PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2011) **366**, 1783–1789
doi:10.1098/rstb.2010.0414

Introduction

Introduction to placebo effects in medicine: mechanisms and clinical implications

Karin Meissner[1,2,*], Niko Kohls[3,4,5] and Luana Colloca[6,7]

[1]*Institute of Medical Psychology, Ludwig-Maximilians-University, Goethestrasse 31 80336 Munich, Germany*
[2]*Institute of General Practice, Klinikum rechts der Isar, Technische Universität, Orleansplatz 47, 81776 Munich, Germany*
[3]*Generation Research Program, Human Science Center, Ludwig-Maximilians-University, Prof.-Max-Lange-Platz 11, 83646 Bad Tölz, Germany*
[4]*Peter Schilffarth Institute for Sociotechnology (PSI), Prof.-Max-Lange-Platz 16, 83646 Bad Tölz, Germany*
[5]*Brain, Mind and Healing Program, Samueli Institute, 1737 King Street, Suite 600, Alexandria, VA 22314, USA*
[6]*National Center for Alternative and Complementary Medicine (NCCAM), and*
[7]*Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, MD, USA*

The field of placebo research has made considerable progress in the last years and it has become a major focus of interest. We know now that the placebo effect is a real neurobiological phenomenon and that the brain's 'inner pharmacy' is a critical determinant for the occurrence of psychobiological and behavioural changes relevant to healing processes and well-being. However, harnessing the advantages of placebo effects in healthcare is still a challenge. The first part of the theme issue summarizes and discusses the various kinds of placebo mechanisms across medical fields, thereby not only focusing on two main explanatory models—expectation and conditioning theory—but also taking into account empathy and social learning, emotion and motivation, spirituality and the healing ritual. The second part of the issue focuses on questions related to transferring knowledge from placebo research into clinical practice and discusses implications for the design and interpretation of clinical trials, for the therapeutic settings in daily patient care, and for future translational placebo research.

Keywords: placebo; nocebo; neurobiology; psychological mechanisms; randomized controlled trials; clinical practice

1. INTRODUCTION

Henry Knowles Beecher (1904–1976), one of the first placebo researchers, noted that soldiers severely wounded in a World War II combat zone much less frequently asked for analgesics to relieve their unbearable suffering than patients with similar injuries in civilian hospitals (25% versus 80%). Beecher reasoned that to the soldiers, being wounded during deployment meant that they had survived, would be removed from the combat zone and then would be treated well, whereas the civilians were probably more worried about their social and financial situation. Thus, Beecher opined that the threatening consequences anticipated by the civilian patients may explain their differing reactions concerning the demand of analgesics [1].

* Author for correspondence (karin.meissner@med.lmu.de).

One contribution of 17 to a Theme Issue 'Placebo effects in medicine: mechanisms and clinical implications'.

This interesting finding is the reason why Beecher got interested in exploring the power of placebos. His seminal paper 'The powerful placebo' written in 1955, in which he claimed that 'placebos have a high degree of therapeutic effectiveness in treating subjective responses' and can also have 'toxic effects' [2, p. 1606], has been cited more than 1000 times to date. Although his conclusions about the overall effect size and significance of placebo effects in clinical trials were biased owing to methodological errors in his analyses [3], his papers have nonetheless encouraged numerous medical doctors and scientists to study what we have come to know as 'placebo effects'.

(a) *Mechanistic placebo research*

A major step in placebo research was achieved by the discovery of the involvement of endogenous opioids in placebo analgesia. In 1978, Levine *et al.* [4] showed that the placebo response in patients with post-operative pain could be blocked by the opiate antagonist naloxone. Several replication studies with more sophisticated

methodological designs and experimental set-ups confirmed these findings [5–8]. However, there were also controversial or non-significant findings [9–11].

It is only owing to advances in neuroscience particularly driven by the insights obtained by neuroimaging techniques that we can be sure that endogenous opioid systems in the brain are indeed involved in many forms of placebo analgesia. For example, using positron emission tomography, Petrovic *et al.* [12] showed that a subset of brain regions was similarly affected by either a placebo intervention or treatment with the opioid agonist remifentanil. In 2005, using molecular imaging techniques, Zubieta *et al.* [13] were able to demonstrate that the expectation of pain relief activates μ-opioid receptor signalling in the human brain. Finally, the opioid antagonist naloxone was shown to reduce not only pain perception but also placebo-induced responses in cortical structures associated with pain modulation as well as in pivotal areas of the descending pain control system [14].

It is important to note that information about expected treatment effects can affect pain both in a positive and in a negative manner. Negative expectations can increase pain sensitivity and attenuate the effects of analgesic drugs [15,16]. This so-called nocebo hyperalgesia may persist for several months and could be demonstrated also by brain imaging techniques [17]. At the neurochemical level, nocebo hyperalgesia is modulated by the cholecystokininergic system [6,18,19].

It may, at a first glance, seem that placebo research has predominantly focused on pain and pain perception. However, while many insights concerning the psychobiological mechanisms of placebo have indeed been obtained from pain research, it is important to note that placebo and nocebo effects also occur in other medical conditions. A finding of comparable importance to the involvement of endogenous opioids in placebo analgesia, for example, was the demonstration that placebo responses in patients with Parkinson's disease are associated with the release of dopamine in the striatum, i.e. the specific brain structure damaged in Parkinson patients [20]. Likewise Benedetti *et al.* [21] were able to demonstrate that the clinical placebo effect in patients with Parkinson's disease was closely associated with the activity of single neurons in the subthalamic nucleus, a key brain area relevant for central motor control.

Additionally, there is a bulk of studies showing that organ functions regulated by the autonomic nervous system (ANS) are amenable to both placebo and nocebo interventions [22]. For example, the majority of studies scrutinizing the nocebo effect have actually been investigated in asthmatic patients, and there is now clear evidence that the expectation of bronchoconstriction impairs lung function. Finally, immunological placebo responses have been demonstrated in animal experiments, healthy subjects and patients, and parts of the physiological mechanisms responsible for these distinct changes in immune functions have recently been described [23]. First studies in patients suggest that conditioned immunosuppression may not only affect allergic responses but actually attenuate the course of disease of autoimmune illnesses [24].

The theories most accepted for explaining psychological mediation of placebo effects are expectation and classical conditioning. As early as 1950, Wolf published a paper entitled 'Effects of suggestion and conditioning on the action of chemical agents in human subjects' [25]. The idea of suggestive processes being relevant for placebo effects was later replaced by the concept of expectation. Inspired by the insights stemming from hypnosis research, Kirsch [26] wondered about the underlying psychological function determining the specific response to a suggestion, and he began to focus on the role of expectancy as a mediating psychological variable. The importance of verbal suggestions and expectations for placebo and nocebo effects has meanwhile been demonstrated in numerous experimental studies [22,27–29]. Furthermore, there is now compelling evidence for the validity of classical conditioning theory for explaining placebo effects, because drug-like effects also occur when active treatments administered repetitively are replaced with pharmacological inert interventions such as saline solutions or sugar pills [24,27,30]. Recent studies have additionally demonstrated that social observational learning represents another psychological mechanism for producing placebo responses [31]. Further important pieces of the placebo puzzle still need to be integrated into the whole picture, for example, motivational aspects [32], emotions [29] and characteristics of the healing ritual itself [33].

Besides all these psychological factors that are related to the therapeutic setting and how the placebo effects are initiated, personality factors may also play a role. While early attempts to define the typical 'placebo reactor' have failed [34], certain personality traits associated with placebo effects have recently been identified. For example, traits related to reward (and, from a neurobiological point of view, the dopaminergic activation), such as novelty seeking and reward responsiveness, accounted for about 25 to 30% of the variance in placebo analgesic responses [35,36]. Additionally, altruism [37], optimism [38–40], empathy [31] and spirituality [32,41] have been found to modulate placebo responses.

In summary, current knowledge about placebo mechanisms allows us to shed some light on the psychobiological mechanisms underlying the placebo (and nocebo) phenomenon, thereby allowing us to tentatively define a theory of the biological basis for the ability of the human body to heal itself. What implications does this knowledge have for clinical decision making and patient care?

(b) *Clinical placebo research*

For more than half a century, the randomized placebo-controlled trial (RCT) has been regarded as the gold standard for testing the efficacy of new clinical interventions and treatments. RCTs include an active treatment group and a placebo treatment group, whereby neither doctors nor patients know which of the two treatments is actually administered to a patient ('double blinding'). The total treatment effect is conceptualized as the sum of the 'specific' treatment effect and the 'unspecific' effects that occur also in the placebo group ('additive model'). A significantly larger effect in the treatment group indicates

superiority of the drug. The model builds upon the idea that placebo responses are of similar size in all study groups, as only then the principle of 'additivity' as a basic conceptual assumption can be employed.

However, the assumption of additivity has interestingly never been thoroughly tested. Moreover, recent analyses suggest that placebo effects may vary considerably both between treatment arms and across studies [42–44]. For example, there is mounting evidence that an increased likelihood to receive active treatment—which may be regarded a proxy for the degree of expectation of improvement—is associated with better outcome in the respective placebo groups, thereby potentially affecting conclusions about the efficacy of active treatment [45–49]. Furthermore, studies that used an 'active' placebo, which mirrored the side effect profile of the drug, increased the response in the placebo group in comparison with an inert placebo that does not exhibit side-effects [50]. In addition, there is evidence that physical placebos, such as sham acupuncture, are associated with larger placebo effects than pharmacological placebos [51–54].

Owing to this apparent variability of placebo effects within and across clinical trials, some treatments may fail to prove superiority above placebo even though their total effects are of clinical relevance and exceed the effect achieved by standard care. This paradox, which has been theoretically described and termed the 'efficacy paradox' [44], has recently become reality in two large acupuncture studies [55,56]. Implications for clinical trial methodology need to be discussed [42,44].

The word 'placebo' is derived from the verb 'placere', meaning 'to please' [34]. During the pre-pharmacological age it was quite customary to distribute sugar pills or other pharmacologically inactive substances to sooth the patient, to test for 'real illness' or to placate people, when no real effective treatment was known [44]. Even nowadays, physicians and nurses use placebo interventions regularly in clinical practice for very similar reasons as the healers did before the rise of modern medicine [57]. However, the deliberate use of placebo interventions bears severe ethical problems as the patient has to be deliberately deceived by the therapist. Therefore, alternative ways to harness the advantages of placebo effects in daily clinical practice are required. As will be debated in this theme issue, several approaches have been suggested, such as the description of placebos without deception, the application of conditioning protocols and the creation of an optimal healing environment [24,30,58].

2. OVERVIEW OF THE THEME ISSUE

The first part of the theme issue summarizes and discusses placebo mechanisms across medical fields, focusing on different explanatory models including conditioning, verbal suggestions, emotions, motivation, spirituality and healing rituals. The second part of the issue focuses on questions related to transfer of that knowledge into clinical practice, discussing implications of placebo research for the design and interpretation of clinical trials, for the therapeutic settings in daily patient care and for future translational placebo research.

Benedetti's team provides a comprehensive overview of neurobiological and pharmacological mechanisms underlying the placebo effect across different conditions [28]. While most of the presented studies are related to the medical context, where pathological conditions are altered following the administration of an inert substance or verbal instructions tailored to induce expectation of change, the review also goes beyond the clinical setting, embracing physical performance with crucial implications for sport competition as well.

Schedlowski's team presents behavioural conditioning as a major mechanism mediating the placebo response on the immune system, and describes underlying mechanisms on the basis of functional interaction between the central nervous system (CNS) and the peripheral immune system, with an emphasis on allergic reactions [24]. Although the exact mechanisms of immune behavioural conditioning are yet largely unknown, there is evidence that both allergic and anti-allergic responses can be 'manipulated' by means of conditioning paradigms, with the potential to promote anti-allergic healing processes.

Specific verbal suggestions accompanying placebo interventions affect not only the perception of symptoms, but also the functioning of inner organs that are modulated by the ANS. Karin Meissner [22] reviews the placebo literature with respect to the cardiovascular, the gastrointestinal and the pulmonary systems and provides relevant background information on the functional organization of the ANS and the central autonomic network. In accordance with previous findings from analgesic placebo research [59,60], her results provide first evidence for the autonomic specificity of autonomic placebo effects. For example, placebo interventions targeting the stomach affected gastric motility, but not cardiovascular or electrodermal functions [61]. She proposes that verbal suggestions during placebo interventions may activate association networks in the brain that store memories of the appropriate autonomic response [22].

In contrast to findings supporting the specificity of placebo effects, it has been postulated that there might be a common mechanism that subserves all types of placebo responses. Flaten *et al.* [29] review the literature with respect to a hypothesis that focuses on the role of emotions for the placebo response. The hypothesis predicts that pain relief following the ingestion of a placebo pill may be due to the reduction of stress and anxiety and a concomitant increase in positive emotions. As these emotions are closely connected to the activation of endogenous opioid systems in the brain, they can explain the occurrence of analgesic placebo responses.

An important question related to the effectiveness of placebo interventions is whether insights into placebo and nocebo mechanisms gained under laboratory conditions can be transferred to the clinical encounter. Starting from a motivational framework of placebo effects, Michael Hyland [32] provides evidence that different placebo mechanisms may apply in different contexts. Whereas response expectancy, conditioning and goal activation may be responsible for short-term placebo effects, long-term placebo responses may be achieved through satisfaction of higher level goals, such as a good relationship with the doctor. This may improve symptoms by reducing stress and thereby attenuating the deleterious effects of stress on health.

In the last years, a new research field has blossomed that is investigating the relationship between spirituality, health and coping with illness and distress. Spirituality may broadly be understood as an implicit or explicit orientation towards, searching for and expressing a reality transcending immediate and mediate personal needs, and a striving for experiencing a universal or transcendental dimension. It is of interest that research looking into spirituality health connection has provided insights that are similar to those obtained in placebo research. For example, there is clear evidence that spirituality is able to alter pain perception [62,63]. Kohls *et al.* [41] suggested that meaningfulness and sense of purpose may be a concept relevant for health-related processes including the placebo effect.

Ted Kaptchuk's contribution [33] is a creative comparative analysis of ceremonials by Navajo healing rituals (the most populous American Indian tribe in the United States), acupuncture, and biomedical treatments. The author describes the different components of the three healing settings and identifies the treatment ritual as the basis of any placebo response. While for biomedicine the placebo effect has primarily been a 'non-specific' process that needs to be controlled, the placebo effect for ritual theory constitutes the 'specific' effect of a healing effort. As placebo research has started to sketch the underlying neurobiological causal pathways of these unspecific effects, it has become clear that a link between placebo studies and ritual theory would be helpful. The author emphasizes the need for mixed-method research methodologies in the field.

The last contribution of the first part provided by Colloca & Miller [27] aims at interpreting, critiquing and conceptualizing the existing experimental and clinical research on placebo (and nocebo) effects though a learning perspective—the process of decoding information and creating expectations. The question whether and how human beings can activate this sort of inbuilt 'endogenous pharmacy' is of utmost interest for all areas of medicine. It is important to understand how individuals can systematically harness innate, environmentally and/or culturally promoted placebo mechanisms for enhancing clinical outcomes, improving their health and well-being, and reducing harmful effects. Therefore, the learning perspective may have innovative implications for a deeper and better knowledge of the placebo phenomenon in science and healthcare.

The second part of the issue covers highlights that range from clinical trial methodology to translational placebo research. Harald Walach [44] introduces the reader to historical notes of the placebo effect when inert substances and procedures were introduced as control conditions. He then describes the efficacy paradox of sham interventions pointing to the fact that sham interventions frequently turn out to be more powerful than proved, evidence-based treatments. Walach uses the efficacy paradox as a conceptual basis for discussing the limits of present conventional trial methodology, thereby raising questions about how efficacy of treatments should be determined. The question whether a treatment is effective can be addressed by considering circumstances, context, patients' choice, and subjective sense of meaningfulness that is attributed to the intervention itself.

Rief's team provides an overview about placebo and nocebo phenomena in antidepressant trials [43]. The authors present a sophisticated meta-analysis of RCTs suggesting large placebo responses to antidepressant medication. Several moderating factors relating to the size of the placebo responses could be identified, such as the method of symptom assessment and year of publication. Nocebo responses, in terms of the side-effect patterns in the placebo groups, depended on the side-effect profiles of the antidepressant drug and notably differed for gender.

Enck *et al.* [42] focus on important but as yet unanswered questions about placebo effects in clinical trials, with an emphasis that questions the additivity model. They propose several novel study designs that may be useful for disentangling placebo and treatment effects in clinical trials in order to get a more reliable and true estimation of the effects of active treatments. For example, a unique although still untested study design would not randomize patients between drug and placebo, but would allow them to 'freely' choose between two pills, one being the active drug and one the placebo. Thus, the assessment of drug versus placebo efficacy would not rely on reports of symptom improvement that may contain reporting bias, but rather on choice behaviour.

Linde *et al.* [57] discuss reasons for using placebos in clinical practice and suggest that the perspectives of physicians, scientists and patients about placebo may substantially diverge. Using placebo interventions in medical practice is rather frequent, but is in contrast with the professional imperative of specific and indicated treatment as it is conventionally taught in medical education, and consequently points to a considerable amount of treatment uncertainty among physicians. At the same time, the widespread use of placebos can be taken as evidence that rituals, myths and plausible explanations have not been barred from modern medicine but still guide therapeutic decisions.

Wayne Jonas [58] discusses some possible dilemmas that may derive from the current framing of placebo research. In particular, he presents the scenario of a physician who has to decide on the utilization of a treatment that is 'not better than placebo' but nonetheless is more effective than standard care. In such a case, Jonas argues, it is important to understand the placebo effect as a meaning response, which can be triggered by manipulating contextual factors. By introducing the concept of an optimal healing environment, Jonas suggests that the therapeutic alliance and the management of patient's expectation may represent an important element of good clinical practice.

Verbal and non-verbal interactions between the patient and the physician may affect the perception of treatment efficacy, which in turn may influence patient expectations, and thus also clinical outcome. Vase *et al.* [64] present qualitative data from interviews with patients who have experienced pain relief following a placebo intervention or active treatment, discussing the extent to which these findings have implications for our understanding of placebo analgesia.

Beyond the scientific interest in exploring the mechanisms of the placebo and nocebo responses and improving clinical trial methodology, the ultimate aim of this research is to develop knowledge that can be translated into improved patient care. In light of the translational placebo research, Colloca & Miller [30] end the issue by analysing salient aspects of theoretical knowledge of the placebo and nocebo effects, discussing the evidence of clinical placebo (and nocebo) responses, and identifying potential strategies for harnessing beneficial placebo responses and diminishing harmful nocebo effects in the clinical encounter consistent with ethical and legal requirements.

3. FUTURE DIRECTIONS

Scientific interest in placebo and nocebo effects has grown dramatically in recent years. A plethora of studies have shown that implicit and explicit psychobiological mechanisms that are inextricably associated with the therapeutic encounter *per se* are important factors for mediating placebo responses. A challenge for the future is to understand commonalities and differences in eliciting the placebo response across different systems and conditions. Additionally, it would be important to identify psychobiological characteristics that serve as biomarkers for predicting placebo responsiveness (placebo responders versus placebo non-responders). The promise of increasingly sophisticated brain imaging techniques is that we will better understand the complex interactions of mind and body in placebo-induced healing processes.

From a methodological point of view, given the uncertainty about the size of placebo and treatment effects in clinical trials and practice, there is a need for more methodologically rigorous study designs that are capable of disentangling the specific and non-specific components of a given treatment. In addition, valid ways to estimate the size of placebo effects in daily patient care have to be developed, and the reasons for using disproven, non-medicated treatments so frequently in daily practice needs to be discussed. In pursuing the goal to translate insights from placebo research into clinics it will be necessary to learn more about the attitudes of patients towards harnessing placebo effects in healthcare, for example, by administering placebo treatments without deception, or by manipulating context factors in order to create an optimal healing environment. Further consideration must be devoted to exploring variables pivotal to the patient–physician relationship and treatment settings influencing patients' perception of symptoms and the outcome of treatments.

It is plausible to argue that research on placebo and nocebo effects may not only prompt a revolutionary shift in thinking of the physician–patient interaction, with the promise to guide strategies for optimizing clinical practice, but will also open promising avenues for improvement within most areas of modern medicine.

A substantial part of the contributions in this theme issue are based on talks held at a symposium on placebo effects from 27th to 28th November 2009 at Lake Starnberg, Germany, organized by Ernst Pöppel, Karin Meissner and Niko Kohls from the Ludwig-Maximilians-University Munich, Germany. We are grateful for the generous support of the Theophrastus Foundation (Germany), the Peter Schilffarth Institute for Sociotechnology (Germany) and the Samueli Institute (USA) that made this conference possible.

REFERENCES

1 Beecher, H. K. 1956 Relationship of significance of wound to pain experienced. *J. Am. Med. Assoc.* **161**, 1609–1613. (doi:10.1001/jama.1956.02970170005002)
2 Beecher, H. K. 1955 The powerful placebo. *J. Am. Med. Assoc.* **159**, 1602–1606.
3 Kienle, G. S. & Kiene, H. 1997 The powerful placebo effect: fact or fiction? *J. Clin. Epidemiol.* **50**, 1311–1318. (doi:10.1016/S0895-4356(97)00203-5)
4 Levine, J. D., Gordon, N. C. & Fields, H. L. 1978 The mechanism of placebo analgesia. *Lancet* **2**, 654–657. (doi:10.1016/S0140-6736(78)92762-9)
5 Levine, J. D. & Gordon, N. C. 1984 Influence of the method of drug administration on analgesic response. *Nature* **312**, 755–756. (doi:10.1038/312755a0)
6 Benedetti, F. 1996 The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* **64**, 535–543. (doi:10.1016/0304-3959(95)00179-4)
7 Benedetti, F., Amanzio, M. & Maggi, G. 1995 Potentiation of placebo analgesia by proglumide. *Lancet* **346**, 1231. (doi:10.1016/S0140-6736(95)92938-X)
8 Amanzio, M. & Benedetti, F. 1999 Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* **19**, 484–494.
9 Gracely, R. H., Dubner, R., Wolskee, P. J. & Deeter, W. R. 1983 Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* **306**, 264–265. (doi:10.1038/306264a0)
10 Grevert, P., Albert, L. H. & Goldstein, A. 1983 Partial antagonism of placebo analgesia by naloxone. *Pain* **16**, 129–143. (doi:10.1016/0304-3959(83)90203-8)
11 Posner, J. & Burke, C. A. 1985 The effects of naloxone on opiate and placebo analgesia in healthy volunteers. *Psychopharmacology* **87**, 468–472. (doi:10.1007/BF00432515)
12 Petrovic, P., Kalso, E., Petersson, K. M. & Ingvar, M. 2002 Placebo and opioid analgesia—imaging a shared neuronal network. *Science* **295**, 1737–1740. (doi:10.1126/science.1067176)
13 Zubieta, J. K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., Nichols, T. E. & Stohler, C. S. 2005 Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J. Neurosci.* **25**, 7754–7762. (doi:10.1523/JNEUROSCI.0439-05.2005)
14 Eippert, F., Bingel, U., Schoell, E. D., Yacubian, J., Klinger, R., Lorenz, J. & Buchel, C. 2009 Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* **63**, 533–543. (doi:10.1016/j.neuron.2009.07.014)
15 Tracey, I. 2010 Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat. Med.* **16**, 1277–1283. (doi:10.1038/nm.2229)
16 Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. 2004 Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol.* **3**, 679–684. (doi:10.1016/S1474-4422(04)00908-1)
17 Rodriguez-Raecke, R., Doganci, B., Breimhorst, M., Stankewitz, A., Buchel, C., Birklein, F. & May, A. 2010 Insular cortex activity is associated with effects of negative expectation on nociceptive long-term

habituation. *J. Neurosci.* **30**, 11 363–11 368. (doi:10.1523/JNEUROSCI.2197-10.2010)
18 Benedetti, F., Amanzio, M. & Thoen, W. 2010 Disruption of opioid-induced placebo responses by activation of cholecystokinin type-2 receptors. *Psychopharmacology* **213**, 791–797. (doi:10.1007/s00213-010-2037-y)
19 Benedetti, F., Amanzio, M., Casadio, C., Oliaro, A. & Maggi, G. 1997 Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. *Pain* **71**, 135–140. (doi:10.1016/S0304-3959(97)03346-0)
20 de la Fuente-Fernandez, R., Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B. & Stoessl, A. J. 2001 Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* **293**, 1164–1166. (doi:10.1126/science.1060937)
21 Benedetti, F., Colloca, L., Torre, E., Lanotte, M., Melcarne, A., Pesare, M., Bergamasco, B. & Lopiano, L. 2004 Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat. Neurosci.* **7**, 587–588. (doi:10.1038/nn1250)
22 Meissner, K. 2011 The placebo effect and the autonomic nervous system: evidence for an intimate relationship. *Phil. Trans. R. Soc. B* **366**, 1808–1817. (doi:10.1098/rstb.2010.0403)
23 Schedlowski, M. & Pacheco-Lopez, G. 2010 The learned immune response: Pavlov and beyond. *Brain Behav. Immunol.* **24**, 176–185. (doi:10.1016/j.bbi.2009.08.007)
24 Vits, S., Cesko, E., Enck, P., Hillen, U., Schadendorf, D. & Schedlowski, M. 2011 Behavioral conditioning as the mediator of placebo responses in the immune system. *Phil. Trans. R. Soc. B* **366**, 1799–1807. (doi:10.1098/rstb.2010.0392)
25 Wolf, S. 1950 Effects of suggestion and conditioning on the action of chemical agents in human subjects; the pharmacology of placebos. *J. Clin. Invest.* **29**, 100–109. (doi:10.1172/JCI102225)
26 Kirsch, I. 1999 Hypnosis and placebos: response expectancy as a mediator of suggestion effects. *Anal. Psicología* **15**, 99–110.
27 Colloca, L. & Miller, F. G. 2011 How placebo responses are formed: a learning perspective. *Phil. Trans. R. Soc. B* **366**, 1859–1869. (doi:10.1098/rstb.2010.0398)
28 Pollo, A., Carlino, E. & Benedetti, F. 2011 Placebo mechanisms across different conditions: from the clinical setting to physical performance. *Phil. Trans. R. Soc. B* **366**, 1790–1798. (doi:10.1098/rstb.2010.0381)
29 Flaten, M. A., Aslaksen, P. M., Lyby, P. S. & Bjørkedal, E. 2011 The relation of emotions to placebo responses. *Phil. Trans. R. Soc. B* **366**, 1818–1827. (doi:10.1098/rstb.2010.0407)
30 Colloca, L. & Miller, F. G. 2011 Harnessing the placebo effect: the need for translational research. *Phil. Trans. R. Soc. B* **366**, 1922–1930. (doi:10.1098/rstb.2010.0399)
31 Colloca, L. & Benedetti, F. 2009 Placebo analgesia induced by social observational learning. *Pain* **144**, 28–34. (doi:10.1016/j.pain.2009.01.033)
32 Hyland, M. E. 2011 Motivation and placebos: do different mechanisms occur in different contexts? *Phil. Trans. R. Soc. B* **366**, 1828–1837. (doi:10.1098/rstb.2010.0391)
33 Kaptchuk, T. J. 2011 Placebo studies and ritual theory: a comparative analysis of Navajo, acupuncture and biomedical healing. *Phil. Trans. R. Soc. B* **366**, 1849–1858. (doi:10.1098/rstb.2010.0385)
34 Shapiro, A. K. & Morris, L. A. 1978 The placebo effect in medical and psychological therapies. In *Handbook of psychotherapy and behaviour change* (eds S. L. Garfield & A. E. Bergin), pp. 369–410. New York, NY: John Wiley.
35 Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H. & Bushnell, M. C. 2009 The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. *J. Neurosci.* **29**, 4882–4887. (doi:10.1523/JNEUROSCI.5634-08.2009)
36 Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A. & Zubieta, J. K. 2008 Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch. Gen. Psychiatry* **65**, 220–231. (doi:10.1001/archgenpsychiatry.2007.34)
37 Mackenbach, J. P. 2005 On the survival of the altruistic trait in medicine: is there a link with the placebo effect? *J. Clin. Epidemiol.* **58**, 433–435. (doi:10.1016/j.jclinepi.2004.09.007)
38 Geers, A. L., Wellman, J. A., Fowler, S. L., Helfer, S. G. & France, C. R. 2010 Dispositional optimism predicts placebo analgesia. *J. Pain* **11**, 1165–1171. (doi:10.1016/j.jpain.2010.02.014)
39 Geers, A. L., Helfer, S. G., Kosbab, K., Weiland, P. E. & Landry, S. J. 2005 Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. *J. Psychosom. Res.* **58**, 121–127. (doi:10.1016/j.jpsychores.2004.08.011)
40 Morton, D. L., Watson, A., El-Deredy, W. & Jones, A. K. 2009 Reproducibility of placebo analgesia: effect of dispositional optimism. *Pain* **146**, 194–198. (doi:10.1016/j.pain.2009.07.026)
41 Kohls, N., Sauer, S., Offenbächer, M. & Giordano, J. 2011 Spirituality: an overlooked predictor of placebo effects? *Phil. Trans. R. Soc. B* **366**, 1838–1848. (doi:10.1098/rstb.2010.0389)
42 Enck, P., Klosterhalfen, S., Weimer, K., Horing, B. & Zipfel, S. 2011 The placebo response in clinical trials: more questions than answers. *Phil. Trans. R. Soc. B* **366**, 1889–1895. (doi:10.1098/rstb.2010.0384)
43 Shedden Mora, M., Nestoriuc, Y. & Rief, W. 2011 Lessons learned from placebo groups in antidepressant trials. *Phil. Trans. R. Soc. B* **366**, 1879–1888. (doi:10.1098/rstb.2010.0394)
44 Walach, H. 2011 Placebo controls: historical, methodological and general aspects. *Phil. Trans. R. Soc. B* **366**, 1870–1878. (doi:10.1098/rstb.2010.0401)
45 Papakostas, G. I. & Fava, M. 2009 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. (doi:10.1016/j.euroneuro.2008.08.009)
46 Sinyor, M., Levitt, A. J., Cheung, A. H., Schaffer, A., Kiss, A., Dowlati, Y. & Lanctot, K. L. 2010 Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. *J. Clin. Psychiatry* **71**, 270–279. (doi:10.4088/JCP.08r04516blu)
47 Diener, H. C., Dowson, A. J., Ferrari, M., Nappi, G. & Tfelt-Hansen, P. 1999 Unbalanced randomization influences placebo response: scientific versus ethical issues around the use of placebo in migraine trials. *Cephalalgia* **19**, 699–700. (doi:10.1046/j.1468-2982.1999.019008699.x)
48 Mallinckrodt, C. H., Zhang, L., Prucka, W. R. & Millen, B. A. 2010 Signal detection and placebo response in schizophrenia: parallels with depression. *Psychopharmacol. Bull* **43**, 53–72.
49 Klosterhalfen, S., Vase, L. & Enck, P. 2010 The likelihood of receiving the drug determines the size of the placebo response. *Neurogastroenterol. Motil* **22**, 1–22. (doi:10.1111/j.1365-2982.2010.01548.x)
50 Moncrieff, J., Wessely, S. & Hardy, R. 2004 Active placebos versus antidepressants for depression. *Cochrane*

Database Syst. Rev. **1**, CD003012. (doi:10.1002/14651858.CD003012.pub2)
51 Hrobjartsson, A. & Gotzsche, P. C. 2010 Placebo interventions for all clinical conditions. *Cochrane Database Syst. Rev.* **1**, CD003974. (doi:10.1002/14651858.CD003974.pub3)
52 Linde, K., Niemann, K. & Meissner, K. 2010 Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. *Forsch Komplementmed* **17**, 259–264. (doi:10.1159/000320374)
53 Linde, K., Niemann, K., Schneider, A. & Meissner, K. 2010 How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. *BMC Med.* **8**, 75. (doi:10.1186/1741-7015-8-75)
54 Kaptchuk, T. J. *et al.* 2006 Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ* **332**, 391–397. (doi:10.1136/bmj.38726.603310.55)
55 Scharf, H. P., Mansmann, U., Streitberger, K., Witte, S., Kramer, J., Maier, C., Trampisch, H. J. & Victor, N. 2006 Acupuncture and knee osteoarthritis: a three-armed randomized trial. *Ann. Intern. Med.* **145**, 12–20.
56 Haake, M., Muller, H. H., Schade-Brittinger, C., Basler, H. D., Schafer, H., Maier, C., Endres, H. G., Trampisch, H. J. & Molsberger, A. 2007 German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch. Intern. Med.* **167**, 1892–1898. (doi:10.1001/archinte.167.17.1892)
57 Linde, K., Fässler, M. & Meissner, K. 2011 Placebo interventions, placebo effects and clinical practice. *Phil. Trans. R. Soc. B* **366**, 1905–1912. (doi:10.1098/rstb.2010.0383)
58 Jonas, W. B. 2011 Reframing placebo in research and practice. *Phil. Trans. R. Soc. B* **366**, 1896–1904. (doi:10.1098/rstb.2010.0405)
59 Montgomery, G. & Kirsch, I. 1996 Mechanisms of placebo pain reduction: an empirical investigation. *Psychol. Sci.* **7**, 174–176. (doi:10.1111/j.1467-9280.1996.tb00352.x)
60 Benedetti, F., Arduino, C. & Amanzio, M. 1999 Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J. Neurosci.* **19**, 3639–3648.
61 Meissner, K. 2009 Effects of placebo interventions on gastric motility and general autonomic activity. *J. Psychosom. Res.* **66**, 391–398. (doi:10.1016/j.jpsychores.2008.09.004)
62 Wachholtz, A. B. & Pargament, K. I. 2005 Is spirituality a critical ingredient of meditation? Comparing the effects of spiritual meditation, secular meditation, and relaxation on spiritual, psychological, cardiac, and pain outcomes. *J. Behav. Med.* **28**, 369–384. (doi:10.1007/s10865-005-9008-5)
63 Giordano, J. & Kohls, N. 2008 Spirituality, suffering, and the self. *Mind Matter* **6**, 179–191.
64 Vase, L., Nørskov, K. N., Petersen, G. L. & Price, D. D. 2011 Patients' direct experiences as central elements of placebo analgesia. *Phil. Trans. R. Soc. B* **366**, 1913–1921. (doi:10.1098/rstb.2010.0402)