How Positive and Negative Expectations Shape the Experience of Visceral Pain

Sigrid Elsenbruch

Contents

Abstract

Knowledge from placebo and nocebo research aimed at elucidating the role of treatment expectations and learning experiences in shaping the response to visceral pain fills an important research gap. First, chronic abdominal pain, such as in irritable bowel syndrome (IBS), is highly prevalent, with detrimental individual and socioeconomic impact and limited effective treatment options. At the same time, IBS patients show high placebo response rates in clinical trials and benefit from placebo interventions. Second, psychological factors including emotions and cognitions in the context of visceral pain have been implicated in the pathophysiology of IBS and other conditions characterized by medically unexplained somatic symptoms. Hence, the study of nocebo and placebo effects in visceral pain constitutes a model to assess the contribution of psychological factors. Herein, the clinical relevance of visceral pain is introduced with a focus

S. Elsenbruch (✉)
Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
e-mail: Sigrid.Elsenbruch@uk-essen.de

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on IBS as a bio-psycho-social disorder, followed by a review of existing clinical and experimental work on placebo and nocebo effects in IBS and in clinically relevant visceral pain models. Finally, emerging research trends are highlighted along with an outlook regarding goals for ongoing and future research.

Keywords
Visceral pain • Functional gastrointestinal disorders • Irritable bowel syndrome • Visceral hyperalgesia

1 Introduction: Visceral Pain and Irritable Bowel Syndrome

Visceral pain is a common symptom of great clinical and socioeconomic significance in many areas of medicine. Patients experience acute, recurrent and/or chronic visceral pain in many medical disciplines, including internal medicine, gynaecology, visceral surgery, urology, and general medicine. Especially in patients presenting with chronic or recurrent abdominal pain, it is often difficult to identify an unequivocal organic cause, at least with established diagnostic tools. After exclusion of a number of common organic conditions such as inflammatory bowel disease (IBD) or esophagitis, chronic abdominal complaints are often classified as one of the *functional gastrointestinal disorders* (FGDs). The FGDs are considered an important public health problem because they are remarkably prevalent, can be disabling, and constitute a major individual, social, and economic burden (Agarwal and Spiegel 2011; Maxion-Bergemann et al. 2006). Irritable Bowel Syndrome (IBS), the most common FGD with prevalence rates of 8–23 % (Choung and Locke 2011; Talley 2008) is characterized by recurrent abdominal pain or discomfort in combination with disturbed bowel habits in the absence of identifiable organic cause. FGDs such as IBS are more prevalent in women (at least in Western countries) and often present with comorbid gastrointestinal, somatic, and psychological/psychiatric symptoms resulting in a significant overlap with other diagnoses. This overlap does not only exist with conditions associated with other, primarily gastrointestinal symptomatology, including chronic pelvic pain, faecal incontinence, or chronic constipation, but also with diagnoses involving extra-intestinal symptoms such as fibromyalgia and chronic fatigue syndrome (Choung and Locke 2011; Frissora and Koch 2005). All these conditions share a high incidence of psychiatric or psychological comorbidities, especially anxiety, depression, and somatization disorder with typical personality alterations including high neuroticism and catastrophizing and altered healthcare-seeking behaviour (Folks 2004; Whitehead et al. 2002). Finally, a history of abuse, early adverse life events and trauma has been linked to the onset of symptoms in a significant proportion of patients with medically unexplained bodily symptoms (Bradford et al. 2012).

Current etiological concepts for FGDs unequivocally assume bio-psycho-social models (Elsenbruch 2011; Tanaka et al. 2011). Consequently, it is assumed that the pathophysiology is multi-factorial encompassing biological, psychological, and social mechanisms mediated by the central, autonomic, neuroendocrine, and immune systems. Whereas earlier concepts focussed on the role of altered motility in FGDs, more recent evidence has led to a paradigm shift with a strong focus on altered afferent and central processing of painful stimuli. Specifically, visceral hyperalgesia (or hypersensitivity) and visceral hypervigilance constitute key concepts in current research on pathophysiological mechanisms. The role of central nervous system mechanisms along the "brain-gut axis" is increasingly appreciated, owing to accumulating evidence from brain imaging studies that the neural processing of painful visceral stimuli is altered in IBS together with long-standing knowledge regarding the contribution of stress and negative emotions to symptom frequency and severity. At the same time, there is growing evidence suggesting that peripheral and local immune mechanisms and disturbed neuro-immune communication could play a role in the pathophysiology of visceral hyperalgesia (Elsenbruch 2011).

Although little mortality is associated with FGDs including IBS, effective treatment is often difficult leading to (or exacerbating) multiple and costly medical procedures, decreased compliance and altered healthcare-seeking behaviour. Existing treatment options range from a number of symptom-oriented pharmacological options to psychological treatments, including psychotherapy and hypnotherapy (Enck et al. 2010). Given the bio-psycho-social disease model (Tanaka et al. 2011), it is recommended that these conditions are treated with interdisciplinary, personalized treatment approaches that require particular attention to the doctor–patient relationship (Palsson and Drossman 2005). Hence, apart from the high clinical relevance of visceral pain in FGDs, these conditions in general and IBS in particular can be viewed as "model conditions" in the development and testing of conceptual approaches aimed at understanding and improving the integration of the psychosocial context into treatment concepts. Indeed, within the field of clinically oriented placebo research, one primary goal is to integrate patient expectations and experiences into more "personalized" treatment approaches that integrate medical and psychological aspects. Interestingly, it is indeed in patients with IBS that the remarkable clinical effectiveness of a placebo-based intervention has been demonstrated in a clinical trial (Kaptchuk et al. 2008, 2010). Clearly, these seminal findings have catapulted visceral pain and IBS into the focus of placebo researchers both in basic and clinical sciences who strive to transfer knowledge from placebo research into clinical application.

2 Relevance of Placebo and Nocebo Effects in Visceral Pain

The seminal results of the above mentioned clinical trial with placebo acupuncture in IBS (Kaptchuk et al. 2008), together with another trial revealing the feasibility and clinical effectiveness of "open" placebo treatment without deception

(Kaptchuk et al. 2010), have impressively demonstrated the putative clinical potential of placebo treatment in IBS. Moreover, there exist at least two additional considerations that drive ongoing efforts to produce more experimental and clinical data on placebo and nocebo effects in visceral pain both in patients and healthy individuals. The first is the fact that IBS patients (and patients with other types of gastrointestinal conditions including IBD and GERD) demonstrate large placebo responses in clinical trials. For example, in a recent meta-analysis Ford et al. found that in 73 eligible RCTs including 8,364 patients with IBS allocated to placebo, pooled placebo response rate across all RCTs was 37.5 % (Ford and Moayyedi 2010). Similar results were reported in an earlier, smaller meta-analysis including 45 placebo-controlled RTCs (Patel et al. 2005). Herein, the population-weighted average placebo response rate was 40.2 % (Patel et al. 2005). Finally, in a meta-analysis of 19 randomized and placebo-controlled complementary and alternative medicine (CAM) trials, the pooled estimate of the placebo response rate was 42.6 %, and hence comparable when compared to "conventional" medical therapy trials (Dorn et al. 2007). However, it should also be noted that placebo response rates in functional bowel disorders (functional dyspepsia, irritable bowel syndrome) trials are similar to those in other pain conditions and are also comparable with other organic gastrointestinal diseases (duodenal ulcer, inflammatory bowel diseases) (Enck et al. 2012). Despite these facts, findings of high placebo response rates in FGDs, irrespective of differences or similarities with other conditions, have in fact contributed to a "negative image" of placebo effects as "nuisance" (Enck et al. 2008) which hinders rather than helps efforts to identify effective treatment options for FGDs. This negative view is only slowly being replaced by a more constructive appreciation of the chances associated with an improved understanding of psychological factors in general and placebo/nocebo knowledge in particular (Enck et al. 2013; Finniss et al. 2010; Price et al. 2008) with interesting contributions to our understanding of the pathophysiology and treatment of chronic abdominal pain (Elsenbruch 2011; Enck et al. 2012; Lu and Chang 2011). This is paralleled by more refined knowledge regarding the conceptualization, design, and analysis of clinical trials (Enck et al. 2013; Rief et al. 2011).

Secondly, there is a growing appreciation for the potential of placebo and nocebo research in interdisciplinary science aimed at elucidating the pathophysiology of chronic abdominal pain and IBS. Indeed, placebo analgesia and nocebo hyperalgesia constitute fruitful experimental models to assess the contribution of psychological factors in altered responses to visceral stimuli in general and visceral hyperalgesia in particular. In fact, it has been prominently noted already several years ago that "...these forms of hyperalgesia are also highly modifiable by placebo and nocebo factors [...], synergistic interactions occur between placebo/nocebo factors and enhanced afferent processing so as to enhance, maintain, or reduce hyperalgesia in IBS" (Price et al. 2009), thereby catapulting placebo/nocebo issues "at the heart" of a multi-factorial, psychosocial disease model. Since then, a number of experimental studies assessing the mechanisms mediating placebo and nocebo effects in IBS and healthy volunteers have been accomplished. These findings, reviewed in the following section, have not only contributed to our understanding

of placebo and nocebo effects in visceral pain, but have also highlighted the pivotal role of psychological factors in the response to visceral pain. Indeed, the study of nocebo and placebo effects in visceral pain constitutes a model to assess the contribution of psychological factors to the pathophysiology of IBS and other clinical conditions associated with chronic abdominal pain and medically unexplained bodily complaints (Elsenbruch 2011).

3 Mechanistic Studies

Knowledge about the neurobiology and neuropsychology underlying placebo and nocebo effects in visceral pain is steadily improving, but overall experimental evidence is much more limited in visceral pain when compared to somatic pain. Of note, separate studies in clinically relevant visceral pain models are important given significant differences between visceral and somatosensory signal processing both in the periphery and within the central nervous system. In fact, several fMRI studies support distinct processing of somatosensory and visceral pain in the human brain (Aziz et al. 2000; Dunckley et al. 2005a, 2007; Eickhoff et al. 2006). Similar differences also appear to exist within the brainstem (Dunckley et al. 2005b). Furthermore, attentional modulation of pain intensity perception for visceral and somatic pain, respectively, is reflected in different brain regions (Dunckley et al. 2007), which is interesting in the context of placebo-induced pain modulation. Finally, recent evidence showed that although statistically significant, the correlation between individual pain thresholds for visceral and somatic stimulation is relatively weak (Horing et al. 2013). Hence, although no studies exist that have directly compared the neural mechanisms mediating placebo analgesia in somatic vs. visceral pain models, it appears highly likely that the brain mechanisms differ. Therefore, studies on *visceral* placebo analgesia in no way duplicate but rather complement and extend findings from research using somatic pain models and/or address other chronic pain conditions. Using a barostat, pressure-controlled distensions of the rectum or oesophagus can be accomplished, and this procedure constitutes a clinically relevant, valid, and reliable visceral pain model. This paradigm represents the "gold standard" in the study of visceral sensitivity, very closely induces ("mimics") visceral discomfort or pain as well as urge-to-defecate (in the case of rectal distension), and is safely applicable in healthy subjects as well as patients. It also allows the determination of sensory thresholds for perception and pain such that individualized stimuli at pre-determined intensity levels for application in studies, including fMRI studies, can be chosen. Of note, with one exception of esophageal distensions (Lu et al. 2010), all experimental placebo and nocebo studies in the visceral pain field, reviewed below, have applied rectal distensions.

3.1 Experimental Placebo Studies

The group around D. Price was the first to conduct experimental placebo studies in the visceral pain field. Several studies, which all used the rectal distension model, were conducted within IBS patients (Price et al. 2007; Vase et al. 2003, 2005): The first study (Vase et al. 2003) documented that IBS patients reported significant reductions in rectal distension-induced pain intensity and pain unpleasantness in the placebo condition (i.e. verbal suggestions for pain relief regarding an inactive gel that was applied to the rectal balloon). The study also included conditions with rectal and oral lidocaine application, respectively. Interestingly, no differences were found between the placebo and either lidocaine condition and given previous findings by the same group showing that rectal lidocaine reversed visceral hyperalgesia (Verne et al. 2005), the authors concluded that "adding a verbal suggestion for pain relief can increase the magnitude of placebo analgesia to that of an active agent" (Vase et al. 2003). As this constituted the very first placebo study in the visceral pain field, this conclusion proved "prophetic" in the sense that today—a decade later—there is good evidence to support that placebo interventions may be used not only to enhance or complement conventional treatment approaches for IBS, but in fact to use them instead of pharmacological treatments (Kaptchuk et al. 2008, 2010). In a second study (Vase et al. 2005), the authors could again show a large placebo effect in a group of IBS patients in the same pain and placebo analgesia paradigm (i.e. rectal distensions delivered with instructions of pain relief). Interestingly, the placebo effect reportedly increased over time, while ratings of expected pain, desire for pain relief and anxiety decreased successively, resulting in more variable placebo responses during later parts of the experimental session. Based on these findings, the authors suggested that a reduction in negative emotions could play a role in placebo analgesia (Vase et al. 2005) (for a more detailed discussion of findings regarding the putative role of emotions, see Sect. 4). Further, the authors found no effect of naloxone treatment on the placebo response, indicating that herein the placebo effect was not associated with (or mediated by) endogenous opioids (Vase et al. 2005). This negative finding is interesting given broad evidence that somatic placebo analgesia involves the endogenous opioid system (Benedetti 1996; Benedetti et al. 2005; Eippert et al. 2009; Petrovic et al. 2002; Zubieta et al. 2005). This raises the question if indeed the mechanisms mediating placebo analgesia may be specific for pain modality and/or condition.

Owing to the growing appreciation of the crucial role of the brain in pain processing in general and placebo analgesia in particular, several groups have since then accomplished mechanistic placebo studies in visceral pain using brain imaging techniques. The first published brain imaging study on placebo effects in visceral pain was a positron emission tomography (PET) study (Lieberman et al. 2004). Herein, the brain response to rectal distensions in IBS patients was analyzed both before and after a 3-week placebo regimen. Increases in ventrolateral prefrontal cortex (VLPFC) activity from pre- to post-placebo treatment predicted self-reported symptom improvement, and this relationship was mediated by changes in dorsal anterior cingulate cortex (Lieberman et al. 2004). The second

brain imaging study (Price et al. 2007) used fMRI to assess rectal distension-induced brain activation in patients with IBS in the same rectal placebo paradigm described above (Vase et al. 2003, 2005). The results revealed large reductions in pain ratings and in distension-induced brain activation within pain-related regions (i.e. thalamus, somatosensory cortices, insula, and anterior cingulate cortex) in the placebo condition. The authors noted that decreases in activity were related to suggestion (i.e. expectation) and a second factor ("habituation/attention/conditioning") (Price et al. 2007). Two re-analyses (Craggs et al. 2007, 2008) of this first fMRI study in IBS patients (Price et al. 2007) were subsequently carried out: One connectivity analysis described the interactions of neural networks during placebo analgesia using structural equation models (Craggs et al. 2007), the other focussed on the temporal characteristics of neural networks activated during placebo analgesia (Craggs et al. 2008).

The above studies were carried out exclusively in patients with IBS. Placebo analgesia and its underlying neural mechanisms were first described for healthy humans in a study utilizing an esophageal distension pain model (Lu et al. 2010). The authors reported large reductions of pain extent and pain ratings, along with reduced brain activity in the visceral pain matrix (i.e. thalamus, somatosensory cortices, insula, prefrontal cortex, and anterior cingulate cortex) in the placebo condition in healthy subjects (Lu et al. 2010). Interestingly, this was also the first study to pay attention to pain anticipation, which appears to play a significant role in subsequent responses to pain. Herein, the VLPFC was associated with increased activity during anticipation of visceral pain, which was interpreted as evidence in support of "top-down control" in the modulation of the pain experience (Lu et al. 2010). Utilizing the rectal distension model, our group has implemented several expectation-induction and learning procedures to study visceral placebo (along with nocebo) responses utilizing behavioural, peripheral, and central measures including fMRI (Benson et al. 2012; Elsenbruch et al. 2012a, b; Kotsis et al. 2012; Schmid et al. 2013, 2014; Theysohn et al. 2014). In this series of studies, our first main goal was to clarify the role of expectation in visceral placebo analgesia in healthy volunteers (Elsenbruch et al. 2012a). To do so, we delivered visceral pain stimuli in three expectation conditions designed to vary the level of expectancy regarding the intravenous administration of a supposed analgesic drug which was in reality saline. In a within-subject design with a counterbalanced order of conditions, participants were told that they had a 100, 50, or 0 % chance of receiving the active drug. The results revealed that the expectation of pain relief effectively reduced perceived painfulness of visceral stimuli in a "dose-dependent" manner, i.e. the greater the expectation of analgesia, the more pronounced the placebo analgesic effect. Analysis of blood-oxygen-level-dependent (BOLD) responses during cued pain anticipation and painful stimulation revealed that placebo analgesia was associated with activity changes in the thalamus, prefrontal, and somatosensory cortices in placebo responders when comparing the 100 % and 0 % expectation conditions (Elsenbruch et al. 2012a). Expectation-induced changes in cortical activation were particularly pronounced for the pain anticipation phase, underscoring the pivotal role of pain anticipation in central pain modulation during

placebo-induced positive expectation, consistent with findings in the oesophageal placebo analgesia study reviewed above (Lu et al. 2010). In a follow-up analysis of the 50 % expectation condition of this dataset, we could show that *perceived* treatment allocation affected behavioural and neural responses to placebo treatment (Kotsis et al. 2012). Given a 50 % probability of receiving active treatment, the magnitude of placebo-induced subjective pain relief and pain-induced neural activation was significantly greater in subjects who believed to be in the active treatment group. These findings have interesting implications for clinical trials where patients are typically told that they have a 50 % chance of receiving the active drug. Our most recent work has subsequently focussed on implementing and testing experimental paradigms to study nocebo hyperalgesia in parallel to placebo analgesia in visceral pain, in order to be able to better understand these opposite effects and their underlying mechanisms at the behavioural and neural levels. These studies (Elsenbruch et al. 2012b; Schmid et al. 2013) are summarized in detail below (see Sect. 3.2).

All studies reviewed thus far were conducted either exclusively within IBS patients or exclusively within healthy controls, which precludes an assessment of possible alterations in the neural response during placebo analgesia in patients with chronic abdominal pain. To this date, there exist only two studies (Lee et al. 2012; Schmid et al. 2014), one of them from our group, that *directly* compared placebo analgesia responses in IBS patients and a healthy control group. In the first study (Lee et al. 2012), placebo analgesia was induced by a combination of verbal suggestions and a prior learning experience (i.e. "pre-conditioning") involving a technical manipulation to simulate a potent analgesic effect. The results of this study revealed comparable placebo analgesia responses in IBS patients compared to healthy controls in subjective parameters, including pain ratings. Interestingly, greater anxiety responses were negatively correlated with the magnitude of placebo-induced subjective pain reduction, which led the authors to suggest that higher affective disturbances in IBS patients may predict a weak placebo effect. Furthermore, despite comparable placebo responses at the behavioural level, there was greater activity in affective and cognitive brain regions, including the insula, cingulate cortex, and VLPFC in IBS patients during placebo analgesia, suggesting altered neural processing of placebo-induced changes in pain perception in IBS (Lee et al. 2012). These data are supported by our own recently published data (Schmid et al. 2014) showing similar behavioural placebo analgesia but altered neural modulation in IBS patients not only when compared to healthy controls but also to patients with ulcerative colitis in remission, suggesting a specific deficit in endogenous pain inhibition due to affective disturbances in IBS (Fig. 1).

Together, these studies impressively demonstrate that placebo-induced cognitive and/or learning processes are highly relevant for central and behavioural pain responses not only in patients but also in healthy controls. At the same time, there exist several areas where more knowledge is urgently needed (for details, see Sect. 4). In this context of mechanistic studies, two aspects appear most important: First, more studies comparing the mechanisms mediating placebo responses in patient groups compared to healthy control groups are clearly needed to

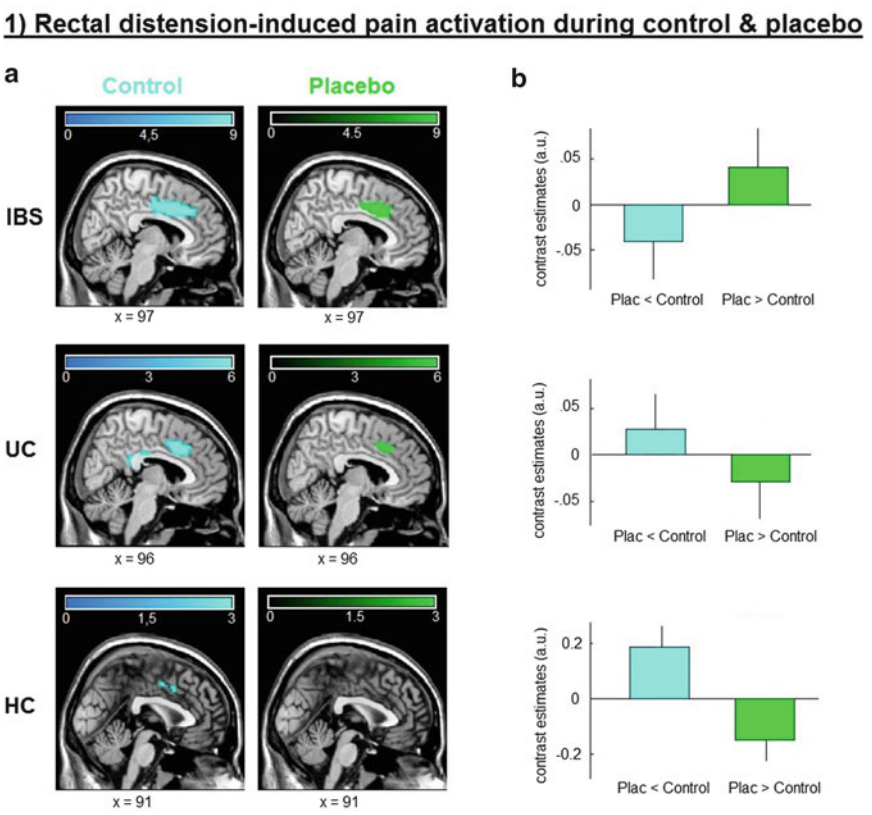

Fig. 1 (**a**) Rectal distension-induced neural activation in the midcingulate cortex in the control condition (i.e. neutral expectations induced by instructions of receiving saline, *left column*, activation shown in *blue colour*) and placebo condition (i.e. expectation of pain-relief induced by deceptive instructions of receiving a spasmolytic drug, *right column*, activation shown in *green colour*) in patients with irritable bowel syndrome (IBS, *upper row*), patients with ulcerative colitis in remission (UC, *middle row*), and healthy controls (HC, *lowest row*). Results of within-group analyses on the contrast (placebo > off) using one-sample *t*-tests revealing significantly reduced pain-induced neural activation in the placebo condition in UC and HC but not in IBS, resulting in significant group differences upon two-sample *t*-tests (not shown). Images overlaid on a structural T_1-weighted MRI used for spatial normalization and thresholded at $p < 0.05$ uncorrected using an anatomical mask for visualization purposes; colour bars indicate *t*-score. (**b**) Plots of contrast estimates of changes in pain-related neural activation in the respective differential contrast within each group for the cingulate cortex, a.u., arbitrary units [Adapted from Schmid et al. (2014)]

complement and extend the only two existing study (Lee et al. 2012; Schmid et al. 2014). Second, although expectation and conditioning have been identified as the two major neuropsychological mechanisms mediating placebo and nocebo effects, in the above reviewed experimental research on visceral placebo analgesia there exists virtually no data addressing the putative role of conditioning/learning

mechanisms. Most published studies have either focussed on placebo paradigms which manipulate expectation alone or utilized verbal suggestions in combination with a prior learning experience (i.e. "pre-conditioning") In those studies, it is not possible to disentangle effects of expectation and learning/conditioning, which is another area where more research is clearly needed (for more details on the putative role of learning/conditioning, see Sect. 4).

3.2 Experimental Nocebo Studies

To this date, virtually no experimental evidence exists regarding nocebo effects in visceral pain. To close this research gap, we recently implemented different experimental approaches to investigate nocebo effects in a clinically relevant visceral pain paradigm (i.e. rectal distensions) in healthy volunteers. In a behavioural study, we implemented a combination of negative verbal suggestions about (supposed) pain sensitization and a prior learning experience of surreptitiously enhanced pain intensity (i.e. "pre-conditioning"). The results revealed significantly greater pain ratings (i.e. nocebo hyperalgesia) and increased anticipatory anxiety in the nocebo group when compared to both a placebo group and a group who received neutral instructions (Elsenbruch et al. 2012b).

In a subsequent fMRI study, we assessed the neural mechanisms mediating visceral nocebo hyperalgesia along with placebo analgesia in a separate group of healthy volunteers (Schmid et al. 2013). To do so, effects of negative (nocebo) and positive (placebo) treatment expectations following intravenous application of an inert substance on the response to painful rectal distensions were analysed in two groups: Whereas the placebo group received positive instructions of pain relief due to the supposed application of a spasmolytic drug with analgesic properties, the nocebo group was instructed about an increase in pain due to the application of the opioid antagonist naloxone. In reality, only saline was administered in all groups. Within each group, there a control condition was implemented (in counterbalanced order) during which participants received truthful neutral instructions of saline application, allowing us to directly contrast positive and negative expectations, respectively, with neutral expectations in analyses of BOLD responses. As expected, results in the placebo group revealed significantly reduced rectal-distension induced perceived pain (Fig. 2a) along with a reduction of pain-induced neural activation within the insula (Fig. 2b). Interestingly, the nocebo group showed increased perceived pain (Fig. 2a), which was paralleled by increased insula activation during painful stimulation when comparing negative and neutral expectations (Fig. 2c) (Schmid et al. 2013).

Given that the insula is crucial for interoception, multi-modal sensory integration as well as pain-related decision making and emotional awareness (Craig 2003; Linnman et al. 2011; Wiech et al. 2010), these findings are an important step in identifying the brain mechanism(s) mediating visceral pain modulation by expectations. Since our insula finding during nocebo hyperalgesia is in line with existing brain imaging data on nocebo hyperalgesia for somatic pain (Bingel

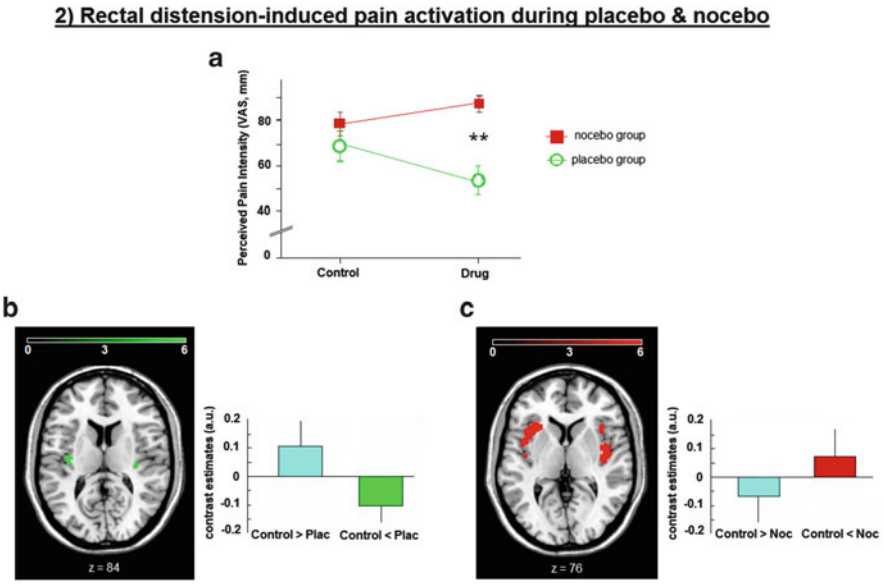

Fig. 2 (**a**) Visual analogue scale (VAS, 0–100 mm) ratings of perceived pain intensity in response to rectal distensions in the placebo and nocebo groups during neutral expectations (control: truthful instructions of saline administration) and deceptive drug-specific expectations (i.e. placebo group: instructions of a spasmolytic drug; nocebo group: instructions of an opioid antagonist). The placebo and nocebo groups differed significantly in perceived pain ratings during drug-specific expectations (**results of post-hoc independent samples *t*-test: $p < 0.001$). Data are shown as mean ± standard error of the mean (SEM). (**b**) Rectal distension-induced modulation of neural activation by deceptive verbal suggestions within the placebo group revealing significantly reduced activation of the insula during positive (placebo) compared to neutral expectations (control). (**c**) Within the nocebo group, insula activation was significantly increased during negative (Noc) when compared to neutral expectations (control). *Left columns* in **b, c**: Images overlaid on a structural T_1-weighted MRI used for spatial normalization and thresholded at $p < 0.01$ using an anatomical mask and uncorrected for visualization purposes. *Colour bars* indicate *t* score. *Right columns* in **b, c**: Plots of parameter estimates of changes in pain-related neural activation in differential contrasts within the insula, a.u., arbitrary units [Adapted from Schmid et al. (2013)]

et al. 2011; Kong et al. 2008), one may conclude that there may exist at least some shared brain regions for central pain modulation by cognitions and/or emotions, irrespective of pain modality. Interestingly, we previously documented more pronounced insula modulation in a negative emotional context, induced by psychosocial stress, in IBS patients (Elsenbruch et al. 2010), supporting a role of the insula in pain modulation also in patients with chronic abdominal pain.

Our nocebo results are especially interesting in light of recent evidence that negative treatment expectancy abolished opioid analgesia in a somatic pain model (Bingel et al. 2011). Together, these findings strongly underscore that negative expectations induced by verbal suggestions shape the response to pain, irrespective of the presence of an actual analgesic drug. Furthermore, they extend our own

previous work in which we induced nocebo hyperalgesia by negative expectations resulting from non-drug-related suggestions about an impending worsening of pain together with surreptitiously increased distension pressures ("pre-conditioning", see above) (Elsenbruch et al. 2012b). Together, these data support that nocebo effects in experimental pain can occur as a result of verbal suggestions in the context of active as well as inert pharmacological substances (Benedetti et al. 2006; Bingel et al. 2011; Scott et al. 2008), and also in situations that induce negative expectations not resulting from drug-related information but rather disease-related information as well as from learning or conditioning (Colloca et al. 2008, 2010; Jensen et al. 2012; Kong et al. 2008). For a transfer of this knowledge into clinical application, it is important to appreciate that in daily clinical routine, negative expectations regarding worsening of symptoms can occur through a number of possible factors which may or may not involve an actual drug or medication (Colloca and Miller 2011). In fact, there is increasing appreciation that it is the *entire* context surrounding medical encounters that shapes patients' expectations and hence placebo and nocebo responses in daily clinical practice (Colloca and Miller 2011). By inference, attempts to systematically reduce or minimize nocebo effects in clinical settings will have to address treatment-specific as well as non-treatment directed negative expectations, which could pose a challenge that researchers will have to overcome once more data becomes available describing nocebo effects in clinical settings—which is thus far not available in the field of visceral pain.

In conclusion, taking together results from experimental pain research in visceral and other pain models unequivocally underscores the "power" of positive and negative expectancies in shaping the response to pain not only at the behavioural level but also within the brain. Indeed, brain imaging studies have made a fundamental contribution to leaving behind earlier criticism that placebo or nocebo responses are merely the result of a response bias (Price et al. 2008) and moving to discerning the neural mechanisms mediating placebo/nocebo-induced alterations in endogenous pain inhibition. At the same time, the role of genetic (Hall et al. 2012) and peripheral mechanisms, including neuroendocrine and immune mediators (Elsenbruch et al. 2012b; Kokkotou et al. 2010), is beginning to emerge. Continuing this work in the visceral pain field will be vital for us to gain a more complete picture encompassing the complex interactions between the central nervous system and the periphery during visceral placebo and nocebo responses as a basis for much needed clinically oriented research not only in IBS patients but also in other gastrointestinal conditions such as inflammatory bowel diseases (Bonaz and Bernstein 2013).

4 Perspectives and Future Research Goals

4.1 Learning/Conditioning

More research is needed to discern the role of learning/conditioning processes in placebo and especially in nocebo effects in visceral pain models and in patients with chronic visceral pain. As reviewed above, there currently exists only very limited experimental and clinical evidence on nocebo effects in visceral pain, and the few existing studies have primarily focused on the role of negative expectations. However, nocebo findings in somatic pain models support a role of learning/conditioning processes in nocebo effects, although available research does remain scarce and heterogeneous also in the somatic pain field. For example, Colloca et al. showed that one session of conditioning (i.e. pairing coloured lights to stimuli that were surreptitiously increased or reduced in intensity) was sufficient to induce nocebo responses to non-painful and painful stimuli (Colloca et al. 2010), but these responses extinguished rapidly. Four sessions of conditioning led to more robust nocebo responses that did not extinguish as rapidly, supporting that the "strength" of learning is related to the magnitude of the nocebo response. On the other hand, in an earlier study, the same group reported that a preconditioning procedure did not increase allodynia and hyperalgesia induced by verbal suggestions alone (Colloca et al. 2008), leading the authors to conclude that learning may be less in important in nocebo hyperalgesia when compared to its role in placebo analgesia. More recently, Jensen et al. implemented visual cues indicating high and low pain to induce nocebo and placebo responses (Jensen et al. 2012). While visual cues were designed to be clearly visible in one experiment, there occurred non-conscious (masked) exposure to the same cues in a second experiment. The results revealed significant nocebo effects for both clearly visible as well as masked visual cues, supporting that nocebo effects can be induced without conscious awareness of the predictive cues (Jensen et al. 2012).

These findings provide an interesting link to another learning-based experimental paradigm that is well-established in the field of learning and memory, namely fear conditioning. Fear conditioning and its extinction is based on the principles of classical conditioning and is an established translational model both in the context of anxiety disorders, drug addiction and relapse, and (chronic) pain (Milad and Quirk 2012). During fear conditioning, neutral stimuli are repeatedly paired with aversive unconditioned stimuli (US). In many studies, the US is a painful stimulus, most commonly electric shock, which is consistently paired with neutral visual stimuli during a learning/conditioning phase (Sehlmeyer et al. 2009). As a result of contingent pairing of neutral stimuli and US, the previously neutral stimuli turn into predictive cues that are now fear-provoking conditioned stimuli (CS) even when presented alone. When applied to the putative conditioning/learning mechanisms mediating nocebo hyperalgesia, this model may prove useful and relevant since conditioned pain-related anticipatory fear likely contributes to hyperalgesia and its underlying central mechanisms. In other words, one may reconceptualise the CSs as pain-signalling predictive cues capable of eliciting (or enhancing) nocebo

responses. Indeed, the concept that classical conditioning is relevant for placebo effects is well-established in classically conditioned immunosuppression, but thus far it has not been systematically studied in the context of nocebo hyperalgesia in pain models. There does, however, exist evidence from human and animal research supporting a link between conditioned fear and hyperalgesia. For example, effects of conditioned fear on somatic pain thresholds have been documented in healthy volunteers (Williams and Rhudy 2007). In animal models of visceral hypersensitivity, learned associations between predictive contextual cues and painful stimuli were reportedly relevant for the development of visceral hypersensitivity (Tyler et al. 2007) and for the retrieval of visceral pain-conditioned passive avoidance (Wang et al. 2011). In IBS patients, conditioning led to reduced pain thresholds (Nozu et al. 2006) and a role of interoceptive fear conditioning in visceral pain has been proposed (De Peuter et al. 2011). Hence, associative learning and extinction processes appear to be involved in hyperalgesia and may thereby contribute to nocebo responses in pain. Although the vast majority of existing human fear conditioning studies utilized non-visceral USs (e.g. electric shock), it is possible to implement fear conditioning with oesophageal or rectal distensions as effective US (Kattoor et al. 2013, 2014; Schmid et al. 2013; Yágüez et al. 2005). Based on these initial studies, more research is needed to provide data addressing the putative role of learning/conditioning in nocebo effects. In doing so, it will be important to disentangle classically conditioned processes that may operate without conscious awareness from primarily "conscious" learning experiences that trigger cognitions because of expectations.

Finally, in the context of learning mechanisms, recent advances have been made pointing to the role of social/observational learning in nocebo hyperalgesia, which may also prove relevant for patients with visceral pain (Swider and Babel 2013; Vögtle et al. 2013). Herein, it will be necessary to develop and test appropriate paradigms to assess observational/social learning in nocebo (as well as placebo) effect using clinically relevant visceral pain models.

4.2 Trait and State Emotions

The putative relevance of psychological trait and state variables is only beginning to be understood, and there is growing evidence from the somatic pain field to suggest a role of emotions in nocebo as well as placebo responses (Flaten et al. 2011). In nocebo effects, the role of negative emotions, especially anxiety and stress, has previously been documented in several pain models, including experimental ischemic arm pain (Benedetti et al. 2006; Johansen et al. 2003), painful mechanical and/or electrical stimulation (Colloca et al. 2008, 2010; van Laarhoven et al. 2011), and heat pain (Kong et al. 2008) in healthy subjects, as well as in patients with postoperative pain (Benedetti et al. 1997). Given the small number of available nocebo studies in visceral pain models, it is difficult to ascertain if negative emotions play a similar role in visceral nocebo hyperalgesia. In our own first nocebo study implementing the rectal distension pain model in

healthy individuals, we observed significantly greater anticipatory state anxiety in the nocebo group (Elsenbruch et al. 2012b). On the other hand, our subsequent fMRI nocebo study revealed significant nocebo hyperalgesia in the nocebo group in the absence of obvious changes in state anxiety or tension (Schmid et al. 2013). Based on these negative findings, we concluded that it is possible for nocebo hyperalgesia to occur in the absence of increased negative emotions.

The notion that placebo effects could be mediated at least in part by reduced negative emotions has been put forward (Flaten et al. 2011) based on the previously established connection between placebo analgesia and reward processing (Petrovic et al. 2005). However, with one recent exception (Lyby et al. 2012), no studies exist thus far which have directly manipulated emotions in order to directly test for changes in placebo and/or nocebo responses. In this study, the authors tested effects of experimentally-induced fear (i.e. anticipation of electric shock) on subsequent placebo analgesia in a somatic pain model. The results supported that induced fear abolished placebo analgesia, especially in participants with high fear of pain (Lyby et al. 2012). These findings fit together nicely with correlative evidence from the study by Lee et al. (see above) showing that within IBS patients, high scores on the Hospital Anxiety and Depression Scale correlated significantly and negatively with indicators of the placebo analgesia response (Lee et al. 2012). These findings led the authors to suggest that affective disturbances (. . .) "might partially predict a weak placebo effect in IBS patients" (Lee et al. 2012), which is clearly supported by our own recent IBS data showing a correlation of weaker placebo analgesia with higher depression scores on the Hospital Anxiety and depression scale (Schmid et al. 2014). Given proper replication also in other pain models and conditions, these findings have important implications for attempts to bring experimental findings from the placebo field into the clinic. Herein, it will then be important to incorporate and systematically take into account emotional state and trait variables of the patient, including fear of pain (Lyby et al. 2011). This would be especially important in clinical settings that are per se anxiety-provoking, such as in the context of receiving treatment following a frightening diagnosis or awaiting a potentially painful treatment such as a surgical intervention. Clearly, more knowledge about effects of trait and state emotions on placebo analgesia and nocebo hyperalgesia is needed to improve our understanding of inter-individual differences in placebo and nocebo responses. Given effects of positive and negative expectations on drug efficacy (Bingel et al. 2011) and effects of patients–provider interaction on the magnitude of placebo effects (Kaptchuk et al. 2008), a more refined understanding about the role of emotional context factors will be crucial for optimizing doctor-patient communication irrespective of treatment with a "real" drug or a placebo. This can ultimately lead to more effective and "personalized" (placebo) treatments while minimizing unwanted nocebo effects.

4.3 Sex/Gender Differences

Knowledge regarding possible sex and/or gender differences in placebo analgesia is scarce, and virtually non-existent in nocebo hyperalgesia (Bjorkedal and Flaten 2012; Swider and Babel 2013). Indeed, a recent review concluded that "studies are urgently required in order to better understand the role of sex-gender on placebo mechanism and its impact on randomized clinical trials outcomes" (Franconi et al. 2012). Attempts to draw conclusions about possible sex differences in placebo/nocebo responses in visceral pain are further complicated by the fact that the role of sex or gender in the response to and central processing of visceral stimuli themselves (without additional placebo/nocebo modulation) remains incompletely understood. Although sex differences in the prevalence of the functional gastrointestinal disorders including IBS are well-documented (Chang et al. 2006b; Fillingim et al. 2009; Mayer et al. 2004; Mogil and Bailey 2010; Unruh 1996), experimental evidence is scares and heterogeneous. Studies on sex differences in visceral sensitivity revealed conflicting and even contradictory results. For example, in healthy subjects, results demonstrated no sex differences (Kern et al. 2001; Sloots et al. 2000; Soffer et al. 2000), reduced perception but normal pain thresholds in females (Kim et al. 2006), and increased discomfort thresholds in females (Chang et al. 2006a). For patients with IBS, current evidence is similarly conflicting (Berman et al. 2000; Chang et al. 2006a; Mertz et al. 1995). At the level of neural processing of visceral stimuli, the few available brain imaging studies supported sex differences in IBS patients (Berman et al. 2000; Labus et al. 2008; Naliboff et al. 2003). In healthy subjects, on the other hand, the few existing fMRI studies revealed contradictory results. Whereas Berman et al. found a trend for greater activation in males in the insula, anterior, and midcingulate cortex compared to females (Berman et al. 2006), Kern et al. reported the opposite result, i.e. an activation of the insula and anterior cingulate cortex (ACC) only in females, but not in males (Kern et al. 2001). In age- and BMI-matched healthy subjects, we assessed sex differences in rectal sensory and pain thresholds along with the neural response to painful rectal stimuli (Benson et al. 2012). Our analysis of rectal thresholds revealed no differences between males and females. At the level of the brain, males and females demonstrated a largely comparable pattern of neural activation in the majority of pain-processing brain regions, although there was a tendency for females to show a slightly different activation of prefrontal regions during cued anticipation and pain (Benson et al. 2012). Building on our fear conditioning work with rectal pain as unconditioned stimulus (Gramsch et al. 2014; Kattoor et al. 2013, 2014), we recently documented sex differences in the neural mechanisms mediating fear conditioning, extinction, and reinstatement in healthy males and females (Benson et al. 2014), with interesting implications for the putative role of learned pain-related fear in nocebo hyperalgesia (Elsenbruch 2011).

Given these complex findings, it is not surprising that current evidence from placebo research is similarly conflicting. There exists some evidence from experimental placebo studies and clinical trials focusing on somatic pain (Aslaksen

et al. 2011; Averbuch and Katzper 2001; Butcher and Carmody 2012; Compton et al. 2003; Flaten et al. 2006), nausea (Klosterhalfen et al. 2009; Weimer et al. 2012), and IBS symptoms (Kelley et al. 2009). Herein, there are results supporting either greater placebo responses in men (Aslaksen et al. 2011; Butcher and Carmody 2012; Compton et al. 2003; Flaten et al. 2006) or in women (Kelley et al. 2009), or suggest no sex differences (Averbuch and Katzper 2001). Hence, it remains elusive if one sex shows larger placebo responses and may hence be considered to be more "placebo-prone". Of note, in this context it is crucial not only to consider the sex of the participant but also that of the investigator which reportedly plays a role at least in somatic pain responses (albeit without placebo modulation) (Aslaksen et al. 2007; Gijsbers and Nicholson 2005). For example, in a heat pain experiment, Aslaksen et al. reported that investigator x subject sex interaction influenced pain ratings with lower pain reports in male subjects given female investigators (Aslaksen et al. 2007). In addition, a recent study on nocebo hyperalgesia induced by social observational learning revealed that the magnitude of nocebo hyperalgesia was greater after a male model was observed, regardless of the sex of the subject (Swider and Babel 2013). Taken together, these initial results clearly indicate that there exist complex interactions between sex, sex hormones and gender (roles) that are likely to contribute to placebo and nocebo effects, which need to be addressed in future studies.

Conclusions

Results from clinical and experimental research in the field of visceral pain complement and extend findings from other pain modalities and in chronic somatic pain conditions. Together, this growing body of evidence unequivocally underscores the "power" of positive and negative expectancies and learning experiencing in shaping the response to pain not only at the behavioural level but also within the brain, with profound clinical implications. Indeed, brain imaging studies have made a fundamental contribution to leaving behind earlier criticism that placebo or nocebo responses may merely reflect response bias and moving to discerning the neural mechanisms mediating placebo/nocebo-induced alterations in endogenous pain inhibition. At the same time, the role of peripheral mechanisms, including mediators of the HPA axis and the autonomic nervous system, is beginning to be understood such that a more complete picture encompassing the complex interactions between the central nervous system and the periphery during placebo and nocebo responses is beginning to emerge. Within a bio-psycho-social conceptualization of placebo and nocebo mechanisms, emotions constitute primary targets for future research aimed at elucidating the *modulators* of placebo and nocebo responses both in experimental and clinical studies in the context of visceral pain and beyond.

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