Psychobiological mechanisms of placebo and nocebo effects in antidepressant trials

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Abstract

Antidepressant treatment is going through a major paradigm shift. Conventional pharmacotherapies show to be less effective than was initially thought, whereas the interest in two other influences steadily grows: that of placebo and nocebo effects. Over the years, these phenomena have outgrown their reputation as a hazard to depression research and developed into valuable research focuses on themselves. The present literature thesis describes where contemporary neuroscience stands in the identification of the psychobiological systems that underlie placebo and nocebo influences in treatment of depression, and how these findings can implicate research, clinical trials and clinical practice. The findings show that placebo and nocebo mechanisms are characterized by prefrontal activation patterns, as well as molecular mechanisms that appear sensitive to cognitive modulation. The latter include the dopamine reward system and hypothalamus-pituitary-adrenal (HPA)-axis activity, which seem to exert a cross-over influence on each other. The placebo and nocebo mechanisms not only closely correspond to conventional, but particularly to newly hypothesized biomarkers of depression itself. This implies that the effects of expectation that are currently framed as placebo- and nocebo-related, in fact reflect the cognitive character of depression itself. Such a theory would explain both the robust placebo- and nocebo effects in depression treatment and the modest efficacy of current antidepressants. Furthermore, this literature study showed that the current randomized placebo-controlled trial (RCT) design may have flaws on many levels. Most importantly: it fails to isolate the genuine placebo effect and it adopts the invalid fundamental assumption of the additive model. New designs are needed to investigate the expectancy component of antidepressant treatment. As for the clinical practice, physicians and clinicians must become aware of their responsibility to improve treatment success. Besides exploiting the therapeutic strength of the placebo effect, a significant improvement can be made with preventing its counteracting nocebo influences.

Key words: placebo mechanisms; nocebo mechanisms; depression; expectancy; neuroimaging; HPA-axis; reward expectation;
Introduction

In clinical trials with antidepressants, the pharmacological effect of a drug is tested against a ‘control group’ that receives placebo treatment. This so-called randomized placebo-controlled trial (RCT) design is still the most commonly used model in depression studies. However, this design has serious flaws\(^1\). The scientific belief grows that current antidepressants are not as effective as was once believed, and that instead, the placebo effect could be responsible for a significant part of antidepressant treatment outcome in clinical trials\(^2\). A second strong modulator of treatment outcome is the less known, negative equivalent of the placebo response: the nocebo effect\(^3\).

The aim of this literature thesis is to describe where contemporary neuroscience stands in the identification of these two mechanisms that are of great influence for the success rates of antidepressant treatment. In order to provide a most complete overview, this thesis should discuss the two research themes that together seem to embody the total amount of neuroscientific placebo and nocebo studies in the context of depression. The first theme in research comprises neuroimaging studies, which attempt to measure those brain alterations during the time course of antidepressant trials that can be specifically correlated with placebo and nocebo mechanisms. Recent theories propose that these expectation-driven phenomena act on the same pathways that are targeted by pharmacological agents\(^4\). I will investigate to what extent imaging results confirm this theory. The second research theme involves a molecular approach, and explores how anticipatory anxiety and reward expectation relate to manipulations of neurotransmitter systems. It is a novel approach to try and make the connection between these two research lines, and subsequently compare these therapeutic effects of the placebo response with those of its counteractive nocebo response. This would shed more light on the mysterious relationship between these two phenomena: is nocebo just the flip side of the placebo mechanism, or has it a distinct mechanism\(^5\)? The fact that there are evident shared statistical characteristics in clinical outcomes of placebo and nocebo effects\(^6\), implies that this comparison is worth a study.

Another important research focus is to establish both shortcomings and potentials of current placebo and nocebo research in clinical trials that investigate antidepressant treatment. On the one side, we have to know by which factors current research is limited and constrained. Also, it is important to recognize which potential this field has to implicate clinical trials of antidepressant research. The latter point comprises three topics. In the first place, the relation to biomarkers of depression itself. This might shed light on the explanation why placebo and nocebo responses are so robust in antidepressant trials. Second, it should provide a careful assessment of the current RCT that currently is the primary source for both placebo and active treatment results. Third, it might provide valuable information that can be translated into clinical practice. For example, fruitful patient-clinician relationships can stimulate placebo responses and prevent nocebo reactions. This literature thesis provides an overview of where contemporary neuroscience stands in the identification of the psychobiological mechanisms that underlie placebo and nocebo effects in antidepressant treatment. Analysis from a neuroimaging and molecular perspective provides a more complete overview of the underlying therapeutic nature of these effects, and implicate research focus, clinical trials and clinical practice.
Research questions:

I. What are the psychobiological mechanisms of placebo effects in antidepressant treatment?
II. What are the psychobiological mechanisms of nocebo effects in antidepressant treatment?
III. How can these insights contribute to the improvement of research, clinical trials and clinical practice of antidepressant treatment?

RESEARCH QUESTION I
Psychobiological mechanisms of placebo effects in antidepressant treatment

Placebo effects represent all positive ‘non-specific’ effects on clinical outcome that are related to the therapeutic environment and that cannot be explained by the ‘specific’ nature of the medical intervention. The mysterious effect of this phenomenon is triggered by the patient’s expectancy of clinical benefit. Since the 1960s, antidepressant clinical trials make use of this contextual character. The RCT has been created to test the pharmacological effects of a drug against a ‘control group’ that receives placebo treatment. Subtracting the clinical benefit of placebo receivers from that of the specific treatment gives the true effect of the drug. For a long time, results showed superiority of antidepressant treatment over placebo. However, Kirsch provided a major challenge to this assumption by showing that pharmacotherapy has only modest benefits over placebo treatment. Moreover, the inclusion of unpublished trial data in this analysis showed that drug benefits even fall below significance levels. This breakthrough has led to shifts in depression research. First, the understanding developed that antidepressants are not as effective as once thought. Second, Kirsch created the modern interpretation of the RCT: the small difference between the two groups is not due to ineffectiveness of the antidepressant per se, it is because of the strong placebo response that occurs in both groups. Meta-analysis showed 50 percent of clinical improvement is an effect of placebo, while 25 percent is due to pharmacological treatment and 25 percent to spontaneous remission. Over the years, compelling evidence confirmed that the therapeutic context is a remarkably strong influence on treatment efficacy: 30 to 50 percent of patients significantly improve after sham treatment, against a remission rate of 45 to 70 percent after receiving pharmacotherapy. Recent findings even show that drug efficacy does not go beyond 30 to 50 percent.

The ‘antidepressant placebo effect’ is very robust compared to other placebo conditions, independent of which therapeutic strategy is used. An explanation for this would be that in depression, patients are particularly responsive to expectancy effects, since hopelessness, as a central feature of depression, is on itself a function of expectancy. This implies that clever modulation of these expectations can offer the key to remission. It is evident that this phenomenon in depression needs further investigation. However, such studies have hardly been performed, due to methodological challenges in this field. Placebo research in other conditions, like pain analgesia and Parkinson’s disease, can be studied by means of short-term designs that exert only a single manipulation to investigate the placebo response. The time course of antidepressant trials however, involves multiple weeks and thus does not allow for such manipulations. Until now, only neuroimaging studies have adapted to this long term time course research that aims to identify brain mechanisms that correlate with placebo remission.

I adopt a novel approach that looks for new insights and theories of the placebo effect in
depression. For this, I include specific characteristics and the ones that can be ‘borrowed’ or translated from other placebo conditions. The specifics involve two research topics: the theories on the psychosocial context of depression, and the brain mechanisms that are obtained by neuroimaging studies. Translational aspects are those that come from molecular studies that manipulate placebo effects in other conditions. The novel approach is to make the connection between these two research lines by integrating and translating their research results and theories in the context of depression.

This overview starts with the qualitative, psychosocial mechanisms that mediate the neurobiological mechanisms, which are provided in section 1.1. Section 1.2 describes results on a neuroimaging level, followed by the molecular measures of placebo effects that are given by section 1.3. Section 1.4 reports the obstacles, shortcomings and bias of current depression-specific placebo research that were encountered during this literature research on placebo responses.

1.1 Psychosocial mechanisms

The psychosocial concepts of placebo effects were initially defined in studies of analgesia, and later in studies of symptom relief in parkinsons’s disease\(^\text{16}\). Expectation and conditioning are the two most important factors that also relate to the placebo response in general\(^\text{4, 17}\). Expectation generally describes the patient’s belief in the success of treatment outcome. In short-term placebo designs of analgesia and Parkinson’s disease, it is regarded to be consciously accessible\(^\text{18}\). Conditioning represents a person’s prior lifetime learning experiences that relate to the upcoming treatment, as well as the observation of that of other persons in similar situations. Other than for expectation, conditioning influences are generally considered to go beyond cognitive factors like attention, and thus to be subconscious\(^\text{19}\). These systems not mutually exclusive: expectations are framed by prior learning experiences\(^\text{20}\).

Despite this clear integration, these two concepts are still pitted against each other in literature. As for the antidepressant placebo effect, this evidently challenges research conduct and results in conflicting results. Future studies must evidently prevent this pitfall\(^\text{17}\). But which novel concepts can provide the solution to do so? First, we must explore how expectations, as an adaptive cognitive advantage, can facilitate increased response to sham treatment\(^\text{17}\). For this, novel psychobiological concepts are needed that are highly translational to neurobiological research. Concepts which’ contribution can explain placebo responses across conditions and treatments, but also for each condition specifically\(^\text{3, 17, 18}\). Only very recent reviews recognize the most comprehensive theory\(^\text{10}\). The placebo response seems directly mediated by two opposite psychobiological mechanisms of expectation: anticipatory anxiety and reward expectation. The degree to which these are experienced by the patient are partly based on prior learning experiences that are derived of the psychosocial treatment environment, which entail reinforced expectations, social learning and conditioning effects\(^\text{10}\).

*Reward expectation and anticipatory anxiety*

Compelling evidence shows shared cognitive mechanisms for placebo effects across diseases, representing the conscious and unconscious self-regulation of affective states\(^\text{10}\). However, these are
known to result in different effects for each specific placebo condition: from physiological pain alleviation in analgesia to elevated dopamine transmission in Parkinson’s disease, and remission in antidepressant trials. A comprehensive view on how these shared cognitive mechanisms still result in heterogeneous outcomes for each condition is given by Haug. The key assumption, he says, is that shared expectation mechanisms trigger different descending pathways and therefore result in very different biomarkers of placebo and nocebo responses. This makes placebo effects seem to be more heterogeneous than they actually are\textsuperscript{21}. In other words, these ‘upstream’ placebo mechanisms of anticipatory anxiety and reward might be similar across diseases, but were initially difficult to recognize since the ‘downstream’ processes are so different.

The growing agreement among neuroscientists is that these upstream placebo mechanisms are measures of reward expectation and anticipatory anxiety that are shown in all conditions\textsuperscript{4, 10, 15, 22} and that explain results on a neurobiological level. In the context of depression, this makes sense. Upstream self-regulating mechanisms are already proposed to trigger the antidepressant placebo effect\textsuperscript{19}. Reward expectation (i.e. anticipation to clinical benefit) is considered to be a direct mediator of positive expectations and thus to improve treatment outcome. This ‘placebo-reward model’\textsuperscript{16} now is a generally accepted paradigm that originated from neuroimaging studies\textsuperscript{10, 16, 23, 24}. As the negative opponent of reward expectation, a patient’s anticipatory anxiety is shown to be inversely proportional to placebo robustness\textsuperscript{4}. Over the years, its involvement has shifted from only the antagonizing influence on placebo, to a direct mediation of nocebo responses; a development I will explain during section 2.1 while discussing nocebo mechanisms. That this took a while to realize, might be related to the relatively unknown character of the nocebo response.

The very key to understand how reward and anxiety determine treatment outcome as a function of placebo or nocebo effects seems to lie in the acknowledgement that these mechanisms, besides triggering their own specific mechanisms, also exert crossover influences on each other. Although this is an overarching conclusion that can be deduced from literature but is hardly phrased explicitly, it seems crucial for an accurate interpretation of results. In antidepressant treatment, a person’s positive reward expectancy intrinsically means that susceptibility to harmful nocebo experiences is reduced. The other way around is when a patient anticipates to negative treatment outcome, high rates of anticipatory anxiety do not allow for reward expectation, thereby preventing that the additive effects of positive expectation can facilitate additive effects of placebo outcome. The following two sections address how reward expectation can strengthen and anticipatory anxiety can reduce the placebo effect. This is approached from both a neuroimaging and molecular perspective\textsuperscript{24}.

1.2 Cues from neuroimaging studies

Already in 2002, imaging studies started to focus on the antidepressant placebo effect, allowing it to become a research focus on itself. These studies search for cortical and subcortical activity patterns that are specific for the expectancy-driven placebo effect during the time course of clinical trials. Most used imaging tools are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Some cues are obtained by electroencephalography (EEG), transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). Differences and similarities of brain activation patterns are compared between patient groups that have received either placebo or specific
pharmacological treatment. The results are quantified in correlation units that indicate the strength of the connection between conditions, but do not contain information of causality and can thus not predict.

I will discuss only those neuroimaging findings that are considered reliable, robust and least unambiguous. Engaging in an in-depth and time consuming analysis will not add relevant conclusions\textsuperscript{19, 25}, since validity and reliability of these detailed activation patterns can be seriously questioned\textsuperscript{1}. That is because they are subject to many experimental limitations and biases, all of which I will discussed in section 1.2.1 and section 1.4.

To investigate how the antidepressant placebo mechanisms might resemble those of active treatment, one must first globally understand which activation patterns and brain areas are associated with clinical benefits. Depression remission is generally associated with the strengthening of prefrontal inhibitory projections over limbic-paralimbic (cingulate, amygdala and insula) and subcortical (striatum, thalamus and brain stem) functioning\textsuperscript{19, 26}. The best replicated finding is that of normalization of frontal activation patterns, which is found across treatments: from psychotherapies and antidepressant medication, to TMS and DBS\textsuperscript{19}. Modern neuroscience beliefs that a significant part of these mechanisms are related to the cognitive state of a person: meaning that the same activation patterns must also be found in placebo groups\textsuperscript{19, 27}. Indeed, the best replicated result in both placebo and active treatment groups is that clinical benefit is correlated with prefrontal normalization patterns\textsuperscript{19}. That these patterns do not significantly differ is, moreover, shown by the fact that even after ten years of imaging research on the antidepressant placebo effect, studies have not managed to come up with major differences between placebo and active treatment evoked activation patterns\textsuperscript{25}. This confirms that the expectancy component between these groups will be responsible for the major part of these prefrontal changes.

This assumption is consistent with findings that go beyond the context of depression, i.e. placebo responses in analgesia and Parkinson’s disease. Compelling evidence shows shared involvement of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dIPFC)\textsuperscript{28}. Faria et al. assume that given their nonspecific character, this might relate to the anticipation of positive and negative affective states in general, and therefore to both conscious and unconscious mediation of reward expectation\textsuperscript{25}. A more recent fMRI study of the same group adds that anxiety-relief is also necessary for establishment of the placebo effect\textsuperscript{27}. However, there remain many inconsistencies concerning the exact parts of these structures that are involved, and the direction of the activity changes. This might again, at least partly, result from design limitations that will be discussed later.

Integrating these findings with the psychosocial concepts of the placebo response that I discussed in the previous section, suggest as explanation that placebo responses are created by a person’s expectations and anticipation to the belief of receiving treatment, a process primarily mediated by the prefrontal cortex. Reward expectation and anticipatory anxiety and seem to be mediators of this prefrontal expectation mechanism. The next question is: how do these prefrontal pathways descend and influence subcortical pathways? This placebo pathway is less easily transferable from other placebo conditions, and still poorly understood. Neuroimaging studies that investigate this particular topic have often included molecular measures in their imaging designs. These imaging findings advocate that direct activity of mesolimbic pathway and the counteracting influence of HPA-axis activity together determine the magnitude of the placebo response. A crucial finding is that the systems that regulate this activity patterns, are directly activated or deactivated by
reward expectation and anticipatory anxiety.

**Reward expectation**

It can be hypothesized that also in antidepressant treatment, clinical improvement (i.e. reward) induces the placebo response by activating the reward circuitry. The 'placebo-reward' mechanism is the first paradigm that explains the general, psychobiological process of reward expectation across placebo conditions. It involves neuronal pathways that relate cognitive, emotional and motor processes to form an integrated response that is also known to underlie the motivational pursuit of natural, monetary and drug rewards. Already in 2001, a study on Parkinson's disease hypothesized that dopamine release in the nucleus accumbens of the ventral striatum was related to a patient’s positive expectations of treatment outcome, and indeed, a common expectancy component is now agreed upon to act across diseases. In 2002, the first PET study on the antidepressant placebo effect showed that increased activity of the ventral striatum and OFC predicted whether someone would turn out to be treatment respondent, either to fluoxetine or placebo. In addition, Scott et al found that placebo and nocebo effects in a pain challenge can be directly evoked by manipulating dopamine release with dopamine agonists and antagonists. People that were sensitive for monetary reward, also experienced high placebo responses. This study also measured cortical activity: placebo mechanisms were related to OFC, insular cortex, nucleus accumbens and amygdala.

**Anticipatory anxiety**

Imaging research also shows that anticipatory anxiety is needed to create placebo responses, and that placebo induces relief of anticipatory anxiety. Although the causal chain remains unspecified, it is inevitable to conclude that anticipatory anxiety and the placebo effect are strongly and inversely related. That the placebo effect is induced by anxiety reduction has been shown in both objective and subjective measures, i.e. as activation of prefrontal and subcortical brain areas that are involved in expectation and processing of emotional stimuli, and as the participant’s subjective appraisal of emotional processing after treatment. In 2005, Petrovic et al. showed that anticipatory anxiety directly antagonizes the placebo response in emotional disturbance when processing affective stimuli. First, they showed that the benzodiazepine midazolam and its antagonist flumazenil can increase or decrease the placebo effect, respectively. Second, and crucial, they showed that the expectation component of getting anxiolytic or anxiogenic drugs can is essential for the drug to exert its effect. That is, when subjects anticipated to getting midazolam but instead got placebo, large placebo responses were obtained. The other way around was also observed: anticipatory anxiety can counteract the anxiolytic drug effect almost completely. Hence, when subjects thought to get placebo before getting the emotional stimuli but actually got midazolam, the placebo effect was completely diminished. Anxiolytic effects of placebo treatment were correlated with increased cerebral blood flow in the OFC and ACC. These activations translated to the subjective report of reduced emotion. For a long time, this was the only imaging study that directly investigated the placebo effect in emotional processing. Although it provided interesting results, its short term time course is not representative for the multi-week process of depression remission.

The follow-up study of Zhang et al. attempted to separate transferable anxiety-reducing placebo effects from condition-specific characteristics of pain analgesia. They showed that transferable mechanisms were indeed characterized by significantly increased activity in the caudate
head and the ACC and reduced activity in the amygdala and insula. Zhang et al. briefly speculate that reward-expectation might have a key role in relief of anxiety-induced placebo effects. Thereby, it is the first study that explicitly advocates the cross-over effect of these two concepts that I hypothesized before.

1.2.1 Shortcomings of neuroimaging studies on the placebo response

Creating the above overview needed assessment of many, often contradicting results. There is great variance in (prefrontal) structures that are reported to be involved, as well as in the nature of these normalization procedures. These can be the result of intrinsic limitations of neuroimaging tools. Next, there are biases that result from either intended manipulations of the experimenter or intrinsic weaknesses of the experimental design, i.e. of the RCT. Those that strongly relate to neuroimaging studies will be discussed below. More general RCT limitations will be discussed in section 1.4 and during section 3.2, since prevention of these must be a driving force in the search for new methodological designs. Klosterhalfen et al. claim that as long as the biases in imaging studies are not ruled out, these technologies will not facilitate progress in placebo research.

Intrinsic limitations of neuroimaging studies

Intrinsic properties of neuroimaging research constrain the measurement of individual response to placebo. The primary weakness and source for variance is that few studies controlled for individual resting state activity levels. Chiesa et al. showed that selection of those studies that did, resulted in more consistent, reliable results. Second, neuroimaging results are only significant above threshold significance, i.e. when they reflect stable and robust activation patterns that are shared across subjects. This makes it inevitable that smaller, more variant and perhaps more meaningful patterns are overlooked. Third, and related to the previous flaw, algorithms that are largely used depend on subjective choices of the experimenter. For example, the choice to perform a region of interest study or whole brain analysis. All these shortcomings make that alternatives outside the imaging world, i.e. molecular/ pharmacological studies, may have more potential to create scientific progress.

Problems with the RCT and placebo imaging

When neuroimaging research tries to identify brain mechanisms that are specific for placebo treatment, they focus on those activation patterns that are specific for placebo groups, compared to active treatment groups. This is a complete misinterpretation. The placebo response occurs in both placebo and active treatment groups, since it is simply a function of the expectation component that is evoked by getting treatment. Whether this is sham or active treatment, patients do not know. Thus theoretically, its magnitude is equal in both groups. Researchers seem to forget that the RCT is developed for and thus measures the effect of a pharmacological agent compared to placebo treatment. Hence, the only interesting differences in brain activations between the two groups are those induced by pharmacological change brain activations, and these are specific for the treatment group. It is remarkable how most neuroimaging studies over the last ten years seem to forget this.

Since the placebo effect is thus captured in both arms of the RCT, isolating its genuine
character needs adjustment of the study design. Creating differences in the expectation component and therefore manipulating the placebo response would need inclusion of a patient group that receives no treatment. This is easier said than done: the many problems and few possible solutions for this change are discussed in section 3.2, which deals with improvements of clinical designs.

1.3 A molecular approach

Molecular studies embody the second research approach to investigate placebo responses. These have the potential to not only correlate, but also to manipulate and predict the placebo response on a molecular level. Most are performed for analgesia and Parkinson’s disease, with a minor extension to studies that explore the placebo effect of emotional processing. As mentioned before, the short time course of these designs allows for direct molecular manipulation, whereas the multi-week time course of depression remission does not. Transferring these studies’ findings might thus be speculative, but nevertheless provide general mechanisms that are likely to underlie the antidepressant placebo effect as well.

Already in 2003, Benedetti et al. found that subconscious cognitive mechanisms are related to endocrine changes in analgesia. From that point on, compelling evidence supports the idea that a person’s expectation of getting treatment can trigger a cascade of molecular changes. These studies make clever use of agonists and antagonists to manipulate the neurotransmitter systems that may mediate placebo responses. I will provide an overview of which neurotransmitters were subject to such interventions, starting with the major one and from that starting point, discussing its influencing side-effects. It is important to keep in mind that despite this separated listing, their function is intensely integrated.

**Gamma-aminobutyric acid (GABA)**

The involvement of GABA in the placebo response is evident. It is a primary focus of pharmacological manipulations that investigate the placebo effect, in analgesia, Parkinson’s disease and emotion regulation. These studies use benzodiazepines and their antagonists, which are modulators of the GABA-A receptor, to decrease and increase anticipatory anxiety. As I discussed before they directly modulated the placebo effect. Therefore it is very remarkable that the same studies do not explicitly recognize GABA as an important modulator of the placebo response. The few placebo studies that mention GABA explicitly, do this only briefly and in combination with glutamate. The latter compound mediates more closely investigated neuronal pathways, like the dopamine reward system. Therefore I will now explicitly advocate the involvement of GABA.

Already in 2003, Benedetti et al. showed that the strong anxiolytic effects of diazepam can be completely eliminated when patients are unaware of this compound being administered. Also, when a patient anticipated to receive diazepam but actually got placebo, this resulted in large placebo effects in the processing of emotional stimuli, accompanied by the participant’s subjective anxiolytic report. This means that the expectation of getting this drug is a crucial mediator for experiencing its benefit, i.e. that its transmission is a function of cognitive modulation. However, the specific mechanisms that it targets were not yet identified, since GABA , together with glutamate, constitutes the vast majority of neurotransmission in the human brain.
In 2006, the breakthrough came. GABA agonists appeared to reduce both experienced anticipatory anxiety and to antagonize HPA-axis activity, which resulted in larger placebo responses. The activity of the HPA axis seems to be boosted by negative expectation, and is now considered to be a direct mediator of the nocebo response, instead of the placebo response. So, more specifics of this stress system will be discussed in section 2.3, when addressing molecular systems in nocebo responses.

GABA is also explicitly mentioned as a modulator in the placebo-reward theory. When an environmental clue is given (i.e. a verbal suggestion by the experimenter) that creates the possibility of reward (i.e. therapeutic benefit), cortical mechanisms are activated that project to the ventral tegmental area (VTA), which include both glutaminergic and GABA-ergic efferents. Later, when the ventral striatum projects back to the prefrontal cortex, is this again modulated by GABA.

Serotonin
Benedetti et al. showed that elevated serotonin levels stimulate the placebo response and counteract the nocebo response in pain experiments and Parkinson’s disease. In this study, healthy subjects expected to be treated with the 5-HT1B/1D agonist sumatriptan. The enhanced serotonin activity also increased growth hormone (GH) levels and decreased cortisol secretion. When these patients received placebo, this appeared also to significantly increase GH and inhibit cortisol secretion. A clue that implies serotonin’s involvement in HPA-axis activity. This is consistent with theories of Goldapple et al., who advocate that serotonin might modulate a person’s expectations on a prefrontal level, and that these expectations trigger more downstream neurobiological pathways that induce the placebo response.

In 2005, Benedetti et al. analyzed those neuroimaging results of Mayberg et al. that showed shared prefrontal and subcortical brain mechanisms between placebo and fluoxetine responders. As an explanation for this congruency, Benedetti suggested serotonergic neurotransmission might mediate those mechanisms of the antidepressant placebo effect that he calls ‘self-regulatory’. In other words, the general circuit that mediates the voluntary, or cognitively controlled, regulation of affective responses. Later, he offers two theories on the causal chain of events. Either serotonin reuptake inhibition may be involved in the antidepressant effect produced by placebo, or serotonin reuptake could be involved only in those brain regions that are affected by fluoxetine. In other words, serotonin could either be involved in placebo mechanisms, or it could simply be a coincidental correlation that emerged from Mayberg’s clinical design which compared placebo responders to fluoxetine responders. With the knowledge we have now, the latter seems unlikely. An elaboration on this view I will give in section 3.1. Unfortunately, there is still no follow-up that gives an answer to the Benedetti’s theory, since molecular studies are still not performed in the context of depression, leaving the role of serotonin in the antidepressant placebo effect unsolved.

Dopamine
In the previous section, I discussed how PET studies have come up with the ‘placebo-reward’ theory that acknowledged involvement of dopamine in the placebo response. The mesolimbic dopaminergic system seems to be an important mediator of expectation-driven molecular systems that are also key characteristics of depression: motivation, emotional response and reward. Research agreed that these affective states can be a function of the therapeutic environment.
In 2004, placebo administration of the dopamine agonist apomorphine was shown to mimic its active drug effect, and thus suggested that dopamine can somehow be cognitively modulated. Colloca tried to extrapolate these findings for Parkinson’s disease patients to a clinical context. Would this imply that when people have prior experience with similar symptoms, a conditioned response can be evoked? Scott and Stohler used both dopamine agonists and antagonists to show that expectancy is a direct function of dopamine manipulation. In fact, as for modulating GABA transmission by benzodiazepines and their antagonists, dopamine modulation seems to be bidirectional: dopamine has a direct relationship with the strength of the placebo response, whereas it can also decrease the placebo response.

1.4 Bias in placebo research

There are many factors that influence and confound the assessment, report and comparison of the genuine magnitude of the placebo response in the depression context. The very diverse nature of these limitations can be subdivided in three clusters: bias by natural course of disease, bias as a consequence of the RCT design, and bias in subjective report of depression remission.

Natural course of disease
Depression research ought to control for the natural course of disease, or spontaneous remission, which is a substantial influence on treatment outcome. Generally, patients are recruited or subscribe for a clinical trial during their peak intensity of their depression. This means that independent of treatment, people are likely to improve anyway. Therefore, spontaneous remission is expected to be a ‘silent contributor’ to placebo responses. Trials would only distinguish spontaneous recovery ratings from the genuine placebo effect by including a no-treatment group. Meta-analyses of Kirsch et al. first estimated 75 percent of clinical benefit to result from placebo-related expectations, leaving 25 percent to the effects of antidepressant drugs. Later, the same authors corrected their own measures, now recognizing that around 25 percent of clinical improvement is a function of spontaneous remission, against 50 percent caused by the ‘genuine’ placebo effect and 25 percent of pharmacological treatment.

Flaws in the RCT design
The RCT design creates a platform for both intentional and unintentional violations of sample homogeneity, which decreases reliability and generalization of results. Randomization is often purposely violated by experimenters who wish to create a more homogenous group, evidently with the aim to improve statistical power of results. For example, studies that aim to show antidepressant superiority over placebo consider placebo-responders a hazard. Meta-analyses show that between 1980 and 2000, many studies have adopted the placebo run-in phase, in which placebo responders are withdrawn from a trial before random assignment to the treatment condition, a procedure that is also called placebo wash-out. Transparency of results is obstructed since many studies do not describe both their subject selection criteria and the number of subjects that dropped from the trial due to early placebo response. Besides these intentional selections in what ought
have been randomized subject groups, there are also unintentional developments that require attention. An evident development through the years is that people with mild symptoms are more often included in depression studies: a group that responds relatively well to placebo, but less to antidepressants\(^8\), \(^{13}\), \(^{44}\). This is also a group which is more prone to spontaneous remission (reference\?). All of these biases call for a uniform, consequent approach that determines which patients are to be ex- and included in clinical trials.

**Subjective report of depression remission**

The subjective report of patients that measures treatment outcome and thus determines treatment success, is a sensitive target for distortion. Since treatment outcome is assessed by qualitative measures of depression severity, usually the Hamilton Depression Rating Scale (HDRS)\(^{42}\), its report can be seriously biased. Two major themes stand out. First, the rating of changes in depression scores after treatment differs substantively between self-rating reports of patients and observer ratings\(^3\), \(^{45}\). This remarkable observation is also called the investigator related expectation pattern or observer bias. This observer bias also underlies a phenomenon that is framed by the slightly ironic name of the ‘publication year effect’: the report of placebo effects in antidepressant trials over the years has grown steadily, while experimental design has stayed the same\(^1\), \(^3\), \(^{46}\). This increase is probably the result of the placebo effect becoming more accepted as a research focus, instead of being just a hazard for antidepressant research. Rief et al. investigated a large bulk of antidepressant trials between 1980 and 2005 and concluded that the publication year effect was only observed when the primary outcome of depression rating was assessed by the observer instead of the patient itself. Clearly, there is a need for objective outcome measures for subjective report\(^3\), \(^{10}\), i.e. a generic assessment of side effects scale (GASE): structured assessment of side effect reports that combines patient and observer ratings for the most valid and reliable results\(^3\).

Second, also from a patient’s perspective there is bias. The magnitude of experienced placebo effects is proportional to a person’s tendency towards optimism and social desirability\(^{40},^{47},^{48}\). Also, pessimists are more prone to nocebo effects\(^{48}\). Geers et al. claim that these dispositional factors must be considered in placebo research, since they may moderate the major individual differences in placebo experience.

**RESEARCH QUESTION II**

**Psychobiological mechanisms of nocebo effects in antidepressant treatment**

The nocebo effect embodies the negative equivalent of the placebo response. The phenomenon remained unknown for a long time, since negative expectations were initially thought to just reduce placebo robustness. From the 1980s, it became clear that negative expectations can be held responsible for the development of side or adverse effects that cannot be explained by the pharmacological ingredients of treatment itself\(^5\). Just like for placebo, nocebo effects are a direct function of the therapeutic environment that accompanies an intervention, and causes significant
reductions of treatment effect, observed for both placebo and active medication. Fifty to sixty percent of patients in antidepressant trials report side effects, of which fifteen to twenty-seven percent discontinue treatment. Barsky et al. advocate that the far majority of these side effects is not drug-related, but rather results from the somatic consequences of emotion or psychosocial stress due to anticipation of getting treatment. Adverse effects are the main cause of non-adherence to treatment or even discontinuation of medication: a quarter of this occurs in the nocebo group that received placebo treatment. These remarkable findings show that anticipatory anxiety can have a tremendous effect on physiological sensations. Even apart from the report of side and adverse effects, the absence of belief in a therapy has strong effects on whether its eventual success. This is reflected by the fact that coercive treatment is often not effective. Also, patients who have indicated to prefer alternative treatment over antidepressant treatment, showed reduced treatment response. Lastly, repeated poor response to previous treatment is known to result in lower placebo response to a novel intervention: these persons are apparently already anticipating a similar outcome.

Nocebo effects might even exert a stronger influence on depression remission than the placebo effect can compensate for. This theory would fit with the observation of Kirsch et al., stating that these patients are already prone to the negative expectancy that a state of affairs will not get better, irrespective of the measures that are taken to improve the situation. All taken together, preventing a nocebo component of antidepressant treatment has the potential to significantly improve the clinical context of patient-clinician communication and disclosure in routine practice, thereby relieving patients from unnecessary stress and preventing the costs of ineffective of terminated treatment attempts. However, implementation can only reach its full benefit after identification of the nocebo effect’s psychobiological nature. Unfortunately, it is still relatively unknown as a topic that deserves attention. Hardly any literature can be found on the nocebo response in antidepressant trials, and the few studies that can be found, plead strongly for more investigations. Neuroscience has a key role in the process towards this goal. Research has already begun to explore how negative expectations can counteract clinical benefit. From around 2006 to the present, the term nocebo effect appears more and more in studies of placebos, since these are reported and advocated to share mechanisms. An important future goal would be to explain how this negative anticipation leads to the experience of side and adverse effects. So far its nature is still poorly understood, and the theories that do exist need replication. Some studies address the key question: is nocebo just the flip side of the positive placebo mechanism, or is it a distinct phenomenon? What are their converging and diverging psychobiological mechanisms? There are definitely shared statistical characteristics in clinical outcomes of placebo and nocebo effects.

As done for placebo mechanisms, I will discuss both the psychosocial and neurobiological mechanisms of the nocebo response in antidepressant trials. Section 2.1 discusses the psychosocial mechanisms, which provide a proper introduction into their less specifically studied neurobiological underpinnings. In section 2.2, the few neuroimaging studies that offer information on nocebo responses are described. Section 2.3 discusses molecular studies, which are the primary source for nocebo biomarkers in general and provide strong clues for its specific role in depression. Lastly, the general difficulties that accompany the study of nocebo effects in antidepressant trials are discussed in section 2.4.
2.1 Psychosocial mechanisms

How can patients experience side and adverse effects when they not even receive active treatment? Clearly, this does not have anything to do with pharmacological treatment. Also, how can it be that when one has negative expectations, treatment is less likely to be effective? As for placebo, the nocebo response seems to be directly mediated by two opposite psychobiological mechanisms that together, determine the degree of negative expectation: anticipatory anxiety and reward expectation. The underlying learning experiences upon which these are based comprise two aspects. First, information (e.g. by the clinician i.e. the informed consent) can form a burden for patients (both before onset and during treatment). The nature of this effect and the solution to overcome such influences will be discussed during sections 3.2 and 3.3. Second, the experiences of prior unsuccessful therapies\textsuperscript{49}, including one’s own as well as observations of others\textsuperscript{52}, and not to forget the general knowledge of antidepressant treatment that is easily picked up these days via internet and other media, since it has also become a topic of societal debate\textsuperscript{3}.

Anticipatory anxiety seems to directly trigger neurobiological pathways and diminishes the positive potential of reward expectation on treatment outcome. This theory is mostly discussed in research of hyperalgesia\textsuperscript{4}, but also confirmed by placebo studies that demonstrate that anxiety can strongly deteriorate placebo effects\textsuperscript{10, 53}, and even now reflected in recent imaging study, all of which will be discussed below. In contrast to placebo studies, the nature of the nocebo effect is scarcely investigated in the antidepressant context. One reason for this is the fact that nocebo insights did not develop from a control group use to an actual research focus. Hence, there is no retrospective research database available to analyze neuroimaging results, nor a well established study design such as the RCT. However, I propose here that there are novel nocebo mechanisms and theories that can be deduced from already existing knowledge. This entails the integration of two fields: knowledge of the nocebo effect that is already known from the antidepressant context, and studies of other nocebo conditions. What is already known in the depression context is that it mainly provides the subjective characteristics of the nocebo effect and the psychosocial concepts that were previously discussed. Also, as I will discuss during section 3.1, the pathophysiology of depression itself provides cues for nocebo mechanisms and vice versa. The other field entails studies of other nocebo conditions. These involve only a handful of neuroimaging studies, but more importantly, there are also valuable molecular studies that relate to translational neurobiological systems of anticipatory anxiety\textsuperscript{4}. Combining the results of these studies provides many clues such as anticipatory anxiety that can also in antidepressant trials, be regarded as a upstream mediator of the nocebo effects\textsuperscript{4, 23, 54}.

2.2 Cues from neuroimaging studies

Few studies tried to identify the neural activation patterns that are triggered by the ‘negative placebo effect’. The first fMRI study that directly addresses the nocebo response in antidepressant treatment was performed in 2004\textsuperscript{55} and did not produce meaningful results. This team was interested in the relation between functional brain mechanisms during an initial placebo lead-in phase and the experience of side effects later on during active treatment. Although this was an interesting perspective, the use of only healthy participants - which most likely got this study to pass ethical constraints - did not allow measurement of genuine depression remission and associated
normalization patterns as a result to treatment. Perhaps because of these reasons, meaningful correlations were not measured.

After this, the long silence in imaging studies was broken in 2008 by Kong et al., whose fMRI study explored the hyperalgesic nocebo effect. Negative expectations induced a cortical network that modulates pain-specific and cognitive aspects of hyperalgesia. The cognitive aspects were considered more non-specific, expectation-related, and involved prefrontal and limbic activations. This group found that activity in bilateral ACC and interconnected left hippocampus was significantly increased by nocebo expectations. Kong et al. report three relevant conclusions. First, as no placebo analgesic study has ever reported hippocampal involvement, its role might be specific for nocebo expectations. Hence, a hypothesis that is not confirmed yet. Second, they observe that their findings of prefrontal normalization patterns fit within the previously report of incongruence of frontal function in placebo and nocebo mechanisms. They provide the explanation that the prefrontal cortex is related to many functions such as expectation generation, memory retrieval and emotion modulation. Again, it is confirmed that establishment of ‘the’ cognitive expectation pathway is very difficult. Third, the authors find their results consistent with the previously described study of Scott, who investigated opposite nocebo and placebo mechanisms in pain, and found the OFC, insular cortex, nucleus accumbens and amygdala important limbic regions, were involved. This also fits with the anxiety-relieving placebo effect that Zhang et al. described, which I discussed for placebo neuroimaging studies. However, it is important to note that these pain hyperalgesic studies are all limited, in that they explored only very short-term nocebo responses, which makes them only partially translatable to depression studies.

One recent nocebo study does explore this long-term context, albeit this still is focused on nociceptive pain experience. It investigates how long negative psychosocial stimuli like clinical information remains relevant in the development and maintaining of negative expectation throughout daily life experience. The authors wanted to address a paradox in nocebo research: although it is generally accepted that negative expectation very strongly shapes modulates attention, arousal, stress and mood, little is known about the nature, long-term effects and strength of these mechanisms. This consideration is certainly translatable to the long term clinical time course of depression, even though Rodriguez-Raecke et al. focus on nociceptive pain in healthy subjects. Also very important, and in contrast with the studies of Kong et al. and Scott et al.: negative expectation was only evoked by verbal suggestions, not via physiological conditioning. This even more resembles the clinical depression context. With fMRI, neurobiological pathways of negative expectation over eight days are measured. As opposed to Kong’s results, this study found nocebo instructions only to correlate to the right insular cortex, an area known to be involved in pain experience. When they lowered significance threshold to normal (p < 0.05), significance also reaches the thalamus and right amygdala.

All results taken together, neuroimaging studies on nocebo effects are not abundant, nor congruent. The expectation-related prefrontal modulation seems replicated only in short term nocebo studies, but these studies seem not very translatable to nocebo effects that harm clinical benefit in antidepressant treatment. Further research needs to be performed to test current hypotheses and build on these to develop novel ones.
2.3 A molecular approach

Molecular studies provide many cues and theories on the nocebo effects in antidepressant treatment. Their outcomes are of great importance, since research in the direct, clinical trial context is still constrained on ethical grounds\textsuperscript{15, 52}. Below, an elaborate discussion is given of those nocebo mechanisms that can be translated from other conditions to the context of depression. The key system seems to be the HPA-axis, which’ activity is modulated by many neurotransmitters that all have their own, specific influence.

The HPA-axis and GABA modulation

GABA manipulations of anticipatory anxiety offered the evidence that the HPA-axis is involved in the nocebo effect, a mechanism that might be particularly related to the depression context (see section 3.1). The findings behind this theory will be explained below. However, one must keep in mind that agonizing and antagonizing GABA receptors can result in strengthening of both placebo and nocebo responses; a process of which the specifics are not yet known.

In 2006, a pioneering study related anticipatory anxiety directly to the HPA-axis, and considered these concepts to be underpinnings of nocebo mechanisms in contrast to placebo\textsuperscript{37}. Besides confirming that GABA-ergic neurotransmission plays a major role in the placebo effect by reducing anxiety, it was indicated that benzodiazepines perform their function by antagonizing HPA-axis hyperactivity. This pain study provided an evident subdivision in placebo mechanisms, i.e., those that are analgesia-specific, and those that seem more upstream, general mechanisms, like HPA-axis activity. Benedetti et al. elegantly showed that when a person’s anticipatory anxiety is blocked by the benzodiazepine diazepam, this antagonizes both HPA activity and pain experience. Administration of the CCK-antagonist proglumide, which directly reduces the pain experience in a dose dependent manner, did not have an effect on the level of experienced anxiety and did also not influence HPA-hyperactivity\textsuperscript{37}. This particular finding implicates that anticipatory anxiety is an upstream mechanism that is modulated by a person’s negative expectations of treatment success, mediated via GABA-ergic neurotransmission and related to the stress regulatory system of the HPA-axis. The finding that both direct verbal suggestions and prior learning experiences can increase or decrease this stress system’s activation\textsuperscript{37}, matches with theories claiming that anxiety is an adaptive system of the stress response, and can influence the HPA-axis on both a short-term and long term basis\textsuperscript{54}. The general character of this mechanism implies that inhibition of its activity could also underlie the antidepressant placebo effect. The specific pathway of how anticipatory anxiety might create its downstream changes in HPA-activity is not yet investigated in nocebo studies.

Monoamine function

A combination of placebo and nocebo studies implies that monoamine function is inversely related to nocebo effects. As already discussed in section 1.3, serotonin is associated with the placebo effect by e.g. inhibition of cortisol secretion, and might be involved in inhibition of nocebo-related HPA-axis hyperactivity. As for GABA, also dopamine acts bidirectional: antagonizing its function decreases the placebo and stimulates nocebo effects, while agonizing stimulates the placebo and reduces nocebo effects in Parkinson’s disease\textsuperscript{24, 33}. 

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2.4 Bias in nocebo research

The primary concern with nocebo studies is that there are so few available: clinical research on nocebo responses is still restricted on ethical grounds\(^1\). Ideas to overcome these restrictions will be discussed during section 3.2, which discusses problems with current design of clinical trials. The relatively unknown character of the nocebo response does confound its assessment in antidepressant treatment in multiple ways\(^46, 58\). To begin with, it is complex to assess whether negative influences on placebo responses are measures of nocebo effects or not \(^4, 10\). Reviews complain that retrospective speculation of nocebo responses from placebo-controlled trials is bound to reach a deadlock, since experimenters often not report nor measure adverse and side effects\(^3\). A vast 80 percent of RCTs did not measure or report side effects at all\(^46\). Also, the frequent withdrawal of subjects and patients as a result of adverse effects is often not documented\(^52\). Besides, physicians and clinical practitioners are often not aware that this information may have significant consequences at later time points during treatment\(^57\). The fact that these burdening instructions to participants are often not given deliberately, makes that they are not reported in the experimental documentation and thus create a silent bias in treatment outcome\(^57\). Second, as in placebo, subjective report of these side effects hampers reliability. The variation in ascertainment strategies influences evaluation of side and adverse effects in clinical trials very strongly\(^3\). Compared to the methods that are used for the establishment of drug effects, measures of nocebo ratings are less intelligent and reliable. Evidently, there is a great need for systematic strategies that assess side and adverse effects in a valid way\(^3\).

**RESEARCH QUESTION III**

How these insights can contribute to research, clinical trials and clinical practice of antidepressant treatment

How can we explain that despite all existing and still growing theories about the placebo and nocebo response, the implementation of this knowledge to benefit research and clinical practice in antidepressant treatment is still so poor? This paradox is recognized in many studies\(^1, 19, 46, 59\). Research just continues to use conventional models\(^19\), ignoring great potential to improve its experimental design. These improvements can be made along three lines. First, they can shed new light on the development of new therapeutic targets for antidepressant treatment. Section 3.1 discusses the observation that conventional, but especially newly identified biomarkers of depression correspond with knowledge of the mechanisms underlying placebo and nocebo responses. Second, the development of novel clinical designs that more reliably measure genuine placebo and nocebo responses. Section 3.2 explains the challenges for current clinical designs that investigate placebo effects, but are based on intrinsically incorrect assumptions. This section also discusses the options for novel clinical trial designs that might evade ethical constraints. Third, the implementation of placebo and nocebo knowledge in clinical practice in order to benefit a patient’s experience and thereby increasing responsiveness to treatment. In section 3.3, implications for clinical practice are
discussed. Last of all, section 3.4 shortly discusses remaining recommendations for further research that are induced from the studied literature.

3.1 The expectancy component of depression remission

Molecular systems that underlie placebo and nocebo mechanisms in antidepressant trials correspond closely with conventional but especially newly biomarkers of depression itself. This section explains what this congruence might imply. Section 3.1.1 introduces which developments are made in contemporary research on depression, and where it stands now in the identification of therapeutic targets. Section 3.1.2 discusses how these run parallel with the placebo and nocebo mechanisms that are starting to be identified. Based on this observation, this section also discusses new theories that centralize the expectation component of depression remission.

3.1.1 Contemporary research on depression

*Challenging the monoamine theory*

In the 1960s, the monoamine theory was proposed as the primary dysfunction in depression. This has led to a major development of antidepressant medication that targets especially serotonergic function, and that has evidently become a routine procedure in our today’s society. In the Netherlands, every year 300.000 first prescriptions for antidepressant medication are reported. This development has become a focus for critique and is now on its return. Patients do not recognize themselves in the diagnosis of their physician anymore, and are not willing to adhere to this routine prescription pharmacological treatment. This results in poor and sometimes adverse responses to treatment.

Neuroscience is also starting to question the monoamine theory of depression: it is now believed that depression is far more complicated and heterogeneous than was initially thought. From a modern perspective, antidepressant efficacy is based on two invalid causality assumptions. First, as discussed earlier, we now know that a significant part of antidepressant drug efficacy can be attributed to non-specific treatment effects. Second, it is a backwards argumentation to deduct monoamine dysregulation as the cause of depression, based on the fact that elevating its levels reduces antidepressant symptoms. This causality issues are underscored by the fact that it is still not explained why the clinical benefit of SSRIs only starts only after three weeks of treatment, while serotonin levels are already elevated within one day.

*New paradigms in depression research*

Already in 2003, Mayberg stated that depression is not simply a dysfunction of certain neurotransmitter systems, but involves failure of maintaining emotional and homeostatic control when there is cognitive or somatic stress. Different forms of treatment modulate different forms of targets that somehow are integrated, and therefore complement chemical and molecular adaptations and homeostatic effects. Consistent with these novel theories, mild effectiveness of antidepressants can be explained by the heterogenic character of depression. With so many integrated and complementary mechanisms, it is evident that these find an ‘entry point’ and thus
cause symptom relief in a certain percentage of patients. In general, this antidepressant-responsive group involves patients that suffer from a major depression, whereas people that are less severe depressed generally do not benefit from these drugs. Around thirty percent of depressed patients does not respond treatment at all. In 2008, Ruhé theorized that this treatment resistant group indicates that current antidepressants do not target the right mechanisms. This would mean that remission in mildly depressed patients by administration of SSRIs would occur by default. We now know that at least a part of these ‘default’ mechanisms results from a patient’s cognitive expectation components that anticipates on treatment outcome.

With this new paradigm in mind, it still appears very difficult to establish quantifiable biomarkers of depression, both on a neuroimaging and molecular level. This all originates from the absence of a ‘golden standard’. Baseline levels of brain activation and neurochemical levels are different for every person, and therefore the pathological dysfunction of these varying baseline levels are very difficult to establish. A recent review showed that 40–60% of the variance in neurochemical responses is attributable to the individual differences between subjects. However, there are strong indications for particular systems to be involved in the pathophysiology of depression, which are more causal biomarkers than dysfunctioning monoamine systems. The bottom line of these novel theories is that there are many dysfunctional systems in the mood regulation pathways of depression, and that the nature of each these system’s contribution can vary for every patient. This increases the challenge for development new therapeutic strategies.

New biomarkers of depression

One theory on depression remission still stands, i.e. that it can be constituted by improving the cognitive control over emotional processing. Patients who are considered to be improved have more cognitive control over their affective processing, which shows in prefrontal modulation of limbic structures like the amygdala and hypothalamus. Contemporary neuroscience advocates the following three theories. Most importantly, a central position in this integrative pathological system is taken by the HPA axis, a focus that is even called the neuropeptide hypothesis of depression, as the new ‘alternative’ for the monoamine theory of depression that was formerly adhered to in neuroscience. In 2010, Werner et al. suggested that administration of neuropeptides and their agonists/antagonists could ameliorate depressive symptoms.

Second, as a highly integrated system that modulates HPA-function, the monoamine function remains acknowledged. However, it is now considered an indirect system underlying depression, since its function is integrated with more central mechanisms as HPA-axis functioning. Also, monoamines exert complicated influences on each other.

Third, a very novel approach in depression research explicitly focuses on altered GABA and glutamate transmission in the integrated psychopathological system of depression. All taken together, the bottom line of novel theories is that there are many dysfunctional systems in the mood regulation pathways of depression, and that the nature of each these system’s contribution can vary for every patient.
3.1.2 The expectation component of depression remission: placebo-, nocebo- or depression-related?

There is a compelling correspondence between the conventional, but particularly newly hypothesized biomarkers of depression and those that are beginning to be recognized for placebo and nocebo mechanisms. This may be explained by presuming that the biomarkers of depression that are cognitively controlled and expectancy-driven might still be related to placebo mechanisms and its counteracting nocebo mechanism. Summarizing for placebo and nocebo studies, the HPA-axis came forward as a ‘modulation hub’ for all kinds of systems: not only for the conscious and unconscious cognitive systems that form a person’s expectation, but also for the molecular underpinnings of monoamines and GABA. In addition, this system seems directly correlated to the physical measures of anticipatory anxiety. The cognitive modulation of the HPA-axis is consistent with the previously mentioned theory that our brain is given the possibility to cognitively control anticipatory anxiety, or fear, to adapt to acute or long term stress, to both of which the HPA-axis is reactive.

This argumentation has the potential to explain both the robustness of expectancy effects in depression treatment as to the mild effectiveness of current pharmacotherapies. As for the first category, it would explain the robustness of nocebo and placebo responses in clinical trials that investigate antidepressant treatment. It could be that what neuroscience has always called placebo mechanisms should not be framed as such, i.e. as effects on treatment outcome that are caused by the administration of ‘inert’ or sham treatment. This thought is shared by Benedetti, who says in a recent review that the term ‘placebo effect’ is too restrictive, and that they should actually be called ‘placebo-related effects’. Taken this thought even further in the specific context of depression, the prefrontally modulated psychobiological systems could instead represent the affective character of depression itself. This would match with the elegant theory of Kirsch et al. who consider expectation to be a fundamental characteristic of depression itself. To reach this conclusion, especially the molecular study of nocebo responses in relation to those of placebo provided very valuable clues. A relationship of anticipatory anxiety with the HPA-axis in nocebo responses indicates that also by means of a prefrontally mediated pathway, recovery rates of depression can be counteracted by negative expectations. The relation between negative expectations and depression remission is only once recognized in literature: Colloca et al. once suggested that side effects may serve as clue for identifying the underpinnings of depression. Interestingly, this theory could have implications for how depression can be regarded as a disorder. Assuming that these placebo- and nocebo-related mechanisms can indeed be assigned to depression itself, these clearly contain both conscious and unconscious cognitive factors (as is agreed upon in placebo and nocebo studies). This is very relevant for the ongoing societal debate about the position of depression: where in between psychology and psychiatry does remission stand?

Second, the mild effect of current antidepressants can now be explained by the assumption that this pharmacotherapy targets these systems in such an indirect way that recovery is slightly stimulated in some patient groups. Already in 2004, Goldapple et al. hypothesized that pharmacological treatment might target and strengthen expectancy-related brain mechanisms, like prefrontal structures and the ventral striatum. He explains this on a molecular level. Early effects of treatment lead to desensitization of serotonin autoreceptors, which initially leads to enhanced serotonin release in the prefrontal cortex. Since the ACC has a strong serotonergic innervation, Goldapple et al. assume that this might directly increase frontal activations in ACC metabolism. This
prefrontal activation could also lead to limbic inhibition, particularly of the amygdala and hypothalamus, which can lead to remission. This is consistent with HPA-axis hypo-activity as a placebo mechanism, and hyperactivity in those of nocebo responses. Their interesting explanation goes even further. This group already proposed GABA to be involved in this expectancy-induced pathways, since limbic inhibition is mediated by regional increase in GABA- and decrease in glutamate levels. Consistent with these findings, agonizing the serotonergic system exerts inversely proportional influences on the HPA-axis and thus the nocebo response. All taken together, modulation of SSRIs might target attenuation of prefrontal and subcortical activity, thereby influencing depression symptomatology.

3.2 Implications for clinical trials

The investigation of placebo and nocebo responses in clinical trials revealed major limitations in current clinical designs, many of which I already discussed in previous sections. Before advocating new trial designs, it is important to reach agreement on the definition of placebo and nocebo effects that need to be investigated. There seems to be a difference between clinical practitioners and neuroscientists. Clinical practitioners might merely be interested how the clinical environment can be optimized to gain optimal treatment effects. They are not that interested in the precise explanation how placebo and depression mechanisms are measures of the same process. This entanglement of non-specific and specific effects of antidepressant medication has also been used for illegitimate reasons: in particular it provided the pharmaceutical industry for several decades with invalid confirmation of antidepressant efficacy. From a neuroscience perspective, it is believed that one must first understand the mechanisms involved in order to be able to treat in a rational way. Therefore, neuroscientists are interested in a design that isolates the genuine placebo effect, and thus controls for spontaneous remission or interactions with pharmacological treatment. Besides, new designs should acknowledge that the antidepressant placebo effect, and with it the influences of nocebo effects, can be very heterogeneous between patient groups; a theory that I discussed in the previous section. Below, I will explain why the so-called ‘additive model’ of the RCT does not take this heterogeneity into account. Subsequently, the major constraints that prevent the development of new designs will be discussed.

The additive model of the RCT

Enck and colleagues formulate sharp critique on current antidepressant trials. They particularly refer to the poor intrinsic validity of the additive model, which is the basic assumption underlying the RCT and states that the pharmacological effect of a drug is calculated by subtracting the treatment effect of a ‘control group’ that receives placebo. This group proposed novel approaches to calculate drug-placebo difference in clinical trials with antidepressants, and found that the additive model does not take into account a significant part of placebo responders are treatment non-responders and vice versa. As I already discussed in section 3.1, reaction to both treatment and placebo seems to be at least partly a function of depression severity. The second assumption of the additive model is that the nonspecific effects of medication can be entirely separated from the pharmacological effects. As described above, there is reason to
believe that pharmacological agents target some mechanisms involved in placebo- and nocebo-related mechanisms. There is no proof that these do not react on a complicated, synergistic and patient specific manner, which would seriously question the presumed additive character of pharmacological effect.  

**New designs**

There are various factors that hold back proper investigation of placebo and nocebo research in clinical trials that investigate antidepressant treatment. There are two options for future research: either the RCT must be adjusted, or a new design must be created. Both perspectives encounter ethical constraints, and great resistance from the pharmaceutical industry. Exploring the placebo effect is of no interest of the pharmaceutical industry, which is a major financer of research on clinical trials.

Adjusting the RCT would be necessary to measure the genuine placebo and nocebo response. I already introduced in section 1.4, that a control group must be included that receives no treatment. This would allow the experimenter to manipulate the expectancy component and control for spontaneous remission. However, it is considered unethical to include a group that receives no treatment. An option to resolve these ethical constrictions is to include an ‘unofficial’ no treatment group: a waiting list for clinical trials, on the condition that patients must first give informed consent that they can be assigned to this group. Investigating nocebo effects with this RCT design encounters even more ethical objections: intentionally provoking ineffectiveness of treatment is certainly not agreed upon.

Creating new designs is advocated by many prominent placebo researchers, since it would serve proper investigation of response expectancy in depression preservation and remission. The most discussed design is the balanced-placebo design, which is considered to resemble real life situations far better than the RCT does. It is developed to disentangle expectancy components from pharmacological aspects, and thereby overcomes the intrinsic flaw of the RCT, i.e. the additive model. Experimenter manipulates both the expectancy of the patients (e.g. receive a drug while telling that they will receive placebo) as what is currently done by the RCT: administration of the drug itself. Although this is essentially a very clever approach, there are both ethical and experimental objections. Since deceiving the patient is an intrinsic characteristic of the design, this encounters ethical constraint. A solution for this problem is to ask subjects permission for active misleading. This so-called ‘authorized deception’ gives research participants the choice to decide whether they agree to participate in scientific research that can involve deception and, if so, authorize to be subject to this. The flaw in this plan is that letting subjects sign for authorized deception, might raise suspicion among these people and thus deteriorates the very intention of the design. The experimental objections bring up the fact that the design is not double-blind anymore, since the experimenter him-/herself has become a factor in the experimental design. This can offer a serious platform for experimenter-induced biases. Miller et al. mentioned in this respect elegantly: ‘deception may be harmful not only to those who are deceived but also to those who practice it’.

All taken together, future research that aims to investigate expectancy-driven components of antidepressant treatment is challenged by many ethical and experimental difficulties.
3.3 Implications for clinical practice

The more knowledge we have of placebo and nocebo effects in antidepressant trials, the better it can be translated to clinical practice and thus improve health care. The placebo effect’s existence advocates human self control over disease development\textsuperscript{19}. Therefore, clinical practice should explore the strength and limits of this phenomenon in order to exploit its therapeutic effects. But a significant improvement can also be made with preventing, or at least diminishing nocebo effects to a minimum\textsuperscript{49}.

In 2002 the nocebo effect was still unknown to three quarters of patients and health care providers\textsuperscript{50}, while current literature confirms that it still is hardly given any attention\textsuperscript{49, 59}. Both from a patient’s wellbeing perspective as for financial reasons it is important to improve efficacy of health care provision. Nocebo effects are considered to result from routine clinical protocols that involve the disclosure of potential benefit and risks like side or adverse effects of anticipated pharmacological treatments that are supposed to alleviate disease symptoms\textsuperscript{69}. Indeed, an important reason for early discontinuation of treatment of diminished belief in its effectiveness often results from the patient’s reattribution of these disease related symptoms to those of the therapeutic strategy\textsuperscript{3, 50}. Physicians and clinicians are often not aware that this information can be a burden for the patient and have significant consequences at later time points during treatment\textsuperscript{57}. They should know that they have the important duty to keep negative expectations low: during the talk-through of the informed consent, procedural information, and follow-up assessments, clinicians must maintain an effective and considerate relationship with the patient to avoid unwarranted and untenable nocebo responses that can last through the entire time course of treatment\textsuperscript{57}. The clinical practitioner must guide the patient through treatment by creating awareness of self-fulfilling prophecies that might silently and slowly exert their negative effect on treatment success\textsuperscript{49}.

Miller and Colloca reconsider informed consent in placebo and nocebo studies with a risk–benefit assessment\textsuperscript{69}. They conclude that it should not be viewed solely through the ethical perspective of promoting and respecting patient autonomy anymore. Instead, physicians and clinical practitioners must reconsider their responsibility in such a way that patient autonomy is still respected. Colloca and Miller also advocate that this progressive consideration deserves attention in future studies\textsuperscript{69}.

In other words, predictive measures are needed to create tailor-made prevention programmes that help a patient with tolerating adverse and side effects of treatment, that might reduce discontinuation of treatment and diminishment of treatment success, irrespective of what nature the pharmacological treatment might be\textsuperscript{49}.

3.4 Remaining suggestions for further research

This emerging field of neuroscientific research puts forward a tremendous amount of new topics that require attention. They are either explicitly mentioned by contemporary reviews, together with those that I recognized as a gap in existing knowledge.

Biomarkers
It would be interesting to further investigate similarities in nocebo and placebo mechanisms with
new experimental designs. It also might be worth investigating the link between new biomarkers for depression and mechanisms of placebo/nocebo modulation. This literature did only approach depression from a placebo and nocebo perspective. Integrating these studies in the search on dysfunctional systems in depression might provide clues about recovery from depression, and guide directions for therapeutic strategies. For instance, there are not only clear gender differences in depression\(^{63}\), but also in the experience of nocebo and placebo mechanisms\(^3,\,14\). Until the present moment, only one study can be found that explicitly targets sex differences in nocebo effects\(^{14}\). Nestoriuc et al. found that female and male patients have a different susceptibility for the development of adverse side effects after taking placebo antidepressant medication.

*Personal differences in placebo and nocebo effects*

Individual differences in the experience of placebo and nocebo responses are already shown to be a function of personality traits, like optimism and pessimism\(^48\). Geers et al. found that optimists are better able to overcome health problems than pessimists, partly because they ‘catch up on’ the placebo component of treatment, whereas pessimists do not. Also, pessimists are more likely to experience side and adverse effects of this same treatment\(^37,\,48\). These differences are currently still regarded as a confound, as described in section 1.4. However, trying to identify such character traits might turn these into to predictors of whether someone will response to certain treatment strategies or not.

*Long term effects of placebo treatment*

Few studies address the long term effects of placebo treatment. Many figures can be found on the comparison of antidepressant placebo response against that of active treatment, obtained by the randomized placebo-controlled design. However, the long term effects of the treatment success rates are discussed by few studies\(^{44}\), an observation shared by Benedetti in 2005\(^{19}\). Only two studies explicitly touch upon this gap in literature. They say it is remarkable that besides Pavlovian conditioning, there is still no other model available that explains the construction and maintenance of the placebo effect\(^6\). Rief and colleagues wonder why all research is focused on optimizing the placebo response in clinical practice when it is still not known whether the long term effects are the same as active treatment\(^{71}\).

**Conclusions**

Both placebo and nocebo responses in antidepressant trials seem directly mediated by a patient’s expectation of treatment outcome, which consist of both conscious and subconscious factors. These expectations are framed by a patient’s prior learning experiences, and mediated by two opposing psychobiological systems: reward expectation and anticipatory anxiety. Whereas placebo mechanisms result from positive expectations that are directly proportional to reward expectancy, nocebo mechanisms are created by negative expectations that seem driven by anticipatory anxiety. These two mediating concepts are highly translational to the neurobiological mechanisms they set in motion. Neuroimaging studies show that placebo and nocebo mechanisms are characterized by
prefrontal activation patterns that dampen or increase limbic activation, respectively. Molecular studies principally show that the dopamine reward system is directly related to reward expectation, and HPA-axis hyperactivity can be directly targeted by anticipatory anxiety. Very importantly, both systems are subject to modulation of a person’s expectation of treatment outcome, and exert cross-over influence on each other. This cognitive modulation is shown to occur via dopamine as well as GABA neurotransmission.

These mechanisms closely correspond with conventional, but particularly to newly hypothesized biomarkers of depression itself. This could imply that the expectation mechanisms that are currently framed as placebo- and nocebo-related, in fact reflect the cognitive character of depression itself. Such a theory would explain both the robust placebo- and nocebo effects in depression treatment and the modest efficacy of current antidepressants. For a disorder where expectancy is such a central feature of disease, this seems conceivable. The inclusion of nocebo mechanisms in this literature study was of great importance to reveal this congruence. Furthermore, this literature study confirmed that the RCT design is defective in measuring the placebo response on many levels: it offers an easy platform for intentional and unintentional biases, it fails to isolate the genuine placebo effect from other factors like spontaneous remission and the pharmacological effect, and it adopts the invalid fundamental assumption of the additive model. Future research must focus on creating new designs that prevent these pitfalls. If it is true that placebo and nocebo effects in antidepressant treatment somehow reflect cognitive aspects of depression, this would mean that they will differ substantially for each subject. This already shows in placebo research: responsiveness differs as a function of depression severity. Last, the acknowledgement of placebo and in particular nocebo responses is crucial for clinical practice. Physicians and clinicians must become aware of their responsibility to improve treatment success rates. First, carefully instructing patients of what they can expect, can prevent detrimental nocebo effects on the patient’s response expectancy and thus treatment outcome. Second, the placebo-related therapeutic effects can be cleverly exploited to stimulate treatment success.

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