill these requirements, a multimodal testing approach has been developed for experimental stimulation of the gut—Fig. 5.2 [11].

Experimental Studies and Pathophysiology of Chronic Abdominal Pain

QST has been used as an attempt to explain the pathophysiology of both functional and organic disorders of the gut. It is generally the belief that the central component of the pain system plays a major role in functional disorders such as functional chest pain, functional dyspepsia, and irritable bowel syndrome (IBS). On the other hand, in organic diseases such as inflammatory bowel disease and chronic pancreatitis, the pain regulatory systems are intact and the

Fig. 5.2 The multimodal probe for electrical, mechanical, cold, warmth, and chemical stimuli. The probe has a bag for mechanical and thermal stimuli, the latter given by recirculating water. Electrodes for electrical stimuli are mounted on the probe above the bag. A side hole in the tube proximal to the bag allows perfusion with acid and other chemicals

balance between afferent activity and local/central pain inhibition is functioning differently. In the following section, selected methods to stimulate and assess the pain system in different examples of functional and organic diseases are highlighted.

In order to unravel abnormal pain processing, several pain assessment methods are available being more or less directly associated with the stimulus. These are for example:

- The subjective response using different rating scales
- The size and localization of the referred pain area
- Detection of viscero-visceral hyperalgesia
- The response to repeated stimulation (a proxy to wind-up or central integration)

The *subjective sensory response to QST* may reflect abnormal processing of the pain. Patients with functional pain disorders, such as functional chest pain and IBS, typically have hyperalgesia and allodynia to experimental stimuli of the organs thought to be diseases [16]. Only 40–60 % of the IBS patients show lowered rectal discomfort thresholds to mechanical stimulation, but when other perceptual abnormalities (altered referral pattern and increased intensity of sensations) were considered, 94 % of IBS patients had at least one abnormality [17]. In order to unravel disease pathogenesis, more advanced methods, such as the multimodal probe, can be used to detect sensory abnormalities. This approach has been used in patients with functional and organic diseases. As stated previously can the TRPV1 receptor be activated by a variety of stimuli, including acid (protons) and increases in temperature that reach the noxious range. Hence, patients with organic diseases, such as nonerosive and erosive esophagitis, were shown to have specific hyperalgesia to heat reflecting activation of the receptor by the natural acid reflux. On the other hand in patients with functional chest pain acid, there was a pathological response to experimental acid perfusion likely reflecting activation of central pain mechanisms [4]. In general, chronic tissue injury and pain has been associated with higher thresholds to mechanical stimulation in different regions of the GI tract. For example, chronic inflammation of the small bowel in patients with inflammatory bowel disease is associated with mechanical hypoalgesia of the rectum [18]. However, the pain response can vary according to the tissues that are stimulated such as seen in patients with chronic pancreatitis. This may reflect the complex pain mechanisms and interaction between sensitization and descending control systems [19, 20]—see also section about viscera-visceral hyperalgesia.

Referred pain is a normal phenomenon seen in clinical practice where pain originating from the viscera is also felt in somatic areas remote from the organ. Convergence between visceral and somatic afferents in the spinal cord seems to be of importance (Fig. 5.3). In organic diseases, it is believed that referred hyperalgesia of somatic tissues is caused by a normal process of central sensitization triggered by massive afferent visceral barrage [21]. However, in functional disorders, abnormal central processing of the afferent stimulation is likely of more importance. Hence, if the patients are properly instructed, the referred pain can be used as a proxy for the central changes. Experimentally, we have found that the referred pain area in healthy volunteers typically changed location after acid perfusion of the esophagus [1–3]. In patients with organic diseases such as those with gastro-esophageal reflux disease (GORD) and chronic pancreatitis, the referred pain area to stimulation of the esophagus and duodenum is increased in size and this is likely reflecting the increased afferent visceral barrage and subsequent activation of second-order neurons [4, 19]. In functional disorders, however, there seems to be a change in localization as well as an increased size of the referred pain area such as seen to experimental visceral stimulation in patients with functional chest pain, functional dyspepsia, and IBS [22].

Changes in the sensitivity and skin temperature in the referred pain area have also been shown in experimental studies of healthy volunteers [23, 24]. Correspondingly, abnormal superficial and deep sensations have been demonstrated in patients with renal stones, appendicitis, and cholecystolithiasis [25–27]. In patients with chronic pancreatitis

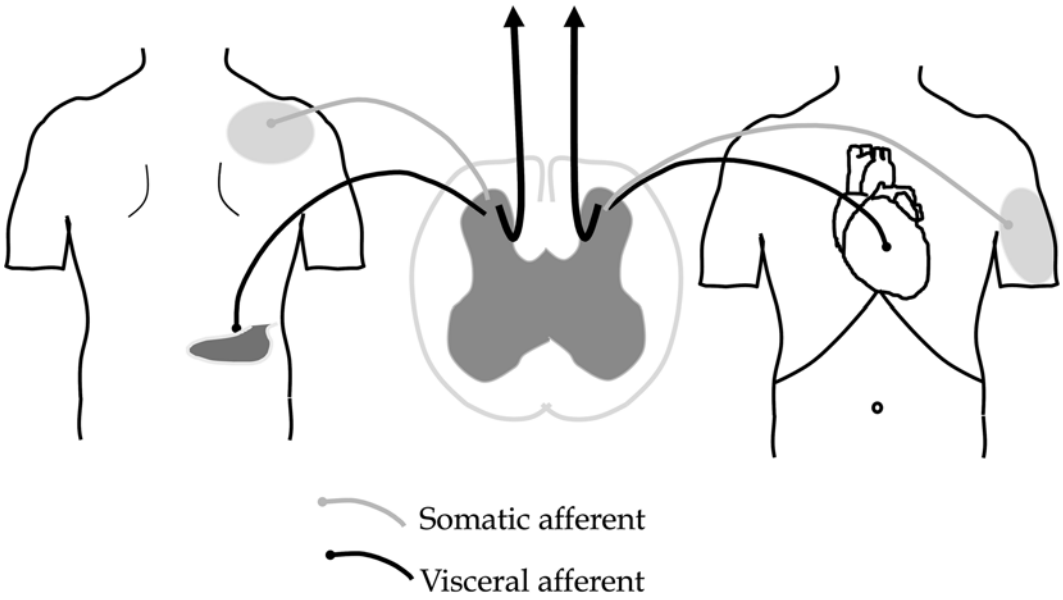

Fig. 5.3 Pain referral to somatic areas remote from the visceral organs is a common finding in GI diseases and known as "referred pain," e.g., pain referral to the right shoulder in acute cholecystitis. The underlying mechanism is related to convergence between visceral and somatic afferents in the spinal cord although in principal more complicated

sensory changes have also been seen in the corresponding "viscerotome" [28]. Such changes in localization and sensitivity of the referred pain areas may be a hallmark of diseased organs and if the experimental methods are improved they may serve as a biomarker of the disease.

Viscero-visceral hyperalgesia is a complex form of hypersensitivity probably explained by more than one mechanism. Since this phenomenon takes place between visceral organs which share their central afferent termination, it is plausible that central sensitization plays an important role [29]. Recently, human experimental studies support the role of viscero-visceral hyperalgesia in GI diseases. Acidification of the distal esophagus resulted in hyperalgesia in the proximal esophagus, and duodenal acidification was shown to induce esophageal hypersensitivity [30]. Recently, we showed that acidification of the esophagus in healthy volunteers involve widespread changes in the perception of experimental pain from remote organs such as the rectum [31]. The widespread visceral hypersensitivity in functional GI disorders (IBS, functional dyspepsia, etc.) may be due to this mechanism. As an example a marked reduction in colonic perception thresholds and alternation in the viscero-somatic referral pattern were seen in patients with IBS after lipid administration in the duodenum [32]. Viscero-visceral hyperalgesia may also explain the epidemiological findings in several clinical conditions with organic diseases such as an increased number of anginal attacks in patients with gallbladder calcinosis, and increased number of colics in dysmenorrheic patients with urinary calculosis [33]. Evidence for viscero-visceral hyperalgesia has also been provided in experimental studies of organic diseases, e.g., in patients with gastro esophageal reflux disease (GERD) where increased sensitivity to gastric distension was shown. Therefore, the frequent airway symptoms in GERD (often refractory to treatment with proton pump inhibitors) may not only be related to direct aspiration of the gastric refluxate, but vasovagal reflex mechanisms evoked by acid-related hyperalgesia may also be important [34].

Repeated stimulations: Sensitization of the spinal neurons is known to occur with prolonged or repeated stimulation ("wind-up" or temporal summation) of the peripheral afferents. Thus, temporal summation results in a short-lasting spinal cord sensitization that persists after discontinuing the peripheral stimulation. In the laboratory, this is perceived as increased pain to a series of stimuli with the same intensity.

Repeated electrical or mechanical stimuli to the small and large intestine in volunteers may cause increased sensation to subsequent stimuli, and this may be used as a model for enhanced central gain [1–3]. In functional pain Munakata et al. showed the importance of central mechanisms. In their study, patients with IBS developed rectal hyperalgesia following repetitive sigmoid distensions [35]. Paterson et al. [36] as well as studies from our group [4] also showed that repeated distensions conditioned the esophagus in functional chest pain patients resulted in higher pain scores. In organic diseases, repeated stimuli were also used to show the central amplification of pain in patients with chronic pancreatitis [37]. This stimulation paradigm can also be used to understand the changes in referred pain. If electrical stimuli are repeated over time, the pain and the area of referred pain increase progressively [23].

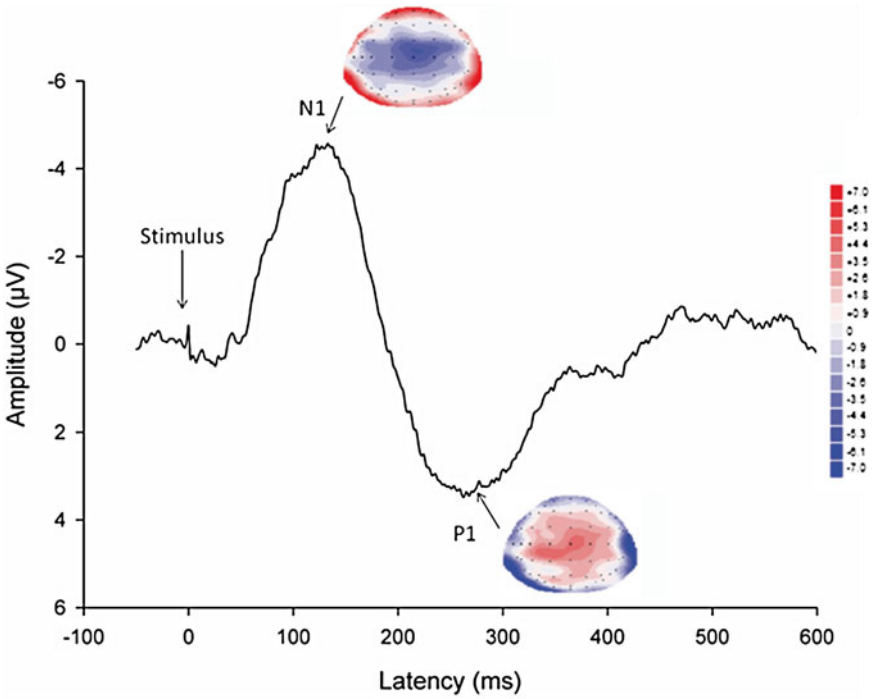

Fig. 5.4 A typical evoked potential (vertex-electrode) recorded after stimulation of the rectosigmoid junction in a healthy volunteer. Note the different peaks denoted N1 and P1, each defined by latency (ms), amplitude (μV), and a corresponding topographic map made from the 64 electrodes covering the head

QST can also be used to unravel pain mechanism at higher centers using electrophysiological and imaging methods. There are several possibilities, but the most used methods are as follows:

- The nociceptive reflex
- Electroencephalography (EEG) and magnetoencephalography (MEG)
- Imaging

The nociceptive (RIII) reflex is a spinal reflex that is elicited by painful stimulation of a sensory nerve. For example, stimulation of the sural nerve at the ankle evokes a flexion reflex that can be measured by quantification of the electromyographic response in the biceps femoris muscle. The connection from the primary afferents to the motor neurons is a polysynaptic pathway, which can be modulated by other afferent input, spinal neuronal excitability, and activity in descending control systems. Bouhassira et al. showed that tonic distension of the stomach and rectum resulted in inhibition of the reflex, whereas phasic mechanical stimuli of the rectum resulted in more complex modulation [38, 39]. Sensitization of the esophagus with acid resulted in a significant increase in the baseline reflex excitability, followed by a gradual inhibition during continuous distension of the organ [1–3]. Analgesics can modify the reflex and hence it may indirectly be used for basic and pharmacological studies of pain pathways in the GI tract [40].

The EEG monitors the brain activity to external stimuli directly in real time. The resting EEG has been used to unravel pain mechanisms in visceral diseases [41]. However, when a repetitive stimulus is applied and the cortical electrical activity is averaged (time-locked to the stimulus), the stimulus-evoked cortical potential (EP) can be extracted from the background electrical activity and is shown in shape of a waveform with different peaks (Fig. 5.4). Each peak in the EP represents a synaptic event associated with the transmission of afferent information from one group of neurons to another. The early peaks are supposed only to be influenced by the stimulation rate, intensity, and localization, and they reflect to a major degree the brain loci that process the pain intensity and localization [42]. EPs have been used to explain abnormal central pain processing in patients with functional disorders such as functional chest pain and IBS, suggesting an increased central nervous system response to visceral stimuli and reorganization of brain activation in the cingulate gyrus among others [43–45]. Studies have also suggested that different subgroups of patients with IBS exist such as those with short latency of the early EP components having sensitization of GI afferent pathways, and those with long latencies and enhanced late responses reflecting hypervigilance and increased affective processing [46].

Inverse modeling of the EPs can be used to identify the original electrical sources in the brain—for details see [47].

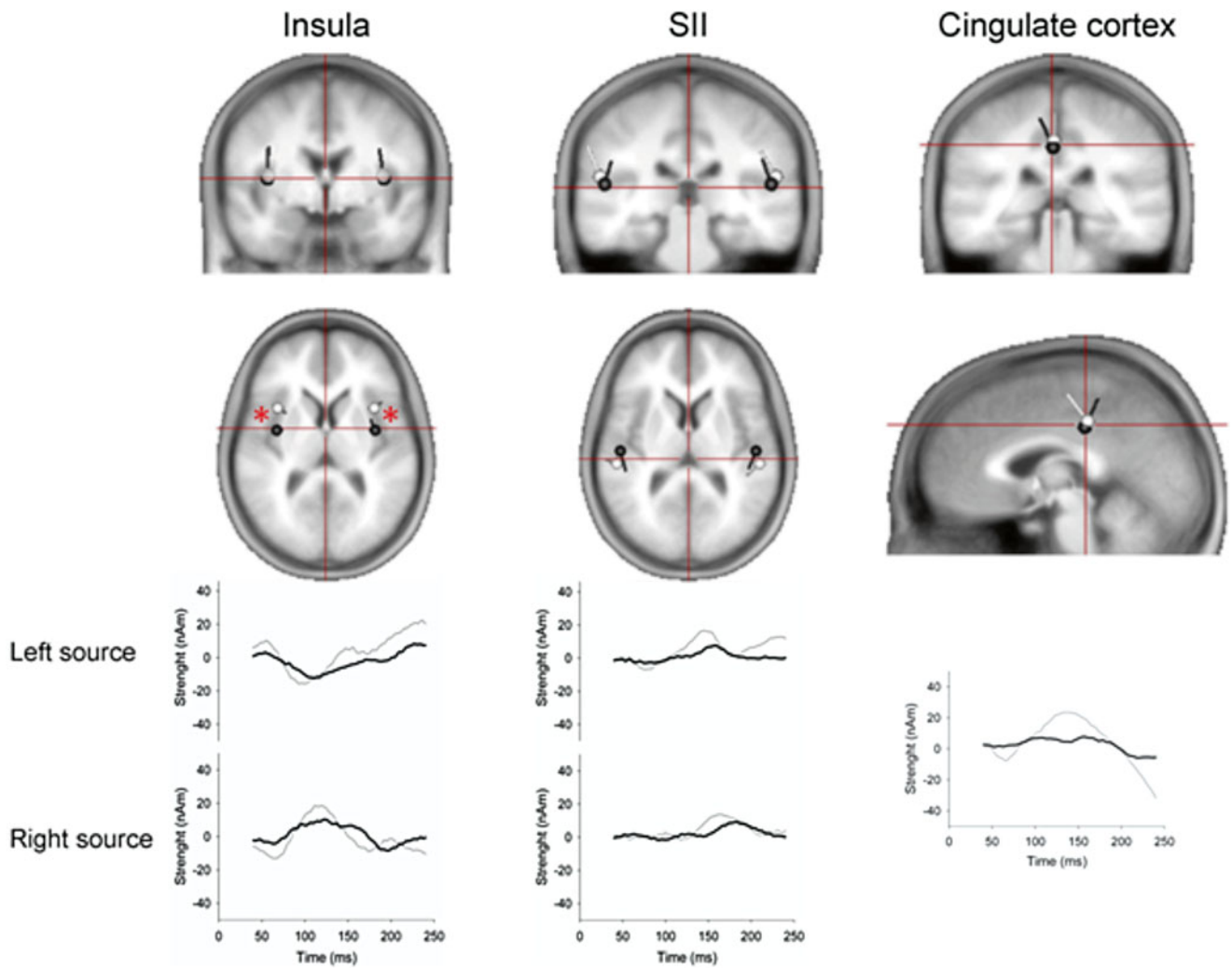

Fig. 5.5 *Top panels*: locations of brain sources evoked by painful stimulation of the sigmoid in patients with chronic pancreatitis (*black*) and healthy volunteers (*white*). The locations of insular sources differed between the groups. *Lower panel*: sequential activity of the brain sources throughout the time window of analysis (40–240 ms) in chronic pancreatitis patients (*black*) and healthy volunteers (*grey*). Modified from Olesen et al. (2011a) [91]

In organic diseases such chronic pancreatitis analysis of the EP topography has revealed a shift in insular dipole localization which was correlated with the patients' clinical pain scores (Fig. 5.5) [48]. Comparable findings have been reported in experimentally induced visceral hypersensitivity in healthy volunteers and may reflect the neurophysiologic correlate of functional reorganization. Insula has an important function for integrating the visceral sensory and motor activity together with limbic integration and is particularly important in pain perception from the gut. Experimental and clinical studies of somatic pain conditions, such as phantom limb pain, have also showed a correlation between clinical pain scores and reorganization, with the most suffering patients showing the most pronounced reorganization (i.e., a maladaptive pain response). Hence, the reorganization in chronic pancreatitis may be due to an "overactivation" of pain areas in the brains pain matrix, inducing a functional reorganization of the insular cortex. Such analysis may increase our understanding of the pain pathogenesis where the pain processing in the brain is of major importance, and there is preliminary evidence that these abnormalities may serve as predictors of treatment response.

MEG is a noninvasive technique for mapping brain activity by recording magnetic fields produced by electrical currents in the brain. MEG is a technically demanding technique and is only available in few specialist centers. Furthermore, it is limited by its incapability to resolve radial currents generated by deep brain sources, e.g., in the cingulate cortex. However, the spatial resolution of more superficial cortical

activity is in the mm range which is better than the EEG (for review see [47]). The methods have been used to follow the brain activation following esophageal electrical stimulation in healthy volunteers, but otherwise studies of visceral pain has until today been very limited [49].

Imaging methods may also be used to explore pain mechanisms following experimental stimulation of the gut. Improved methods for brain imaging techniques (fMRI, PET, and SPECT) have vastly increased our understanding of the central processing of GI sensation and pain in both healthy volunteers as well as in patients suffering from GI disorders.

Magnetic resonance imaging (MRI) allows imaging of both brain structure and activity. Brain activity measured by functional MRI (fMRI) has most commonly been acquired by the blood oxygenation level dependent (BOLD) technique, which is based on different paramagnetic properties of oxy- and deoxyhemoglobin in the blood. fMRI has an excellent spatial resolution (2–5 mm) and operates in a noninvasive and nonradioactive environment allowing subjects to be studied repetitively. The BOLD signal reflects simultaneously changes in local blood flow, volume, and deoxyhemoglobin content, which derive from changes in neuronal activity [50]. Regions of activation are identified by subtracting regional BOLD signal during a control/resting condition from the signal during a stimulus condition—Fig. 5.6. Recently, other techniques such as arterial spin labeling which allows the measurement of whole brain cerebral blood flow in absolute units through the use of magnetically labeled endogenous water in blood allowing assessment of the temporal dynamics of the neural activation induced by pain. This has been used to detect changes in regional cerebral blood flow associated with a standard cutaneous heat pain [49] and infusion of hypertonic saline [51]. Arterial spin labeling is particularly suited to studies of prolonged pain since it becomes increasingly more sensitive than BOLD to changes in neural activation as the stimulus duration exceeds one minute [52]. A new technique called signal enhancement by extravascular water protons has been used in fMRI of the spinal cord, which is essential in the complete mapping of the pain system, and spinal cord and brain stem sensory-related neural activity has been consistently observed in a number of studies. Recently also, resting state fMRI has been applied in pain research including connectivity analysis between multiple brain networks [53]. Additionally, structural information obtained by other MRI techniques can been superimposed on the functional data: diffusion tensor imaging with assessment of microstructural integrity in sensory-related brain areas, tractography with tracing of nerve fibers, volumetry of cortical regions with assessment of the neuroplastic response to long-standing pain, and spectroscopy assessing the concentration of metabolites [54–57]. This allows more explanatory information on the neural structures, function, and connections between the centers involved in pain processing.

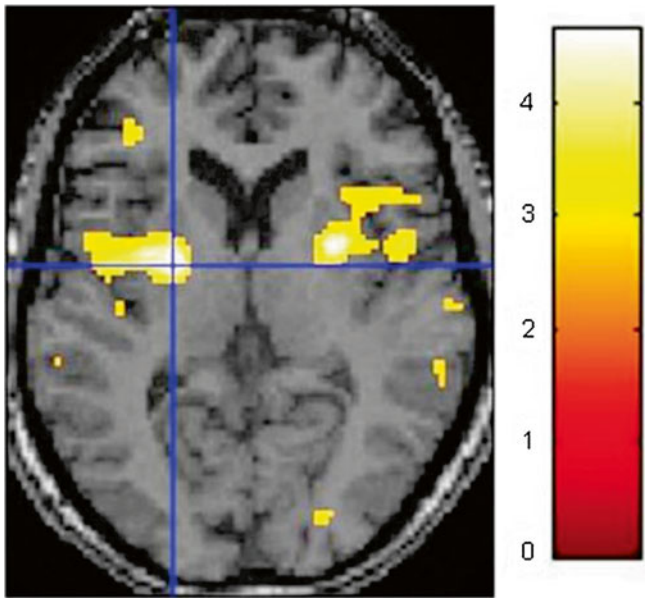

Fig. 5.6 Functional magnetic imaging (fMRI) with illustration of the brain activity induced by painful thermal stimulation of the right forearm in a single subject. This is based on the BOLD technique, which is based on different paramagnetic properties of oxy- and deoxyhemoglobin in the blood where the color code shows signal intensity. Regions of activation (here in the insular regions) are identified by subtracting regional BOLD signal during a resting condition from the signal during the painful stimulus

fMRI has been used in several studies for demonstrating abnormal brain processing in particular functional GI disorders. Few studies have also been conducted in organic diseases such as inflammatory bowel disease. Kwan et al. identified abnormal event-related sensations in five brain regions following rectal distensions in IBS [58]. In the primary somatosensory cortex, urge-related responses in the IBS group were seen compared to the control group. This could be interpreted as upregulated afferent input underlying visceral hypersensitivity or "visceral allodynia." In the IBS group, pain-related responses were seen in the medial thalamus and hippocampus, but not in the control group. However, pronounced urge- and pain-related activations were present in the right anterior insula and the right anterior cingulate cortex in the control group, but not the IBS group. Finally, lack of activation in right anterior insula was found in IBS patients, interpreted by the authors as either a ceiling effect or a dysfunction in interoceptive processing or control of visceromotor responses. In controls, patients with inflammatory bowel disease and IBS patients, Bernstein et al. performed rectal balloon distention to a sensation of stool and to a sensation of pain while undergoing fMRI [59]. All three groups share similar loci of activations to visceral sensations of stool and pain, but both activation and deactivation of particular regions of interest was differentiated between the groups. Finally, fMRI has been used to evaluate the effect of the

tricyclic antidepressant amitriptyline, which is believed to be of clinical benefit in IBS patients [60]. Amitriptyline reduced pain-related cerebral activations in the pACC and the left posterior parietal cortex compared to placebo, but only during mental stress [61].

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are nuclear imaging techniques that can trace radiolabeled molecules injected into the blood stream, whereby the distribution, density and activity of receptors in the brain can be visualized. This provides an insight into the organization of functional networks in the brain, which cannot be achieved by morphologic investigations or imaging of blood flow and metabolism [62]. Using this molecular imaging technique, pharmaceutical compounds can be used as radiolabeled tracers combined with kinetic models allowing quantification of receptor sites and enzyme function [63]. PET is superior in imaging radiopharmaceuticals and/or other ligands as it offers the ability to study receptor distribution and explore the site of action.

Both SPECT and PET have been used in studies investigating which brain areas are activated during painful stimuli [64]. Nevertheless, it has not been used very widely in clinical pain studies. A study by Fukumoto et al. assessed regional cerebral blood flow of the contralateral thalamus in ten patients with reflex sympathetic dystrophy syndrome [65], but has so far not been used in the investigation of visceral pain. Several studies have used PET for investigating brain activation during visceral pain [66–68], but to our knowledge no studies of specific receptor systems have been conducted.

Assessment of Analgesic Effects by Visceral QST

The effect of analgesics on visceral pain is difficult to evaluate in the clinic, due to the deep and diffuse nature of the pain and the accompanying autonomic symptoms [1–3]. Application of experimental pain models in a crossover study design with appropriate baseline recordings offers a unique opportunity of revealing analgesic effects [5]. It has been recommended to include pain models in various tissues as, e.g., opioid analgesia can exhibit tissue dissimilarities [69]. Moreover, different modalities activate distinct pain mechanisms and make it possible to investigate on a mechanistic basis how analgesics work. The effect on pain from deeper structures (muscle and viscera) is considered most important as, e.g., opioid analgesia is more robust in deep pain [69].

To induce deep pain, experimental pain has been evoked in different parts of the GI tract [1–3, 12, 13]. Sensitization of the nervous system is also possible by, e.g., perfusion of the gut with chemical substances. Thus, peripheral and central mechanisms relating to the clinical situation can be evoked, and the effect on pharmacological modulation evaluated. Experimental pain studies can be conducted in healthy volunteers or in patients to evaluate analgesic effects. In the next section, some examples are discussed, for more comprehensive review the reader is referred to [69, 70].

Healthy Volunteers

Experimental pain in healthy volunteers appears to be suited to investigate the analgesic effects, especially when deep pain and hyperalgesia is evoked to mimic the clinical situation [5, 6, 69, 70].

Ketamine is an NMDA-antagonist that has been widely studied in experimental pain in healthy volunteers. Animal studies that investigated the analgesic role of NMDA receptors proposed that NMDA-receptor-related transmission is more important in acute nociceptive responses involving visceral tissues, whereas involvement in somatic nociception may be more dependent on mechanisms active in inflammation and hyperalgesia [71–73]. Therefore, visceral stimulations should be included in the experimental pain model when investigating effects of NMDA-antagonists. However, only one study investigated the effect of ketamine in a model including visceral sensory stimulations. It was found that pain from visceral distension was decreased by ketamine [74]. The findings on analgesic effects of ketamine in acute visceral pain in humans are in agreement with these animal data since the ketamine-related attenuation of pain intensity appeared more pronounced for noxious visceral than for cutaneous stimulation [74].

Morphine and oxycodone are opioids and have both been tested in experimental visceral pain studies in healthy volunteers. They were both effective against mechanical and electrical esophageal pain, but only oxycodone attenuated thermal pain [5, 6, 75]. Moreover, oxycodone and morphine have been tested in esophageal hyperalgesia induced by a combination of acid and capsaicin. In visceral hyperalgesia, only oxycodone showed effect on pain to electrical stimulation and the referred pain area to heat stimuli [76]. Morphine and oxycodone also showed different effects comparing somatic and visceral pain. This reflects the clinical situation where visceral pain in contrast to somatic pain can be difficult to treat with traditional μ-opioid agonists, and oxycodone has in a few clinical studies been found more effective than morphine [77, 78].

New drugs: Human experimental pain models in healthy volunteers have also been used to evaluate analgesic effects of new drugs. For example, the effect of a new TRPV1 antagonist (AZD1386) was assessed by our group in experimentally induced esophageal pain. It was found that it increased pain thresholds to heat stimuli of the esophagus, whereas pain thresholds to other stimuli were unaffected. AZD1386 treatment also attenuated, but did not prevent, acid-induced hyperalgesia [79].

Patients

Pain experienced and reported by healthy volunteers is different from clinical pain, and in the laboratory it is not possible to reproduce the pathophysiology and the full complexity of the pain experience in patients [80, 81]. As described previously, pain in patients is accompanied by several factors such as fear, emotions, anxiety, etc. influencing the overall sensory experience [82]. Hence, improvement in, e.g., depression during treatment with a new drug can result in less pain ratings. It can therefore be difficult to evaluate analgesic effects and specific mechanisms in patients with pain, and even studies with well-known analgesics, such as NSAIDs, are frequently inconclusive [83]. However, experimental pain models can be applied in patient groups to investigate analgesic effect in the actual patient group providing controlled stimuli and quantitative assessments. Below some examples are provided to give insight into this testing.

Gabapentin and pregabalin decreases hyperalgesia and allodynia and are widely used in treating neuropathic pain. Gabapentin and pregabalin also exert antinociceptive effects in animal models of neuropathic, surgical, inflammatory, acute, and chronic pain. This was supported by positive findings in the described human experimental pain models in patients [84, 85]. The mechanism of action is not fully known, but part of the therapeutic action on neuropathic pain is thought to involve voltage-gated calcium ion channels [86, 87]. Gabapentin has been investigated in experimental visceral pain in patients with diarrhea-predominant IBS where pain was evoked by rectal distensions. The distending pressure triggering a first sensation of defecation was not altered, but threshold pressures for bloating, discomfort, and pain were increased [85]. Pregabalin was also studied in patients with IBS. Rectal sensitivity was assessed using a Barostat technique and pregabalin significantly increased the sensory thresholds, desire to defecate and pain [84]. In patients with chronic pancreatitis thought to have a strong neuropathic pain component [88], pregabalin was also tested. Here, the experimental measures were translated into a clinical efficacy, confirmed by traditional questionnaire endpoints [89]. In these patients, perceptual thresholds to electrical stimulation of the sigmoid with recording of corresponding evoked brain potentials were also obtained. Pregabalin increased pain threshold to electrical gut stimulation, whereas no differences in evoked brain potential characteristics or corresponding brain sources were seen. It was concluded that the antinociceptive effects of pregabalin is mediated primarily through subcortical mechanisms [90].

Opioids: In an experimental pain study in patients with chronic pancreatitis, it was found that mechanical, heat, and electrical pain in skin and mechanical and electrical muscle pain was unaffected by morphine. However, morphine increased esophageal mechanical pain-tolerance threshold, whereas esophageal heat and electrical pain thresholds were unaffected [91]. Another study investigated the effect of morphine in patients with chronic pancreatitis and found no effect on rectal distension thresholds [92]. In patients undergoing abdominal hysterectomies, morphine increased pain tolerance to rectal distension, whereas no effect on transcutaneous electric sensation or skin electric pain-tolerance thresholds was found [93]. The effect of oxycodone was only investigated in one experimental pain study in patients with chronic pancreatitis. Oxycodone showed more pronounced effects than morphine on skin, muscle, and visceral stimulations [91] again demonstrating a differential effect on opioids.

QST in Prediction of Response to Analgesics

It has recently been shown that QST has the potential to stratify patients into responders and nonresponders to analgesic treatment. Such results are promising and indicate that the methods may be useful as a clinical tool in tailoring individualized therapy. For example, heat pain threshold was correlated to the effect of oxycodone on pain following cold pressor testing in healthy volunteers [94]. Likewise, electrical, heat, and pressure-evoked pain have been shown predict postoperative analgesic consumption in surgical patients. Hence, *electrical* pain stimulation was correlated to postoperative consumption of acetaminophen and morphine after caesarean section and percutaneous nephrolithotomy [95, 96]. *Pressure* pain was correlated to morphine consumption following hysterectomy [97]. Finally, preoperative *heat* stimulations predicted morphine use following knee arthroplasty and caesarean section [98, 99], as well as ibuprofen requirement within the first ten postoperative days following laparoscopic tubal ligation [100]. In contrast, three studies have been unable to find a relationship between electrical pain thresholds and subsequent analgesic consumption [101–103]. These apparently conflicting results regarding electrical stimulation are most likely related to differences in study methodology across studies.

In *patients with neuralgia*, Edwards et al. [104] found that heat pain sensitivity predicted the effect of morphine, but not the responses to nortriptylin or placebo. Likewise, Attal et al. [105] reported a correlation between baseline heat pain and the effect of lidocaine and mexiletine. Recently, Yarnitsky et al. [106] suggested that in patients with painful diabetic neuropathy those with less efficient conditioned pain modulation were most likely to benefit from duloxetine. Finally, in patients with *chronic pancreatitis*, Olesen et al. [107] showed that the effect of pregabalin was associated with increased sensitivity to electrical stimulation in the pancreatic viscerotome compared to a control area. In summary, the evidence

remains insufficiently robust to suggest any specific QST measure to discriminate between patients who are likely to respond to analgesic treatment. However, results are promising and call for future well designed and sufficiently powered studies focusing on different modalities of experimental pain modulation rather than a single static pain paradigm.

Conclusion

Painful sensations from the gut tract are very common in the clinic, but underlying diseases can be difficult to diagnose and treat successfully. Findings from basic, experimental, and clinical research have gained new insight about the GI pain system, and evidence for sensitization at both the peripheral and the central level seems to be of major importance in the explanation and treatment. The methods have also been used to test the effect and mechanisms of existing and new drugs and in prediction of the responses to treatment. This information and knowledge should be implemented in the clinic leading to the right diagnosis and directing future treatment approaches against underlying visceral pain mechanism.

References

1. Drewes AM, Gregersen H, Arendt-Nielsen L. Experimental pain in gastroenterology: a reappraisal of human studies. Scand J Gastroenterol. 2003;38:1115–30.
2. Drewes AM, Pedersen J, Liu W, Arendt-Nielsen L, Gregersen H. Controlled mechanical distension of the human oesophagus: sensory and biomechanical findings. Scand J Gastroenterol. 2003;38: 27–35.
3. Drewes AM, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multi-modal induction and assessment of allodynia and hyperalgesia in the human oesophagus. Eur J Pain. 2003;7:539–49.
4. Drewes AM, Reddy H, Pedersen J, Funch-Jensen P, Gregersen H, Arendt-Nielsen L. Multimodal pain stimulations in patients with grade B oesophagitis. Gut. 2006;55:926–32.
5. Staahl C, Christrup LL, Andersen SD, Arendt-Nielsen L, Drewes AM. A comparative study of oxycodone and morphine in a multimodal, tissue-differentiated experimental pain model. Pain. 2006; 123:28–36.
6. Staahl C, Reddy H, Andersen SD, Arendt-Nielsen L, Drewes AM. Multi-modal and tissue-differentiated experimental pain assessment: reproducibility of a new concept for assessment of analgesics. Basic Clin Pharmacol Toxicol. 2006;98:201–11.
7. Brock C, Nissen TD, Gravesen FH, Frokjaer JB, Omar H, Gale J, Gregersen H, Svendsen O, Drewes AM. Multimodal sensory testing of the rectum and rectosigmoid: development and reproducibility of a new method. Neurogastroenterol Motil. 2008; 20:908–18.
8. Sengupta JN, Gebhart GF. Gastrointestinal afferent fibers and sensation. In: Johnson LR, editor. Physiology of the gastrointestinal tract. New York, NY: Raven; 1994. p. 483–519.
9. van der Schaar PJ, Lamers CB, Masclee AA. The role of the barostat in human research and clinical practice. Scand J Gastroenterol Suppl. 1999;230:52–63.
10. Gregersen H, Kwiatek MA, Schwizer W, Tutuian R. Contribution of sensitivity, volume and tone to visceral perception in the upper gastrointestinal tract in man: emphasis on testing. Neurogastroenterol Motil. 2007;19:47–61.
11. Drewes AM, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multimodal assessment of pain in the esophagus: a new experimental model. Am J Physiol Gastrointest Liver Physiol. 2002;283:G95–103.
12. Olesen AE, Staahl C, Brock C, Arendt-Nielsen L, Drewes AM. Evoked human oesophageal hyperalgesia: a potential tool for analgesic evaluation? Basic Clin Pharmacol Toxicol. 2009;105: 126–36.
13. Olesen SS, Olesen AE, Gravesen F, Poulsen JK, Funch-Jensen P, Gregersen H, Drewes AM. An endoscopic method for thermal and chemical stimulation of the human oesophagus. Neurogastroenterol Motil. 2009;21:1250–e116.
14. Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. Pain. 1990;41:167–234.
15. Sarkar S, Hobson AR, Furlong PL, Woolf CJ, Thompson DG, Aziz Q. Central neural mechanisms mediating human visceral hypersensitivity. Am J Physiol Gastrointest Liver Physiol. 2001; 281:G1196–202.
16. Rossel P, Drewes AM, Petersen P, Nielsen J, Arendt-Nielsen L. Pain produced by electric stimulation of the rectum in patients with irritable bowel syndrome: further evidence of visceral hyperalgesia. Scand J Gastroenterol. 1999;34:1001–6.
17. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology. 1995;109:40–52.
18. Bernstein CN, Niazi N, Robert M, Mertz H, Kodner A, Munakata J, Naliboff B, Mayer EA. Rectal afferent function in patients with inflammatory and functional intestinal disorders. Pain. 1996;66: 151–61.
19. Dimcevski G, Schipper KP, Tage-Jensen U, Funch-Jensen P, Krarup AL, Toft E, Thorsgaard N, Arendt-Nielsen L, Drewes AM. Hypoalgesia to experimental visceral and somatic stimulation in painful chronic pancreatitis. Eur J Gastroenterol Hepatol. 2006;18:755–64.
20. Olesen SS, Brock C, Krarup AL, Funch-Jensen P, Arendt-Nielsen L, Wilder-Smith OH, Drewes AM. Descending inhibitory pain modulation is impaired in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2010;8:724–30.
21. Arendt-Nielsen L, Laursen RJ, Drewes AM. Referred pain as an indicator for neural plasticity. Prog Brain Res. 2000;129:343–56.
22. Drewes AM, Pedersen J, Reddy H, Rasmussen K, Funch-Jensen P, Arendt-Nielsen L, Gregersen H. Central sensitization in patients with non-cardiac chest pain: a clinical experimental study. Scand J Gastroenterol. 2006;41:640–9.
23. Arendt-Nielsen L, Drewes AM, Hansen JB, Tage-Jensen U. Gut pain reactions in man: an experimental investigation using short and long duration transmucosal electrical stimulation. Pain. 1997;69:255–62.
24. Arendt-Nielsen L, Schipper KP, Dimcevski G, Sumikura H, Krarup AL, Giamberardino MA, Drewes AM. Viscero-somatic reflexes in referred pain areas evoked by capsaicin stimulation of the human gut. Eur J Pain. 2008;12:544–51.
25. Vecchiet L, Giamberardino MA, Dragani L, Albe-Fessard D. Pain from renal/ureteral calculosis: evaluation of sensory thresholds in the lumbar area. Pain. 1989;36:289–95.
26. Stawowy M, Funch-Jensen P, Arendt-Nielsen L, Drewes AM. Somatosensory changes in the referred pain area in patients with cholecystolithiasis. Eur J Gastroenterol Hepatol. 2005;17: 865–70.
27. Stawowy M, Rossel P, Bluhme C, Funch-Jensen P, Arendt-Nielsen L, Drewes AM. Somatosensory changes in the referred pain area following acute inflammation of the appendix. Eur J Gastroenterol Hepatol. 2002;14:1079–84.

28. Buscher HC, Wilder-Smith OH, van Goor H. Chronic pancreatitis patients show hyperalgesia of central origin: a pilot study. Eur J Pain. 2006;10:363–70.
29. Qin C, Malykhina AP, Akbarali HI, Foreman RD. Cross-organ sensitization of lumbosacral spinal neurons receiving urinary bladder input in rats with inflamed colon. Gastroenterology. 2005;129:1967–78.
30. Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. Lancet. 2000;356:1154–9.
31. Frokjaer JB, Andersen SD, Gale J, Arendt-Nielsen L, Gregersen H, Drewes AM. An experimental study of viscero-visceral hyperalgesia using an ultrasound-based multimodal sensory testing approach. Pain. 2005;119:191–200.
32. Simren M, Abrahamsson H, Bjornsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. Gut. 2001;48:20–7.
33. Giamberardino MA. Recent and forgotten aspects of visceral pain. Eur J Pain. 1999;3:77–92.
34. Fass R, Achem SR, Harding S, Mittal RK, Quigley E. Review article: supra-oesophageal manifestations of gastro-oesophageal reflux disease and the role of night-time gastro-oesophageal reflux. Aliment Pharmacol Ther. 2004;20 Suppl 9:26–38.
35. Munakata J, Naliboff B, Harraf F, Kodner A, Lembo T, Chang L, Silverman DH, Mayer EA. Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. Gastroenterology. 1997;112:55–63.
36. Paterson WG, Wang H, Vanner SJ. Increasing pain sensation to repeated esophageal balloon distension in patients with chest pain of undetermined etiology. Dig Dis Sci. 1995;40:1325–31.
37. Dimcevski G, Staahl C, Andersen SD, Thorsgaard N, Funch-Jensen P, Arendt-Nielsen L, Drewes AM. Assessment of experimental pain from skin, muscle, and esophagus in patients with chronic pancreatitis. Pancreas. 2007;35:22–9.
38. Bouhassira D, Chollet R, Coffin B, Lemann M, Le Bars D, Willer JC, Jian R. Inhibition of a somatic nociceptive reflex by gastric distention in humans. Gastroenterology. 1994;107:985–92.
39. Bouhassira D, Sabate JM, Coffin B, Le Bars D, Willer JC, Jian R. Effects of rectal distensions on nociceptive flexion reflexes in humans. Am J Physiol. 1998;275:G410–7.
40. Curatolo M, Petersen-Felix S, Arendt-Nielsen L. Sensory assessment of regional analgesia in humans: a review of methods and applications. Anesthesiology. 2000;93:1517–30.
41. Olesen SS, Hansen TM, Graversen C, Steimle K, Wilder-Smith OH, Drewes AM. Slowed EEG rhythmicity in patients with chronic pancreatitis: evidence of abnormal cerebral pain processing? Eur J Gastroenterol Hepatol. 2011;23:418–24.
42. Valeriani M, Le Pera D, Tonali P. Characterizing somatosensory evoked potential sources with dipole models: advantages and limitations. Muscle Nerve. 2001;24:325–39.
43. Frobert O, Arendt-Nielsen L, Bak P, Funch-Jensen P, Peder BJ. Pain perception and brain evoked potentials in patients with angina despite normal coronary angiograms. Heart. 1996;75:436–41.
44. Hollerbach S, Bulat R, May A, Kamath MV, Upton AR, Fallen EL, Tougas G. Abnormal cerebral processing of oesophageal stimuli in patients with noncardiac chest pain (NCCP). Neurogastroenterol Motil. 2000;12:555–65.
45. Rossel P, Pedersen P, Niddam D, Arendt-Nielsen L, Chen AC, Drewes AM. Cerebral response to electric stimulation of the colon and abdominal skin in healthy subjects and patients with irritable bowel syndrome. Scand J Gastroenterol. 2001;36:1259–66.
46. Arebi N, Bullas DC, Dukes GE, Gurmany S, Hicks KJ, Kamm MA, Hobson AR. Distinct neurophysiological profiles in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2011;300:G1086–93.
47. Frokjaer JB, Olesen SS, Graversen C, Andresen T, Lelic D, Drewes AM. Neuroimaging of the human visceral pain system—a methodological review. Scand J Pain. 2011;2:95–104.
48. Olesen SS, Frokjaer JB, Lelic D, Valeriani M, Drewes AM. Pain-associated adaptive cortical reorganisation in chronic pancreatitis. Pancreatology. 2010;10:742–51.
49. Hobson AR, Furlong PL, Worthen SF, Hillebrand A, Barnes GR, Singh KD, Aziz Q. Real-time imaging of human cortical activity evoked by painful esophageal stimulation. Gastroenterology. 2005;128:610–9.
50. Turner R. Magnetic resonance imaging of brain function. Am J Physiol Imaging. 1992;7:136–45.
51. Owen DG, Clarke CF, Ganapathy S, Prato FS, St Lawrence KS. Using perfusion MRI to measure the dynamic changes in neural activation associated with tonic muscular pain. Pain. 2010;148:375–86.
52. Wang J, Aguirre GK, Kimberg DY, Roc AC, Li L, Detre JA. Arterial spin labeling perfusion fMRI with very low task frequency. Magn Reson Med. 2003;49:796–802.
53. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010;62:2545–55.
54. Nucifora PG, Verma R, Lee SK, Melhem ER. Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity. Radiology. 2007;245:367–84.
55. Frokjaer JB, Bouwense SA, Olesen SS, Lundager FH, Eskildsen SF, van Goor H, Wilder-Smith OH, Drewes AM. Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2012;10:434–8.e1.
56. Frokjaer JB, Olesen SS, Gram M, Yavarian Y, Bouwense SA, Wilder-Smith OH, Drewes AM. Altered brain microstructure assessed by diffusion tensor imaging in patients with chronic pancreatitis. Gut. 2011;60:1554–62.
57. Fregni F, Potvin K, Dasilva D, Wang X, Lenkinski RE, Freedman SD, Pascual-Leone A. Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain. Eur J Pain. 2011;15:53–60.
58. Kwan CL, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology. 2005;65:1268–77.
59. Bernstein CN, Frankenstein UN, Rawsthorne P, Pitz M, Summers R, McIntyre MC. Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. Am J Gastroenterol. 2002;97:319–27.
60. Clouse RE, Lustman PJ. Use of psychopharmacological agents for functional gastrointestinal disorders. Gut. 2005;54:1332–41.
61. Morgan V, Pickens D, Gautam S, Kessler R, Mertz H. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. Gut. 2005;54:601–7.
62. Heiss WD, Herholz K. Brain receptor imaging. J Nucl Med. 2006;47:302–12.
63. Wirrwar A, Schramm N, Vosberg H, Muller-Gartner HW. High resolution SPECT in small animal research. Rev Neurosci. 2001;12:187–93.
64. Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. Science. 1991;251:1355–8.
65. Fukumoto M, Ushida T, Zinchuk VS, Yamamoto H, Yoshida S. Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome. Lancet. 1999;354:1790–1.
66. Ladabaum U, Minoshima S, Hasler WL, Cross D, Chey WD, Owyang C. Gastric distention correlates with activation of multiple cortical and subcortical regions. Gastroenterology. 2001;120:369–76.

67. Vandenbergh J, Dupont P, Fischler B, Bormans G, Persoons P, Janssens J, Tack J. Regional brain activation during proximal stomach distention in humans: a positron emission tomography study. Gastroenterology. 2005;128:564–73.
68. Stephan E, Pardo JV, Faris PL, Hartman BK, Kim SW, Ivanov EH, Daughters RS, Costello PA, Goodale RL. Functional neuroimaging of gastric distention. J Gastrointest Surg. 2003;7:740–9.
69. Staahl C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM. Assessing analgesic actions of opioids by experimental pain models in healthy volunteers—an updated review. Br J Clin Pharmacol. 2009;68:149–68.
70. Staahl C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM. Assessing efficacy of non-opioid analgesics in experimental pain models in healthy volunteers: an updated review. Br J Clin Pharmacol. 2009;68:322–41.
71. Ji Y, Traub RJ. Spinal NMDA receptors contribute to neuronal processing of acute noxious and nonnoxious colorectal stimulation in the rat. J Neurophysiol. 2001;86:1783–91.
72. McRoberts JA, Coutinho SV, Marvizon JC, Grady EF, Tognetto M, Sengupta JN, Ennes HS, Chaban VV, Amadesi S, Creminon C, Lanthorn T, Geppetti P, Bunnett NW, Mayer EA. Role of peripheral N-methyl-D-aspartate (NMDA) receptors in visceral nociception in rats. Gastroenterology. 2001;120:1737–48.
73. Olivar T, Laird JM. Differential effects of N-methyl-D-aspartate receptor blockade on nociceptive somatic and visceral reflexes. Pain. 1999;79:67–73.
74. Strigo IA, Duncan GH, Bushnell MC, Boivin M, Wainer I, Rodriguez Rosas ME, Persson J. The effects of racemic ketamine on painful stimulation of skin and viscera in human subjects. Pain. 2005;113:255–64.
75. Arendt-Nielsen L, Olesen AE, Staahl C, Menzaghi F, Kell S, Wong GY, Drewes AM. Analgesic efficacy of peripheral kappa opioid receptor agonist CR665 compared to oxycodone in a multimodal, multi-tissue experimental human pain model: selective effect on visceral pain. Anesthesiology. 2009;111:616–24.
76. Olesen AE, Staahl C, Arendt-Nielsen L, Drewes AM. Different effects of morphine and oxycodone in experimentally evoked hyperalgesia: a human translational study. Br J Clin Pharmacol. 2010;70:189–200.
77. Lenz H, Sandvik L, Qvigstad E, Bjerkelund CE, Raeder J. A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. Anesth Analg. 2009;109:1279–83.
78. De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil. 2004;16:383–94.
79. Krarup AL, Ny L, Astrand M, Bajor A, Hvid-Jensen F, Hansen MB, Simren M, Funch-Jensen P, Drewes AM. Randomised clinical trial: the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. Aliment Pharmacol Ther. 2011;33:1113–22.
80. Curatolo M, Arendt-Nielsen L, Petersen-Felix S. Central hypersensitivity in chronic pain: mechanisms and clinical implications. Phys Med Rehabil Clin N Am. 2006;17:287–302.
81. Arendt-Nielsen L, Curatolo M, Drewes A. Human experimental pain models in drug development: translational pain research. Curr Opin Investig Drugs. 2007;8:41–53.
82. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1:277–99.
83. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ. 2004;329:1317.
84. Houghton LA, Fell C, Whorwell PJ, Jones I, Sudworth DP, Gale JD. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. Gut. 2007;56:1218–25.
85. Lee KJ, Kim JH, Cho SW. Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2005;22:981–8.
86. Field MJ, Cox PJ, Stott E, Melrose H, Offord J, Su TZ, Bramwell S, Corradini L, England S, Winks J, Kinloch RA, Hendrich J, Dolphin AC, Webb T, Williams D. Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci U S A. 2006;103:17537–42.
87. Bauer CS, Rahman W, Tran-van-Minh A, Lujan R, Dickenson AH, Dolphin AC. The anti-allodynic alpha(2)delta ligand pregabalin inhibits the trafficking of the calcium channel alpha(2) delta-1 subunit to presynaptic terminals in vivo. Biochem Soc Trans. 2010;38:525–8.
88. Drewes AM, Krarup AL, Detlefsen S, Malmstrom ML, Dimcevski G, Funch-Jensen P. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. Gut. 2008;57:1616–27.
89. Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141:536–43.
90. Olesen SS, Graversen C, Olesen AE, Frokjaer JB, Wilder-Smith O, van Goor H, Valeriani M, Drewes AM. Randomised clinical trial: pregabalin attenuates experimental visceral pain through sub-cortical mechanisms in patients with painful chronic pancreatitis. Aliment Pharmacol Ther. 2011;34:878–87.
91. Staahl C, Dimcevski G, Andersen SD, Thorsgaard N, Christrup LL, Arendt-Nielsen L, Drewes AM. Differential effect of opioids in patients with chronic pancreatitis: an experimental pain study. Scand J Gastroenterol. 2007;42:383–90.
92. Wilder-Smith CH, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. Dig Dis Sci. 1999;44:1107–16.
93. Wilder-Smith CH, Hill L, Wilkins J, Denny L. Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. Anesthesiology. 1999;91:639–47.
94. Eisenberg E, Midbari A, Haddad M, Pud D. Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects. Pain. 2010;151:104–9.
95. Buhagiar L, Cassar OA, Brincat MP, Buttigieg GG, Inglott AS, Adami MZ, Azzopardi LM. Predictors of post-caesarean section pain and analgesic consumption. J Anaesthesiol Clin Pharmacol. 2011;27:185–91.
96. Pedersen K, Olesen A, Osther P, Arendt-Nielsen L, Drewes A. Prediction of postoperative pain after percutaneous nephrolithotomy: can preoperative experimental pain assessment identify patients at risk? Urolithiasis. 2013;41(2):169–77.
97. Hsu YW, Somma J, Hung YC, Tsai PS, Yang CH, Chen CC. Predicting postoperative pain by preoperative pressure pain assessment. Anesthesiology. 2005;103:613–8.
98. Martinez V, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. Anesth Analg. 2007;105:815–21.
99. Pan PH, Coghill R, Houle TT, Seid MH, Lindel WM, Parker RL, Washburn SA, Harris L, Eisenach JC. Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement. Anesthesiology. 2006;104:417–25.
100. Rudin A, Wolner-Hanssen P, Hellbom M, Werner MU. Prediction of post-operative pain after a laparoscopic tubal ligation procedure. Acta Anaesthesiol Scand. 2008;52:938–45.
101. Nielsen PR, Norgaard L, Rasmussen LS, Kehlet H. Prediction of post-operative pain by an electrical pain stimulus. Acta Anaesthesiol Scand. 2007;51:582–6.

102. Wilder-Smith OH, Tassonyi E, Crul BJ, Arendt-Nielsen L. Quantitative sensory testing and human surgery: effects of analgesic management on postoperative neuroplasticity. Anesthesiology. 2003;98:1214–22.
103. Aasvang EK, Hansen JB, Kehlet H. Can preoperative electrical nociceptive stimulation predict acute pain after groin herniotomy? J Pain. 2008;9:940–4.
104. Edwards RR, Sarlani E, Wesselmann U, Fillingim RB. Quantitative assessment of experimental pain perception: multiple domains of clinical relevance. Pain. 2005;114:315–9.
105. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology. 2004;62:218–25.
106. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain. 2012;153:1193–9.
107. Olesen SS, Graversen C, Bouwense SAW, van Goor H, Wilder-Smith OHG, Drewes AM. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. PLoS One. 2013;8(3):e57963.