Placebo effects and their determinants in gastrointestinal disorders

Sigrid Elsenbruch and Paul Enck

Abstract | Placebo effects in clinical trials have sparked an interest in the placebo phenomenon, both in randomized controlled trials (RCTs) and in experimental gastroenterology. RCTs have demonstrated similar short-term and long-term placebo response rates in gastrointestinal compared to other medical diagnoses. Most mediators and moderators of placebo effects in gastrointestinal diseases are also of similar type and size to other medical diagnoses and not specific for gastrointestinal diagnoses. Other characteristics such as an increase in the placebo response over time and the placebo-enhancing effects of unbalanced randomization were not seen, at least in IBS. Experimental placebo and nocebo studies underscore the 'power' of expectancies and conditioning processes in shaping gastrointestinal symptoms not only at the level of self-reports, but also within the brain and along the brain–gut axis. Brain imaging studies have redressed earlier criticism that placebo effects might merely reflect a response bias. These findings raise hope that sophisticated trials and experiments designed to boost positive expectations and minimize negative expectations could pave the way for a practical and ethically sound use of placebo knowledge in daily practice. Rather than focusing on a 'personalized' choice of drugs based on biomarkers or genes, it might be the doctor–patient communication that needs to be tailored.

Elsenbruch, S. & Enck, P. *Nat. Rev. Gastroenterol. Hepatol*. **12**, 472–485 (2015); published online 21 July 2015; doi:10.1038/nrgastro.2015.117

Introduction

Placebo research is a highly dynamic and rapidly evolving field, involving many disciplines spanning from the basic neurosciences to clinical medicine. Indeed, the placebo phenomenon is now receiving attention not only from scientists and clinicians striving to understand the underlying mechanisms and their implications in a treatment context, but also from other health-care professionals, policy makers and the general public. Until the initiation of dedicated experimental work about one decade ago, the term 'placebo' was primarily referred to in the context of clinical trials in which a placebo treatment or group had proven essential as a comparator to establish clinical efficacy of the experimental treatment. The remarkably large placebo effects in clinical trials, across medical diagnoses and treatments, resulted in a rather negative connotation of placebo effects as a 'nuisance' hampering advances in the development and testing of new drugs. Since then, much progress has been made owing to substantial advances in our understanding of the mechanisms and determinants driving placebo effects in clinical trials, paralleled by an improved mechanistic knowledge from experimental research. Today, the 'placebo effect' or 'placebo response' refers to the therapeutic outcome following an administration of an inert treatment, which is shaped by the entire psychosocial context surrounding a patient.[1] The definition of these terms are subject to an ongoing debate,[2–4] but we will herein use the terms nearly synonymously (see Glossary in Box 1). Now, a more constructive appreciation has arisen of placebo research as a fruitful model for neurogastroenterology and neuroscience, and a tool to advance the design and interpretation of clinical trials. A broad consensus exists across disciplines that placebo effects constitute real psychobiological phenomena with fundamental implications for the pathophysiology and treatment of medical conditions, which this Review aims to delineate specifically for the gastrointestinal field.

Institute of Medical Psychology & Behavioural Immunobiology, University Hospital Essen, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany (**S.E.**). Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, University Hospital, Tübingen University, Frondsbergstrasse 23, 72076 Tübingen, Germany (**P.E.**)

Correspondence to: P.E. paul.enck@uni-tuebingen.de

Competing interests
The authors declare no competing interests.

Historical perspective

"Success has many fathers, but failure is an orphan."
Tacitus, *Agricola* (c. 98AD)

In gastroenterology, the historical origins of the placebo concept and its underlying mechanisms are not well-known. Two scientific sources can be identified that explored the mechanisms of placebo effects with some reference to gastroenterology, shortly after placebo-controlled trials had become the standard in pharmacological research. The first is attributable to Henry K. Beecher's prominent statement referring to the 'powerful placebo'[5] and emphasizing the need for a placebo group in clinical trials. The closest Beecher came to gastroenterology was a referral to a study on nausea during seasickness[6] in which placebo response rates as high as 38% were noted. In his summary of the literature, Beecher[5] already referred to Steward Wolf and his

Key points

- Placebo response rates in randomized controlled trials in gastroenterology are of similar size, and mediators and moderators are of similar type to those in other medical subspecialties
- Some trends found in other medical subspecialties—for example, an increase of the placebo response over time and high placebo responses with unbalanced randomization—have been avoided in gastroenterology
- Experimental gastroenterology has shown that the placebo response (for example, in visceral pain and nausea) follows established rules and mechanisms (learning, expectations)
- Brain imaging studies have demonstrated that the placebo response is not merely a response bias, but exhibits neurobiological and psychobiological properties along the gut–brain axis
- With improved doctor–patient communication, it might be possible to boost the efficacy of drug treatment by utilizing the placebo mechanisms in daily practice

Box 1 | Glossary

Placebo
The word placebo is the Latin word for "I shall please". It is used to indicate sham treatments or inert substances such as sugar pills or saline infusions.

Nocebo
The term nocebo ("I shall harm") was introduced in analogy to 'placebo' to distinguish the positive from the noxious effects of placebos, when an inert substance is given in a negative context inducing negative expectations about the outcome, for example adverse events in placebo-controlled trials, or experimental hyperalgesia and nausea in the laboratory.

Placebo effect
The placebo effect is defined as average improvement of a symptom or physiological condition following a placebo intervention in a RCT. It includes methodological factors (regression to the mean, response bias), the natural course of the disease, and context factors (expectation, learning). The 'true' placebo effect is the placebo effect cleared for other contributing (or in fact confounding) factors such as the natural course of the disease or spontaneous symptom fluctuations. However, RCTs usually do not control for the natural course because this would require a 'no treatment' control group; instead, it is assumed that the natural course is equal in the drug and the placebo arm, which might not be the case.

Placebo response
The placebo response refers to the outcome caused by a placebo manipulation. It reflects the neurobiological and psychophysiological response of an individual to an inert substance or sham treatment and is mediated by various factors that make up the treatment context.

Natural course of a disease
This term describes the course and outcome of an illness in the absence of any treatment or intervention; the disease is left 'to run its natural course' that includes spontaneous variation in symptom severity, which is an immanent phenomenon in most chronic clinical conditions.

Placebo mediators, moderators
Predictors of the placebo response and/or effect can be divided into patient-based (personality, symptoms, history, etc.) and design-based factors (duration, intensity, frequency of interventions, etc.) that either are mediators, which are required to elicit the response (a neural pathway, a clinical condition) or are moderators that modulate the response (age, sex).

Locus of Control
The concept of a locus of control describes the belief of an individual of who or what is in control of events (health, well-being, social life, etc.) affecting them.[182] A person's locus of control is conceptualized as either being internal (believes to personally control his or her life) or external (believes to be controlled by others, by environmental factors that cannot be influenced, or by chance). The locus of control is part of an individual's personality (trait). A similar concept is the theory of 'self-efficacy'.[183] An external locus of control has been found to be related to higher placebo response than an internal locus of control.[122,184]

Abbreviation: RCT, randomized controlled trial.

work.[7] In a series of ingenious experiments in patients with gastric and other fistulae, Wolf and co-workers[8] explored psychological and physiological consequences, mostly intestinal changes following drug and placebo applications. Utilizing the mechanisms still discussed today to elicit placebo responses, namely expectations and associative learning (for example, Pavlovian conditioning [see Box 2]), the authors meticulously documented in two case studies that the nauseogenic effects of ipecac, a herbal drug to induce mild vomiting, could be completely abolished with convincing instructions suggesting improvement of nausea.[7] Along the same lines, gastric hypermotility after repeated neostigmine application onto the gastric mucosa could also be elicited by application of tap water or lactose when used deceptively.[7] This finding could well constitute the first documented experimental evidence of what we now refer to as the nocebo effect. In an almost forgotten landmark paper in 1959, Wolf summarized the 'pharmacology of placebos',[9] with extensive references to cardiology, pulmonology, infectious disease, psychiatry, surgery, and of course to gastroenterology. Research into the placebo response was then forgotten until the 1990s, when dedicated work in many disciplines started to emerge.

Placebo responses in clinical trials

Since the beginning of randomized and placebo-controlled trials (RCTs) in pharmacology,[10] placebo responses in RCTs have received great attention when they exceeded expectations; as was the case in early gastric and duodenal ulcer treatment trials of antacids and histamine-2 receptor antagonists[10,11] with placebo response rates of ≥50%.[10] These high placebo response rates and the strong positive correlation between the responses to drug and placebo were thought to indicate a major contribution of spontaneous ulcer remission.[10] Unless a 'no treatment' control group is integrated into a RCT (which is not the case in the majority of trials for ethical reasons), the relative contribution of the spontaneous course of the disease will be a substantial fraction of the placebo response. Usually, patients on the waiting list are thought to be a suitable representation of the 'natural disease course', but as we have elucidated,[12] this assumption is not the case as waiting for a future treatment might improve or worsen the symptoms by itself. Only novel RCT designs might be able to overcome this limitation, as might experimental work through inclusion of proper control groups (see section on mechanisms of placebo response). The contribution to the placebo response in RCTs of spontaneous symptom improvement was evaluated across different clinical conditions and was shown to be ~50% and it was >50% in nausea RCTs.[13]

A number of meta-analyses and systematic reviews have discussed the size of the placebo response in RCTs in gastrointestinal disorders, such as IBD, functional bowel disorders (IBS, functional dyspepsia), gastric and duodenal ulcerations and GERD. These disease-oriented meta-analyses are listed in Table 1, together with major

Box 2 | Psychological mechanisms—expectancy and learning

Expectancy is in most experiments manipulated by specific information, typically delivered via verbal suggestions or written study or drug-related materials, about the efficacy (or outcome) of a drug or therapeutic intervention. Experiments in somatic pain models have often used simple verbal cues to induce positive (placebo) or negative (nocebo) expectations to induce placebo analgesia or nocebo hyperalgesia, respectively.

Learning, comprising classical conditioning, instrumental learning and social observation, constitutes another principle mechanism underlying placebo and nocebo effects. In classic conditioning, repeated associations between a neutral stimulus and an active drug (unconditioned stimulus) or an aversive symptom can result in the ability of the neutral stimulus by itself to elicit a response characteristic of the unconditioned stimulus. Instrumental and social learning have been shown to induce or enhance placebo analgesia[185–187] and nocebo analgesia[188,189] in somatic pain models.

patient-based or design-based factors associated with high or low placebo response rates.

A rather early analysis of the placebo response in IBS by Klein was published in 1988 and summarized data from 43 trials conducted between 1959 and 1987.[14] According to his analysis, the average placebo response rate was as high as 55%, but as we will discuss later , these early trials lack adequate disease definition, responder definition and sample size, and thus do not represent overall RCT outcomes any longer. Klein summarized his findings with the provocative statement that "not a single study offers convincing evidence that any therapy is effective in treating the IBS symptom complex", which might have been true at that time, but certainly not after the development of standardized diagnostic criteria such as the Rome criteria, the formulation of adequate primary end points and responder definitions for RCTs, and adequate sample sizes.

According to the listed meta-analyses in Table 1, the pooled placebo response ranges between 20–35% in IBD, and 20–40% in IBS, functional dyspepsia, gastric and duodenal ulcer and GERD, with marginal differences between functional and somatic disorders (see Table 1). These differences are mainly due to the definitions of treatment response: clinical and/or endoscopic remission of IBD on the one hand; symptom improvement with patient or doctor-reported outcomes in functional bowel disorders on the other hand. Most gastrointestinal RCTs have used binary outcome definitions (that is, percent of responders). Comparison of these data to trials that have used continuous outcomes (for example, improvement in depression or pain ratings on a clinical visual analogue scale score) are difficult. However, a meta-analysis published in 2015 of nonvisceral pain trials using a 30% or 50% improvement as the binary outcome, revealed that the placebo response was responsible for the outcome at the following levels: 14% for central neuropathic pain; 23% for peripheral neuropathic pain; and 26% for diabetic neuropathic pain[15] compared to 20% for pancreatic pain treatment.[16] Placebo response rates in gastrointestinal trials are also comparable to trials in psychiatric diseases such as depression and schizophrenia with an average 40% pooled placebo response across many RCTs.[17]

Determinants of the placebo response

As indicated in Table 1, some of the determinants of the placebo response for the listed diseases might be unspecific for gastrointestinal disorders, but others might well be specific.

IBD

Mild or moderate symptoms at baseline in patients with Crohn's disease[18] constituted among the most frequently noted predictor of a high placebo response in psychiatric trials[17] as well as other and nonpsychiatric medical areas.[19] Similarly, a high number of study visits by patients with IBD[18,20] is associated with increased placebo response rates and indicates that one of the driving factors for the placebo response is the frequency of doctor–patient interactions.[21] The reason(s) why European trials or trials with European centre participation, generate higher placebo responses in patients with ulcerative colitis[22] than trials without European involvement remains uncertain. Trial organization, including the frequency of doctor visits and the type and intensity of contacts between patients and health professionals (for example, telephone, study nurse) might be different between US and European trials[23]; these factors have also been found to influence the placebo response rate in RCTs outside gastroenterology.[17]

IBS

Patient-reported outcomes have lower placebo responses than doctor-reported measures.[24] Similar to IBD, placebo responses in IBS trials are higher with longer trial duration[25,26] and shorter run-in periods,[25] but contradictory evidence exists[24] presumably owing to a different trial selection for the analyses. In addition, studies conducted earlier (that is, before 1990) had overall higher placebo responses than trials during the last 20 years' studies, which is also different from studies in depression[27] and schizophrenia.[28] The apparent contradiction between two of the analyses[25,29] with respect to the relevance of the frequency of study visits for the placebo response is due to the fact that the authors either calculated the total number of patient–doctor contacts[25] or the number of contacts divided by duration of trials.[29]

Functional dyspepsia

Specific predictors of the placebo response were found in functional dyspepsia. A higher BMI was associated with higher placebo response,[30,31] as was nonsmoking status, low symptom severity at baseline and symptoms progression during run-in,[31] but since these data were found in only a few trials independent validation is required.

Duodenal ulcers and GERD

The schedule of treatment regimens (two versus four doses per day) predicted a higher placebo response in patients with duodenal ulcers.[32] The presence of erosive oesophagitis was associated with reduced placebo response rates. PPI trials had lower placebo responses in comparison to earlier histamine-2 antagonist trials in patients with GERD.[33]

Table 1 | Contribution of patient-based and design-based factors to the placebo response*

Author	*n*	PPR	Disease	Age effects	Sex effects	Factors associated with increased placebo response
Ilnyckyj *et al.* (1997)[20]	38	26.7	Ulcerative colitis	NR	NR	Higher number of study visits
Garud *et al.* (2008)[22]	110	32.1	Ulcerative colitis	NR	NR	European studies, longer trial duration, higher number of patients
Su *et al.* (2004)[18]	21	19.0	Crohn's disease	No	No	Lower symptoms at baseline, concurrent therapy, higher number of visits
Gallahan *et al.* (2010)[23]	20	33.8	Crohn's disease	NR	NR	None reported
Pitz *et al.* (2005)[25]	84	36.0	IBS	Yes	No	Higher frequency of intervention, longer trials, shorter run-in, earlier studies
Patel *et al.* (2005)[29]	45	40.2	IBS	No	No	Lower number of study visits, Rome criteria at entry
Dorn *et al.* (2007)[26§]	19	42.6	IBS	No	No	Longer trial duration, more office visits
Ford *et al.* (2010)[24]	73	37.5	IBS	No	No	European studies, shorter trial duration, physician reported outcome
Talley *et al.* (2006)[30]	4‡	35.0	Functional dyspepsia	No	No	Higher BMI, inconsistent symptom pattern, gastric emptying delayed at baseline
Enck *et al.* (2009)[31]	1‡	22.2	Functional dyspepsia	No	No	Non-smoking, higher BMI, low symptoms at baseline, increase during run-in
Capurso *et al.* (2012)[16]	7	19.9	Pain in pancreatitis	NR	NR	Multicentre trials, short run-in
De Craen *et al.* (1999)[32‖]	79	36/44	Duodenal ulcers	No	No	None reported
Cremonini *et al.* (2010)[33]	24	18.9	GERD	No	No	Less in erosive oesophagitis, less in PPI therapies

*In published meta-analyses. ‡Individual patient data available. §Complementary and alternative medicine treatment. ‖For 4 per day versus 2 per day regimens. Yes or no, these factors were evaluated for their contribution to the PR. Abbreviations: BMI: body mass index; *n*, number of studies included; NR, not reported; PPR, pooled placebo response (%) based on a binary primary endpoint and the percentage of patients meeting the definition in the placebo arm.

Specifics of the placebo response

Unbalanced randomization

In RCTs concerning migraine,[34] depression,[35] and schizophrenia[36] it had been noted that randomly assigning more patients to an active treatment arm than to placebo, which is done for different reasons (for example, ethical, dose-testing, motivational) will result in higher placebo responses and drug responses because more patients know that they will receive active treatment. When Ford *et al.*[24] compared studies with a 50:50 randomization to all others they found a difference in the placebo response of ~4% in favour of 50:50 trials (contrary to the hypothesis), which was not statistically significant. This relationship indicates that an unbalanced randomization does not seem to affect the placebo response in RCTs in IBS (see Figure 1a); the reason for this observation will be discussed later. Instead, the variability of the placebo response seems to be a function of the number of patients included and with higher patient numbers (<100) it reaches a rather stable 40%, whilst with lower numbers it might be either very high (up to 80%) or very low due to large error margins.

Change of the placebo response over time

Again, depression and schizophrenia RCT meta-analyses have demonstrated a constant increase of the placebo response in trials published between 1980 and 2005.[27,28,37,38] Quite the opposite seems to be true for IBS. The placebo response showed a trend towards a negative correlation with the year of study publication for IBS trials published between 1975 and 2005 (see Figure 1b); this negative trend became significant ($r = -0.201$, $P = 0.045$) when studies conducted between 2000 and 2015 were added.[39] A similar trend was recognized by others.[25] This trend, however, confounds two contributing variables: more recent trials and the number of patients included; more recent trials have included many studies with large patient numbers (>100 patients per arm) that were drug-industry-initiated and generated overall smaller placebo responses than investigator-driven studies performed before 2000. Certainly, the commonly used responder definition based on Rome criteria initially,[40] and then on the FDA and the European Medicines Agency (EMA) approved primary end point definitions (for example, subjective global assessment, adequate relief),[41,42] have favoured this development towards lower placebo response rates and better discrimination between the effect of the drug and placebo on disease course.

Placebo response and trial duration

In the analysis of early IBS RCTs conducted between 1959 and 1987,[14] the trial duration varied between 2 weeks and 24 weeks and was on average only 6 weeks. 10 years later in 1999, Spiller[43] proposed a model predicting the placebo response might decrease to 20% or below with longer trial durations (>12 weeks); however, this prediction was based on a small number of long-term trials (see Figure 1b). This assumption was confirmed in the

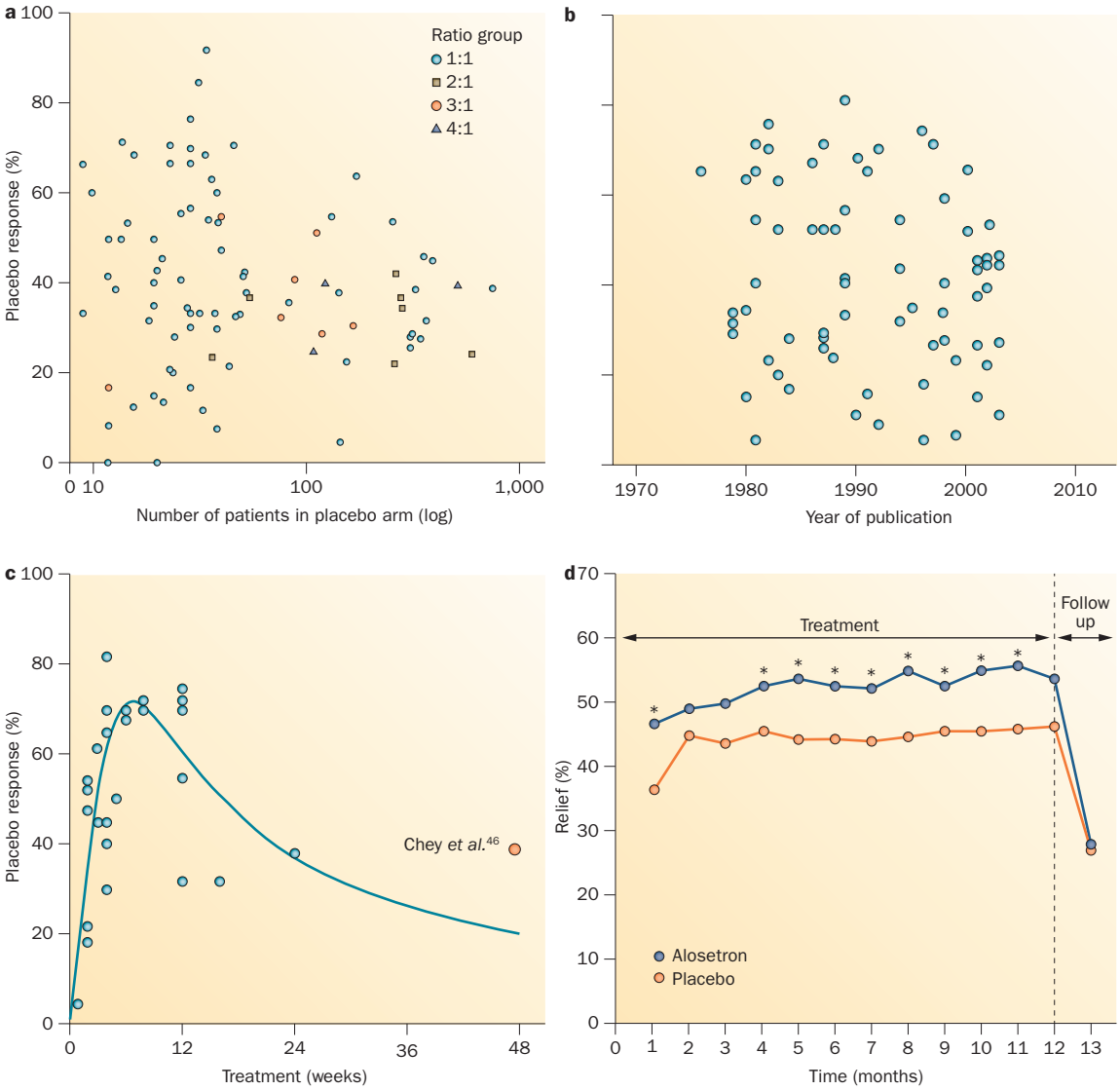

Figure 1 | Placebo responses in IBS. **a** | Placebo effect size (% responder) in RCTs in patients with IBS, as a function of the number of patients included. Randomization schedules (drug:placebo) vary (1:1,>1:1) indicating different probabilities of patients receiving active treatment. No effect of the unbalanced randomization on the placebo effect is seen. Modified with permission from Springer © Weimer, K. & Enck, P. *Handb. Exp. Pharmacol*. **225**, 237–272 (2014).[12] **b** | Placebo effect size (% responder) in the RCT in IBS as a function of the year of publication. A trend towards lower placebo response rates in recent years is evident. Modified with permission from Thieme © Enck, P. & Klosterhalfen, S. *Z. Gastroenterol.* **44**, 257–266 (2006).[190] **c** | Placebo effect sizes (% responder) in RCTs published between 1976 and 1998 as a function of treatment duration. Modified with permission from Elsevier Ltd. © Spiller, R. C. *Am. J. Med.* **107**, 91S–97S (1999).[43] According to the nonlinear regression model, the placebo effect should be below 20% in studies lasting 48 weeks or longer. The red dot indicates the placebo response illustrated in d. **d** | Placebo and drug response rates (% responder) in a 1-year RCT with alosetron in patients with IBS. Reproduced with permission from Nature Publishing Group © Chey, W. D. *et al. Am. J. Gastroenterol.* **99**, 2195–2203 (2004).[44] Note that the placebo response stays at around 40% for the entire treatment period. Abbreviations: RCT, randomized controlled trial.

meta-analysis by Ford *et al.*[24] in which short-term trials in IBS (that is, 1–4 weeks duration; $n = 19$) had a pooled placebo response of 46%, this response dropped to 39.8% in trials lasting 5–8 weeks ($n = 11$) and 34% in trials lasting >8 weeks ($n = 43$). Some meta-analyses indicated the opposite,[25,26] but that result could be due to their trial selection. Meanwhile, IBS trials include studies of even longer durations (26–52 weeks) and it has been found that the placebo response can stay as high as 40% for the entire period of treatment,[44] with substantial recurrence of symptoms after placebo withdrawal (see Figure 1d). Similar long-term effects are known from RCTs in other diseases.[45–49]

Another specific characteristic of some IBS trials is the proof of drug efficacy (the difference in effect between drug and placebo) proposed by the EMA, with multiple drug phases, to mimic symptom waxing and waning. Respective trials with the same drug indicate that the

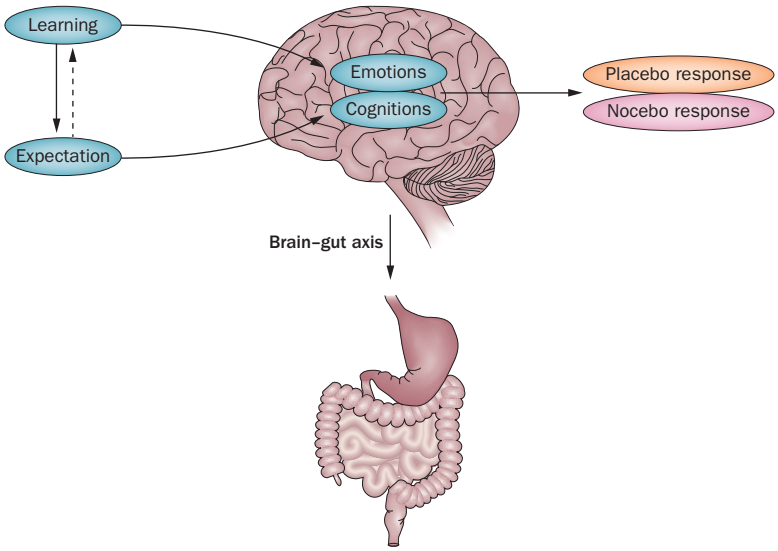

Figure 2 | Expectancy and learning as the two best-characterized principle mechanisms that mediate placebo and nocebo effects. Learning processes include classical conditioning, instrumental learning and social observation. These processes shape expectations about a treatment involving both emotions (state anxiety, fear, hope) and cognitions. They are centrally mediated, involve multiple brain regions and influence gastrointestinal sensory and motor functions along the bidirectional brain–gut axis. The entire psychosocial treatment context, including the factual information that is provided to the patient about a treatment, the quantity and quality of the patient–provider communication and features of the medical setting, shape placebo and nocebo responses through learning and expectation. See Box 2 for further information.

placebo response in a second drug phase can be even higher than with the first.[50] In addition, conditioning effects (for example, on bowel movements or abdominal pain) that one would expect following 12 weeks of drug treatment are rather low when a blinded randomized switch from drug to placebo occurs.[51]

Other features of placebo-controlled trials

A meta-analysis published in 2015 related the efficacy of IBS drug treatments to the number and severity of adverse events recorded during the treatment.[52] A positive and statistically significant correlation between both measures was evident and the authors concluded that spontaneous unblinding has occurred during these trials: the more adverse events experienced, the more the patient might be convinced of being treated by an effective drug, and as a consequence values the drug higher. This perception could be the reason for rather low placebo responses in more recent trials (after 2000) with drugs, for example, rifaximin, which have lower adverse event rates.[53]

Another interpretation of the same phenomenon of low placebo response and high drug efficacy in rifaximin trials in IBS was proposed by Kim *et al.*[54] Patient responses to mock informed consent forms of trials, testing either an antidepressant (desipramine), a prokinetic (alosetron), or a local antibiotic (rifaximin) were evaluated. Patients expected the highest efficacy for treatments they were familiar with (antibiotics), which the authors called a 'pre-cebo' effect.[54]

The increased use of social media by patients enrolled in RCTs might also corrupt true blinding and a fair assessment of drug efficacy. Through these networks, patients communicate with other patients, and exchange information about drugs and their adverse effects; it has been noted[55] that this information informs patients about their group assignment and so unblinds drug studies.

Finally, in RCTs planned for remission maintenance in chronic conditions with disease recurrence phases such as IBD[23] or ulcers, placebo response rates serve another purpose, namely to test the relapse rate in a 'natural course' condition. Although, a contribution of a true placebo effect (of expectations and conditioning) cannot be excluded. Relapse as determined by a Crohn's disease activity index (CDAI) score of >150 after surgery was 23% and recurrence of Crohn's disease detected endoscopically within 6 years of treatment was 50%.[56] Recurrence of gastric or duodenal ulcers within 24 weeks of treatment was 3.29% after placebo treatment.[57]

Mechanisms of the placebo response

Most experimental placebo studies have been carried out in the context of nausea and visceral pain, which has provided valuable information about the role of verbally induced expectations and associative learning (conditioning) in shaping the experience of gastrointestinal symptoms (Box 2). More importantly, experimental work encompassing laboratory and clinical studies is essential to elucidate the central and peripheral mechanisms mediating placebo effects in the gastrointestinal system (Figure 2). Furthermore, by inclusion of proper control groups or conditions, experimental studies can adequately control for spontaneous symptom fluctuations or other factors not attributable to the placebo response.

Nausea

Laboratory experiments in healthy volunteers addressing placebo effects in nausea have primarily focused on motion sickness induced by rotation chair or optokinetic drum, as elegantly reviewed elsewhere.[58] These efforts are complemented by field studies on nausea resulting from going on a naval cruise and clinical work in cancer patients suffering from nausea in the context of chemotherapy. Laboratory findings in healthy individuals support that nausea symptoms can be improved with placebo interventions that are based on the principles of Pavlovian conditioning, a manipulation of expectancies (typically by verbal instructions) or a combination of both.[12] Experimental techniques aiming to reduce conditioned responding and/or to enhance extinction of the conditions response might constitute promising tools leading to effective interventions. Indeed, two proof-of-concept studies in healthy volunteers show that anticipatory nausea can be successfully reduced by repetitive pre-exposure to the nausea-inducing environment (called 'latent inhibition' in learning psychology terms)[59] and by providing a different, salient beverage before nausea induction (called 'overshadowing').[60] Although more work is underway,[61] only a single small-scale clinical experiment has applied conditioning-based

interventions to successfully reduce nausea in patients with cancer undergoing chemotherapy.[62]

Changing expectations about nausea in a presumed 'nauseogenic' situation could constitute another approach capable of improving nausea symptoms. Administration of a placebo pill[63] or verbal instructions associated with distinct gustatory stimuli have improved nausea symptoms.[64,65] In line with these experimental data, naval cadets experienced less sea sickness and performed better after a psychological intervention aimed at reducing anticipatory fear and improving self-efficacy.[66] However, other studies attempting to modify expectations by verbal instructions have provided counterintuitive effects: symptoms of motion sickness were lower in a group with negative instructions suggesting more symptoms when compared with a group with positive instructions suggesting reduced symptoms, and a control group.[63] At the same time, gastric tachyarrythmias were lower in the negative expectancy group compared with the positive expectancy group.[63] Two studies produced negative results.[67,68] These inconsistencies could in part be explained by sex differences between participants[64,65] and/or complex interactions between the sex of the participant and the sex of the experimenter.[65] Ultimately, interventions combining the principles of conditioning with verbally-induced expectations could be most promising for an effective alleviation of nausea symptoms. Testing this combined approach in healthy volunteers, we implemented a combination of verbal instructions and surreptitiously reduced rotation speed in preceding trials (conditioning) and found substantially alleviated symptoms, fewer nauseogenic head movements and longer rotation tolerance in a subsequent test for conditioning effects.[69] Although experimental studies such as this one might seem highly artificial from a clinical standpoint, they are invaluable to disentangle the psychological mechanisms that have a role in the initiation, worsening and improvement of nausea. At the same time, they offer the opportunity to elucidate the central and peripheral mechanisms underlying placebo effects in nausea. Indeed, a few studies have suggested that verbally-induced expectations do not only affect behavioural readouts of nausea, but also induce changes in gastric slow wave rhythm, as measured by electrogastrography (EGG),[68] although findings are scarce and not unequivocal.[63,65,69] Some efforts have been made to characterize peripheral neuroendocrine and immune mediators of the stress systems such as cortisol and cytokines,[59,60,70,71] but replication and extension in healthy volunteers and patients is needed before the putative role of the hypothalamic–pituitary–adrenal axis and immune systems in placebo effects for nausea can be clarified. Of note, the search for the neurobiological mechanisms underlying placebo effects in nausea are being complemented by experimental approaches using brain imaging to address central mechanisms.[72,73]

The clinical application of placebo-based interventions aimed at reducing nausea in patients is built upon the above-reviewed experimental studies together with accumulating evidence that nausea in cancer patients undergoing chemotherapy can be predicted by pretreatment expectancies.[74] The few existing interventional studies designed to improve nausea in patients on chemotherapy by enhancing positive expectations have provided conflicting results.[75,76] This disparity is in line with results coming from efforts to prevent or reduce seasickness symptoms by verbally-induced expectations.[66,67] Though the search for predictors of individual placebo responses is ongoing, it seems that prior expectations (assessed with questionnaires) regarding nausea might be a crucial predictor.[77] Clearly, in clinical settings, the improvement of positive treatment-related expectations along with a reduction of pretreatment worries might not be effective in all individuals. As such, an improved understanding of interindividual variability in placebo responses is an important research goal,[1] which might lead to more personalized intervention strategies based on placebo principles. A rather early attempt in this direction was made with patients undergoing major abdominal surgery:[78] patients received either specific verbal instructions regarding intestinal mechanisms resolving postoperative ileus, or unspecific information, for example, on relaxation and breathing techniques. Both were mixed with personalized information on favourite food, friends and family obtained during a pre-intervention interview. The group with specific verbal instructions had a clinically relevant shorter average time to return of intestinal motility (2.6 versus 4.1 days), time to discharge was 6.5 versus 8.1 days, and an average saving of US$1,200 per patient for this 5 min intervention.[78]

Visceral pain

All existing experimental placebo studies on visceral pain have utilized pressure-controlled oesophageal or rectal distensions to evoke pain, and have primarily focused on the role of verbally induced expectations in placebo analgesia. The first experimental work, conducted by Donald Price and colleagues in patients with IBS,[79–81] collectively showed that verbal instructions effectively reduced rectal-distension-induced perceived pain and unpleasantness and were as similarly effective as lidocaine treatment.[79] This finding proved prophetic as there now exists intriguing evidence that placebo interventions might represent effective 'stand-alone' treatments.[82,83] Several groups have accomplished mechanistic placebo work using brain imaging techniques. In a PET study, the brain response to rectal distensions in patients with IBS were analysed both before and after a 3-week placebo regimen.[84] Increases in ventrolateral prefrontal cortex activity from pre-placebo to post-placebo treatment predicted self-reported symptom improvement and this relationship was mediated by changes in dorsal anterior cingulate cortex activity.[84] Subsequent functional MRI research in a group of patients with IBS revealed reductions in distension-induced brain activation within multiple pain-related brain regions in the placebo condition,[81] along with specific connectivity changes[85] and changes in the temporal characteristics of activated neural networks.[86] Data from healthy volunteers undergoing oesophageal[87] or rectal[88–90] distensions, essentially confirmed that reductions in reported pain resulting from verbally induced

instructions are paralleled by reduced neural activation during painful stimulation. Multiple brain regions and networks appear to be involved in the modulation of pain during placebo analgesia, consistent with evidence from the broader somatic pain field.[91,92]

To date, only two brain imaging studies exist[93,94] that directly compared neural mechanisms involved in placebo analgesia responses in patients with IBS and healthy individuals as controls. At the behavioural level, both studies conclusively revealed similar reductions in rectal-distension-induced perceived pain in the placebo condition in patients with IBS and healthy controls. At the same time, placebo-induced neural modulation during rectal pain differed in patients with IBS as compared with healthy controls, involving multiple brain regions.[93,94] Specifically, in the study by Schmid *et al.*,[93] healthy individuals as well as patients with ulcerative colitis in remission showed reduced activation in pain-related brain areas during placebo analgesia, whereas no changes could be observed in patients with IBS. These differences in neural modulation were most impressive in the cingulate cortex. In the study by Lee *et al.*[94] altered activation of the cingulate cortex (and other regions) during placebo analgesia was also seen in patients with IBS, leading us and others to speculate that IBS might be characterized by impaired cognitive pain modulation, in line with earlier suggestions and evidence from similar work outside of placebo research.[95–99] Interestingly, in both placebo studies psychiatric comorbidity (that is, anxiety, depression) appeared to at least contribute to these group differences, allowing us to speculate that affective disturbances in patients with IBS could contribute to altered cognitively driven pain modulation.[93,94] Furthermore, patients with IBD did not reveal such alterations in the central processing of pain during visceral placebo analgesia, supporting the specificity of findings for IBS.[80]

Until research results directly comparing placebo effects in various pain modalities and across chronic pain conditions become available, it is difficult to conclusively say whether placebo effects in visceral and somatic pain are similar or whether they involve different pathways. However, evidence does exist to support 'specificity' for the visceral domain. This specificity is based on evidence documenting differences between visceral and somatosensory signal processing in the periphery and within the central nervous system,[100–104] and data indicating that attentional modulation of pain intensity perception for visceral and somatic pain, respectively, is reflected in different brain regions.[101] Furthermore, unlike in somatic placebo analgesia (reviewed elsewhere[105]), placebo analgesia in a visceral pain model was not modulated by endogenous opioids.[80] The possible role of other neurotransmitters, neuropeptides or hormones, including oxytocin,[106,107] the endocannabinoid system,[108] nitric oxide,[109] or dopamine[110,111] remains to be studied in gastroenterology (neurobiological mechanisms in somatic placebo analgesia has been reviewed elsewhere[112]). Finally, the correlation between individual pain thresholds for visceral and somatic stimulation is reportedly weak.[113] Hence, studies on visceral placebo responses in no way duplicates, but rather complements and extends findings from research using somatic pain models or in patients with other chronic pain conditions.[91,114,115]

Predictors and mediators

Age and sex

As early as 1955, Henry Beecher explored the difference between placebo responders and nonresponders and found that "…there were no differences in sex ratio or in intelligence. [but]… significant differences in attitude, habits, educational background and personality structure between consistent reactors and nonreactors".[5] In a review of the placebo response across many medical conditions,[19] no evidence was found that sex contributes to the placebo response despite occasional reports from experimental settings suggesting otherwise,[65] and only marginal evidence that age might have a role, with younger adult patients exhibiting larger placebo response rates than older adults. This larger placebo response rate was the case in one of the IBS meta-analyses,[24] but it has also been noted that children with functional gastrointestinal diseases in general might exhibit larger placebo responses in RCTs than adolescents and adults,[116] similar to findings in attention deficit hyperactivity disorder and depression.[117] Although meta-analyses of depression trials in children[38,118] confirmed an increased placebo response, they also found that the placebo determinants that are effective in adults (for example, the intensity and frequency of doctor–patient contacts) do not drive the placebo response in children,[118] but are rather mediated by 'proxies' (that is, parents, siblings, family members, friends).[119]

Personality

Although some studies indicate a personality characteristic (for example, anxiety) to be associated with a higher placebo response in specific experimental and clinical settings, for example, in motion sickness and pain,[120] poor evidence has been collected that this association is true across all conditions tested. Certainly, a strong publication bias is present, as most investigators use a large battery of psychometric tests and usually report only those that were found to be linked to the placebo response and statistically nonsignificant results are often not published.[121] In a secondary analysis of one of the nausea experiments, we found the concept of self-efficacy and 'locus of control' (LoC, see glossary in Box 1) linked to the placebo response, with low self-esteem and an external LoC as predictors of a high placebo response.[122] High self-esteem and an internal LoC were reliable predictors of treatment success in depression RCTs, whether with a drug or with placebo.[123] An external LoC was associated with a higher placebo response than an internal LoC in a performance-decrementing task following consumption of an alcohol-placebo.[124]

Genes

The search for biomarkers of the placebo response (or placebo responders) has received little attention in times when whole or candidate human genome analysis was not readily available. In a subset of patients with IBS

selected for a sham acupuncture study,[83] the authors investigated whether serum biomarkers would mirror a change of symptoms during therapy and would predict placebo responsiveness from baseline data.[125] Of the 10 biomarkers tested, only one single marker, osteoprotegerin, yielded statistical significance for the placebo response, but since the analysis did not correct for multiple testing, this result might be a type I error.

The authors also found that people with the catechol-*O*-methyltransferase Val158Met polymorphism had a higher placebo response than those without the polymorphism,[126] a finding that replicates data from a depression trial.[127] The polymorphism was also found to be associated with nocebo responses in an immune-conditioning trial.[128] However, this association might not be specific for the placebo response, as the same polymorphism was found to be associated with sleep regulation, attention deficit hyperactivity disorder, Parkinson disease, eating disorders and other diseases and their response to treatments.[129] A good prediction of the placebo response was found in an immune-conditioning task in healthy individuals by measuring plasma noradrenaline level and state anxiety, predicting nearly 60% of the variance in conditioned IL-2 response, but these findings probably do not transfer beyond psycho-immunology and require replication.[130]

Nocebo effects

The term nocebo (Latin for "I shall harm"), created in analogy to placebo (Latin for "I shall please"), has been used consistently only in the past decade, although some of the experiments of Stewart Wolf clearly are 'nocebo' experiments[7] and the term has been 'invented' already decades ago.[131] Only 306 citations for this search term (last accessed Jul 5, 2015) are listed on PubMed, whereas the number of genuine 'placebo' publications addressing the placebo effect *per se* (excluding placebo-controlled trials) is in the range of 3,000.[17] Initially, nocebo was primarily used to describe adverse events reported by patients that received placebo in RCTs.[132,133] These adverse events usually mimic the information provided in informed consent leaflets, and might have led to drop-outs in the placebo arm of RCTs. This observation has been documented in RCTs including patients with fibromyalgia[132,133] and migraine.[134] Unfortunately, similar analyses are not available for adverse events in placebo arms of RCTs in gastrointestinal disorders. The term nocebo is also used when referring to symptom reporting after reading drug information leaflets,[135] inappropriate doctor–patient communication[136] and symptom occurrence after false or falsely understood diagnoses.[133] In principle, the nocebo effect includes all negative expectations and consequences of past negative experiences with any medical therapy. As such, it is especially pertinent in chronic conditions associated with waxing and waning of symptoms such as IBS or IBD, with invasive diagnostic procedures such as endoscopy, and with often ineffective treatments despite various treatment attempts (as found in medical histories of patients with functional gastrointestinal disorders). Nocebo studies involving patients is urgently needed. Relatively few experimental studies have specifically addressed nocebo effects and so the neurobiology of this phenomenon is incompletely understood,[136,137] but might involve cholecystokinin and related mediators.[138,139] Of note, to properly study the nocebo phenomenon, controlling for confounding factors such as natural disease history, spontaneous symptom fluctuations is important and can usually only be accomplished in experiments and controlled clinical trials.[140] In the following section, we will refer to three clinical topics in which nocebo responses have been the subject of clinical and/or experimental investigations, namely nausea, food intolerances and visceral pain.

Nausea and related gastrointestinal symptoms

Laboratory studies support that Pavlovian conditioning can induce or worsen symptoms of nausea and urge-to-vomit, reduce rotation tolerance and result in conditioned taste aversion.[64,70] Pavlovian conditioning might also contribute to anticipatory nausea in patients undergoing chemotherapy.[141,142] The few studies that have experimentally increased negative expectations—for example, by administration of an inert pill together with verbal instructions suggesting symptoms exacerbation—in healthy individuals have provided inconsistent findings of either protective effects (that is, a reduction of nausea)[63,68] or no effect on symptoms.[64] An effect of conditioning on rotation tolerance has been reported in one study, with larger effects in men compared with women.[64] In patients undergoing chemotherapy, greater negative pretreatment expectations regarding nausea are correlated with enhanced chemotherapy-induced nausea.[74,77,143] Attempts to systematically improve negative pretreatment expectations about nausea in a clinical oncology setting are scarce and support a complex interaction of expectancy manipulation with pre-existing expectancies.[75] In patients with functional dyspepsia, the putative role of negative expectancies in symptom induction is increasingly appreciated and extended to other upper gastrointestinal functions, such as postprandial fullness and bloating in health and obesity.[144] In their elegant trial on cognitive factors regulating symptoms in functional dyspepsia, patients were provided either correct or false information about the fat content of high fat yoghurt that patients ingested over 2 days. The results revealed that both the fat content, but also the information affected symptoms of fullness and bloating, whereas nausea scores, plasma cholecystokinin and gastric volumes were unaffected by the information provided. These findings support that expectations, shaped by prior negative experiences with specific foods, might trigger symptoms.[145] These conclusions illustrate that in patients, symptoms are probably shaped by an interaction between conditioning and expectancies in ways that could be challenging to disentangle in much-needed experimental work.

Food intolerances

Although many patients with gastrointestinal disorders, especially those with presumed functional disorders, claim to have 'food intolerances' to a variety

of nutrients and nutrient components,[146] the true prevalence of food allergies is low.[147] The prevalence of specific malabsorption syndromes (such as lactose, fructose intolerance) is well-established in many countries,[148] but in health surveys many more individuals claim to be lactose intolerant.[149] A similar puzzle seems to be arising with the claims of noncoeliac gluten sensitivity.[150] In a study of >300 patients with a negative hydrogen breath test following lactose challenge, nearly 10% reported abdominal symptoms during the test, and when they were deceptively given glucose before another breath test, half of them reproduced their symptoms, as did 25% of those with lactose malabsorption.[151] Similarly, among patients with claimed hypersensitivity towards milk products, one-third had a negative hydrogen breath test after lactose challenge,[152,153] and most tolerated moderate amounts of milk (that is, 250 ml daily) with minor symptoms. Symptoms are usually higher in the home environment than in the laboratory setting,[154] and symptoms reports were associated with increased somatization scores and other psychopathological characteristics,[155] indicating that the reported symptoms of lactose intolerance in many patients might constitute nocebo responses to reports in public media, patient communication and other sources of information.

Visceral pain

Experimental evidence regarding nocebo effects in visceral pain is emerging. Building on the first nocebo experiment involving rectal distensions and deceptive instructions in patients with IBS,[79] we implemented a combination of negative verbal instructions and a prior learning experience of surreptitiously enhanced distension pressure (pre-conditioning) in healthy volunteers. The results revealed substantially greater distension-induced pain when compared with a control group who had received truthful instructions.[90] In a subsequent functional MRI study, negative instructions led to more reported pain along with greater distension-induced activation of the insula cortex when compared with control instructions (truthful neutral suggestions).[88] Further data confirm and extend these findings and support that negative pain-related instructions (rather than treatment-related instructions) can also result in nocebo hyperalgesia involving the insula cortex.[156] Given that the insula is crucial for interoception (sensations arising from inside of the body), multimodal sensory integration as well as pain-related decision-making and emotional awareness,[157–159] these findings are an important step in identifying the brain mechanism(s) mediating visceral nocebo hyperalgesia. These emerging nocebo results are especially interesting in light of evidence that negative treatment expectancy abolished opioid analgesia in a somatic pain model.[160] Hence, nocebo effects could shape the response to medical interventions and aversely affect drug efficacy,[136,161] which has extensive implication for clinical routine and informed consent.

Pavlovian conditioning mechanisms might also have a role in nocebo effects relating to visceral pain. Building on earlier evidence that classical conditioning with oesophageal pain is feasible, experimental efforts have implemented Pavlovian conditioning with rectal distensions as unconditioned stimuli. Analogous to classically-conditioned taste aversion in rotation-chair induced motion sickness, pairing neutral stimuli (such as, visual cues) with visceral pain results in a learned emotional response to formerly neutral cues.[162–164] Intriguingly, this effect of emotional learning through association with aversive visceral cues seems to be disturbed in patients with IBS, in part owing to changes in the corticotropin-releasing factor system.[165] Whether and how classical conditioning contributes to hyperalgesia and pain chronicity is a subject of ongoing work, and this might involve perceptual discrimination.[166] Meanwhile, new cognitive-behavioural treatments based on extinction learning support that the principles of conditioning and its subsequent extinction can be harnessed in the treatment of patients with IBS.[167,168]

Future directions

Placebo effects in clinical trials have sparked broad interest in the placebo phenomenon. Analyses of clinical trial data has increased the appreciation that more clinical and experimental work is needed to advance our understanding of the determinants, underlying mechanisms and clinical implications of the placebo effect. Future work has to demonstrate whether predictors found in RCTs can be substantiated and explored in experimental studies. Whether findings from experiments can shape the design of RCTs also needs to be explored. Directions for future work on placebo effects in clinical trials and experimental approaches can be found within various medical specialties including gastroenterology. First and foremost, the placebo acupuncture trial in patients with IBS[83] represents a milestone in the possible clinical application of placebos. This trial supports the notion that these interventions might constitute effective 'stand-alone' treatments, provided that ethical considerations are met.[83] While awaiting much-needed replication in the field of gastroenterology, similar findings from trials in patients with chronic back pain[169] and asthma[170] invoke cautious optimism that placebo interventions could indeed prove to be at least as efficacious as conventional therapy. Indeed, based on the above-mentioned trial in patients with asthma comparing active treatment with an albuterol inhaler, a placebo inhaler, sham acupuncture or no intervention, the authors wrote that placebo effects "…can rival the effects of active medication in patients with asthma".[170]

These findings also raise the possibility that placebo treatment might be effective in 'boosting' the efficacy of active drugs. Evidence supporting this notion comes from a trial in patients with episodic migraine attacks.[171] In this sophisticated trial, variations in medication labelling were shown to modify not only placebo, but also drug effects and drug efficacy could be improved by increasing positive information, presumably by enhancing positive expectations.[171] Experimental data lend further support for this notion and are beginning to unravel the underlying neural correlates of expectancy-drug interactions,[160,172] with partially inconsistent results.[173]

Conclusions

The efficacy of placebo interventions appears to be shaped by the quality of the patient–provider relationship,[83] although more evidence is needed to confirm this suggestion. The notion that doctor–patient communication could constitute a predictor of outcome is more readily accepted in some areas, for example, in functional bowel disorders such as IBS; however, in other areas in which diagnoses are of unequivocally 'organic' aetiology, a more systematic integration of psychological concepts and a substantive broadening of views from both doctors and patients would be required. This integration of psychological concepts fits in to the concept of a bidirectional brain–gut axis that 'operates' in virtually all types of gastrointestinal diagnoses, irrespective of psychological contributions to aetiology or pathophysiology. As psychologists with a psychophysiology background we might be biased, but the evidence convincingly suggests that older dualistic concepts separating the 'mind' from the 'body' in the treatment of medical conditions is not only outdated, but simply falls short of current knowledge gathered during and since the 'decade of the brain'. What is crucial might be the brain rather than the 'mind', but semantics should neither stand in the way of scientific progress nor of improved clinical care.

Lastly, ethical considerations surrounding deception and informed consent arise from clinical and experimental placebo research alike. Although a full discussion of ethical aspects is beyond the scope of this article (reviewed elsewhere[174,175]), it is important to draw attention to emerging evidence from clinical trials in patients with IBS,[83] major depression[176] and migraine[171] that 'open-label' placebo treatment might be efficacious and is also supported by experimental data.[177,178] Similarly, application of conditioning principles could pave the way to reduce the amount of medication needed[179,180] and/or to reduce adverse events such as conditioned nausea.[142,181] These improvements in care could be achieved with the informed consent of patients and thereby overcome ethics restraints in this field. These findings raise hope that sophisticated trials and experiments designed to boost positive expectations and minimize negative expectations could lead to a practical and ethically sound use of placebo knowledge to benefit patients. Together, knowledge from the evolving placebo field might change how we think about informed consent in clinical encounters as well as in RCTs and be the basis for us to re-conceptualize 'personalized medicine'. Rather than focusing on a 'personalized' choice of drugs based, for example, on biomarkers or genes, it could be the psychosocial treatment that needs to be tailored to the patient. Ultimately, placebo and nocebo knowledge from basic, preclinical and clinical work has made one fundamental aspect of patient care crystal clear: the largest potential for a positive clinical outcome lies in the interaction between patient and clinician. If nothing else, placebo research underscores the pivotal role of psychosocial factors, ranging from doctor-patient communication over informed consent to the entire treatment setting. Transferring this knowledge to everyday practice is certainly ambitious, perhaps even visionary, but only achievable with the combined interdisciplinary efforts involving researchers, clinicians, healthcare providers and policy makers.

1. Enck, P., Bingel, U., Schedlowski, M. & Rief, W. The placebo response in medicine: minimize, maximize or personalize? *Nat. Rev. Drug Discov.* **12**, 191–204 (2013).
2. Kirsch, I. The placebo effect revisited: lessons learned to date. *Complement. Ther. Med.* **21**, 102–104 (2013).
3. Benedetti, F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* **84**, 623–637 (2014).
4. Price, D. D., Finniss, D. G. & Benedetti, F. A comprehensive review of the placebo effect: recent advances and current thought. *Ann. Rev. Psychol.* **59**, 565–590 (2008).
5. Beecher, H. K. The powerful placebo. *J. Am. Med. Assoc.* **159**, 1602–1606 (1955).
6. Gay, L. N. & Carliner, P. E. The prevention and treatment of motion sickness; seasickness. *Bull. Johns Hopkins Hosp.* **84**, 470–490 (1949).
7. Wolf, S. Effects of suggestion and conditioning on the action of chemical agents in human subjects; the pharmacology of placebos. *J. Clin. Invest.* **29**, 100–109 (1950).
8. Wolf, S. & Wolff, H. G. Function of the stomach as observed in fistulous human subjects, with special reference to the action of drugs and the effects of vagotomy. *Am. J. Med.* **3**, 127 (1947).
9. Wolf, S. The pharmacology of placebos. *Pharmacol. Rev.* **11**, 689–704 (1959).
10. de Craen, A. J., Kaptchuk, T. J., Tijssen, J. G. & Kleijnen, J. Placebos and placebo effects in medicine: historical overview. *J. R. Soc. Med.* **92**, 511–515 (1999).
11. Weihrauch, T. R. & Gauler, T. C. Placebo—efficacy and adverse effects in controlled clinical trials. *Arzneimittelforschung.* **49**, 385–393 (1999).
12. Weimer, K. & Enck, P. Traditional and innovative experimental and clinical trial designs and their advantages and pitfalls. *Handb. Exp. Pharmacol.* **225**, 237–272 (2014).
13. Krogsboll, L. T., Hrobjartsson, A. & Gotzsche, P. C. Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Med. Res. Methodol.* **9**, 1 (2009).
14. Klein, K. B. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology* **95**, 232–241 (1988).
15. Arakawa, A., Kaneko, M. & Narukawa, M. An investigation of factors contributing to higher levels of placebo response in clinical trials in neuropathic pain: a systematic review and meta-analysis. *Clin. Drug Investig.* **35**, 67–81 (2015).
16. Capurso, G., Cocomello, L., Benedetto, U., Camma, C. & Delle, F. G. Meta-analysis: the placebo rate of abdominal pain remission in clinical trials of chronic pancreatitis. *Pancreas* **41**, 1125–1131 (2012).
17. Weimer, K., Colloca, L. & Enck, P. Placebo effects in psychiatry: mediators and moderators. *Lancet Psychiatry* **2**, 246–257 (2015).
18. Su, C., Lichtenstein, G. R., Krok, K., Brensinger, C. M. & Lewis, J. D. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology* **126**, 1257–1269 (2004).
19. Weimer, K., Colloca, L. & Enck, P. Age and sex as moderators of the placebo response—an evaluation of systematic reviews and meta-analyses across medicine. *Gerontology* **61**, 97–108 (2015).
20. Ilnyckyj, A., Shanahan, F., Anton, P. A., Cheang, M. & Bernstein, C. N. Quantification of the placebo response in ulcerative colitis. *Gastroenterology* **112**, 1854–1858 (1997).
21. Benedetti, F. Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* **93**, 1207–1246 (2013).
22. Garud, S., Brown, A., Cheifetz, A., Levitan, E. B. & Kelly, C. P. Meta-analysis of the placebo response in ulcerative colitis. *Dig. Dis. Sci.* **53**, 875–891 (2008).
23. Gallahan, W. C., Case, D. & Bloomfeld, R. S. An analysis of the placebo effect in Crohn's disease over time. *Aliment. Pharmacol Ther.* **31**, 102–107 (2010).
24. Ford, A. C. & Moayyedi, P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **32**, 144–158 (2010).
25. Pitz, M., Cheang, M. & Bernstein, C. N. Defining the predictors of the placebo response in irritable bowel syndrome. *Clin. Gastroenterol. Hepatol.* **3**, 237–247 (2005).
26. Dorn, S. D. *et al.* A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. *Neurogastroenterol. Motil.* **19**, 630–637 (2007).

27. Walsh, B. T., Seidman, S. N., Sysko, R. & Gould, M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* **287**, 1840–1847 (2002).
28. Kemp, A. S. *et al.* What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophr. Bull*. **36**, 504–509 (2010).
29. Patel, S. M. *et al.* The placebo effect in irritable bowel syndrome trials: a meta-analysis. *Neurogastroenterol. Motil.* **17**, 332–340 (2005).
30. Talley, N. J. *et al.* Predictors of the placebo response in functional dyspepsia. *Aliment. Pharmacol. Ther*. **23**, 923–936 (2006).
31. Enck, P., Vinson, B., Malfertheiner, P., Zipfel, S. & Klosterhalfen, S. The placebo response in functional dyspepsia—reanalysis of trial data. *Neurogastroenterol. Motil*. **21**, 370–377 (2009).
32. de Craen, A. J. *et al.* Placebo effect in the treatment of duodenal ulcer. *Br. J. Clin. Pharmacol.* **48**, 853–860 (1999).
33. Cremonini, F. *et al.* Meta-analysis: the effects of placebo treatment on gastro-oesophageal reflux disease. *Aliment. Pharmacol. Ther*. **32**, 29–42 (2010).
34. Diener, H. C., Dowson, A. J., Ferrari, M., Nappi, G. & Tfelt-Hansen, P. Unbalanced randomization influences placebo response: scientific versus ethical issues around the use of placebo in migraine trials. *Cephalalgia* **19**, 699–700 (1999).
35. Papakostas, G. I. & Fava, M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur. Neuropsychopharmacol.* **19**, 34–40 (2009).
36. Woods, S. W., Gueorguieva, R. V., Baker, C. B. & Makuch, R. W. Control group bias in randomized atypical antipsychotic medication trials for schizophrenia. *Arch. Gen. Psychiatry* **62**, 961–970 (2005).
37. Yildiz, A., Vieta, E., Tohen, M. & Baldessarini, R. J. Factors modifying drug and placebo responses in randomized trials for bipolar mania. *Int. J. Neuropsychopharmacol*. **14**, 863–875 (2011).
38. Bridge, J. A., Birmaher, B., Iyengar, S., Barbe, R. P. & Brent, D. A. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am. J. Psychiatry* **166**, 42–49 (2009).
39. Enck, P., Horing, B., Weimer, K. & Klosterhalfen, S. Placebo responses and placebo effects in functional bowel disorders. *Eur. J. Gastroenterol. Hepatol*. **24**, 1–8 (2012).
40. Longstreth, G. F. *et al.* Functional bowel disorders. *Gastroenterology* **130**, 1480–1491 (2006).
41. US Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research. Guidance for industry. Irritable bowel syndrome—clinical evaluation of drugs for treatment. *FDA* [online], http://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf (2012).
42. European Medicine Agency. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. *European Medicines Agency* [online], http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf (2013).
43. Spiller, R. C. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. *Am. J. Med*. **107**, 91S–97S (1999).
44. Chey, W. D. *et al.* Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am. J. Gastroenterol*. **99**, 2195–2203 (2004).
45. Potkin, S. *et al.* Placebo response trajectories in short-term and long-term antipsychotic trials in schizophrenia. *Schizophr. Res*. **132**, 108–113 (2011).
46. McRae, C. *et al.* Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. *Arch. Gen. Psychiatry* **61**, 412–420 (2004).
47. Moseley, J. B. *et al.* A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N. Engl. J. Med*. **347**, 81–88 (2002).
48. Quessy, S. N. & Rowbotham, M. C. Placebo response in neuropathic pain trials. *Pain* **138**, 479–483 (2008).
49. Khan, A., Redding, N. & Brown, W. A. The persistence of the placebo response in antidepressant clinical trials. *J. Psychiatr. Res*. **42**, 791–796 (2008).
50. Tack, J. *et al.* A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* **54**, 1707–1713 (2005).
51. Rao, S. *et al.* A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am. J. Gastroenterol*. **107**, 1714–1724 (2012).
52. Shah, E., Triantafyllou, K., Hana, A. A. & Pimentel, M. Adverse events appear to unblind clinical trials in irritable bowel syndrome. *Neurogastroenterol. Motil*. **26**, 482–488 (2014).
53. Schoenfeld, P. *et al.* Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. *Aliment. Pharmacol. Ther*. **39**, 1161–1168 (2014).
54. Kim, S. E., Kubomoto, S., Chua, K., Amichai, M. M. & Pimentel, M. "Pre-cebo": an unrecognized issue in the interpretation of adequate relief during irritable bowel syndrome drug trials. *J. Clin. Gastroenterol*. **46**, 686–690 (2012).
55. Lipset, C. H. Engage with research participants about social media. *Nat. Med*. **20**, 231 (2014).
56. Renna, S. *et al.* Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. *Gastroenterology* **135**, 1500–1509 (2008).
57. Yuan, Y. H., Wang, C., Yuan, Y. & Hunt, R. H. Meta-analysis: incidence of endoscopic gastric and duodenal ulcers in placebo arms of randomized placebo-controlled NSAID trials. *Aliment. Pharmacol. Ther*. **30**, 197–209 (2009).
58. Quinn, V. F. & Colagiuri, B. Placebo interventions for nausea: a systematic review. *Ann. Behav. Med*. **49**, 449–462 (2014).
59. Klosterhalfen, S. *et al.* Latent inhibition of rotation chair-induced nausea in healthy male and female volunteers. *Psychosom. Med.* **67**, 335–340 (2005).
60. Stockhorst, U., Hall, G., Enck, P. & Klosterhalfen, S. Effects of overshadowing on conditioned and unconditioned nausea in a rotation paradigm with humans. *Exp. Brain Res*. **232**, 2651–2664 (2014).
61. Stockhorst, U. *et al.* Effects of overshadowing on conditioned nausea in cancer patients: an experimental study. *Physiol. Behav*. **64**, 743–753 (1998).
62. Geiger, F. & Wolfgram, L. Overshadowing as prevention of anticipatory nausea and vomiting in pediatric cancer patients: study protocol for a randomized controlled trial. *Trials* **14**, 103 (2013).
63. Levine, M. E., Stern, R. M. & Koch, K. L. The effects of manipulating expectations through placebo and nocebo administration on gastric tachyarrhythmia and motion-induced nausea. *Psychosom. Med*. **68**, 478–486 (2006).
64. Klosterhalfen, S. *et al.* Gender and the nocebo response following conditioning and expectancy. *J. Psychosom. Res.* **66**, 323–328 (2009).
65. Weimer, K. *et al.* Effects of ginger and expectations on symptoms of nausea in a balanced placebo design. *PLoS ONE* **7**, e49031 (2012).
66. Eden, D. & Zuk, Y. Seasickness as a self-fulfilling prophecy: raising self-efficacy to boost performance at sea. *J. Appl. Psychol*. **80**, 628–635 (1995).
67. Tyler, D. B. The influence of a placebo, body position and medication on motion sickness. *Am. J. Physiol.* **146**, 458–466 (1946).
68. Williamson, M. J., Thomas, M. J. & Stern, R. M. The contribution of expectations to motion sickness symptoms and gastric activity. *J. Psychosom. Res*. **56**, 721–726 (2004).
69. Horing, B. *et al.* Reduction of motion sickness with an enhanced placebo instruction: an experimental study with healthy participants. *Psychosom. Med*. **75**, 497–504 (2013).
70. Klosterhalfen, S. *et al.* Pavlovian conditioning of taste aversion using a motion sickness paradigm. *Psychosom. Med*. **62**, 671–677 (2000).
71. Meissner, K. Effects of placebo interventions on gastric motility and general autonomic activity. *J. Psychosom. Res*. **66**, 391–398 (2009).
72. Napadow, V. *et al.* The brain circuitry underlying the temporal evolution of nausea in humans. *Cereb. Cortex* **23**, 806–813 (2013).
73. Farmer, A. D. *et al.* Visually induced nausea causes characteristic changes in cerebral, autonomic and endocrine function in humans. *J. Physiol.* **539**, 1183–1196 (2015).
74. Colagiuri, B. & Zachariae, R. Patient expectancy and post-chemotherapy nausea: a meta-analysis. *Ann. Behav. Med*. **40**, 3–14 (2010).
75. Roscoe, J. A. *et al.* An exploratory study on the effects of an expectancy manipulation on chemotherapy-related nausea. *J. Pain Symptom Manage*. **40**, 379–390 (2010).
76. Shelke, A. R. *et al.* Effect of a nausea expectancy manipulation on chemotherapy-induced nausea: a university of Rochester cancer center community clinical oncology program study. *J. Pain Symptom Manage.* **35**, 381–387 (2008).
77. Roscoe, J. A. *et al.* Insight in the prediction of chemotherapy-induced nausea. *Support. Care Cancer* **18**, 869–876 (2010).
78. Disbrow, E. A., Bennett, H. L. & Owings, J. T. Effect of preoperative suggestion on postoperative gastrointestinal motility. *West J. Med*. **158**, 488–492 (1993).
79. Vase, L., Robinson, M. E., Verne, G. N. & Price, D. D. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. *Pain* **105**, 17–25 (2003).
80. Vase, L., Robinson, M. E., Verne, G. N. & Price, D. D. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* **115**, 338–347 (2005).
81. Price, D. D., Craggs, J., Verne, G. N., Perlstein, W. M. & Robinson, M. E. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* **127**, 63–72 (2007).

82. Kaptchuk, T. J. *et al.* Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS ONE* **5**, e15591 (2010).
83. Kaptchuk, T. J. *et al.* Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* **336**, 999–1003 (2008).
84. Lieberman, M. D. *et al.* The neural correlates of placebo effects: a disruption account. *Neuroimage* **22**, 447–455 (2004).
85. Craggs, J. G., Price, D. D., Verne, G. N., Perlstein, W. M. & Robinson, M. M. Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia. *Neuroimage* **38**, 720–729 (2007).
86. Craggs, J. G., Price, D. D., Perlstein, W. M., Verne, G. N. & Robinson, M. E. The dynamic mechanisms of placebo induced analgesia: Evidence of sustained and transient regional involvement. *Pain* **139**, 660–669 (2008).
87. Lu, H. C. *et al.* Neuronal correlates in the modulation of placebo analgesia in experimentally-induced esophageal pain: a 3T-fMRI study. *Pain* **148**, 75–83 (2010).
88. Schmid, J. *et al.* Neural mechanisms mediating positive and negative treatment expectations in visceral pain: A functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. *Pain* **154**, 2372–2380 (2013).
89. Elsenbruch, S. *et al.* Neural mechanisms mediating the effects of expectation in visceral placebo analgesia: an fMRI study in healthy placebo responders and nonresponders. *Pain* **153**, 382–390 (2012).
90. Elsenbruch, S. *et al.* How positive and negative expectations shape the experience of visceral pain: an experimental pilot study in healthy women. *Neurogastroenterol. Motil.* **24**, 914–e460 (2012).
91. Colloca, L., Klinger, R., Flor, H. & Bingel, U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain* **154**, 511–514 (2013).
92. Amanzio, M., Benedetti, F., Porro, C. A., Palermo, S. & Cauda, F. Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum. Brain Mapp.* **34**, 738–752 (2013).
93. Schmid, J. *et al.* Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. *Gut* **64**, 418–427 (2015).
94. Lee, H. F. *et al.* Enhanced affect/cognition-related brain responses during visceral placebo analgesia in irritable bowel syndrome patients. *Pain* **153**, 1301–1310 (2012).
95. Berman, S. M. *et al.* Reduced brainstem inhibition during anticipated pelvic visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. *J. Neurosci.* **28**, 349–359 (2008).
96. Wilder-Smith, C. H. The balancing act: endogenous modulation of pain in functional gastrointestinal disorders. *Gut* **60**, 1589–1599 (2011).
97. Wilder-Smith, C. H. & Robert-Yap, J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. *World J. Gastroenterol.* **13**, 3699–3704 (2007).
98. Wilder-Smith, C. H., Schindler, D., Lovblad, K., Redmond, S. M. & Nirkko, A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut* **53**, 1595–1601 (2004).
99. Piche, M., Arsenault, M., Poitras, P., Rainville, P. & Bouin, M. Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome. *Pain* **148**, 49–58 (2010).
100. Eickhoff, S. B. *et al.* Segregation of visceral and somatosensory afferents: an fMRI and cytoarchitectonic mapping study. *Neuroimage* **31**, 1004–1014 (2006).
101. Dunckley, P. *et al.* Attentional modulation of visceral and somatic pain. *Neurogastroenterol. Motil.* **19**, 569–577 (2007).
102. Dunckley, P. *et al.* Cortical processing of visceral and somatic stimulation: differentiating pain intensity from unpleasantness. *Neuroscience* **133**, 533–542 (2005).
103. Aziz, Q. *et al.* Cortical processing of human somatic and visceral sensation. *J. Neurosci.* **20**, 2657–2663 (2000).
104. Dunckley, P. *et al.* A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. *J. Neurosci.* **25**, 7333–7341 (2005).
105. Kong, J. & Benedetti, F. Placebo and nocebo effects: an introduction to psychological and biological mechanisms. *Handb. Exp. Pharmacol.* **225**, 3–15 (2014).
106. Kessner, S., Sprenger, C., Wrobel, N., Wiech, K. & Bingel, U. Effect of oxytocin on placebo analgesia: a randomized study. *JAMA* **310**, 1733–1735 (2013).
107. Enck, P. & Klosterhalfen, S. The story of O—is oxytocin the mediator of the placebo response? *Neurogastroenterol. Motil.* **21**, 347–350 (2009).
108. Benedetti, F., Amanzio, M., Rosato, R. & Blanchard, C. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. *Nat. Med.* **17**, 1228–1230 (2011).
109. Fricchione, G. & Stefano, G. B. Placebo neural systems: nitric oxide, morphine and the dopamine brain reward and motivation circuitries. *Med. Sci. Monit.* **11**, MS54–MS65 (2005).
110. Scott, D. J. *et al.* Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* **55**, 325–336 (2007).
111. Scott, D. J. *et al.* Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch. Gen. Psychiatry* **65**, 220–231 (2008).
112. Buchel, C., Geuter, S., Sprenger, C. & Eippert, F. Placebo analgesia: a predictive coding perspective. *Neuron* **81**, 1223–1239 (2014).
113. Horing, B., Kugel, H., Brenner, V., Zipfel, S. & Enck, P. Perception and pain thresholds for cutaneous heat and cold, and rectal distension: associations and disassociations. *Neurogastroenterol. Motil.* **25**, e791–e802 (2013).
114. Klinger, R., Colloca, L., Bingel, U. & Flor, H. Placebo analgesia: clinical applications. *Pain* **155**, 1055–1058 (2014).
115. Lu, C. L. & Chang, F. Y. Placebo effect in patients with irritable bowel syndrome. *J. Gastroenterol. Hepatol.* **26** Suppl. 3, 116–118 (2011).
116. Benninga, M. A. & Mayer, E. A. The power of placebo in pediatric functional gastrointestinal disease. *Gastroenterology* **137**, 1207–1210 (2009).
117. Weimer, K. *et al.* Placebo effects in children: a review. *Pediatr. Res.* **74**, 96–102 (2013).
118. Rutherford, B. R. *et al.* Deconstructing pediatric depression trials: an analysis of the effects of expectancy and therapeutic contact. *J. Am. Acad. Child Adolesc. Psychiatry* **50**, 782–795 (2011).
119. Grelotti, D. J. & Kaptchuk, T. J. Placebo by proxy. *BMJ* **343**, d4345 (2011).
120. Horing, B., Weimer, K., Muth, E. R. & Enck, P. Prediction of placebo responses: a systematic review of the literature. *Front. Psychol.* **5**, 1079 (2014).
121. Hrobjartsson, A., Kaptchuk, T. J. & Miller, F. G. Placebo effect studies are susceptible to response bias and to other types of biases. *J. Clin. Epidemiol.* **64**, 1223–1229 (2011).
122. Horing, B., Weimer, K., Muth, E. R. & Enck, P. Prediction of symptom change in placebo versus no-treatment group in experimentally Induced motion sickness. *Appl. Psychophysiol. Biofeedback* http://dx.doi.org/10.1007/s10484-015-9284-y
123. Reynaert, C., Janne, P., Vause, M., Zdanowicz, N. & Lejeune, D. Clinical trials of antidepressants: the hidden face: where locus of control appears to play a key role in depression outcome. *Psychopharmacology (Berl)* **119**, 449–454 (1995).
124. Breckenridge, R. L. & Dodd, M. O. Locus of control and alcohol placebo effects on performance in a driving simulator. *Percept. Mot. Skills* **72**, 751–756 (1991).
125. Kokkotou, E. *et al.* Serum correlates of the placebo effect in irritable bowel syndrome. *Neurogastroenterol. Motil.* **22**, 285–e81 (2010).
126. Hall, K. T. *et al.* Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. *PLoS ONE* **7**, e48135 (2012).
127. Leuchter, A. F., McCracken, J. T., Hunter, A. M., Cook, I. A. & Alpert, J. E. Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder. *J. Clin. Psychopharmacol.* **29**, 372–377 (2009).
128. Wendt, L. *et al.* Catechol-O-methyltransferase Val158Met polymorphism is associated with somatosensory amplification and nocebo responses. *PLoS ONE* **9**, e107665 (2014).
129. Froehlich, T. E. *et al.* Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **50**, 1129–1139 (2011).
130. Ober, K. *et al.* Plasma noradrenaline and state anxiety levels predict placebo response in learned immunosuppression. *Clin. Pharmacol. Ther.* **91**, 220–226 (2012).
131. Kennedy, W. P. The nocebo reaction. *Med. World* **95**, 203–205 (1961).
132. Hauser, W., Bartram, C., Bartram-Wunn, E. & Tolle, T. Adverse events attributable to nocebo in randomized controlled drug trials in fibromyalgia syndrome and painful diabetic peripheral neuropathy: systematic review. *Clin. J. Pain* **28**, 437–451 (2012).
133. Hauser, W., Hansen, E. & Enck, P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch. Arztebl. Int.* **109**, 459–465 (2012).
134. Amanzio, M., Corazzini, L. L., Vase, L. & Benedetti, F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* **146**, 261–269 (2009).
135. Tan, K., Petrie, K. J., Faasse, K., Bolland, M. J. & Grey, A. Unhelpful information about adverse drug reactions. *BMJ* **349**, g5019 (2014).
136. Bingel, U. & The Placebo Competence Team. Avoiding nocebo effects to optimize treatment outcome. *JAMA* **312**, 693–694 (2014).
137. Elsenbruch, S. How positive and negative expectations shape the experience of visceral pain. *Handb. Exp. Pharmacol.* **225**, 97–119 (2014).

138. Benedetti, F., Lanotte, M., Lopiano, L. & Colloca, L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* **147**, 260–271 (2007).
139. Carlino, E., Frisaldi, E. & Benedetti, F. Pain and the context. *Nat. Rev. Rheumatol*. **10**, 348–355 (2014).
140. Petersen, G. L. *et al.* The magnitude of nocebo effects in pain: a meta-analysis. *Pain* **155**, 1426–1434 (2014).
141. Stockhorst, U., Enck, P. & Klosterhalfen, S. Role of classical conditioning in learning gastrointestinal symptoms. *World J. Gastroenterol.* **13**, 3430–3437 (2007).
142. Stockhorst, U. *et al.* Anticipatory symptoms and anticipatory immune responses in pediatric cancer patients receiving chemotherapy: features of a classically conditioned response? *Brain Behav. Immun*. **14**, 198–218 (2000).
143. Colagiuri, B. *et al.* Does assessing patients' expectancies about chemotherapy side effects influence their occurrence? *J. Pain Symptom. Manage*. **46**, 275–281 (2013).
144. Feinle-Bisset, C., Meier, B., Fried, M. & Beglinger, C. Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia. *Gut* **52**, 1414–1418 (2003).
145. Feinle-Bisset, C. & Azpiroz, F. Dietary and lifestyle factors in functional dyspepsia. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 150–157 (2013).
146. Hayes, P., Corish, C., O'Mahony, E. & Quigley, E. M. A dietary survey of patients with irritable bowel syndrome. *J. Hum. Nutr. Diet.* **27** Suppl. 2, 36–47 (2014).
147. Monsbakken, K. W., Vandvik, P. O. & Farup, P. G. Perceived food intolerance in subjects with irritable bowel syndrome— etiology, prevalence and consequences. *Eur. J. Clin. Nutr*. **60**, 667–672 (2006).
148. Suchy, F. J. *et al.* National Institutes of Health Consensus Development Conference: lactose intolerance and health. *Ann. Intern. Med*. **152**, 792–796 (2010).
149. Kull, M., Kallikorm, R. & Lember, M. Impact of molecularly defined hypolactasia, self-perceived milk intolerance and milk consumption on bone mineral density in a population sample in Northern Europe. *Scand. J. Gastroenterol*. **44**, 415–421 (2009).
150. Fasano, A., Sapone, A., Zevallos, V. & Schuppan, D. Non-celiac Gluten Sensitivity. *Gastroenterology* **148**, 1195–1204 (2015).
151. Vernia, P., Di, C. M., Foglietta, T., Avallone, V. E. & De, C. A. Diagnosis of lactose intolerance and the "nocebo" effect: the role of negative expectations. *Dig. Liver Dis*. **42**, 616–619 (2010).
152. Suarez, F. L., Savaiano, D. A. & Levitt, M. D. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N. Engl. J. Med*. **333**, 1–4 (1995).
153. King, T. Comparison of symptoms after the consumption of milk or lactose-hydrolysed milk by people with self-reported severe lactose intolerance. *Clin. Nutr*. **15**, 97–98 (1996).
154. Casellas, F., Aparici, A., Casaus, M., Rodriguez, P. & Malagelada, J. R. Impact of orocecal transit time on patients perception of lactose intolerance. *Rev. Esp. Enferm. Dig*. **105**, 13–17 (2013).
155. Tomba, C., Baldassarri, A., Coletta, M., Cesana, B. M. & Basilisco, G. Is the subjective perception of lactose intolerance influenced by the psychological profile? *Aliment. Pharmacol. Ther*. **36**, 660–669 (2012).
156. Schmid, J. *et al.* Neural underpinnings of nocebo hyperalgesia in visceral pain: a fMRI study in healthy volunteers. *Neuroimage* http://dx.doi.org/10.1016/j.neuroimage.2015.06.060
157. Craig, A. D. Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* **13**, 500–505 (2003).
158. Wiech, K. *et al.* Anterior insula integrates information about salience into perceptual decisions about pain. *J. Neurosci*. **30**, 16324–16331 (2010).
159. Linnman, C., Rougemont-Bucking, A., Beucke, J. C., Zeffiro, T. A. & Milad, M. R. Unconditioned responses and functional fear networks in human classical conditioning. *Behav. Brain Res*. **221**, 237–245 (2011).
160. Bingel, U. *et al.* The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci. Transl. Med*. **3**, 70ra14 (2011).
161. Colloca, L. & Miller, F. G. The nocebo effect and its relevance for clinical practice. *Psychosom. Med*. **73**, 598–603 (2011).
162. Icenhour, A. *et al.* Neural circuitry of abdominal pain-related fear learning and reinstatement in irritable bowel syndrome. *Neurogastroenterol. Motil*. **27**, 114–127 (2015).
163. Gramsch, C. *et al.* Learning pain-related fear: neural mechanisms mediating rapid differential conditioning, extinction and reinstatement processes in human visceral pain. *Neurobiol. Learn. Mem*. **116**, 36–45 (2014).
164. Kattoor, J. *et al.* Fear conditioning in an abdominal pain model: neural responses during associative learning and extinction in healthy subjects. *PLoS ONE* **8**, e51149 (2013).
165. Labus, J. S. *et al.* Impaired emotional learning and involvement of the corticotropin-releasing factor signaling system in patients with irritable bowel syndrome. *Gastroenterology* **145**, 1253–1261 (2013).
166. Zaman, J., Vlaeyen, J. W., Van Oudenhove, L., Wiech, K. & Van Diest, I. Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain. *Neurosci. Biobehav. Rev*. **51**, 118–125 (2015).
167. Craske, M. G. *et al.* A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behav. Res. Ther.* **49**, 413–421 (2011).
168. Ljotsson, B. *et al.* Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. *BMC Gastroenterol.* **11**, 110 (2011).
169. Haake, M. *et al.* German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch. Intern. Med*. **167**, 1892–1898 (2007).
170. Wechsler, M. E. *et al.* Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N. Engl. J. Med*. **365**, 119–126 (2011).
171. Kam-Hansen, S. *et al.* Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci. Transl. Med*. **6**, 218ra5 (2014).
172. Schenk, L. A., Sprenger, C., Geuter, S. & Buchel, C. Expectation requires treatment to boost pain relief: an fMRI study. *Pain* **155**, 150–157 (2014).
173. Atlas, L. Y. & Wager, T. D. How expectations shape pain. *Neurosci. Lett.* **520**, 140–148 (2012).
174. Miller, F. G. & Colloca, L. The placebo phenomenon and medical ethics: rethinking the relationship between informed consent and risk-benefit assessment. *Theor. Med. Bioeth*. **32**, 229–243 (2011).
175. Finniss, D. G., Kaptchuk, T. J., Miller, F. & Benedetti, F. Biological, clinical, and ethical advances of placebo effects. *Lancet* **375**, 686–695 (2010).
176. Kelley, J. M., Kaptchuk, T. J., Cusin, C., Lipkin, S. & Fava, M. Open-label placebo for major depressive disorder: a pilot randomized controlled trial. *Psychother. Psychosom*. **81**, 312–314 (2012).
177. Schafer, S. M., Colloca, L. & Wager, T. D. Conditioned placebo analgesia persists when subjects know they are receiving a placebo. *J. Pain* **16**, 412–420 (2015).
178. Martin, A. L. & Katz, J. Inclusion of authorized deception in the informed consent process does not affect the magnitude of the placebo effect for experimentally induced pain. *Pain* **149**, 208–215 (2010).
179. Wendt, L., Albring, A. & Schedlowski, M. Learned placebo responses in neuroendocrine and immune functions. *Handb. Exp. Pharmacol.* **225**, 159–181 (2014).
180. Albring, A. *et al.* Preserving learned immunosuppressive placebo response: perspectives for clinical application. *Clin. Pharmacol. Ther.* **96**, 247–255 (2014).
181. Stockhorst, U., Steingrueber, H. J., Enck, P. & Klosterhalfen, S. Pavlovian conditioning of nausea and vomiting. *Auton. Neurosci*. **129**, 50–57 (2006).
182. Rotter JB. Generalized expectancies for internal versus external control of reinforcement. *Psychol. Monogr*. **80**, 1–28 (1966).
183. Bandura A. in: *Encyclopedia of Human Behavior*. Vol. 4 (ed. Ramachandran, V. S.) 71–81 (San Diego Academic Press, 1994).
184. Breckenridge RL & Dodd MO. Locus of control and alcohol placebo effects on performance in a driving simulator. *Percept. Mot. Skills* **72**, 751–756 (1991).
185. Au Yeung, S. T., Colagiuri, B., Lovibond, P. F. & Colloca, L. Partial reinforcement, extinction, and placebo analgesia. *Pain* **155**, 1110–1117 (2014).
186. Hunter, T., Siess, F. & Colloca, L. Socially induced placebo analgesia: a comparison of a pre-recorded versus live face-to-face observation. *Eur. J. Pain* **18**, 914–922 (2014).
187. Colloca, L. & Benedetti, F. Placebo analgesia induced by social observational learning. *Pain* **144**, 28–34 (2009).
188. Swider, K. & Babel, P. The effect of the sex of a model on nocebo hyperalgesia induced by social observational learning. *Pain* **154**, 1312–1317 (2013).
189. Vögtle, E., Barke, A. & Kroner-Herwig, B. Nocebo hyperalgesia induced by social observational learning. *Pain* **154**, 1427–1433 (2013).
190. Enck P, Klosterhalfen S. Placebo response in functional bowel disorders [German]. *Z. Gastroenterol*. **44**, 257–266 (2006).

Author contributions

All authors contributed equally to all aspects of the manuscript.