Neurophysiology and Psychobiology of the Placebo Response

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Curr Opin Psychiatry. 2008;21(2):189-195. ©2008 Lippincott Williams & Wilkins
Posted 03/31/2008

Abstract and Introduction

Abstract

Purpose of review: The placebo literature has substantially increased in 2006 and 2007, and more and more medical and psychological subspecialties have added empirical data to our knowledge.

Recent findings: The theoretical framework of our understanding of the placebo response needs extension to account for findings that cannot be attributed to (Pavlovian) conditioning or suggestions alone. In addition, imaging studies need to address individual responses rather than group means, and to expand beyond experimental pain research. Gender aspects have been demonstrated for the placebo response but still widely ignored, especially in neurophysiological studies. It has been shown that nocebo research needs a methodological and ethical framework that allows its exploration. Finally, analyses of clinical trial data, either as metaanalyses or as reanalyses of trial raw data, may allow us to identify factors that subsequently can be used in experimental work.

Summary: Novel findings will allow better planning of clinical drug trials, better handling of clinical trial data in the future, and finally, may eventually result in improved patient management.

Introduction

The placebo response is the beneficial effect of a treatment with a drug or other medicinal tool that is thought to not be specific to the drug but rather to ‘unspecific’ circumstances of the treatment; the nocebo response is the worsening of symptoms due to these unspecific factors. In clinical trials of new compounds, these effects are controlled for so as not to overestimate the efficacy of the new drug; in clinical routine, placebo and nocebo responses occur with any treatment, but cannot easily be separated from the specific effects.

Such ‘unspecific’ treatment effects are believed to include predisposing individual factors on the side of both the physician and the patient, for example training, empathy, suggestions, expectancies, worries and concerns, previous illness experience and a history of successful or failed therapy, and health behaviours; it also includes mechanisms based on their interaction, for example time, duration and intensity of patient-doctor communication. Hence, the placebo response may represent an ideal behaviour medicine paradigm to study the interaction between physiological and psychological properties of any medical treatment.

The placebo response (as well as the nocebo response, which has been studied to a lesser degree) is thought to be generated by a few basic mechanisms. First, learning of symptoms by either Pavlovian or by instrumental (rewarding) conditioning; in this case, previous illness experience codetermines the response to a medical intervention. Pavlovian learning has been shown to contribute to the placebo response in a number of clinical symptoms, such as increased blood pressure, nausea, and pain.

The other mechanism that is thought to be involved is the effects of suggestions (on the side of the physician) and expectancies (on the side of the patient) on symptom perception. Placebo analgesia is an established paradigm to study this: prior to an experimental pain application, patients receive an inert pain treatment (by injection, a pill, or a locally applied cream) with the instruction that this is a powerful pain killer, and subsequent tolerance to the pain is measured. Expectancies have also been shown to contribute to motor performance in Parkinson's disease, and to symptom relief in depression.

PUBMED lists between 5000 and 10 000 papers per year for the term ‘placebo’, and among them around 100 that are not placebo-controlled trial reports but deal with the placebo effect per se. The literature published in 2007 and preceding years was screened and reviewed with respect to five aspects: theoretical framework - conditioning versus expectation; neurophysiology, especially brain imaging (functional MRI (fMRI), PET and electroencephalography (EEG)); gender differences in placebo response; nocebo responses and their similarities to the placebo response; and results of systematic reviews, metaanalyses, and reanalyses of clinical trials with respect to determinants of the placebo response.

Expectations and Conditioning

Across clinical conditions, it has been suggested that the placebo response is generated by two distinct mechanisms: suggestions and expectation, and learning via (Pavlovian) conditioning. The relationship between these two mechanisms is unclear but has been subject to experimental research in recent years: Benedetti et al. showed that conditioning is able to override suggested responses, but that suggestions are not able to manipulate conditioned responses - at least in experimental pain and with motor function in Parkinson's disease. Other explanations, however, have been put forward, such that expectancies, achieved through verbal instructions, may also be seen as conditioning stimuli that reactivate earlier stimulus association.

In a set of experiments, Colloca and Benedetti recently demonstrated that prior experience is able to shape placebo analgesia: patients who were conditioned to experience placebo analgesia in an acute paradigm demonstrated reduced pain experiences for up to 7 days, and exhibited reduced extinction of responses in a range of minutes. Repetition of a negative (painful) procedure after 1 week resulted in reduced placebo analgesia.

This work emphasizes that previous experience with successful or unsuccessful treatment of pain will have lasting effects on how a second or subsequent treatment of the same (and of other?) conditions is perceived. The analogy to clinical conditions is evident, but relative, and is noted by the authors: while experimental pain is phasic and acute, clinical pain is usually chronic, and long lasting. Whether and to what degree previous pain treatment contributes to the experience of placebo analgesia in a clinical trial - usually a sixth of the effect size achieved in experimental pain conditions - probably needs a different experimental or clinical approach to be tested (see section on 'Placebo and nocebo').
It is puzzling that, beyond the laws of Pavlovian learning studied for almost a century now, there is basically no model available that allows the maintenance of a strong placebo response to be predicted in a clinical trial that may last for a year or longer. In such a trial, extinction does not seem to occur at all, and previous experience with this drug [a 5-hydroxytryptamine (HT)-3 antagonist or a similar compound] did not shape the response. Hence, one may speculate that if conditioning (learning) were to be part of this placebo response, it cannot be of a Pavlovian nature (see next section).

### Brain Imaging

The number of brain imaging papers on the placebo response has increased over the last few years (Table 1). These papers focus mainly on the area of pain and placebo analgesia processing and to a much lesser degree on other areas of neurological and psychiatric diseases (e.g. Parkinson's disease, depression, or irritable bowel disorder). A number of recent review articles have summarized these findings. As can be seen from this summary, the corotical network thought to be responsible for processing the placebo response is reasonably well established for experimental pain, both peripheral as well as visceral: it includes different cortical (prefrontal cortex, anterior cingulate cortex, insular cortex, supplementary motor area) and subcortical structures (amygdala, periaqueductal grey, thalamus) and seems to differentiate between the sensory component of pain signals and their emotional and affective components, as one would expect from the older pain-imaging literature. A PET binding study indicates that the µ-opioid system is involved, but it has also been proposed that other neurochemical systems contribute to the placebo effect, and among them especially the dopaminergic system, nitric oxide, and cholecystokinin (CCK).

Two recent studies by Zubieta and his groups have used combined but not simultaneous PET (for the pain and placebo response recording) and fMRI imaging (for the recording of dopaminergic reward system response during a incentive task) that allowed the identification of individual response characteristics in a pain paradigm. They found that the nucleus accumbens is activated and releases dopamine during placebo administration.

Whether or not gender differences that have been found in placebo studies (see below) may account for some of the variance in the imaging studies is still missing. The ‘nitric oxide’ hypothesis is based on experimental findings of nitric oxide to affect dopaminergic and glutamate pathways, but direct evidence in humans is still lacking.

One of the pitfalls of most imaging studies is that they rely on a stable and dominant activation pattern across all subjects, since group means are necessary for adequate data analysis. In consequence, placebo nonresponders in small samples of subjects are frequently excluded or used as a type of control. As long as this is the case, individual responsiveness to placebo, which has become a major area of research outside the imaging laboratory (e.g. see also below), will not advance the field.

Other neurophysiological and psychobiological mechanisms of placebo analgesia and placebo response are currently under discussion: it was shown that placebo analgesia following heat pain application may change spinal cord pain processing via descending pathways, and therefore is not merely altered pain reporting. In another experimental (laser) pain condition, the placebo response was not attributable to habituation and compliance with the experimental instruction.

Whether or not gender differences that have been found in placebo studies (see below) may account for some of the variance in the imaging studies is not discussed in any of these papers. In fact, in many of them the gender ratio among patients and volunteers is not even reported (see Table 1). Cortical processing independently of the placebo response, however, has shown significant gender variation both in volunteers and in patients, for example with somatic and visceral pain and with nonpainful stimuli. Future studies should take this into account.

### Gender Effects

Gender effects of the placebo response have rarely been documented in clinical trials but have occasionally been noted in experimental settings. In an experimental setting with placebo analgesia during ischaemic pain, Flaten et al. noted that males responded to the manipulation of expectancies by pain information, while women did not, but they could not exclude an experimenter effect, as all their experimenters were female nurses, and that could have induced a reporting bias. Gender effects have also been noted in an acupuncture trial with male and female practitioners, with females inducing greater trust than males.

We recently studied gender differences of the placebo/nocebo effects in two experiments using a motion-sickness paradigm and found that conditioning was effective predominantly in women, while in the suggestion experiment men exhibited a significantly greater reduction in rotation tolerance and responded more strongly to rotation and to suggestions than women (Fig. 1). We concluded that both procedures were effective in inducing nocebo but not placebo responses but that learning was more effective in women, while suggestions showed a higher efficacy in men.
Figure 1.
Change in rotation tolerance. Change in rotation tolerance(s) in healthy males (dotted lines) and females (solid lines) in two independent experiments with conditioning (cond) and with suggestion (sugg) of nausea symptoms in a rotation chair paradigm, compared with respective control (cont) conditions. Reproduced from [41] (see [42] for technical details).

This calls to our attention that the placebo response in any test, especially in large-scale clinical trials (see below), may be brought about by different components of the same setting, of which some may act on males and others may affect females; the results may be identical and cannot be distinguished based on clinical data alone. Our results, however, may be specific for nausea, for which gender differences are well established.[40,42]

In a nicotine trial,[43] women were more responsive than men towards instructions given with the nicotine patch.

Placebo and Nocebo

The fact that we were unable to induce a placebo response in our experiments with rotation (see above, Fig. 1) has some similarities to other experimental results published recently. Levine and colleagues[44] were using a rotation paradigm and the electrogastrogram (EGG) as a measure of motion response to manipulations of expectancies of symptom worsening or relief; they also found a stronger effect on suggestions of inducing tachygastria, the biological marker of motion sickness, than of bradygastria. In another similar experiment, Meissner et al.[45] were able to modulate the EGG signal in both directions but also preferentially towards tachygastria. From these experiments one may conclude that the placebo response and the nocebo response may be ruled by different laws, but this needs further validation.

Nocebo responses are much less well characterized in the current literature. Usually, nocebo responses are referred to as adverse events that occur in the placebo arm of clinical drug trials.[46] The prevalence of symptoms occurring during placebo treatment of drugs tested are, however, frequently much lower than those found in the general population independently of drug treatment, and have to be viewed with caution.[47] It was noted that adverse events occurring during a placebo run-in phase of an antidepressant trial were associated with prefrontal cortex activation in healthy volunteers.[23,24]

Naturally, experimental nocebo research is limited because of ethical concerns and restrictions.[48,49] When Benedetti et al.[49] employed their 'hidden treatment' paradigm in patients with Alzheimer receiving venepuncture, the placebo analgesia that occurred with open treatment was lost due to loss of expectation. Similarly, hyperalgesia was induced by verbal suggestion and an injection of an inert substance during experimental ischaemic pain, and was associated with increased activity of the hypothalamic-pituitary-adrenal axis as indicated by increased cortisol release; both were blocked by diazepam, while a CCK antagonist blocked only the hyperalgetic effect.[50]

Placebo and nocebo phenomena obviously share some similarities with respect to efficacy, at least in the laboratory. It remains to be shown, however, whether both are ruled by similar mechanisms, for example expectations and conditioning, and whether and how they can be present and operate simultaneously, both in the laboratory as well as in 'real life'; an initial model has been proposed by Benedetti et al.[48,49]

Clinical Trials

An entirely different approach unravelling the mechanisms of the placebo response has been to metaanalyse the results of clinical trials using a placebo arm - with mixed results.

The placebo effect in randomized controlled trials in irritable bowel syndrome (IBS) has recently been subject to two metaanalyses,[51,52] that came to similar conclusions about the overall placebo response rate (40%) in these studies.[1] This placebo response is similar to studies with alternative medicines in the same group of patients,[53] or in other medical conditions such as restless leg syndrome.[54] and is somewhat higher than in depression (29%) and bipolar mania (31%).[55] The reason for variable placebo response rates within one indication but across trials is unknown but may include the sample size,[1] the year of study,[55,57] design characteristics[58] and recruitment pattern.[59]

When analysing the determinants of the placebo response in IBS, the two metaanalyses,[51,52] however, came to opposite conclusions with respect to the direction of effects of the number of study visits on the placebo effect size. We compared the published trial reports that had been selected for metaanalyses, for consistency and agreement of the extracted data between both analyses, with respect to the following: trial design, number of study visits, and response rates (%) in study arms. To test for a systematic error, for example if one analysis would not count initial visits before enrolment while the other would, or would count contacts of the patient with the study nurse while the other would count only doctor contacts, we checked for systematic differences between both analyses in case of disagreement.

The results were surprising: from more than 100 randomized placebo-controlled trials on IBS that have been published over the last 25 years, one
analysis carried out a literature search and found 96 papers and selected 45 that matched their quality criteria for further analysis; while the other selected 54 out of a total of 84 using similar quality criteria. The overlap between both samples was only 26 papers (35% of the 73 trial reports that qualified for at least one of the analyses), and agreement between both was found in only six of these 26. As reported in a recent paper, [60] data extraction from published trials for meta-analysis contains a high rate of errors that may lead to false findings and conclusions.

This may well apply to the frequently cited meta-analyses by Hróbjartsson and Gøtzsche [61,62] which concluded that the placebo response is powerful only because of a lack of "no treatment" control groups in most studies. When the same studies that were included in their meta-analyses were reevaluated with respect to the nature of the primary endpoints (biochemical versus physical) it became evident that the lack of effects of the placebo response can be attributed to studies using biochemical measures, while neurally mediated placebo endpoints would be highly effective overall. [63]

Other contributing factors to the placebo response rate in clinical trials were the origin of patients - response rates in migraine prophylaxis were higher in Europeans than in North Americans, [59] personal expectations, for example in acupuncture trials, [54] and the loss thereof, for example in Alzheimer's disease. [60] The study centre, [60] and patient recruitment and physician training. [59] Reanalysis of the raw data of published clinical drug trials allowed poor prediction of placebo response in functional dyspepsia in one study [67] but a significant association of the placebo response with nonsmoking in another. [68] In addition, placebo responders had lower run-in symptoms and reported symptom increases during drug-free run-in. The latter finding is similar to results described for depression [69,70] and epilepsy. [71]

**Conclusion**

Our analysis of the 2007 literature shows that a theoretical framework of our understanding of the placebo response needs to be extended to account for responses that cannot be attributed to (Pavlovian) conditioning or suggestion alone. Imaging studies need to address individual responses rather than group means, and to expand beyond experimental pain research. In addition, gender aspects are present but widely ignored, especially in neurophysiological studies. Finally, nocebo research needs a methodological and ethical framework that allows its exploration, and analyses of clinical trial data may allow one to identify factors that subsequently can be used in future experimental work.

**Table 1. Brain Activation Studies of the Placebo Response in Various Medical Conditions**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Reference</th>
<th>Participants</th>
<th>Gender*</th>
<th>Technique</th>
<th>Design</th>
<th>Placebo activation</th>
<th>Discussed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrovic</td>
<td>2003</td>
<td>[7]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo injection versus opioid</td>
<td>ACC, PFC</td>
<td>Related mechanisms of placebo analgesia and analgesia</td>
</tr>
<tr>
<td>Wagner</td>
<td>2004</td>
<td>[8]</td>
<td>Poor, healthy volunteers</td>
<td>NR &amp; MR</td>
<td>PET</td>
<td>Placebo cream versus pain, no medication</td>
<td>Increase in PFC, decrease in ACC, Th, IC</td>
<td>Antagonism of pain (PFC) inhibits pain experience (ACC)</td>
</tr>
<tr>
<td>Patrono</td>
<td>2005</td>
<td>[9]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Sham acupuncture versus skin prick</td>
<td>PFC, ACC, insula (PAG)</td>
<td>Acupuncture is superior and specific compared with skin prick</td>
</tr>
<tr>
<td>Zubieta</td>
<td>2006</td>
<td>[10]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo injection versus pain, no medication</td>
<td>Intravenous PFC, ACC</td>
<td>Cognitive factors (expectation)</td>
</tr>
<tr>
<td>Bingel</td>
<td>2006</td>
<td>[11]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo cream versus pain, no medication</td>
<td>Right ACC, Ml, PAG</td>
<td>Subcortical 'learning' centres are connected to ACC.</td>
</tr>
<tr>
<td>Kong</td>
<td>2006</td>
<td>[12]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Sham acupuncture versus pain, no medication</td>
<td>Right ACC, lateral PFC, anterior IC, prefrontal PL</td>
<td>Placebo response mediated through multiple brain centres and pathways.</td>
</tr>
<tr>
<td>Wagner</td>
<td>2007</td>
<td>[13]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo injection versus piperazine antagonist</td>
<td>IC, PAG, DPC, PFC, ACC, thalamus</td>
<td>Expectations affect two distinct endogenous opiod circuits</td>
</tr>
<tr>
<td>Nemeroff</td>
<td>2007</td>
<td>[14]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo tablet for 7 days</td>
<td>PFC, PL</td>
<td>In responders, rest activity is increased as well</td>
</tr>
<tr>
<td>de la Fuente-Fernández</td>
<td>2007</td>
<td>[15]</td>
<td>Poor, healthy volunteers</td>
<td>NR</td>
<td>PET</td>
<td>Placebo versus acute amphetamine injection</td>
<td>Increased activation in striatum</td>
<td>Subcortical dopaminergic 'rewarding' system</td>
</tr>
<tr>
<td>Leuchter</td>
<td>2007</td>
<td>[16]</td>
<td>Depression</td>
<td>NR</td>
<td>EGG</td>
<td>9-week treatment, EEG during rest</td>
<td>PFC activation, early onset</td>
<td>Distinct different mechanisms of drug and placebo</td>
</tr>
<tr>
<td>Mayborg</td>
<td>2007</td>
<td>[17]</td>
<td>Depression</td>
<td>NR</td>
<td>PET</td>
<td>4-week antidepressant treatment, PET during rest</td>
<td>PFC activation</td>
<td>Top-down in placebo, bottom-up activation in medication</td>
</tr>
<tr>
<td>Hunter</td>
<td>2006</td>
<td>[18]</td>
<td>Healthy volunteers</td>
<td>NR</td>
<td>EGG</td>
<td>1-week placebo run-in, 4-weeks antidepressant or placebo</td>
<td>PFC activation</td>
<td>PFC during run-in associated with end effects during medication</td>
</tr>
<tr>
<td>Hunter</td>
<td>2007</td>
<td>[19]</td>
<td>Depression</td>
<td>NR</td>
<td>PET</td>
<td>1-week placebo run-in, 4-weeks antidepressant or placebo</td>
<td>PFC activation</td>
<td>PFC deactivation associated with medication response</td>
</tr>
<tr>
<td>Lieberman</td>
<td>2004</td>
<td>[20]</td>
<td>Patients with IBS</td>
<td>NR</td>
<td>PET</td>
<td>Placebo injection versus pain, no medication</td>
<td>ACC, PFC, DPC, SM</td>
<td>Disruption of an ACC/PFC-RI network in IBS</td>
</tr>
<tr>
<td>Giaglis</td>
<td>2007</td>
<td>[21]</td>
<td>Patients with IBS</td>
<td>NR</td>
<td>PET</td>
<td>Placebo versus rectal distension pain alone</td>
<td>ACC, PFC, SMA</td>
<td>Self-reinforcing feedback loop of cognitive and affective centres</td>
</tr>
</tbody>
</table>

NR, not reported; ACC, anterior cingulate cortex; PFC, prefrontal cortex; IMRI, functional MRI; Th, thalamus; IC, insular cortex; PAG, periaqueductal grey; AM, amygdala; PL, parietal lobe; OFC, orbitofrontal cortex; EEG, electroencephalography; IBS, irritable bowel syndrome; SMA, supplementary motor area.

*Gender, male: female.

**References**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

13. ** Wagner TD, Scott DJ, Zubieta JK. Placebo effects on human µ-opioid activity during pain. Proc Natl Acad Sci U S A 2007; 104:11056-11061. This important paper identifies - by connectivity analysis of fMRI data - two major cortical networks that contribute to the placebo response in experimental pain: one that processes the noxious stimulus and one that is activated in anticipation of pain; both are based on µ-opioid activity, but show individual variation.
24. * Beauregard M. Mind does really matter: evidence from neuroimaging studies of emotional self-regulation, psychotherapy, and placebo effect. Prog Neurobiol 2007; 81:219-236. This review paper summarizes and links neuroimaging studies in the field of psychophysiology (emotion), psychotherapy, and the placebo effect and proposes a translational concept of psycho-neural understanding.
29. ** Scott DJ, Stohler CS, Egnatuk CM, et al. Individual differences in reward responding explain placebo-induced expectations and effects. Placence 2007; 55:325-336. This important paper associates placebo analgesia as measured by PET dopamine binding with individual responsiveness to a monetary reward game (in an fMRI paradigm) to allow assessment of individual variation in placebo analgesia formation.
48. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. Neuroscience 2007; 147:260-271. This important paper is the first comprehensive review on the nocebo phenomenon and postulates similar mechanisms.


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