Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice

Manfred Schedlowski, Paul Enck, Winfried Rief, and Ulrike Bingel

Institute of Medical Psychology and Behavioral Immunobiology (M.S.) and Department of Neurology (U.B.), University Clinic Essen, Essen, Germany; Department of Internal Medicine VI, Psychosomatic Medicine, University Hospital Tübingen, Tübingen, Germany (P.E.); and Department of Psychology, University of Marburg, Marburg, Germany (W.R.)

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Address correspondence to: Dr. Manfred Schedlowski, Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, 45122 Essen, Germany. E-mail: manfred.schedlowski@uk-essen.de

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The placebo effect has often been considered a nuisance in basic and particularly clinical research. This view has gradually changed in recent years due to deeper insight into the neuro-bio-behavioral mechanisms steering both the placebo and nocebo responses, the evil twin of placebo. For the neuroscientist, placebo and nocebo responses have evolved as indispensable tools to understand brain mechanisms that link cognitive and emotional factors with symptom perception as well as peripheral physiologic systems and end organ functioning. For the clinical investigator, better understanding of the mechanisms driving placebo and nocebo responses will allow the control of these responses and thereby help to more precisely define the efficacy of a specific pharmacological intervention. Finally, in the clinical context, the systematic exploitation of these mechanisms will help to maximize placebo responses and minimize nocebo responses for the patient’s benefit. In this review, we summarize and critically examine the neuro-bio-behavioral mechanisms underlying placebo and nocebo responses that are currently known in terms of different diseases and physiologic systems. We subsequently elaborate on the consequences of this knowledge for pharmacological treatments of patients and the implications for pharmacological research, the training of healthcare professionals, and for the health care system and future research strategies on placebo and nocebo responses.

I. Introduction

More than 55 years ago, Stewart Wolf (Wolf, 1959) published a paper in this journal entitled, “The Pharmacology of Placebo,” in which he stated that the chosen title itself may present a “picturesque contradiction,” because by definition pharmacology is concerned with the chemical properties of drugs and their effects on biologic mechanisms. It was common knowledge at that time that the pharmacological action of drugs as well as “other forces at play and the circumstances surrounding their administration” contribute to the overall treatment effect (Wolf, 1950). Empirical data revealed that placebo effects that endow inert agents with potency or modify the treatment effects of active pharmacological substances are not only subjective in nature but that they can also be associated with measurable and thus objective changes in end organ functions. However, the underlying mechanisms remained largely unclear.

The placebo effect itself—the symptom improvement after inert treatments in clinical trials—is composed of different factors, such as the natural history of a disease or fluctuation of symptoms, response biases, effects of cointerventions, and statistical phenomena, such as regression to the mean (Fig. 1). These factors can be distinguished from the actual placebo response that is mediated via three interdependent factors: patients’ expectations about treatment benefits, the quality and quantity of doctor-patient communication, and associative (conditioning) learning processes (Fig. 2). These psychologic factors trigger complex neurobiological phenomena distinctly involving the central nervous system (CNS) as well as system-specific peripheral physiologic and end-organ changes. Confusion persists even within the scientific community about how to define the terms “placebo,” “placebo effect,” and “placebo response.” In this review, we will refer to the term placebo responses, thereby focusing on the effects of the neuropsychological mechanisms of expectation, communication, and conditioning that drive the placebo response (Table 1).

The past two decades have witnessed groundbreaking advances in the understanding of neurobiological and neuropsychological mechanisms of placebo and nocebo responses in various medical conditions (Moerman, 2002; Brody, 2008; Benedetti, 2008, 2011). This knowledge is not only pivotal for more detailed analyses of the neuropsychological mechanisms driving...
the placebo response—it also paves the way for systematic exploitation of this knowledge with the aim to minimize placebo responses in clinical trials and in the context of drug development and to maximize the placebo response in clinical practice to improve treatment outcomes and patient benefit (Jubb and Bensing, 2013).

In this review we will particularly emphasize the neuro-bio-behavioral mechanisms of placebo and nocebo responses, their effects on pharmacological treatments, and potential predictors of interindividual differences in these effects. On this basis, we will outline the relevance of placebo responses on the assay sensitivity in randomized clinical trials (RCTs) and on therapeutic outcomes in clinical practice. Finally, we will discuss implications for the training of health care professionals and the health care systems themselves and propose future research directions.

II. The Origin of the Placebo Concept: From the Ancient Healer to Modern Medicine

Since the dawn of experimental placebo research in the 1990s, many papers (Fig. 3) and books (Spiro, 1986; Harrington, 1999; Thompson, 2005; Benedetti, 2008; Shapiro and Shapiro, 2010) have referred to the history of the placebo concept and its origins long before evidence-based medicine became the gold standard in Western medicine. In the following section, we briefly refer to three aspects of these historical roots of the placebo concept: etymological considerations, methodological aspects, and a “meaning” aspect (Moerman and Jonas, 2002).

i. The origin of the word “placebo” from the Latin verb “placere” (pleasing), in the sense of “I may please” or “it may please,” has been greatly
stressed as the background of a “placebo” application that helps without any underlying scientific background. There is evidence that an even earlier use of the word referred to “singing a placebo” as someone mourning at a funeral as a paid service (Shapiro, 1964). The term placebo remains stuck with this negative connotation, because it is ethically regarded as deception of the patient and is thus only allowed under restricted circumstances, e.g., those of the Declaration of Helsinki (World Medical Association, 2013). The use of placebos is still predominantly

### Placebo/nocebo terminology

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>The word placebo is the Latin term for “I shall please.” It is used to indicate sham treatments or inert substances such as sugar pills or saline infusions.</td>
</tr>
<tr>
<td>Placebo effect</td>
<td>The placebo effect is defined as any improvement in a symptom or physiologic condition of subjects after placebo treatment. There are different mechanisms underlying this phenomenon, including spontaneous remission, regression to the mean, natural course of a disease, biases, and placebo responses.</td>
</tr>
<tr>
<td>Placebo response</td>
<td>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 within the treatment context. Importantly, placebo responses are not restricted to placebo treatments—they can also modulate the outcome of any active treatment.</td>
</tr>
<tr>
<td>Active placebo</td>
<td>An active placebo is a substance or treatment that mimics the side effects of the active compound being tested and is thus by definition not an inert substance. In clinical trials, active placebos are administered to avoid un-blinding due to the different side-effect profiles of drugs and placebo treatments.</td>
</tr>
<tr>
<td>Nocebo</td>
<td>The term nocebo (I shall harm) was introduced in contrast to “placebo” to distinguish the positive from the noxious effects of placebos, when an inert substance is given within a negative context, inducing negative expectations about the outcome.</td>
</tr>
</tbody>
</table>

![Fig. 3. Number of genuine placebo (solid line) and nocebo publications (broken line) in PubMed per year between 1950 and 2013 (from Weimer et al., 2015b, with permission).](image-url)
gave it because it is necessary to give a medicine, and as what I call a placebo” (Cullen, 1772, cited in Jütte, 2013, pp 1). Later, Samuel Hahnemann, founder of homeopathy in the 18th century, frequently used treatments such as milk sugar (lactose), which he deemed ineffective: “In the meantime, until the second medicament is given, one can soothe the patient’s mind and desire for medicine with something inconspicuous such as a few teaspoons a day of raspberry juice or sugar of milk” (Hahnemann, 1814, cited in Jütte, 2014, pp 210). Although he never used the term placebo, Hahnemann was obviously aware of its clinical “potency.” Similarly, the famous “Nuremberg Salt Test” of 1835 (Stolberg, 2006) (designed to disprove Hahnemann’s homeopathic concept) used “pure snow water” as a control for the “saline treatment” that was a popular homeopathic treatment around that time, also without mentioning the term placebo. For more details/information on this and other examples, we refer the interested reader to Ted Kaptchuk’s article on the history of blind assessment and placebo controls in medicine (Kaptchuk, 1998).

iii. A recent publication in the British Medical Journal (BMJ) sought to investigate the “meaning” of the term placebo appearing in articles published in the BMJ in the early days of evidence-based medicine between 1840 and 1899, made possible thanks to the fact that the BMJ’s complete archive has been digitized (Raicek et al., 2012). They identified 71 articles mentioning the term “placebo,” of which 47 (66%) were in specific sections in the BMJ such as “Correspondence” (10%), “Original communications” (10%), and “Reports of societies” (4%), with the remaining 42% distributed among 23 other categories. Twenty-four of the citations (34%) were in non-specified sections. They assigned the use of the term placebo to nine categories: no effect or pejorative, (31%), natural history (25%), satisfy patient (20%), medical performance (10%), buy time (4%), financial gain (4%), placebo control (3%), has clinical effect (1%), and unclear (1%). Taken together, only two articles (of 1886 and 1889) used placebos as controls to test the effects of a medical treatment, and only one mentioned its being clinically effective. According to the authors, all placebo applications were deceptive and did not debrief the patients after completion of the study.

Our brief history of placebo use in medicine illustrates the three aspects that are still evident in today’s use of placebos: the negative connotation of the term placebo, the suspicion that the use of placebos implies the deception of patients, and the speculation that placebos may be ineffective in helping patients. Experimental and clinical data from the last two decades has clearly demonstrated that it is about time these assumptions were overcome.

III. Placebo Effects and Effect Sizes in Clinical Trials

A. Effect Sizes of Symptom Improvement across Different Medical Conditions

When compared with the effect of drugs in randomized placebo-controlled trials, placebo effects can vary substantially, ranging from under 10% to over 60%, even within single clinical entities. Requiring a 50% symptom improvement to qualify as a treatment responder resulted in 26% placebo responders in diabetic neuropathic pain (Arakawa et al., 2015) but this was lower in other pain conditions (e.g., dental pain: 16%; Averbuch and Katzper, 2001). Similar response rates were reported in migraine (29%; Macedo et al., 2006), fibromyalgia (45%; Hauser et al., 2011), and pancreatic pain (20%; Capurso et al., 2012) investigations.

It is, however, almost impossible to compare the placebo response data from different meta-analyses of RCTs in various clinical conditions. RCTs with a binary outcome that allow for the differentiation of placebo responders and nonresponders usually report the percentage of responders in the placebo arm, and the meta-analyses of such trials report the “pooled placebo response” (Weimer and Enck, 2014). Most RCTs with gastroenterological patients take this approach, revealing pooled placebo response rates ranging between 25% and 45% (Weimer et al., 2013a; Elsenbruch and Enck, 2015). Trials with continuous outcome measures (symptom scale improvements, e.g., in depression, schizophrenia, Parkinson’s disease, attention deficit hyperactivity syndrome, etc.) usually report effect sizes in the placebo arm, but their interpretation depends on a clinically meaningful grading of the scale that can vary according to the condition. In sleep disorders, for instance, the placebo response accounts for 60% of the response in the drug arm of respective trials when assessed by polysomnographic measures (Winkler and Rief, 2015).

Placebo effects are more pronounced when assessed via patient-reported outcomes (symptoms, symptom ratings, quality of life measures) compared with biomarkers (Meissner, 2005) or disease markers. However, even with biologic indicators of disease activity such as the Crohn’s Disease Activity Index or endoscopic assessment of disease activity, the placebo response can remain as high as 25% (Su et al., 2004). Biomarkers such as the “forced expiratory volume” in asthma, however, display very weak placebo responses (Wang et al., 2012), and they are known to correlate poorly with patient-reported outcomes or clinical assessments of disease severity (Wechsler et al., 2011). The highest
(around 40%) and most homogeneous placebo response rates are reported in psychiatric trials [e.g., in depression (Papakostas and Fava, 2009)] but also in functional gastrointestinal disorders, such as irritable bowel syndrome (IBS) or functional dyspepsia, disorders known to coincide with depression and anxiety (Ford and Moayyedi, 2010). In contrast, placebo responses are known to be lower in neurologic disorders (epilepsy, Parkinson’s disease) (Goetz et al., 2008; Rheims et al., 2008) and in treating addiction, i.e., smoking cessation (Moore and Aubin, 2012) (Tables 2 and 3).

One of the pitfalls when assessing placebo responses in RCTs is the fact that they can be confounded by spontaneous symptom improvements (Fig. 1) assumed to be similar across all the trial’s arms and therefore not controlled for. Whether the placebo response in RCTs is still of a clinically relevant effect size after ignoring the contribution of spontaneous symptom variation is debatable (Hrobjartsson and Gotzsche, 2001, 2004). A meta-analysis of three-arm trials in 8 different clinical conditions including a “no treatment” control group revealed that about 50% of the placebo response could be explained by spontaneous remission/variation (Krogsboll et al., 2009). Although only involving 10 trials, a similar meta-analysis in major depression disorder (Rutherford et al., 2012) indicated that “waiting” had an effect size of approximately 0.5 (Cohen’s d), the equivalence of a 4-point, clinically relevant improvement on the Hamilton Depression Scale. However, a waiting list is a poor means of placebo responders (Parkinson et al., 2011; Yildiz et al., 2011; Agid et al., 2013; Arakawa et al., 2015), a recent review (Weimer et al., 2015a) of 75 systematic reviews and meta-analyses including more than 1500 trials, 150,000 patients, and 40 medical indications revealed that age and sex were not significant predictors of placebo responses in RCT, despite occasional evidence from experimental research (Aslaksen et al., 2006; Weimer et al., 2013b).

A more detailed meta-analysis of patient-related factors driving the placebo effect in psychiatric disorders recently revealed consistent positive associations between placebo effects with lower disease severity at baseline and shorter disease duration in the treatment-naive patients (Weimer et al., 2015b). Similarly, low symptom severity at study entry was also found to correlate positively with a placebo response in other diseases such as fibromyalgia (Hauser et al., 2011), diabetic neuropathic pain (Hauser et al., 2011), binge-eating

### TABLE 2
Systematic reviews and meta-analyses of the placebo response in RCTs in neurologic disorders, pain syndromes, and in psychiatric disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>N*</th>
<th>Disease</th>
<th>PR Is Higher with...**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheims et al., 2008</td>
<td>32</td>
<td>Epilepsy (children, adults)</td>
<td>younger age</td>
</tr>
<tr>
<td>Fulda and Wetter, 2008</td>
<td>36</td>
<td>Restless Leg Syndrome</td>
<td>longer trial duration</td>
</tr>
<tr>
<td>Goetz et al., 2008</td>
<td>11*</td>
<td>Parkinson’s Disease</td>
<td>higher baseline severity</td>
</tr>
<tr>
<td>Dienert et al., 1999</td>
<td>15</td>
<td>Migraine</td>
<td>higher drug probability</td>
</tr>
<tr>
<td>Machedo et al., 2006</td>
<td>98</td>
<td>Migraine</td>
<td>European studies</td>
</tr>
<tr>
<td>Hauser et al., 2011</td>
<td>72</td>
<td>Fibromyalgia syndrome</td>
<td>lower baseline severity</td>
</tr>
<tr>
<td>Hauser et al., 2012</td>
<td>70</td>
<td>Diabetic neuropath pain</td>
<td>lower baseline severity</td>
</tr>
<tr>
<td>Capurso et al., 2012</td>
<td>7</td>
<td>Pancreatitis</td>
<td>more study sites</td>
</tr>
<tr>
<td>Papakostas and Fava, 2009</td>
<td>182</td>
<td>Depression, adults</td>
<td>more study sites</td>
</tr>
<tr>
<td>Bridge et al., 2009</td>
<td>12</td>
<td>Depression, children</td>
<td>more study sites</td>
</tr>
<tr>
<td>Agid et al., 2013</td>
<td>50</td>
<td>Psychosis</td>
<td>younger age, more recent trials</td>
</tr>
<tr>
<td>Yildiz et al., 2011</td>
<td>38</td>
<td>Bipolar mania</td>
<td>more study sites, female sex</td>
</tr>
<tr>
<td>Cohen et al., 2010</td>
<td>40</td>
<td>MDD, OCD, ANX (children)</td>
<td>children than in adolescents</td>
</tr>
<tr>
<td>Newcorn et al., 2009</td>
<td>10</td>
<td>ADHD (children)</td>
<td>comorbid MDD, non-white</td>
</tr>
<tr>
<td>Buirla et al., 2012</td>
<td>10*</td>
<td>ADHD (adults)</td>
<td>higher baseline severity</td>
</tr>
<tr>
<td>Blom et al., 2014</td>
<td>10*</td>
<td>Binge Eating Disorder</td>
<td>lower baseline severity</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; ANX, anxiety disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PR, placebo response.

* Indicates availability of individual patient data; number of RCTs included in analysis.

** Only the most important influential variable listed.

B. Influence of Patient Characteristics

There tends to be very broad interindividual variation in the placebo response of healthy individuals and patients. Thus, to keep the placebo response low in RCTs, the search for predictors of placebo responses in RCTs applied post hoc reanalyses and sensitivity tests of individual RCTs to identify putative predictors of the placebo response that could then be used to identify and exclude so called “placebo responders” from trials. Among the patient characteristics frequently accused of driving the placebo response are sex (with larger placebo responses in women) and (younger) age. Although these factors were shown to be relevant in some trials (Thijss et al., 1990; Freeman and Rickels, 1999; Rheims et al., 2008; Cohen et al., 2010; Yildiz et al., 2011; Agid et al., 2013; Arakawa et al., 2015), a recent review (Weimer et al., 2015a) of 75 systematic reviews and meta-analyses including more than 1500 trials, 150,000 patients, and 40 medical indications revealed that age and sex were not significant predictors of placebo responses in RCT, despite occasional evidence from experimental research (Aslaksen et al., 2006; Weimer et al., 2013b).
disorder (Blom et al., 2014), or asthma (Wang et al., 2012), but not in attention deficit hyperactivity disorder (Buitelaar et al., 2012) or Parkinson’s disease (Goetz et al., 2008). Meta-analyses of more trials in different medical conditions also failed to clearly identify predictors of the placebo response, which can at least be partially explained by limited access to individualized data, as Tables 2 and 3 illustrate. Individual patient data were available in only 6 of the listed 30 meta-analyses, usually in small data sets. Although more recent experimental approaches have begun focusing on identifying behavioral or genetic traits of placebo or nocebo response differences, no consistent concept has emerged so far (see section VI).

C. Influence of Randomized Clinical Trial Characteristics

When it was first noted that the rate of placebo responses had increased over the years in RCTs for depression (Walsh et al., 2002; Bridge et al., 2009) and schizophrenia (Agid et al., 2013; Rutherford et al., 2005; Mallinckrodt et al., 2010), and psychosis (Agid et al., 2013). It is, however, unclear whether this represents a specific effect in neuropsychiatric disorders, because it has not been observed in other conditions, such as IBS (Ford and Moayyedi, 2010; Elsenbruch and Enck, 2015).

D. Head-to-Head Trials: No Placebo Arm but Even Stronger Placebo Effects

Because placebo responses are immanent in all medical treatments, the omission of a placebo arm in RCTs does not prevent placebo responses—it only renders their systematic assessment more difficult. The evaluation of enrichment trials, or unbalanced randomization in experiments and clinical trials (Weimer and Enck, 2014), has shown that providing a 100% probability of receiving an active treatment increases the response in both drug and placebo groups, as opposed to the 50:50 probability in placebo-controlled trials. In head-to-head trials, in which both treatment arms receive an active component, it is impossible to

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**TABLE 3**

Systematic reviews and meta-analyses of the placebo response (pooled PR, percent) in RCTs in various diseases in internal medicine

Note that this list is incomplete, as it reports only the meta-analysis with the largest number of studies included for the given disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>N*</th>
<th>Disease Description</th>
<th>PR Is Higher With...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilnyckyj et al., 1997</td>
<td>38</td>
<td>Ulcerative colitis</td>
<td>higher number of visits</td>
</tr>
<tr>
<td>Su et al., 2004</td>
<td>21</td>
<td>Crohn’s Disease</td>
<td>longer study duration</td>
</tr>
<tr>
<td>Ford et al., 2010</td>
<td>73</td>
<td>IBS</td>
<td>European studies</td>
</tr>
<tr>
<td>Talley et al., 2006</td>
<td>4*</td>
<td>FD</td>
<td>inconsistent symptoms</td>
</tr>
<tr>
<td>de Craen et al., 1999a</td>
<td>79</td>
<td>Duodenal ulcers#</td>
<td>higher application frequency</td>
</tr>
<tr>
<td>Cremonini et al., 2010</td>
<td>24</td>
<td>Reflux disease</td>
<td>nonerosive reflux disease</td>
</tr>
<tr>
<td>Thijs et al., 1990</td>
<td>1*</td>
<td>Hypertension</td>
<td>older age</td>
</tr>
<tr>
<td>Cho et al., 2005</td>
<td>29</td>
<td>CPS</td>
<td>high intervention intensity</td>
</tr>
<tr>
<td>Freeman et al., 1999</td>
<td>2*</td>
<td>PMS</td>
<td>younger age</td>
</tr>
<tr>
<td>Lamel et al., 2012</td>
<td>31</td>
<td>Psoriasis</td>
<td>higher drug probability</td>
</tr>
<tr>
<td>Narkus et al., 2013</td>
<td>6</td>
<td>Allergy</td>
<td>subcutaneous administration</td>
</tr>
<tr>
<td>Wang et al., 2012</td>
<td>34</td>
<td>Asthma</td>
<td>lower baseline severity</td>
</tr>
</tbody>
</table>

CFS, chronic fatigue syndrome; FD, functional dyspepsia; PMS, premenstrual syndrome; PR, placebo response.

*Indicates availability of individual patient data; number of RCTs included into analysis.

**Only the most influential variable listed.**
specifically assess a placebo response. However, analyses of the treatment responses in head-to-head trials compared with placebo-controlled trials enable us to indirectly assess the contribution of expectancy/placebo mechanisms to the efficacy of active treatment (see section VI).

A meta-analytic comparison of head-to-head trials and placebo-controlled trials of the same drugs for treating depression demonstrated that comparative trials enhance the drug response compared with placebo-controlled trials of the same compounds. This effect is explained solely by the patient’s 100% assurance to receive a drug, and it resulted in an additional 15% “placebo response” to the established average of 40% from placebo-controlled drug trials for depression (Rutherford et al., 2012). Similar data have been reported in schizophrenia (Woods et al., 2005). This creates an ethical dilemma: head-to-head trials need up to four times more patients to statistically test “non-inferiority” than conventional placebo-controlled trials (Leon, 2012), a factor that contradicts the Declaration of Helsinki request (World Medical Association, 2013) that the minimum number of patients be included in RCTs. These trials are also associated with substantially higher trial costs, in particular when the appropriate comparator drug selected is not the property of the sponsoring company and needs to be produced and the provision of double-dummy technology is needed (Marušić and Ferencić, 2013). Finally, the comparator’s selection may force substantial methodological considerations and concerns if more than one potential comparator is available on the market (Dunn et al., 2013).

In summary, the substantial effect sizes of placebo treatments in RCTs are based on both patient-related factors (e.g., age, sex, disease history, and severity), most of which vary greatly in their contribution to the placebo response depending on the clinical condition, and by design-related factors that appear more homogeneous between conditions (e.g., unbalanced randomization, frequency of doctor-patient contacts, trial duration) but lack controllability across different conditions. Finally, public and scientific access to previous RCTs on the individual patient-data level are required (Tudur Smith et al., 2014; Lo, 2015) to further explore the contribution of these factors to the effect size of placebos as long as placebo-controlled trials are the gold standard in the evaluation of new drugs.

IV. Neuro-Bio-Behavioral Mechanisms of Placebo Responses

A. Pain

Among all the placebo responses, it is placebo analgesia (referring to the phenomenon of reduced pain ratings after application of a sham treatment) that is the most thoroughly examined and neurobiologically best characterized placebo response (Tracey, 2010a). The advent of modern noninvasive neuroimaging techniques has provided the unique opportunity to study the neural mechanisms of placebo analgesia and other placebo responses (Benedetti, 2014).

1. Placebo Analgesia Involves Changes in the Pain Processing Network. One of the key questions that has intrigued neuroscientists and clinicians alike is whether the subjective reductions in pain ratings during placebo analgesia are associated with activity changes in the "pain processing network"—the set of brain regions most closely associated with the experience of pain—and, if so, in which of its components?

The majority of neuroimaging studies addressing placebo analgesia report that the reduced pain ratings during placebo analgesia are accompanied by decreased activity in the classic pain-processing areas, including the thalamus, insula, somatosensory cortex, and mid-cingulate regions (Wager et al., 2004; Bingel et al., 2006; Eippert et al., 2009a; Lui et al., 2010; Elsenbruch et al., 2012a; Geuter et al., 2013) (Fig. 4). Electroencephalography (EEG) studies have further confirmed that placebo analgesia is associated with reduced amplitudes of event-related potentials to experimental pain stimuli (Wager et al., 2006; Watson et al., 2007; Aslaksen et al., 2011).

Fig. 4. The CNS mechanisms initiating and mediating placebo responses are best characterized for placebo analgesia and involve the descending pain modulatory network, which includes the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), the amygdala (Am), and the PAG. Similar regions of the brain have been shown to contribute to emotional placebo responses. The shared and distinct contributions of different brain networks in other types of placebo responses are currently unknown.
Evidence from spinal cord forced magnetic resonance imaging (fMRI), which only recently became technically feasible in both humans and animals, has revealed that pain-related activity in the ipsilateral dorsal horn, corresponding to painful stimulation, is substantially reduced under placebo (Eippert et al., 2009b) and rises under expectations of increased pain (nocebo) (Geuter and Büchel, 2013). Together these studies support the notion that altered pain experience during placebo analgesia is not simply the result of report bias but can, at least in part, result from the active inhibition of nociceptive activity, even involving very early stages of neural processing. However, this does not exclude other brain mechanisms’ relevance and contribution to placebo analgesia.

2. Placebo Analgesia Engages Descending Pain Modulatory Networks. These observations have raised the question which brain processes mediate changes in pain processing and perception. The pioneering positron emission tomography (PET) study on placebo analgesia by Petrovic et al. (2002) first revealed a shared neural network in the rostral anterior cingulate cortex (rACC) and the brain stem underlying both opioid and placebo analgesia. The relevance of this network for placebo analgesia has been substantiated by several subsequent studies using various procedures to induce placebo analgesia, including placebo analgesic creams, sham acupuncture, and others (Wager et al., 2004, 2007; Zubieta et al., 2005; Bingel et al., 2006; Kong et al., 2006; Eippert et al., 2009a). These studies showed that placebo analgesia involves the activation of cingulofrontal brain regions together with subcortical structures such as the midbrain periaqueductal gray (PAG), hypothalamus, and amygdala. Connectivity analyses further revealed that the behavioral placebo analgesic effect is related to enhanced functional coupling of the rACC with brain stem areas, such as the PAG (Wager et al., 2004, 2007; Eippert et al., 2009a), and that individual activity and connectivity changes within this network predict the behavioral analgesic effect (Wager et al., 2004; Eippert et al., 2009a).

These studies support the notion that the top-down activation of endogenous analgesic activity via the descending modulatory system represents one mechanism of placebo analgesia. The prefrontal cortex seems to play a crucial role in this mechanism. Activity in the dorsolateral prefrontal cortex was found in the period preceding noxious stimulation, which correlated with activity in the PAG and the subsequent placebo analgesic response (Wager et al., 2004; Eippert et al., 2009a; Lui et al., 2010). Intriguingly, both temporary functional lesions in the prefrontal cortex by repetitive transcranial magnetic stimulation (Krummenacher et al., 2010) as well as degenerated and disconnected frontal lobes in Alzheimer’s disease (Benedetti et al., 2006) are associated with a reduction in or complete loss of verbally induced placebo analgesic responses. These findings implicate the prefrontal cortex as a brain region critical to the initiation of expectancy-related effects on pain perception.

3. Neurotransmitter Systems Involved in Placebo Analgesia. Levine et al. (1978) first demonstrated that placebo analgesia can be antagonized by naloxone, suggesting the involvement of endogenously released opioids. Since then, the contribution of opioidergic neurotransmission in placebo analgesia has been corroborated by indirect pharmacological approaches using opioid antagonists and PET studies using in vivo receptor binding approaches with opioidergic ligands (Amanzio and Benedetti, 1999; Zubieta et al., 2005; Wager et al., 2007; Eippert et al., 2009a). These PET studies have substantiated that the placebo-related activity and connectivity changes within cingulofrontal and subcortical networks including the PAG observed with fMRI involve μ-opioidergic neurotransmission (for review, see Peciña and Zubieta, 2015). The contribution of opioidergic neurotransmission is further substantiated by pharmacological fMRI studies, i.e., by showing that naloxone blocks placebo-related activity in the PAG and rostral ventromedial medulla and PAG-rACC connectivity along with impaired behavioral analgesia (Eippert et al., 2009a), as well as in seminal studies linking variability in genes modulating opioidergic mechanisms with an individual’s placebo analgesic response (Hall et al., 2012; Peciña et al., 2013a,b, 2014, 2015).

The endogenous opioid system is not the only one involved in placebo analgesia. Functional molecular imaging investigating changes in the binding potential of $^{11}$C-labeled raclopride has shown increased dopaminergic neurotransmission in the nucleus accumbens, putamen, and caudate nucleus that correlated with the individual placebo analgesic response (Scott et al., 2007, 2008). Furthermore, Schweinhardt et al. (2009) reported a close positive relationship between gray matter density in the ventral striatum and the magnitude of placebo analgesia, as well as dopamine-related personality traits (e.g., novelty, fun, and sensation seeking) using voxel-based morphometry, whereas others have directly linked reward responsiveness and placebo analgesia experimentally (Scott et al., 2007). These findings suggest a potentially relevant role of the dopaminergic system and the striatum in particular in placebo analgesia. It is, however, unclear whether striatal dopaminergic activity is causally involved in generating analgesia or rather reflects reward processes associated with pain relief. The expectation of dopamine release enhanced reward learning and modulated learning-related signals in the striatum and ventromedial prefrontal cortex (Schmidt et al., 2014). In a recent fMRI study on placebo analgesia, the administration of the D$_2$ antagonist haloperidol blocked placebo-related activity in the striatum but had no effect on analgesia or on activity in brain regions believed to
encode pain intensity (Wrobel et al., 2014). Taken together, although these data suggest endogenous dopaminergic pathways somehow contributing to the individual placebo analgesic response, the distinct role of the dopaminergic system in placebo analgesia requires further investigation (Peciña et al., 2013a).

Placebo analgesia was also recently linked to the cannabinoid system (Benedetti et al., 2011). This system seems to underlie placebo analgesia after pharmacological conditioning with the nonsteroidal anti-inflammatory drug ketorolac. In this case, placebo analgesic responses were reversed by the cannabinoid 1 receptor antagonist rimonabant, indicating that the effects elicited by nonsteroidal anti-inflammatory drug conditioning are partially mediated by the endogenous release of cannabinoids (Benedetti et al., 2011).

Overall, these findings support the notion that the neurobiological effects of placebo analgesia are related to distinct brain mechanisms and neurochemical pathways that are activated in various contexts contributing to placebo analgesia.

4. Unresolved Issues and Remaining Questions Regarding the Mechanisms of Placebo Analgesia. Although the aforementioned lines of evidence support the view that descending pain modulatory mechanisms, even those involving the spinal cord, are a critical pathway underlying placebo analgesia, there is also evidence supporting the relevance of intracortical mechanisms to placebo analgesia. Recent novel methodological approaches including multivariate pattern analysis and meta-analyses of brain-imaging studies suggest that most behavioral variance in placebo analgesia is explained by activity changes in intracortical, emotion-related circuitry, rather than changes in sensory brain areas (Wager et al., 2011), as one would expect were placebo analgesia determined solely by descending inhibition. Defending this view, a recent laser-evoked potential study reported that effective behavioral placebo analgesia can occur without changes in N1 amplitude, which represents the earliest recordable in vivo cortical response to afferent spinothalamic input (Martini et al., 2015).

However, in contrast to the latest perspectives that either highlight descending or intracortical pathways, it is conceivable that several not mutually exclusive pathways can contribute to placebo analgesia, depending on the individual disposition and the context in which placebo analgesia is induced. Further research needs to explore the interactions between the different systems involved in placebo analgesia under physiologic and pathologic conditions (e.g., acute and chronic pain).

B. Parkinson’s Disease

Marked improvements in Parkinson symptoms have been observed in the placebo arm of clinical trials testing pharmacological and surgical treatments for Parkinson’s disease (Shetty et al., 1999; Goetz et al., 2002, 2008; McRae et al., 2004; Diederich and Goetz, 2008). Although placebo rates in clinical trials do not allow for dissociating between “true” placebo responses (induced by positive expectation, doctor-patient communication, or prior experience) and natural fluctuations in the underlying disease unless a “no treatment” arm is included, these high placebo response rates in clinical trials of Parkinson’s disease have motivated deeper examination of the neurobiological mechanisms underlying clinical improvements following placebo treatments in Parkinson’s disease.

De la Fuente-Fernandez et al. (2001) were the first to study the involvement of the endogenous dopamine system for placebo responses in Parkinson patients by using raclopride-PET. After the administration of a placebo that patients believed to be apomorphine (a powerful anti-Parkinsonian treatment), the authors observed increasing dopaminergic neurotransmission in the striatum. The release of dopamine in the dorsal striatum was greater in those patients who reported clinical improvement, suggesting a relationship between placebo-induced changes in dopaminergic neurotransmission in the dorsal striatum and individual clinical benefit. Interestingly, no such association was observed between clinical benefit and changes in dopaminergic neurotransmission in the ventral striatum, which was linked with patients’ expectations of symptom improvement that can also be considered reward anticipation. The contribution of the dopaminergic system to placebo responses in Parkinson’s disease was later corroborated by two other dopamine-ligand PET studies on placebo responses in Parkinson patients (Strafella et al., 2006; Lidstone et al., 2010). The latter study by Lidstone and colleagues specifically investigated how the strength of expectation of clinical improvement influences the changes in dopaminergic neurotransmission in the striatum in response to a placebo treatment. Parkinson patients were told they had a specific probability (25%, 50%, 75%, or 100%) of receiving an active dopaminergic medication, but they in fact received a placebo. Intriguingly, significant dopamine release was only documented in those patients with the 75% probability expectation. The response to prior medication appeared to be a major determinant of placebo-induced dopamine release in the motor (dorsal) striatum, which might be explained by a preconditioning phenomenon. In contrast, the expectation of clinical improvement was additionally required to trigger dopamine release in the ventral striatum (Lidstone et al., 2010), which likely reflects reward-related processes associated with the expectation of clinical improvement (de la Fuente-Fernandez et al., 2004).

Single cell recordings in patients undergoing surgery for implantation of a deep brain stimulator (stimulation of the nucleus subthalamicus) provided the unique
opportunity to directly investigate any neuronal changes in the basal ganglia underlying placebo responses in Parkinson’s disease. Benedetti et al. (2004) were the first to record activity from single neurons in the subthalamic nucleus in awake Parkinson’s disease patients before and after placebo administration following a pharmacological preconditioning procedure using apomorphine (Fig. 2). They reported a significant decrease in the firing rate and bursting activity after the placebo intervention compared with baseline that was associated with the patients’ subjective report of well-being and a reduction in muscle rigidity at the wrist, as rated by a blinded neurologist. In their later study, those observations were expanded by recordings from thalamic nuclei and the substantia nigra (Benedetti et al., 2009), showing complex changes in the entire subthalamic-nigral-thalamic motor circuitry associated with the improvements following placebo administration (for a review, see Frisaldi et al., 2014).

Taken together, several lines of evidence support the notion that placebo responses in Parkinson’s disease are associated with changes in neuronal activity and dopaminergic neurotransmission in the brain circuitry involved in the pathophysiology of the disease itself (for review, see Murray and Stoessl, 2013). These findings have important implications for the interpretation of clinical trials and the clinical care of Parkinson patients.

How reward-related and potential disease-specific processes associated with the placebo response in Parkinson’s disease combine and interact and how long these short-term experimental observations last and contribute to clinical improvements over the longer term (weeks to months) will have to be determined in future studies.

C. Neuropsychiatric Diseases and Behavioral Disorders

Numerous clinical studies and meta-analyses provide compelling evidence for pronounced placebo effects in psychiatric conditions such as depression, schizophrenia, or anxiety disorders (Cavanna et al., 2007; Murray and Stoessl, 2013; Weimer et al., 2015b). Compared with pain or Parkinson’s disease, however, the neurobiological mechanisms underlying placebo responses in these disorders are much less well understood, which is partly because of the lack of experimental models suitable to investigate such mechanisms in healthy volunteers and patients.

1. Depression. Comprehensive reviews and meta-analysis indicate that the drug-placebo difference in clinical studies of depression are relatively small, reporting placebo response rates up to 70% (Kirsch and Sapirstein, 1998; Kirsch et al., 2008; Rief et al., 2009a; Gueorguieva et al., 2011; Mora et al., 2011) (see section III). In addition, 79% of placebo responders remained well within the continuation phase in the studies lasting over 12 weeks, suggesting a long-lasting effect of the antidepressive placebo response (Khan et al., 2008). The neurobiological mechanisms underlying these responses have been analyzed by employing quantitative electroencephalography (Leuchter et al., 2002). Placebo responders showed a significant increase in prefrontal brain activity that was not observed in placebo nonresponders or in patients responding or not responding to the medication.

Changes in glucose metabolism in depressive male patients were analyzed after 6 weeks’ treatment with the antidepressant fluoxetine or placebo via PET (Mayberg et al., 2002). The placebo response was associated with metabolic increases in prefrontal, anterior cingulate, premotor, parietal, and posterior cingulate cortex and decreases in the subgenual cingulate, parahippocampus, and thalamus. These changes in brain activity revealed at least some shared neurobiological pathways for placebo responses in pain and depression in conjunction with expectation and emotion- and reward-related circuitry involvement (Benedetti et al., 2005; Wernicke and Ossanna, 2010; Murray and Stoessl, 2013). These neurobiological findings are accompanied by observations that increased subjective reward experience affects treatment efficacy with antidepressive medication (Wichers et al., 2009). In addition, the expectancy of improvement is affected by the probability of receiving active antidepressant medication, which in turn seems to influence the antidepressive response (Rutherford et al., 2013). These neuropsychological post hoc data justify administering active placebos in clinical trials analyzing the effectiveness of antidepressive treatment (Salamone, 2000; Moncrieff et al., 2004; Edward et al., 2005; Enck et al., 2013; Weimer et al., 2015b).

2. Schizophrenia. Placebo responses reported in clinical trials in schizophrenia are similar in magnitude, quality, and impact to those observed in depression trials (Kinon et al., 2011). The difference in responder rates between antipsychotic and placebo treatments in psychosis is reported to be 18% (Leucht et al., 2009, 2013). Results suggest significant variability in the magnitude of the placebo response due to patient characteristics and trial design factors, with the magnitude of placebo effects increasing over time (Agid et al., 2013; Rutherford et al., 2014) (see section III).

To date, the underlying neurobiological mechanisms steering placebo responses in schizophrenic patients have not been studied; they are difficult to investigate mainly because there is no generally accepted experimental model for schizophrenia. Moreover, schizophrenia’s symptoms are classified into three groups: positive symptoms, such as hallucinations and delusions, negative symptoms, such as apathy and social withdrawal, and cognitive symptoms, such as poor executive functioning and working memory (Murray...
and Stoessl, 2013; Kingwell, 2014), all of which could react differently to placebo mechanisms. Experimental approaches in this field might be further complicated by the fact that patients’ expectations may vary considerably because of a false interpretation of the term placebo, and positive psychotic symptoms may be classified as rewarding (Dunn et al., 2006).

There is thus an urgent need to characterize the neuropsychological mechanisms underlying placebo responses in schizophrenia to ensure continued support for investment and progress in CNS drug development.

3. Anxiety Disorders. For anxiety disorders such as generalized anxiety, panic disorder, or social phobia, placebo effects in clinical trials have been reported ranging between 10% and 60% (Loebel et al., 1986; Mavissakalian, 1988; Mellered and Rosenberg, 1990; Piercy et al., 1996; Huppert et al., 2004; Khan et al., 2005; Stein et al., 2006). Moreover, in RCTs investigating the anxiolytic effect of the benzodiazepine alprazolam, improvement in the placebo arm remained stable after the pill intake was discontinued, whereas patients in the drug arm suffered relapses to baseline levels (Ballenger et al., 1988; Mavissakalian, 1988; Mellered and Rosenberg, 1990; Piercy et al., 1996; Huppert et al., 2004; Khan et al., 2005; Stein et al., 2006). PET analyses showed that placebo responses in patients with social anxiety disorders were accompanied by attenuated amygdala activity, a brain region crucial for emotional processing. Intriguingly, this only applied to those subjects homozygous for the long allele of the serotonin transporter–linked polymorphic region or the G variant of the G-703T polymorphism in the tryptophan-hydroxilase-2 gene promoter. In the same study, the tryptophan-hydroxilase-2 polymorphism significantly predicted placebo responses, whereby homozygosity for the G allele was associated with more pronounced improvement in anxiety symptoms (Furmark et al., 2008). Likewise, anxiety-relieving placebo responses in healthy subjects decreased activity in emotionally responding brain areas such as the amygdala, insula dorsal ACC, and increased activity in the subgenual anterior cingulate cortex and ventral striatum, indicating a reward-related response induced by cognitive factors such as volunteers’ expectations (Zhang et al., 2011). In patients with social anxiety, connectivity changes between the amygdala and dorsolateral prefrontal cortex and rACC areas have been shown to be associated with the individual anxiolytic response to SSRI treatment and placebo, as demonstrated in PET. These observations support the notion that similar cognitive or expectancy-related mechanisms are involved in improving emotion regulation in patients taking anxiolytic drugs and placebo responders (Faria et al., 2014).

Placebo responses in neuropsychiatric disorders have been documented in both RCTs and experimental studies (Weimer et al., 2015b). A few experimental studies have reported at least some shared neurobiological pathways for placebo responses in neuropsychiatric disorders and pain with the involvement of expectation and emotion- and reward-related circuitry. A thorough understanding of the mechanisms steering these often profound placebo responses will be essential to exploiting this knowledge and to maximizing these unspecific treatment effects in daily clinical care for the patient’s benefit and to minimize placebo responses for the development of effective drugs (Enck et al., 2013).

D. Immunologic Responses

Meta-analyses and reviews have demonstrated the susceptibility to “inert” treatments of various immune-related pathologic conditions such as ulcerative colitis (Ilnyckyj et al., 1997), duodenal ulcer (de Craen et al., 1999b), Crohn’s disease (Su et al., 2004), or multiple sclerosis (La Mantia et al., 1996). However, few attempts have been made to specifically investigate placebo responses and the underlying mechanisms directly modulating peripheral immune functions in human subjects (Pacheco-Lopez et al., 2006). These experimental data indicate that peripheral immune functions seem to be predominantly affected by associative learning or conditioning paradigms rather than by cognitive factors alone, such as the expectation of subjects or patients of a given treatment’s benefit.

Learned placebo responses in immune functions can be demonstrated by employing associative learning paradigms in experimental animals, healthy humans, and patients (Enck et al., 2008; Schedlowski and Pacheco-Lopez, 2010). A prerequisite for the classic conditioning of immune functions is intense bidirectional communication between the CNS and the peripheral immune system (Meisel et al., 2005; Tracey, 2009, 2010b) that constantly exchange information on efferent and afferent pathways. The classic conditioning of immune responses is one of the most impressive examples of communication between these major physiologic systems (Exton et al., 2001; Ader, 2003; Pacheco-Lopez et al., 2006; Schedlowski and Pacheco-Lopez, 2010).

I. Studies in Experimental Animals. Most insights into the neurobiological mechanisms steering learned placebo responses in immune functions came from studies in experimental animals. The majority of experiments in rodents usually employ the so-called taste aversion paradigm (Garcia et al., 1985) in which
a novel taste (conditioned stimulus [CS]) is paired with the administration of an immunomodulating drug (unconditioned stimulus [US]) during acquisition. When the CS is re-presented at a subsequent time point during the evocation or memory phase, animals demonstrate a modification of immune parameters as a conditioned response that generally mimic the actual drug (US) effect. Experimental evidence over the last 3 decades has demonstrated behaviorally conditioned stimulatory or inhibitory effects in rodents, both in humoral and cellular immunity, with behavioral conditioning able to re-enlist changes in lymphocyte circulation and proliferation, cytokine production, natural killer cell activity, or endotoxin tolerance (reviewed in Exton et al., 2001; Hucklebridge, 2002; Ader, 2003; Pacheco-Lopez et al., 2006; Riether et al., 2008; Schedlowski and Pacheco-Lopez, 2010).

The underlying central, efferent, and afferent neurobiological mechanisms steering learned immunosuppressive placebo responses are the best understood to date and are thus described here in greater detail. Employing the immunosuppressants cyclophosphamide or cyclosporine A (CsA) as a US demonstrated that the insular cortex and amygdala are key central structures in the behaviorally conditioned suppression of antibody production (Ramirez-Amaya et al., 1996), lymphocyte activity, as well as cytokine production [interleukin (IL)-2, interferon (IFN)-γ] and cytokine mRNA expression (Pacheco-Lopez et al., 2005; Schedlowski and Pacheco-Lopez, 2010). Employing the CsA-taste conditioning paradigm, the learned immunosuppressive responses are mediated on the peripheral efferent arm via the splenic nerve via noradrenaline and adrenoceptor-dependent mechanisms (Exton et al., 1998, 1999, 2002; Pacheco-Lopez et al., 2009; Riether et al., 2011). However, this neuroanatomical pathway with the splenic nerve mediating the learned immunosuppression appears to be just one of many efferent neural routes mobilized during learned immunosuppression, because the learned inhibition of the contact-hypersensitivity reaction (employing the identical CsA-taste paradigm) was independent of sympathetic splenic innervation (Exton et al., 2000).

Other approaches analyzed afferent mechanism(s) enabling the CNS to receive information regarding specific drug-induced immune changes or pharmacological effects induced by the drug employed as a US. Acute peripheral CsA administration induced behavioral changes such as decreased ambulatory activity in the open field 6 hours after CsA injection (von Horsten et al., 1998). These changes coincide with increased neuronal activity detected in the insular cortex and amygdala 1 to 6 hours after intraperitoneal CsA injection, as evident in intracortical EEG telemetry, as well as c-Fos expression and increased noradrenaline levels in the amygdala as determined by microdialysis (Doenlen et al., 2011; Pacheco-Lopez et al., 2013). These immediate alterations appeared to be a direct effect of CsA and not indirectly mediated via the vagus nerve, because a vagal deafferentation before CsA injection did not prevent the increased neural activity. However, CsA levels were detected in the cerebellum, insular cortex, and amygdala 2 to 4 hours after CsA administration (Pacheco-Lopez et al., 2013). Overall, at present it is incompletely understood how the CNS detects the changes induced by different substances and drugs employed in paradigms of learned immune responses, and we still need to elucidate which molecules are the messengers that activate the brain during the acquisition or learning phase of a conditioning protocol (Hadamitzky et al., 2013).

2. Human Studies. The data from experimental animals together with deeper understanding of the mechanisms responsible for learned immune functions formed the basis for studying this interesting placebo phenomenon in humans (Vits et al., 2011). The CsA-taste-immune paradigm was expanded from just being applied in experimental animals to being applied in healthy humans, revealing the behaviorally conditioned significant suppression of T-cell function detected via impaired cytokine (IL-2 and IFN-γ) production, reduced cytokine mRNA expression, and inhibited T-cell proliferation (Goebel et al., 2002). This learned immunosuppression can be repeatedly recalled by exposing the conditioned subjects to the CS again after an 11-day break (Wirth et al., 2011). Moreover, plasma noradrenaline concentration, state anxiety, and baseline levels of IL-2 predicted nearly 60% of the conditioned immunosuppressive response (Ober et al., 2012), providing evidence for biologic and psychologic predictors of conditioned placebo responses in general and learned immune responses in particular. Further studies employing the CsA-taste conditioning paradigm in humans showed that immunosuppression could not be induced by just manipulating the expectancy of test subjects (Albring et al., 2012). In addition, experimental evidence confirms previous observations in rodents (Niemi et al., 2007), namely that inducing a pronounced learned response in immune functions requires multiple CS-US combinations during acquisition and evocation (Goebel et al., 2005; Albring et al., 2012; Grigoleit et al., 2012).

3. Toward the Clinical Application of Learned Immune Responses. A number of studies in rodents have meanwhile demonstrated the potential clinical relevance of learned responses in immune functions. Specifically, the morbidity and mortality of animals with autoimmune disease was abated via the learned immunosuppressive response (Ader and Cohen, 1982; Klosterhalfen and Klosterhalfen, 1983, 1990; Jones et al., 2008). In addition, asthma-like symptoms, anaphylactic shock (Noelpp and Noelpp-Eschenhagen, 1951a,b; Djuric et al., 1988; Palermo-Neto and Guimaraes,
2001, 2002, 2004), or delayed-type hypersensitivity response (Bovbjerg et al., 1987; Rouddebah and Bryant, 1991; Exton et al., 2000) were affected by learned immunosuppressive responses. Behavioral conditioning as supportive therapy has also been studied in the context of experimental cancer therapies (Hiramoto et al., 1991; Spector, 1996; Bovbjerg, 2003), in which the learned immune response reduced tumor growth and prolonged survival time in conditioned tumor-bearing mice (Ghanta et al., 1985, 1988, 1990).

Another example of the potential clinical relevance of the behaviorally conditioned immune response is illustrated by grafting experiments (Gorczynski et al., 1982). Behaviorally conditioned CsA-immunosuppressive effects prolonged the survival time of heterotopically transplanted heart allografts in rats (Exton et al., 1998; Grochowicz et al., 1991). Moreover, combining the conditioning procedure with the administration of subtherapeutic doses of the immunosuppressive drug CsA together with daily re-exposure to the CS led to long-term graft survival in 20–30% of the animals (Exton et al., 1999), indicating synergistic effects via a combination of behaviorally conditioned immunosuppression and subtherapeutic dosing of an immunosuppressive drug.

Early observations in humans, namely, that allergic symptoms can be induced in affected patients despite the absence of allergens, support the notion that learning mechanisms contribute to asthma’s pathophysiology (Turnbull, 1962). This assumption is supported by a study in patients with allergic rhinitis, whereby elevated measures of mast cell tryptase in mucosa were conditioned behaviorally (Gauci et al., 1994). Similarly, allergic subjects re-exposed to an olfactory cue (CS) formerly paired with a grass-allergen challenge displayed increased histamine release (Barrett et al., 2000). Reversely, the antihistaminergic properties of the H1-receptor antagonist desloratadine was behaviorally conditioned in patients suffering from allergic house-dust-mite rhinitis, whereby the learned placebo response significantly reduced subjective symptoms, the allergic response to the skin prick test, and basophile activation (Goebel et al., 2008).

That study was recently confirmed and expanded upon by demonstrating reproducible placebo responses in the allergic response induced by both expectation and learning (Vits et al., 2013). The effectiveness of the conditioning procedure on another type of allergic reaction (delayed-type hypersensitivity response) was tested in healthy volunteers undergoing monthly tuberculin skin tests. All subjects presented significantly blunted symptom severity as a result of the conditioning process (Smith and McDaniel, 1983). However, employing a similar approach, those results could not be replicated (Booth et al., 1995). The efficiency of learned immune responses was also tested in patients with multiple sclerosis who receiving cyclophosphamide infusions continuously paired with a novel taste during the learning phase. Re-exposure to the CS alone during evocation significantly reduced peripheral leukocyte numbers (Giang et al., 1996). Furthermore, by pairing subcutaneous IFN-γ injections with a strongly flavored drink (CS), elevated levels of neopterin and quinolinic acid serum were induced after re-exposing healthy volunteers to the CS (Longo et al., 1999).

Together, these experimental data form a “proof of principle that associative learning protocols may be taken seriously as supportive treatment options during immune pharmacological regimens (Schedlowski and Pacheco-Lopez, 2010; Doering and Rief, 2012; Enck et al., 2013). However, as with other learning processes, behaviorally conditioned immunosuppression is subject to extinction, that is, the learned immunosuppressive response gradually decreases over time. This constitutes a considerable problem for the systematic application of conditioning paradigms as a treatment option supporting immunopharmacological regimens. Attempting to overcome this drawback, a recent study demonstrated that extinction of the learned immunosuppressive response (IL-2 production and IL-2 mRNA-expression) in healthy humans can be inhibited by combining the CS re-exposure during evocation with administration of subtherapeutic doses of CsA (Albring et al., 2014). Similarly, a recent partial reinforcement schedule in which patients received a full dose of medication 25 to 50% of the time and placebo medication the other times significantly reduced the amount of corticosteroid needed to treat cutaneous lesions in psoriasis patients (Ader et al., 2010).

Although the clinical exploitation of conditioned immune responses is still in a very early stage, these preliminary results provide evidence that extinction processes might be overcome by systematically modifying learning protocols such as partial reinforcement strategies (Ader et al., 2010; Doering and Rief, 2012; Hadamitzky et al., 2013; Au Yeung et al., 2014).

E. Neuroendocrine Responses

The experimental designs employed in studies investigating learned placebo responses in neuroendocrine functions basically resemble the conditioning protocols used to induce learned placebo responses in immune functions. During acquisition, the conditioning group receives the pairing of a CS (e.g., stimulus compound, injection procedure, novel tasting drink, or novel olfactory stimulus) and a US (e.g., administration of adrenaline, insulin, dexamethasone, glucose, IFN-β-1a, sumatriptan), which induces alterations in neuroendocrine responses. The experimental group is then re-exposed to the CS during evocation and alterations in neuroendocrine functions (e.g., concentrations of adrenaline, glucose, cortisol, insulin, norepinephrine, glucagon, vasopressin, ACTH, somatropin)
are analyzed, reflecting the conditioned response. Although learned placebo responses in neuroendocrine functions have been demonstrated in experimental animals (Ader, 1976; Buske-Kirschbaum et al., 1996; Janz et al., 1996; Pacheco-Lopez et al., 2004), there are few studies reporting these effects in humans, and those that do mainly employed insulin as a US measuring blood glucose or insulin levels as a conditioned response (Fehm-Wolfsdorf et al., 1993; Stockhorst et al., 1999, 2004, 2011; Klosterhalfen et al., 2000; reviewed in Wendt et al., 2014b). Two human studies reported conditioned changes in plasma cortisol concentrations. One study observed an increase in plasma cortisol levels by re-exposing subjects to a novel tasting drink (CS) that had been paired with an injection of dexamethasone (US) (Sabbioni et al., 1997). A decrease in cortisol and an increase in growth hormone were observed when sumatriptan was used as a US during the conditioning procedure (Benedetti et al., 2003). These changes in cortisol and growth hormone levels were induced via the associative learning protocol but not via mere expectation, resembling the observations in learned immune responses. However, there are currently no data on the neurobiological mechanisms mediating these conditioned neuroendocrine responses, which might explain why we are unaware of any such protocols that have been transferred to clinical conditions.

This experimental evidence demonstrates the potential applicability of such behavioral conditioning protocols in clinical practice. However, future studies will have to analyze the kinetics of the behaviorally conditioned endocrine response and to elucidate whether and to what extent these conditioned responses can be reconditioned on multiple occasions. Only with this information and more detailed knowledge of the mechanisms driving the CNS-endocrine system interaction will it be possible to design conditioning protocols that can be employed in clinical situations to the patients’ advantage.

F. Autonomic Organ Functioning

The innervation of most peripheral organs by sympathetic and the parasympathetic branches of the autonomic nervous system (ANS) forms the anatomic and neurophysiological basis of placebo responses in end-organ functioning (Jänig, 2006). The ANS is under inhibitory and excitatory control of a number of cortical and subcortical structures such as the anterior and mid-cingulate cortices, the insula, dorsolateral prefrontal cortex, amygdala, hippocampal formation, and the hypothalamus (Beissner et al., 2013), brain areas known to mediate placebo responses in pain, nausea, and Parkinson’s disease. Among the ANS-regulated functions, cardiovascular, pulmonary, and intestinal functions have been subjected to placebo investigations.

1. Cardiovascular Functions. A drop in blood pressure is regularly observed in the placebo groups of clinical trials of hypertension (Preston et al., 2000; Weber, 2008). However, the inclusion of no-treatment control groups have revealed that these effects seem to be largely due to confounding factors such as spontaneous fluctuation and regression to the mean of habituation effects (Hrobjartsson and Gotzsche, 2010).

In studies of placebo analgesia, pain relief is accompanied by a reduction in heart rate and heart rate variability (Pollo et al., 2003). This placebo response in pain perception and heart rate was naloxone reversible but was unaffected by muscarinic blockade with atropine. In contrast, $\beta$-adrenoceptor blockade with propranolol did not affect placebo analgesia but did antagonize a pain-induced heart rate increase, suggesting that placebo analgesia is independent from heart rate changes (Pollo et al., 2003). This notion is supported by observations where placebo analgesia was associated with a reduction in subjective stress levels, heart rate, and heart rate variability. The reduction in sympathetic activity appeared to be a factor involved in anticipatory placebo analgesia rather than simply a direct consequence of pain reduction (Aslaksen and Flaten, 2008; Aslaksen et al., 2011). These placebo responses reflected in the heart rate appear to be mediated via the prefrontal cortex, because the impaired connectivity of the prefrontal lobes in Alzheimer patients has been associated with both absent placebo analgesia and a heart rate reduction (Benedetti et al., 2006). Whether placebo responses evident in cardiovascular functions in placebo analgesia studies are a direct cause of the placebo instruction or secondary to the altered pain perception is still not clear.

Placebo responses on cardiovascular functions outside the context of pain-related changes in sympathetic activity have been reported in experimental settings, but they are inconsistent and scarce. Placebo-induced drops in systolic but not diastolic blood pressure in normo- and hypertensive patients have been reported (Agras et al., 1982; Suchman and Ader, 1992; Amigo et al., 1993). More recently, verbally induced expectation reduced systolic blood pressure without affecting diastolic blood pressure or other autonomic responses, such as skin conductance and sympathetic and parasympathetic components of heart rate variability in healthy volunteers (Meissner and Zep, 2011). Another study reported stress responses induced by a placebo-spray administered with the suggestion that it would either raise or lower blood pressure. Within the total study sample, blood pressure was significantly higher after the placebo spray independent of the associated suggestions (Zimmermann-Viehoff et al., 2013). A systolic drop in blood pressure was evident after placebo intake plus verbal suggestion but vanished when participants believed that the medication had
been switched from a trademark to a generic drug (Faasse et al., 2013). Finally, verbal suggestions have been shown to affect coronary diameter in chest pain patients. Surprisingly, the verbal suggestion of vasodilatation induced significant vasconstriction but was associated with lower pain ratings in this patient group without affecting stress ratings, heart rate, or blood pressure (Ronel et al., 2011).

Employing the open versus hidden infusion paradigm, the \( \beta \)-blocker propranolol was more effective in reducing heart rate when given by the doctor (open) compared with the computer-infusion (hidden) condition (Colloca and Benedetti, 2005) (for details, see section VI). Similarly, the acetylcholine muscarinic antagonist atropine induced a more pronounced increase in heart rate when administered overtly compared with the hidden condition (Benedetti et al., 2003).

Taken together, there is evidence of placebo responses on systolic blood pressure, yet other effects on the cardiovascular system require further clarification.

2. Pulmonary Functions. The autonomic nervous system regulates smooth muscle constriction in the respiratory tract; sympathetic activation via catecholaminergic mechanisms induces bronchodilation, whereas bronchoconstriction is predominantly mediated via vagal efferents (Canning and Fischer, 2001). Several studies reported bronchoconstriction in asthmatic patients induced by the use of a fake bronchodilator containing pure saline solution (Isenberg et al., 1992a,b). Verbally induced expectations of bronchoconstriction were antagonized by anticholinergic agents, suggesting these nocebo responses are mediated via enhanced vagal activation of lung functions (Luparello et al., 1968; Butler and Steptoe, 1986). More recently, in an experimental approach, a placebo bronchodilator significantly reduced nonspecific airway hyperreactivity in asthmatic patients (Kemeny et al., 2007). In contrast, another study identified clear and pronounced placebo responses in subjective asthma symptoms but observed no placebo responses on objective outcome measures as measured with spirometry (Wechsler et al., 2011). Taken together, whether and to what extent subjective placebo and nocebo responses are associated with physiologic lung function parameters will have to be analyzed in experimental approaches and clinical investigations.

Both heart rate and respiratory responses appear to be affected during placebo analgesia. Patients treated with the opioid buprenorphine for pain relief after surgery presented a reduced respiratory response as one common side effect of the opioid administration. When injected with NaCl instead of the opioid, patients reported placebo-induced pain relief and displayed a reduced respiratory response that was antagonized with the opioid antagonist naloxone (Benedetti et al., 1998, 1999).

3. Nausea. Nausea was known to demonstrate high placebo response rates as early as 1955, when Beecher (1955) cited a study with average placebo response rates of 40% with seasickness in individuals working on seagoing vessels (Gay and Carliner, 1949). The emetogenic properties of ipecac, a herbal drug to induce mild nausea in intoxication, was completely blocked by verbal suggestions of nausea relief in fistulated individuals (Wolf, 1950). A recent review on laboratory experiments in healthy volunteers addressing placebo responses in nausea concludes that nausea symptoms can be alleviated with placebo interventions based on the principles of Pavlovian conditioning, manipulating expectancies, or a combination of both (Quinn and Colagiuri, 2015).

Attempts to relieve nausea by performing Pavlovian conditioning build on laboratory and clinical evidence that anticipatory nausea, the urge to vomit, taste aversion, and rotation tolerance can be classically conditioned. Experimental techniques aiming to reduce conditioned responding and/or to enhance extinction may constitute promising tools leading to effective interventions. Studies in healthy volunteers confirm that anticipatory nausea is reduced by repetitive pre-exposure to the nausea-inducing environment (“latent inhibition”) (Klosterhalfen et al., 2005) and by providing a different, salient beverage before nausea induction (“overshadowing”) (Stockhorst et al., 2014). Only a single study to date has conducted conditioning-based interventions in a clinical setting to reduce nausea in cancer patients undergoing chemotherapy (Stockhorst et al., 1998), although more work is underway in this promising field (Geiger and Wolfram, 2013).

Changing expectations about nausea has been accomplished in laboratory experiments by the intake of placebo pills (Levine et al., 2006) or by delivering positive suggestions associated with distinct gustatory stimuli (Klosterhalfen et al., 2009; Weimer et al., 2012). Other studies attempting to modify expectations have provided counterintuitive, i.e., reverse effects of suggestions (Levine et al., 2006) or negative results (Williamson et al., 2004). These inconsistencies may in part be explained by sex differences (Klosterhalfen et al., 2009; Weimer et al., 2012) and/or complex interactions between the participant’s sex and that of the experimenter (Aslaksen et al., 2007; Weimer et al., 2012). Ultimately, interventions combining the principles of conditioning with optimized expectations may be most promising for effective alleviation of nausea symptoms. A combination of positive instructions and surreptitiously reduced rotation speed in preceding trials (i.e., conditioning) detected significantly alleviated symptoms, fewer nauseogenic head movements, and longer rotation tolerance in a subsequent trial (Horing et al., 2013).

Exploring the central mechanisms of nausea relief with placebo (and drugs) is difficult given the risk of aspiration during brain-scanner investigations with
RCTs including 8364 patients with IBS allocated to interventions (Enck et al., 2012; Elsenbruch, 2014). Experimental visceral pain is affected by placebo interventions, and genetic contributions (Elsenbruch, 2011). Research for biomarkers includes immunologic, endocrinological, and genetic contributions (Elsenbruch, 2011). The evidence is accumulating that nausea in cancer patients undergoing chemotherapy can be predicted by pretreatment expectancies (Colagiuri et al., 2011). To date, the few interventional studies designed to improve nausea in the context of chemotherapy by enhancing positive expectations have yielded conflicting results (Shelke et al., 2008; Roscoe et al., 2010). This is in line with similar results originating in efforts to prevent (or reduce) seasickness symptoms by manipulating expectancies (Quinn et al., 2015). Galvanic vestibular stimulation induced a sensory mismatch that proved highly effective in conditioning nausea; it was also independent of other experimental context variables. This phenomenon will allow a more in-depth analysis of the central pathways mediating the placebo response in nausea in the future.

Investigating the peripheral mechanisms underlying placebo responses in nausea appears much easier. Studies have suggested that expectancies affect both the behavioral effects of nausea and induce changes in gastric slow-wave rhythm as measured by electrogastrography (Williamson et al., 2004). However, there is a paucity of findings and many are somewhat contradictory (Levine et al., 2006; Weimer et al., 2012; Horig et al., 2013).

Efforts have been made to characterize peripheral neuroendocrine and immune mediators associated with stress responses, such as cortisol and cytokines (Stockhorst et al., 1998, 2014; Klosterhalfen et al., 2005; Meissner, 2009). However, replication and extension to healthy volunteers and patients is needed before the putative role of the hypothalamic-pituitary-adrenal axis and immune systems in placebo responses for nausea can be clarified.

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G. Gastrointestinal System/Irritable Bowel Syndrome

Of all the gastrointestinal disorders, functional bowel diseases of the IBS type represent the largest subgroup with a population prevalence of around 15% in most Western countries (Choung and Locke, 2011). Its major clinical characteristic is abdominal pain in the absence of macroscopically identifiable organic causes. The pathophysiology of IBS is largely unknown, but the search for biomarkers includes immunologic, endocrinological, and genetic contributions (Elsenbruch, 2011). Experimental and clinical studies suggest that experimental visceral pain is affected by placebo interventions (Enck et al., 2012; Elsenbruch, 2014).

A recent meta-analysis reported that in 73 eligible RCTs including 8364 patients with IBS allocated to placebo, the pooled placebo response rate across all RCTs was 37.5% (Ford and Moayyedi, 2010). These observations are confirmed by experimental data in IBS patients in which augmented practitioner-patient communication increases the beneficial effect of placebo acupuncture on symptom severity and quality of life (Kaptchuk et al., 2008a) and in which an open-label placebo produced significantly higher global-improvement scores in these patients (Kaptchuk et al., 2010).

Our understanding of the neurobiological and neuropsychological mechanisms steering placebo responses in visceral pain is much more limited compared with somatic pain (Zhou and Verne, 2014). This is also due to differences in the processing of visceral and somatosensory signals in the periphery and the brain (Aziz et al., 2000; Eickhoff et al., 2006). Most experimental placebo studies in the visceral-pain field employ a rectal distension model in which pressure- or volume-controlled distension of the gastrointestinal compartments is carried out, resulting in reliable pain models. Verbal suggestions for pain relief induced a significant reduction in rectal distension-induced pain intensity in IBS patients (Vase et al., 2003). These placebo responses in visceral pain seemed to correlate negatively with anxiety and negative emotions but were not associated with endogenous opioidergic mechanisms, because naloxone did not affect the placebo response (Vase et al., 2005). The brain responses of IBS patients were analyzed employing glucose-PET imaging before and 3 weeks after a placebo intervention, revealing that prefrontal regions (the right ventrolateral prefrontal cortex) predicted self-reported symptom improvement in these patients with this relationship mediated by changes in the dorsal anterior cingulate cortex (Lieberman et al., 2004). Similarly, an fMRI study reported that decreases in activity in pain-related brain regions in the placebo condition were related to verbal suggestion and “habituation, attention, and conditioning” (Craggs et al., 2007, 2008; Price et al., 2007).

A series of studies analyzed the role of expectation in visceral placebo analgesia in healthy volunteers (Benson et al., 2012; Elsenbruch et al., 2012a,b; Kotsis et al., 2012; Schmid et al., 2013, 2015; Theysohn et al., 2014). When visceral pain stimuli were delivered with a cover story of receiving with varying likelihood (0%, 50%, 100%) an intravenous pain killer, the volunteers reported a “dose-dependent” pain reduction (Elsenbruch et al., 2012a). This placebo analgesia was associated with activity changes in the thalamus, prefrontal, and somatosensory cortices, especially in the pain-anticipation phase, consistent with findings in conditioned esophagal placebo analgesia (Lu et al., 2010). In addition, in the “50% condition,” the placebo-induced pain relief was more pronounced in those subjects who believed they were in the active-treatment group (Kotsis et al., 2012). A direct comparison in the placebo
response to visceral pain between IBS patients and healthy volunteers demonstrated similar placebo responses at the behavioral level (magnitude of placebo analgesia) but a more pronounced neural response in affective and cognitive brain regions (insula, cingulate cortex, prefrontal cortex), suggesting altered neural processing of placebo-induced changes in pain perception in IBS and in patients with ulcerative colitis in remission (Lee et al., 2012; Schmid et al., 2015).

Together, these experimental data demonstrate that placebo responses in visceral pain on the behavioral and a corresponding neural level are induced predominantly by expectation in healthy volunteers and patients with IBS, particularly those with gastrointestinal disorders (Zhou and Verne, 2014). Interestingly, only one study thus far has reported successful conditioning of visceral (esophageal) analgesia in healthy volunteers (Lu et al., 2010), whereas placebo analgesia studies with lower gastrointestinal pain (as in IBS) are still lacking. Until cross-modality comparisons of placebo effects involving different pain models and clinical conditions are available, it is impossible to conclusively determine whether placebo effects in visceral and somatic pain are similar or whether they involve different pathways. In the meantime, there is evidence to support “specificity” for the visceral domain (Eickhoff et al., 2006).

**H. Sleep Disorders**

Placebo responses in insomnia can be assessed on the subjective and objective level. Objectively assessed sleep parameters derived from polysomnographic assessments (PSG) are total sleeping time (TST), sleep onset latency (SOL; time in bed before sleep onset), wake after sleep onset (WASO), and sleep quality (quotient between sleeping time and time in bed).

Subjective and objective improvements in sleep quality in placebo arms of insomnia trials were very recently subjected to meta-analyses (Winkler and Rief, 2015). Results in the placebo groups accounted for 64% of the subjective benefits reported in the drug groups and for 54% of physiologically assessed improvements. The effect sizes for objective versus subjective outcome parameters in the placebo groups did not differ (e.g., TST $d = 0.43$ derived from diaries; $d = 0.42$ derived from PSG). No predictors for strong placebo responses were identified, although other studies reported large baseline variance in SOL and TST and longer SOL to predict placebo responses (Ogawa et al., 2011). These meta-analytically described placebo responses are in accordance with a re-analysis of placebo arms in four drug trials, also indicating the long-term persistence and robustness of positive effects in the placebo arms (Perlis et al., 2005). Other meta-analyses reported a modest difference between drug arms (Z-drugs) and placebo arms in insomnia trials, and the differences in some objective variables (TST, WASO) were even nonsignificant (Huedo-Medina et al., 2012). To further disentangle the effects of expectation, regression to the mean, and social desirability on subjective outcomes in placebo arms of insomnia studies, studies directly examining these influences have been conducted (McCall et al., 2011) that found evidence for the contribution of all three effects (however, with varying degrees) on different outcome variables. Significant improvements in subjective TST were also reported for the comparison between placebo arms and waiting list groups/no treatment groups (McCall et al., 2005; Belanger et al., 2007).

Although clinical trials only enable limited conclusions about the underlying mechanisms, several experimental approaches addressed placebo responses in insomnia directly. In a pilot study, patients with insomnia received a placebo pill for the second night after baseline assessments of the first night. Although this study did not control the so-called “first-night effect” (reduced sleeping time during the first night in the sleep laboratory), the improvements during the second night were larger than would be expected, with a TST increase of 1.3 hours and a WASO reduction to 57% of the first-night assessments. Additionally, the working group reported a trend toward longer rapid eye movement sleep periods after placebo intake (Rogev and Pillar, 2013). Their result is in line with an experiment examining whether the first-night effect can be reduced when placebo pills are administered. Using this laboratory model for insomnia in healthy controls, the investigators showed that the first-night effect is associated with rapid eye movement sleep reductions and that this effect can be counteracted by taking placebo pills (Suetsugi et al., 2007). Further studies investigating healthy controls with experimentally balanced designs confirmed the positive effects of placebo pill intake versus no treatment on WASO on objective and subjective parameters (Fratello et al., 2005). Placebo application can also stimulate alterations in circadian rhythms (Reinberg et al., 1994).

Learning has also been shown to influence sleep quality. Alpha/theta neurofeedback was used to learn the transition into presleep states. This transition is accompanied by reduced activity in the brain areas responsible for external monitoring of sensory input (Kinreich et al., 2014), contributing to a reduction in physiologic arousal.

The neurobiological underpinnings of placebo responses in insomnia are poorly understood. Further investigation is needed to assess which functional and neurophysiological aspects of sleep regulation beyond PSG/EEG parameters are affected by placebo mechanisms. We need to discover which biologic system and physiologic processes in sleep regulation are vulnerable to expectation and conditioning influences (e.g., the ascending neuronal system including the reticular formation, thalamus, and forebrain neurons; the
descending neuronal pathways encompassing neuronal activities in the hypothalamus, brain stem, and spinal cord; neurotransmitter systems such as the glutamatergic system, GABA, noradrenaline, dopamine, and serotonin sensitive receptors; behavioral arousal and muscle tone (Jones, 2011). Sleep is closely associated with the restoration of physiologic systems, such as nocturnal blood pressure dipping and changes in immune functions (Rief et al., 2010; Euteneuer et al., 2014), but it is also relevant for processes such as recreation and memory consolidation (Weber et al., 2014), and placebo responses in these sleep-associated factors also need to be addressed.

V. Neuro-Bio-Behavioral Mechanisms of Nocebo Responses

Nocebo responses describe negative treatment effects that are not directly attributable to the drug's pharmacokinetics. Two variants of these nocebo responses exist: one is characterized by new symptoms or a symptom aggravation associated with drug or placebo intake, although the chemical agent itself is not able to trigger these symptoms. Another variation of nocebo responses is the reduced efficacy of clinical interventions due to negative expectations or prior experiences. The underlying mechanisms steering these two types of nocebo responses are not usually distinguished.

A. Nocebo Effects in Clinical Trials and Clinical Practice

In double-blinded RCTs, the rate of unwanted side effects reported in placebo groups is notoriously high, although these symptoms obviously cannot be the direct consequences of drug effects. Many patients discontinue drug intake because of unwanted side effects, although being in the placebo arm, or because the reported adverse effects are in discordance with the pharmacokinetic of the drug (Rief et al., 2006, 2009a; de la Cruz et al., 2010; Stathis et al., 2013).

Nocebo mechanisms are also considered responsible for epidemic waves of reports of adverse events. In New Zealand, public blaming of a thyroxine product on television led to a dramatic increase in adverse events reported to the authorities responsible for drug monitoring (Faasse et al., 2012). The typical problems observed when switching from a brand to a generic drug are related to nocebo mechanisms as documented in antihypertensive treatments with placebo pills in counterbalanced experimental approaches (Faasse et al., 2013).

Several studies have confirmed that the unwanted side-effect profiles of the placebo arms “mimic” the expected side-effect profiles of the drug arms. The side effects reported by placebo arms in multiple sclerosis treatments have been substantially higher when disease-modifying drugs were investigated compared with trials investigating symptomatic treatments (Papadopoulos and Mitsikostas, 2010). Similar effects were reported from different groups of migraine drugs (Amanzio et al., 2009) and antidepressants (Rief et al., 2009a). Such a mimicking effect can hamper adequate detection of drug-related adverse events.

B. Psychologic Mechanisms Contributing to Nocebo Responses

Negative expectations are powerful determinants and predictors of side-effect development and drug tolerability (Nestoriuc et al., 2010). Research paradigms therefore use verbal suggestion to manipulate expectations, frequently amplifying this effect through negative pre-experiences via Pavlovian conditioning. Although conditioning paradigms are more powerful in triggering placebo effects, both verbal suggestion and learning induce similar effects on nocebo development (Colloca et al., 2008).

Observational learning such as watching and/or listening to others who report serious problems after taking a specific drug is another powerful tool for symptom development, sometimes even more powerful than the mere verbal suggestion of side effects (Vögtle et al., 2013). The social dissemination of somatic symptoms was demonstrated elegantly in a recent study (Benedetti et al., 2014). The authors informed just one person in a group about hypoxia-induced headache before the group was to be exposed to hypobaric conditions in the Alps. This symptom report “infected” other group members depending on the intensity of social contacts with that particular individual.

C. Neurobiological Pathways of Nocebo Responses

Neuroimaging studies have confirmed that the mere expectation of symptoms can already activate the brain structures responsible for symptom perception before any sensory stimulation has occurred, thus sensitizing the person to the perception of discomfort (Koyama et al., 2005; Keltner et al., 2006). Pain expectation is associated with significant activations in nociceptive regions in the thalamus, second somatosensory cortex, and insular cortex. When people expect highly intense, noxious thermal stimuli, significant differences appear in the caudal anterior cingulate cortex, head of the caudate, cerebellum, and contralateral nucleus cuneiformis compared with the expectation of pain stimuli of low intensity (Keltner et al., 2006).

Furthermore, although repeated pain stimulation leads to habituation, this effect can be blocked via verbal instructions such as: “with every assessment day, pain intensity will increase,” inducing negative expectations. This blockage of habituation is associated with diverse activities in the brain’s right parietal operculum (Rodriguez-Raecke et al., 2010).
Different descriptions of a cream as being either sensitizing for pain perception or neutral has revealed different activities even on the spinal level (Geuter and Büchel, 2013). The authors demonstrated that activation was higher under the nocebo instruction at the level of stimulated dermatomes C5/C6 in the spinal cord. Pain-related activity in the ipsilateral dorsal horn of the spinal cord was enhanced. The effect of expectancy, stimulus processing, and perception has been demonstrated across different sensory modalities. These effects are displayed on a behavioral and neuronal level (Summerfield and de Lange, 2014). Because expectation facilitates the perception of a specific sensation and of stimulus categories, this effect helps clarify why side effects often occur as a cluster of multiple symptoms.

From a neurochemical point of view, nocebo responses have been best characterized in the field of pain. Nocebo responses have been associated with variations in the dopaminergic, opioidergic and cholecystokinin (CCK) systems (Benedetti et al., 2007). CCK is involved in the activation of descending pronociceptive pathways from the midbrain PAG in mediating anxiety-induced hyperalgesia as well as in the development and maintenance of hyperalgesia associated with peripheral neuropathy (Lovick, 2008). Accordingly, blockade of CCK pathways via the CCK antagonist proglumide leads to the abolition of the nocebo response (Benedetti et al., 1997).

In the study investigating nocebo effects in high-altitude conditions, Benedetti’s working group reported a higher frequency of headache and examined biologic trajectories of the nocebo via observation effect. They identified significantly increased prostaglandin levels (prostaglandin E2, prostaglandin F2) in the verbally “infected” group that mediated vasodilation and subsequently the occurrence of headache (Benedetti et al., 2014).

After examining pain relief caused by a placebo mechanism versus pain amplification based on nocebo effects, Scott et al. (2008) postulated that these may just be different facets of the same pathways. However, the very same person can suffer simultaneously from nocebo responses while experiencing benefits from placebo mechanisms. Even more, nocebo effects can be (mis-)interpreted as signs of potent drugs, thus amplifying placebo effects. Consequently, moderate drug-onset effects can amplify placebo responses in analgesic therapies (Rief and Glombiewski, 2012). This shift in the meaning of somatic symptoms from disturbing side effect to indexing a powerful treatment is associated with the activation of opioid and cannabinoid systems, especially in pain symptoms (Benedetti et al., 2013). However, considering the broad range of potential physiologic systems and drugs’ side effects, various exchanges between placebo and nocebo mechanisms may be occurring for each symptom and physiologic system (Enck et al., 2008). A recent study reported distinct patterns of neural activation induced by positive or negative expectancies, however, that resulted in a correlated placebo and nocebo behavioral response (Freeman et al., 2015).

Taken together, the underlying mechanisms of nocebo responses are much less well understood than those of placebo responses. In particular, the contribution of similar overlapping and distinct trajectories mediating nocebo versus placebo responses require further investigation.

VI. The Effect of Placebo Responses on Pharmacological Treatments

Placebo responses contribute significantly to clinical outcome in most if not all medical treatments including pharmacotherapy. Patients’ expectations are a key factor that codetermines treatment efficacy. The crucial role of expectation in the therapeutic outcome is best illustrated in the so-called open/hidden drug paradigm. In this paradigm, identical concentrations of the same drug are administered under two conditions: an open condition in which the patient is aware of the time point at which the medication is administered by a health care provider and of the intended treatment outcome (e.g., analgesia) and a hidden condition in which the patient is unaware of the medication being administered by a computer-controlled infusion. This paradigm enables the dissociation of the treatment’s genuine pharmacodynamic effect (hidden treatment) from the additional benefit of the psychosocial context in which the treatment is provided. Studies based on an open/hidden paradigm have revealed that psychosocial factors such as the awareness of a drug being given can considerably enhance its analgesic effect (Levine and Gordon, 1984). Conversely, the hidden administration attenuates the analgesic effect of nonsteroidal anti-inflammatory drugs to nonsignificance, and even the effects of opioids are substantially reduced by hidden application (Colloca et al., 2004). Because of its hidden application, the drug dosage had to be doubled to achieve the same result as during open application, a fact highlighting the economic relevance of placebo responses.

This phenomenon is not limited to analgesics, because similar pharmacotherapeutic effects have also been reported in other domains, such as motor function in Parkinson’s disease and anxiety-related disorders (Amanzio et al., 2001; Colloca et al., 2004). Findings from these studies using the open/hidden drug paradigm are supported by investigations that implicitly modulated the expectancy concerning a given drug by verbal instructions (Lyerly et al., 1964; Kirk et al., 1998; Metrik et al., 2009). The detrimental influence of negative expectations on the drug response became, for instance, apparent in a behavioral experimental study by Dworkin et al. (1983), who reported a reversal of
analgesia by nitrous oxide in dental pain when participants expected the drug to increase awareness of bodily sensations. Although this is not the focus of this review, it should be noted that substantial expectation effects are also observed in nonpharmacological interventions such as acupuncture (Linde et al., 2007).

Similarly, learning effects modulate the response to pharmacological treatments (see above). The effect of prior experience on treatment outcome is evident in results from crossover studies (i.e., drug trials in which subjects receive an active drug and a placebo in randomized order), showing that the order in which the placebo or active treatment is given substantially modulates the treatment response. Generally speaking, the response to the active treatment is stronger when active treatment is given first and weaker when it follows the placebo treatment. This can be explained by the fact that the treatment experience, which can be assumed to be less substantial during placebo, carries over into the active treatment and vice versa. For instance, in a double-blind crossover placebo, this effect was observed by the patients' hypertension when administered first (Suchman and Ader, 1992). Yet, when placebos were administered after a week-long use of atenolol, they produced a significantly greater antihypertensive response than the "no treatment" condition. Sequence effects of drug efficacy have also been proposed in conjunction with analgesic therapies for musculoskeletal pain (Batterman and Lower, 1968), indicating that not only was the placebo medication more effective after active and effective treatment but also that the active drug was less effective when it followed an ineffective placebo treatment. Similar sequence effects were recently reported in conjunction with the analgesic effect of active compared with sham repetitive transcranial magnetic stimulation for chronic pain (Andre-Obadia et al., 2011). Observations from clinical trials were recently corroborated experimentally in an analysis of whether prior experience with one treatment can influence the response to a second treatment by employing experimental models of two analgesic treatments in healthy volunteers. In comparison with those subjects with a positive treatment history, participants who experienced no analgesia from the first treatment continued to show a substantially reduced response to a second, different analgesic treatment. These behavioral effects were substantiated in neuroimaging data showing significant activation differences in brain regions coding pain and analgesia between groups (Kessner et al., 2014). In sum, behavioral studies have proven that the effect of drug treatment is determined by the drug's pharmacological profile and (at least partially) by expectancy and learning mechanisms.

A. Neural Mechanisms Underlying the Effect of Expectations on Drug Efficacy

Recent studies have begun exploring the effects of expectation and prior experience on opioid analgesia by using functional brain imaging. Analgesia was studied in response to the opioid remifentanil under three conditions: without expecting analgesia (hidden application), expecting a positive analgesic effect, and not expecting analgesia, i.e., the expectation of hyperalgesia (Bingel et al., 2011). Results show that the positive treatment expectancy doubled the analgesic benefit of remifentanil, whereas the negative treatment expectation interfered with the analgesic potential of remifentanil so severely that its analgesic effect was completely abolished. Importantly, these changes in pain perception were accompanied by significant alterations in the neural response to noxious thermal stimulation in core brain regions of the pain and opioid-sensitive brain networks such as the thalamus, mid-cingulate cortex, and primary somatosensory cortex, brain areas that have consistently displayed correlations with the intensity of nociceptive input and resultant pain perception (Apkarian et al., 2005; Tracey and Mantyh, 2007), and may therefore serve as an objective index of analgesic efficacy (Bingel et al., 2011). With respect to underlying mechanisms Bingel et al. observed that the individual benefit from positive treatment expectancy during remifentanil analgesia was associated with activity in the descending pain modulatory system, including cingulofrontal and subcortical brain areas, resembling mechanisms of placebo analgesia. In contrast, the negative expectancy that abolished the opioid's analgesic effect was selectively associated with increased activity in the hippocampus and medial prefrontal cortex. These brain areas have been implicated in the exacerbation of pain by mood and anxiety in patients and healthy controls (Ploghaus et al., 2001; Schweinhardt et al., 2008).

These initial experimental data on the expectancy modulation of opioid analgesia substantiate the significant contribution of cognitive factors to the overall benefit from pharmacological treatments. Similar interactions between pharmacodynamic and psychologic effects on regulatory brain mechanisms have been reported in conjunction with methylphenidate administration in cocaine-addicted patients (Volkow et al., 2003). Together with evidence from experimental placebo and nocebo studies, these findings reveal that the effects of expectancy and prior experience converge with pharmacological effects within the very same biologic systems, involving distinct CNS and peripheral physiologic mechanisms. However, despite the unequivocal effect of expectancy and learning on pharmacological treatments, research into its underlying mechanisms remains at a very early stage, leaving many unanswered questions.
B. Additive versus Interactive Effects

One of the crucial questions still unanswered is whether cognitive effects and pharmacologically induced analgesia combine in an additive or interactive manner (Fig. 5). This is the crucial basic assumption behind double-blinded RCTs, postulating that the difference between drug and placebo arms reveals the “real” drug effect. However, depending on the drug, exogenous, pharmacologically induced mechanisms and endogenous cascades triggered by expectancy, learning, and their combination may combine in an additive manner with one substance but combine interactively with another. One approach to investigate additive versus interactive effects of drug and placebo is to adopt a balanced placebo design (Rohsenow and Marlatt, 1981), in which the factors expectancy and drug alternate in a $2 \times 2$ factorial manner. Employing just such a design, Atlas et al. (2012) observed additive rather than interactive effects in conjunction with the influence of positive expectation on remifentanil analgesia. Their results were substantiated by a complementary fMRI study investigating pain-related responses during the open and hidden administration of varying remifentanil dosages, also allowing inferences about potential interactions: no interactive effects of drug and expectation were observed at the neural level. This finding does not exclude the possibility that other drugs, i.e., nonopioid analgesics show interactive analgesic effects with expectation-induced analgesia. Future neuroscientific investigations involving neuroimaging of the influence of expectation and learning mechanisms on pharmacological treatments constitute a new and promising avenue of research. Instead of studying the effect of one of them in isolation by controlling the other, it is time we unraveled how both mechanisms combine on the neurobiological level. Deeper neurobiological understanding of their potential interaction promises to ultimately optimize treatment outcomes, encouraging the development of personalized treatment strategies.

VII. Predictors of Placebo and Nocebo Responses

The presence of placebo responses varies tremendously in both healthy volunteers and patients in experimental and clinical settings. The individual placebo response can range from no effect (“nonresponders”) to profound changes in symptom or disease severity (“responders”). Given that placebo responses contribute so substantially to the overall treatment outcome, knowledge about the individual magnitude of their occurrence would not just guide therapeutic decisions to optimize treatment outcomes in clinical practice, it could also help to clarify poorly understood inconsistencies in clinical trials (Enck et al., 2013).

How knowledge of an individual’s placebo responsiveness may inform clinical decision making is highlighted in an open/hidden study of local anesthesia in patients suffering from Alzheimer’s dementia (Benedetti et al., 2006). These patients, neurobiologically characterized by impaired connectivity of the prefrontal lobes (known to be placebo-relevant brain areas) presented reduced pain relief from the open compared with the hidden application of lidocaine, a local anesthetic. Loss of their ability to form expectations reduced overall treatment efficacy, and they needed dose increases to experience adequate analgesia. This study illustrates that the individual contribution of placebo mechanisms to therapeutic outcome is, at least in part, determined by an individual’s neurobiological makeup; it highlights the necessity to adjust drug treatment approaches depending on the individual predisposition for placebo responses.

Seeking deeper knowledge of individual traits and states susceptible to placebo responses, currently major effort is undertaken to identify any psychologic or

![Fig. 5.](image_url) The additive model assumes unspecific effects of equal size in both the placebo and drug arm or groups of studies or experiments. The interactive model, however, suggests that drug-specific effects interact with the placebo responses and will result in unequal placebo effects in the two study arms or experimental groups. (Modified from Enck et al., 2013, with permission.)
system (in the gene coding fatty acid amide hydrolase, the major degrading enzyme of endocannabinoids) was also linked to the placebo analgesic response in the same dataset (Peciña et al., 2014).

Furthermore, an individual’s brain anatomy (including structural and functional measures) predicts the capacity for placebo analgesic responses in healthy subjects. Stein et al. (2012) indicated that white matter integrity in the dorsolateral prefrontal and rostral anterior cingulate cortices and their pathways to the periaqueductal gray are positively associated with individual placebo analgesic responses in healthy subjects. This finding supports the importance of structural brain connectivity in determining the individual ability to form placebo (analgesic) responses. Along these lines, resting-state functional connectivity between prefrontal and insular/parietal cortices is also known to predict individual placebo analgesic responses in patients suffering from chronic low back pain (Hashmi et al., 2012) and the expectancy-related modulation of pain in healthy volunteers (Kong et al., 2013).

Psychologic, physiologic, and neurobiological predictors of placebo responses have also been identified for placebo responses in other physiologic systems and diseases. Placebo responses in anxiety disorders and depression, for instance, have been correlated with psychologic and genetic traits. An association with the locus of control has been suggested for placebo responses in depression (Reynaert et al., 1995), whereas cultural variations seem to influence placebo responses in anxiety disorders (Moerman, 2000). Serotonin-related gene polymorphisms have been found to influence the individual placebo response in social anxiety at the behavioral and neural level (Furmark et al., 2008), and genetic polymorphisms modulating monoaminergic tone have been related to degree of placebo responsiveness in major depressive disorder (Leuchter et al., 2009).

Regarding learned placebo responses on immune functions, state anxiety and plasma noradrenaline levels were identified as predictors for a learned placebo response in cytokine release (Ober et al., 2012) (see also section IV).

Beyond the known contribution of psychologic factors to nocebo responses (e.g., general drug sensitivity, negative drug effects in the past, anxiety, etc.), little is known about the neurobiological predictors of nocebo responses. Wendt et al. (2014a) reported more drug-specific and drug-unspecific side effects in healthy male subjects with Val/Val variations of the Val158Met polymorphisms of the catechol-O-methyltransferase gene. Their observations further confirm a link between the dopaminergic system and the occurrence of nocebo responses, as the valine genotype is associated with a 3–4 times higher catabolic rate of brain dopamine than the methionine variant (Lachman et al., 1996).
The search of predictor variables in placebo and nocebo responses remains in a very preliminary stage. Studies have often enrolled small cohorts, which might explain the heterogeneous results (Kaptchuk et al., 2008b). Furthermore, it is statistically complicated to sufficiently dissociate the contribution of state from trait variables. Finally and most importantly, we do not know whether and, if so, how placebo responsiveness in one system influences the placebo responsiveness in another; large placebo responses in one condition do not necessarily predict large placebo responses in other conditions as well (Whalley et al., 2008). A deeper and more detailed understanding of the neurobiological and physiologic mechanisms of placebo responses will help unravel the shared and distinct pathways and predictors for placebo responses across different system and conditions (Zhang et al., 2011).

VIII. Relevance and Implications of Placebo Responses

A. Randomized Clinical Trials

The use of placebos in RCTs is without a doubt necessary to develop new drugs, despite the current preference of drug-approval authorities for head-to-head trials comparing novel compounds to drugs already on the market (comparative effectiveness research [CER]). CER requires that more patients be included for noninferiority statistics (Gardiner et al., 2000). However, CER trials raise the placebo response without being able to assess it (Weimer and Enck, 2014). Some propose that future drug trials be designed as three-arm trials: the drug under investigation, a comparator (the best drug available or on the market), and a placebo (Hida and Tango, 2011). This would increase the likelihood of patients receiving effective treatment, in case of 1:1:1 randomization, to a 66% drug chance compared with conventional 50% in 1:1 drug-placebo randomized RCTs. Such “enrichment design,” however, may increase the drug and placebo responses in some conditions (depression, schizophrenia, migraine) (Diener et al., 1999; Papakostas and Fava, 2009; Rutherford et al., 2009) but not in others such as IBS (Ford and Moayyedi, 2010; Elsenbruch and Enck, 2015). At the same time, it accommodates ethical arguments that more patients require and receive effective medication (World Medical Association, 2013).

Two major critical issues arise from the use of placebos in RCTs that may also apply to CER: the risk of unblinding and the control for the spontaneous variation of symptoms.

The traditional concept to reduce between-subject data variance is the use of crossover designs that carry the intrinsic risk of unblinding because patients may identify the drug and the placebo phase by directly comparing side-effect profiles rather than effects (Boutron et al., 2006; Machado et al., 2008), whereas in parallel-group designs, this risk is much lower. At the same time, crossover studies risk results being affected by conditioning (learning) effects (Suchman and Ader, 1992; Colloca, 2014).

In the early 21st Century, RCTs occasionally employed active placebos that mimic adverse events (e.g., in treatment trials of depression) to prevent or reduce such unblinding (Moncrieff et al., 2004), and such unblinding caused by adverse events substantially determines treatment results (Rief and Glombiewski, 2012). However, overall poorer discrimination between drug and active placebo will result in larger patient numbers to prove a drug’s superiority over placebo, making them expensive. As an alternative, parallel group designs are currently the gold standard (Weimer and Enck, 2014).

Onset and offset effects may likewise enable the unblinding of study-arm allocation (Bello et al., 2014), an effect that is minimized by randomized run-in and/or withdrawal designs where patients are enrolled and/or withdrawn from active treatment with variable (but double-blinded) periods of placebo application before and thereafter, respectively (Ivanova and Tamura, 2011; Enck et al., 2013).

Another more recently reported risk for RCT unblinding are social networks where patients enrolled in the same or other studies communicate their experience. Via communicating effects and adverse event profiles of the drugs under investigation, patients may easily determine the treatment arm to which they have been allocated (Lipset, 2014). It has been suggested that rather than allowing this in uncontrolled manner, investigators should try to incorporate network communication into their patient management strategy in RCTs (Nicholas et al., 2013).

A meta-analysis of RCTs of IBS patients demonstrated that the higher overall adverse event profiles of some drugs (e.g., spasmyotics, tricyclic antidepressants) in comparison with others (e.g., local antibiotics, 5-HT3 antagonists) resulted in higher overall drug efficacy (drug minus placebo). These observations argue for studies to be unblinded—for the investigators, but not for individual patients (Shah et al., 2014), something that clearly calls for improved blinding methods, e.g., the re-implementation of “active placebos” (Edward et al., 2005; Rief and Glombiewski, 2012).

Finally, placebo responses may also be driven by pretrial beliefs in the drug being tested: In the mock informed-consent forms of three putative trials testing either an antidepressant (desipramine), a prokinetic (alosetron), or a local antibiotic (rifaximin), IBS patients expected the highest efficacy from treatments with which they were familiar (i.e., antibiotics), which the authors called a “pre-cebo” effect, i.e., preconceived notions from being familiar with the drug class (Kim et al., 2012).
To assess the placebo response in RCTs, it would be important to know how much of the overall placebo effect is attributable to spontaneous symptom variation and the disease’s natural course (Enck et al., 2013). Attempts have been made to estimate this contribution by comparing placebo controls to “no treatment controls” in trials where patients have been allocated to a waiting list. Such a comparison is quite common under conditions where a placebo control group is not readily available for methodological reasons, e.g., in psychotherapy trials. When waiting control and placebo groups are compared, about 50% of the placebo effect is attributable to spontaneous variation of symptoms, at least in the clinical conditions tested such as depression or nausea (Krogsbøll et al., 2009). However, in most cases, especially in cases of severe disease, a “no treatment” or waiting control group would be unacceptable for ethical reasons (World Medical Association, 2013). Waiting controls also develop their own dynamics; on the one hand, patients may improve while waiting because of being assured of receiving active treatment soon (Beck et al., 2015), similar to the effects seen in placebo run-in phases (Enck et al., 2009). On the other hand, it may be regarded as a punishment for patients not to be included in the active treatment condition (Furukawa et al., 2014). If waiting list controls are included, a “step-wedge” design may be superior, because it allows a “dose-response” assessment of waiting for treatment (Fig. 6) (De Allegri et al., 2008; Weimer and Enck, 2014).

Despite these complex considerations it remains crucial to assess and dissociate the spontaneous courses of disease from placebo and drug responses. The “cohort multiple randomized controlled trial” (Relton et al., 2010) is a reinvention of the “Zelen design” (Zelen, 1979) that recruits patients for a monitoring study (e.g., via a patient registry) before recruiting and randomizing a subgroup of the same patients for a placebo-controlled or CER study (Fig. 6). A number of approaches have been published (Cockayne et al., 2014). Finally, initial attempts have been made to avoid involving patients that receive placebo and instead use historic placebo controls from large trial databases (Desai et al., 2013).

Growing knowledge about the mechanisms of placebo and nocebo responses is accompanied by a number of critical consequences concerning the conduct of RCTs, of which the two discussed above are major. First, if trials are not truly blinded for both patients and doctors, the development of novel therapies is jeopardized. Second, if the natural courses of disease symptoms are not controlled, the validity of such novel therapies is questionable. Third and most importantly, knowledge about the moderating and mediating factors of placebo and nocebo responses enables us to assess, control, and homogenize these responses in a clinical trial setting and thereby promises to improve assay sensitivity. For further details regarding these strategies, see Enck et al. (2013).

**B. Training Health Care Professionals**

Given the crucial contribution of placebo and nocebo effects to treatment outcomes, health care professionals must be trained to comprehend the mechanisms of action of therapeutic interventions. Careful assessment of patients’ expectations and pretreatment experiences should be incorporated when documenting medical histories. The physician should be able to judge whether treatment expectations are helpful or dysfunctional and whether pretreatment experiences might limit the treatment response and/or make nocebo effects likely. Special emphasis must be given to patients who fulfill one of these risk factors for a suboptimal treatment response.
At present, very few psychologic interventions have been evaluated that aim to optimize patient’s expectations and to minimize the risk of nocebo development. One successful approach assessed how to optimize patients’ expectations after experiencing myocardial infarction, replicated with an additional tool targeting partners’ treatment expectation as well (Petrie et al., 2002; Broadbent et al., 2009). An optimal therapeutic relationship seems to provide a solid basis from which to benefit from placebo responses and to avoid nocebo responses (Kaptchuk et al., 2008a). Of note, even these relationship effects are becoming better understood thanks to neuroimaging: there is evidence that pain stimuli are better tolerated in the presence of pictures of sympathetic people and that this effect is associated with increased activity in the ventromedial prefrontal cortex (Eisenberger et al., 2011).

The effects of treatment value (Waber et al., 2008; Espay et al., 2015) and open applications reveal the necessity to express the expected positive effects of the intervention and to draw patient’s attention to the visible cues of open treatment applications. Finally, the role of observational learning can be used more systematically. Role models (e.g., per video clips) could be presented to patients, expressing some pretreatment concerns but then confirming positive treatment effects. These models for observational learning could be selected according to mechanisms that facilitate observational learning (e.g., similarities in age, gender, general attitudes).

The systematic use of Pavlovian learning to improve medical interventions needs further evaluation, despite initially promising results (Ader et al., 2010). The use of placebo-controlled drug reduction (Doering and Rief, 2012) in particular promises to maintain drug efficacy despite a systematic reduction in drug dosage (Albring et al., 2014). Applying effective pretreatments with low side effects is another option to further optimize patients’ treatment expectations.

In addition to optimizing treatment effects for the patient’s benefit, we now know that authentic and empathic doctor-patient communication protects from unwanted side effects. For instance, medical jargon is likely to cause misunderstandings and trigger fear in patients. A patient-centered communication style is therefore required when explaining diagnostic procedures, their results, and the rationale and implementation of any intervention (Barsky et al., 2002; Colloca and Finniss, 2012).

Nocebo research has clinical implications for the prevention of side effects. Health care professionals should be trained to offer balanced information on expected positive treatment outcome and the risk of side effects. Moreover, the patient’s own ability to cope with side effects (should they develop) should be emphasized. Although internet portals usually offer threatening information, new Web-based information systems should be developed and approved that offer valuable and accurate information (see below). Finally, if withdrawal symptoms are likely, “hidden withdrawal” procedures could be used to minimize negative expectation effects (for further recommendations, see Colloca and Finniss, 2012; Bingel, 2014).

Taken together, knowledge about placebo and nocebo responses and their underlying mechanisms should be integral elements in the curricula for health care professionals. Furthermore, possessing the skills to maximize placebo responses while minimizing nocebo responses is essential from a clinical application perspective.

C. Health Care System

The past decades have seen groundbreaking advances in the development of new diagnostic tools and treatments. However, this progress has also led to increased specialization and shorter consultation time and thus to frequently low therapeutic alliance due to an inadequate doctor-patient communication, as reflected in the report that in the United States, 50% of patients leave their doctor’s office without having adequately understood what their physician told them (Bodenheimer, 2008). In addition, patients explaining their problem to a physician were interrupted after an average of 23 seconds (Bodenheimer, 2008); similar numbers have been reported for primary care practices in European countries (Deveugele et al., 2002). These disturbing findings are certainly not due to uncommunicative practitioners in general but because doctors are often overstressed by having to see too many patients in too little time. In addition, medical care compensation systems such as the “diagnosis-related group” raise pressure on clinicians by often leaving them with too little time for adequate doctor-patient communication. Serious communication takes time, which calls for a fundamental reorganization of reimbursement structures in medical care to significantly upgrading the time spent communicating with the patient.

In addition to improving the basic conditions for adequate communication, improved patient information systems such as drug information leaflets (package inserts) should be designed to reduce negative expectations regarding unwanted treatment side effects (Bingel, 2014). At present, all potential adverse events must be listed for legal reasons and in standardized terminology, although the empirical evidence of a causal link between drug and unwanted side effects is notoriously weak. Instead, lay and patient-oriented language and the description of positive and unwanted effects should be an integral part of any information leaflet. This should include ways to convey abstract information (such as the probability of the occurrence of side effects) in an intuitive fashion—a future challenge for the drug authorities.
Harnessing placebo mechanisms strategically within health care systems promises to fundamentally improve the effectiveness of treatment strategies by optimizing drug treatment regimens, drug efficacy, drug adherence, and the context characteristics within the overall medical setting. Ultimately, these approaches should lower health care costs and improve patient care.

IX. Placebo Research: What Next?

The advances during the last two decades in our understanding in the neurobiological and neuropsychological mechanisms of placebo and nocebo responses have been made possible by the employment of sophisticated experimental designs and tools, such as neuroimaging, in vivo receptor binding, and single-neuron recording in awake subjects and patients. However, our knowledge about the mechanisms underlying these responses remains limited and several key issues need to be addressed in future research. We have to learn which medical conditions and physiologic systems are affected by which placebo mechanisms and whether these effects are clinically relevant. For example, somatic placebo analgesia can be mediated by cognitive factors such as patients’ expectation about a treatment’s benefit, as well as by associative learning processes (Colloca et al., 2008; Tracey, 2010a; Colloca, 2014), whereas visceral placebo analgesia seems less responsive to conditioning. In contrast, neuroendocrine or immune function appears to be affected primarily by conditioning and not by patient expectation (Wendt et al., 2014b). We also need to discover when placebo and nocebo responses occur and to analyze the specific situational circumstances and patient characteristics that are particularly amenable to placebo or nocebo responses (Kaptchuk et al., 2008b). This knowledge about genetic and/or psychologic predictors will form the basis from which to exploit placebo responses and avoiding nocebo responses in daily clinical routine.

How placebo responses work remains a key issue, because we need to better understand the brain mechanisms at both the macroscopic level (in particular, the brain regions and their interactions with peripheral physiologic functions), as well as on the microscopic (cellular and molecular) levels involved. The data demonstrating that placebo responses can affect pharmacological treatments introduces fascinating clinical perspectives. It will be important to better understand the interactions between placebo mechanisms and pharmacological effects to exploit this phenomenon in daily clinical care for the patient’s benefit.

Similarly, thorough knowledge of the basic mechanisms steering the behavioral conditioning of pharmacological responses will be essential, not just to better understand the brain mechanisms involved in these learning processes but especially to achieve the long-term goal of learned pharmacological responses: to employ these learning paradigms in clinical situations as supportive therapy together with standard pharmacological regimen, the aim being to maximize the therapeutic outcome (Doering and Rief, 2012; Wendt et al., 2014b). Finally, another fascinating scientific question is why did placebo responses develop during evolution (Kaptchuk, 2002, 2011)?

X. Conclusion

Placebo and nocebo responses are mediated by expectations, associative learning processes, and the quality of the patient-physician interaction. They modulate fundamentally symptom perception, the course of diseases, and the efficacy and tolerability of medical treatment. Converging evidence from experimental and clinical studies has demonstrated that these positive and negative effects on health outcomes are based on complex neurobiological phenomena involving the contribution of distinct CNS as well as peripheral physiologic mechanisms.

Recent insights into the psychologic, neurobiological, and peripheral-physiologic processes underlying placebo and nocebo responses provide the unique opportunity to systematically modulate these responses depending on the context in which they occur. In clinical care, the systematic use of placebo mechanisms is a promising target to improve health outcomes. In the context of RCTs, placebo and nocebo responses represent a substantial risk of bias that hampers drug development and assay sensitivity. Strategies to homogenize and control placebo responses and to prevent nocebo responses in a strategy-based manner promise to improve drug development by increasing the sensitivity to detect drug-specific effects and improve the efficacy and tolerability of drug treatment regimens, drug adherence, and context characteristics within the general medical setting.

The full potential of these strategies critically depends on continued characterization of the neurobiological and peripheral-physiologic mechanisms underlying placebo and nocebo responses and, importantly, identification of the predictor variables that influence an individual’s placebo and nocebo response in a context- and disease-specific manner. This knowledge will build the foundation for the exploitation of placebo and nocebo responses based on mechanism-based and personalized clinical decisions.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Schedlowski, Enck, Rief, Bingel.

References

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