Optimizing placebo effects in medical contexts: utilizing learning theories and exploring communication strategies

Smits, R.M.

Calculate indecision,
can't cradle fear no more.
Bear the shame of the incision,
all lain cold across the floor.
Your heart pounds with precision,
a king dies inside his courts.
Your heart pounds with precision,
a king dies inside these doors.

Let it all work out.

Sisay, S. (Sampha). L., (2013). Indecision. On *Dual.*

2. The role of placebo effects in immune-related conditions: mechanisms and clinical considerations.

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ABSTRACT

Introduction: Placebo effects are powerful modulators in clinical outcomes and can either result in treatment benefits or harms, known as placebo and nocebo effects. To harness these outcomes it is important to focus on the underlying processes that steer these effects, namely by learning through expectations and conditioning. In this review, we focus on the influence of placebo effects on subjective and physiological levels of immune-related conditions (e.g. lymphocyte proliferation, cytokine production or other inflammatory markers).

Areas covered: A literature search is conducted in the databases PubMed and PsycInfo by making use of keywords such as “expectations”, “classical conditioning”, “cytokines”, “immune system”, “learned immunosuppression”, and covers studies done in animals, experimental studies in healthy controls as well as studies performed in immune-related patient populations.

Expert Commentary: We report on the presence of placebo effects in RCTs in immune-related conditions and review findings that demonstrate the ability to learn immune responses in both experimental animal and human placebo studies making use of conditioning paradigms with immunomodulating drug agents. We also discuss results to utilize placebo effects by means of classical conditioning principles in medication regimens for patient populations and elaborate on promising findings of preliminary studies focusing on this topic.

Keywords: classical conditioning; cytokines; immune system; inflammation; learned immunosuppression; nocebo effects; placebo effects

INTRODUCTION

The word "placebo" is translated from Latin as “I shall please” and is often described as an inert treatment that by itself does not impact any bodily functions [1]. However, the notion that placebo treatments are merely perceived as ineffective pills has been controversial since the beginning of randomized controlled trials (RCTs), as it was first noticed that patients in the late 40s showed improvement by solely receiving placebo treatment [2, 3]. Placebo’s in RCTs have been used as the gold standard in testing efficacy of drugs and other treatments for several decades [4].

Placebo effects and placebo responses

To fully comprehend the concept of placebo effects, it is important to distinguish placebo effects from placebo responses, as recently outlined by an expert group in the placebo and nocebo field [5]. In medical treatments, a part of the treatment outcome is shaped by the drug effect itself and a large part is also explained by unspecific factors such as spontaneous improvement (regression to the mean), natural history, bias from patients or other factors that play part in the natural course of disease [5]. These changes are termed placebo responses and are seen in both experimental and placebo (control) groups. Eventually, the outcome difference between the experimental group and the placebo group define the treatment effect of the experimental drug under trial conditions [6]. On the other hand, there are placebo effects, factors that shape treatment outcomes by expectations, for example by purposely inducing verbal suggestions about treatment efficacy or manipulating clinical context. More specifically, placebo effects involve neurobiological and psychological learning mechanisms of expectations and conditioning that can be employed to improve treatment outcomes (see Figure 1) [5]. Conversely, there is now convincing evidence from both experimental and clinical studies that the expectation of receiving treatment by itself (placebo effects) have moderate to strong effects in various conditions, as demonstrated in several RCTs that have included a third untreated control arm in their research design, for example in a waiting list group [7]. In these research designs both the placebo and untreated groups do not receive any form of active treatment, thereby highlighting the specific influences of expectations in placebo groups and controlling for factors such as natural course of disease, as

these influences are also present in untreated groups. Interestingly, comparing placebo groups to untreated groups often show pronounced differences in treatment outcomes for placebo groups, whereas outcomes of untreated groups often remain unaffected [8]. In light of these and many other findings of placebo effects, attention have shifted from the traditional view where the occurrence of placebo effects were perceived as a nuisance in RCTs, to the potential of benefitting from these placebo effects and translating these findings to clinical practice in order to optimize treatment outcomes [9].

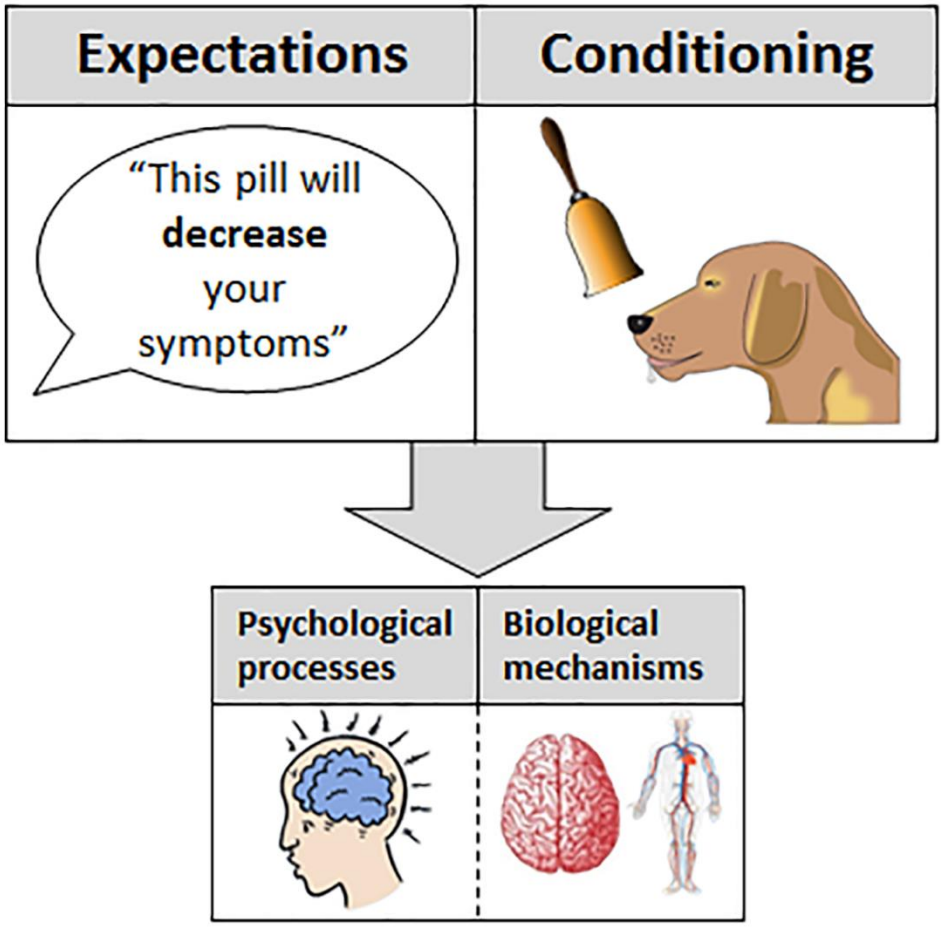

Fig 1. Two main learning mechanisms steer placebo effects: expectations and conditioning. Both mechanisms exert influence on a subjective (through psychological processes) and a physiological level (through biological mechanisms).

Mechanisms that drive placebo effects

At least two main learning mechanisms have been proposed to play a pivotal role in steering the placebo effect: expectations and conditioning [10]. Expectations about

treatment outcomes can either be purposely induced by verbal suggestions or formed by the subject, for example by the patient-physician relationship, hopeful thoughts on treatment outcomes or other factors in clinical context (Figure 1)[1, 10, 11]. The importance of expectations has been extensively studied in the field of pain research. For example, patients instructed by verbal suggestions about forthcoming pain often show increased activation in brain regions involved in pain processing. On the other hand, when expectations are manipulated towards pain reduction, subjective levels of pain experience and activation involved in pain processes significantly decrease [12]. These and other findings show the modulatory effect of verbal suggestions on pain experience and have been demonstrated in several studies [1, 13, 14]. Conversely, nocebo effects (Latin: “I shall harm”) have shown that expectations induced by verbal suggestions can also significantly worsen treatment outcomes and are often associated with increased side effects [15, 16]. The importance of minimizing these nocebo effects in clinical practice has become more evident and strategies on how to prevent nocebo effects have been provided by clinical experts from the placebo research field [5]. Interestingly, there is also some evidence that dopaminergic pathway are influenced by verbal suggestions. For example, patients with Parkinson’s disease showed differences in dopaminergic activation for different probabilities of receiving treatment. In this study, patients in the 75% probability group showed significant improvement signified by enhanced dopamine release and improved motor functions compared to patients receiving lower probability expectations. Noteworthy, patients in the 100% probability group did not show improvement, which the authors explained by the notion that dopaminergic activation was only seen when high reward was expected but not absolutely certain. This implies that learning processes after verbal suggestions including reward prediction may not occur when the outcome is certain, at least when involving dopaminergic pathways [17, 18].

Another factor that plays a pivotal role in the placebo effect is the learning mechanism based on classical conditioning. In classical conditioning, multiple presentations of a stimulus can lead to a learned association, resulting in a learned bodily response, similar to Pavlov’s famous salivation experiment [19]. This principle can also be applied in treatment regimens, like a pharmacological agent paired with contextual cues such as the color, smell or taste of a capsule, or other features in

clinical context, that result in a learned association and eventually cause for comparable drug effects induced by these cues. This learned association between a pharmacological agent and a contextual cue is termed pharmacotherapeutic conditioning (see Figure 2) [20]. By utilizing these placebo effects through classical conditioning, promising treatment outcomes have been found in studies on pain [21] and neuroendocrine and immune-related outcomes [22, 23]. Evidence for the ability to learn an immunologic response was demonstrated in several experiments involving validated conditioning paradigms in both animal and human studies. These studies demonstrated that immunological outcomes can be induced by learned associations and furthermore showed several prerequisites in order for a learned immune response to occur, which is very insightful for possible clinical applications in drug regimens and will be further discussed below.

The aim of this narrative review is to investigate the role of placebo effects in immune-related conditions. To further elaborate on the influence of the placebo effect in immune-related outcomes, we included all data that involved immune parameters, which brought forth a broad range in outcomes, for example from inflammatory diseases such as arthritis or Crohn's disease to immune parameters influenced by placebo effects, such as cytokine proliferation. A literature search was carried out by RMS from January 2018 to April 2018, in the databases PubMed and PsychInfo. Main keywords focused on learning effects such as "expectations", "classical conditioning" and immune-related outcomes as "cytokines" "immune system" and "learned immunosuppression". Moreover, cross-referencing was used for this literature study. Data extraction was completed by RMS and DSV. First, we will discuss several study findings that demonstrate the presence and magnitude of placebo effects in RCTs. In addition, we will give an overview of the results of conditioning paradigms that examined how placebo effects can be integrated to achieve a learned immunological response as used in experimental animal and human studies. Furthermore, we will elaborate on several preliminary studies that have demonstrated beneficial effects of integrating placebo therapy into clinical practice and discuss how these insights can be best translated to clinical trials and practice.

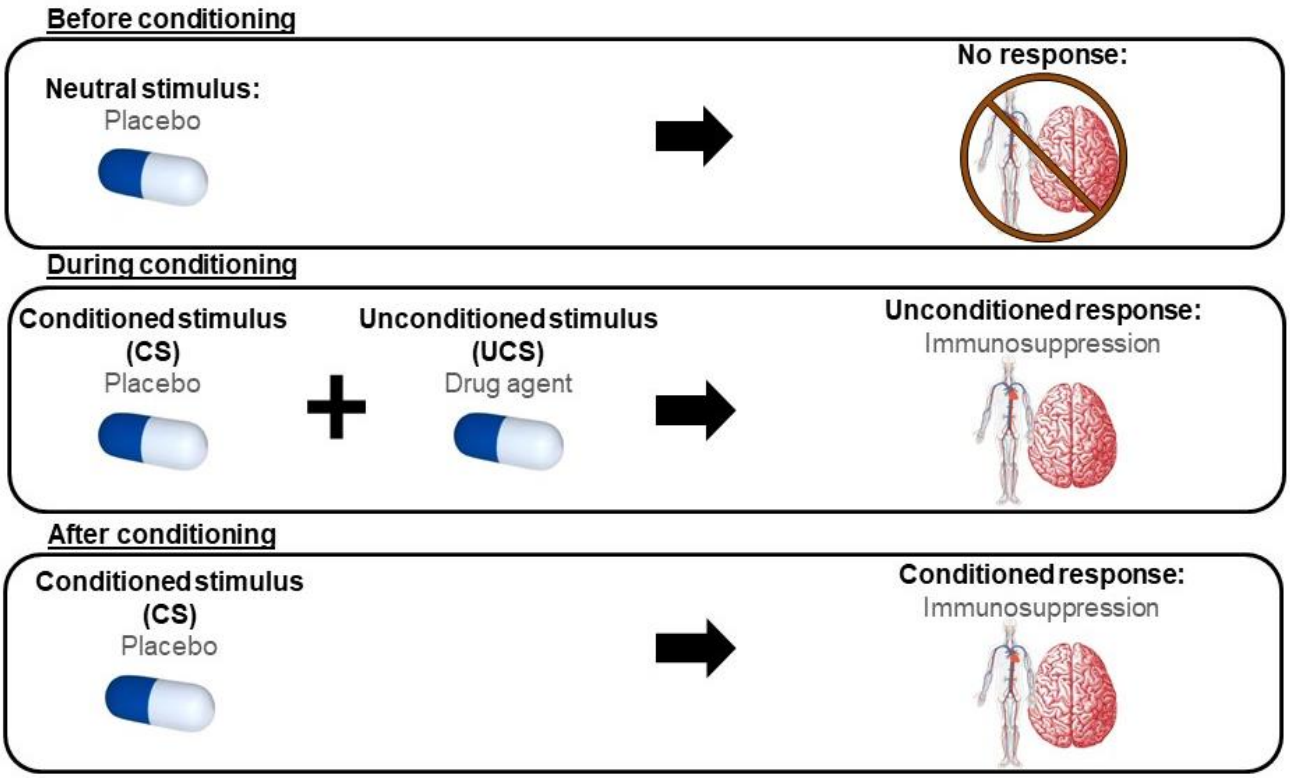

Fig 2. Pharmacotherapeutic conditioning is based on Ivan Pavlov's classical condition experiments (1927) where repeated pairings of stimuli result in a learned association and a physical response.

The placebo effect in immune-related conditions

Numerous efforts have been made to outline the magnitude of placebo effects in meta-analysis among immune-related diseases [24, 25, 26, 27]. To address the magnitude of placebo effects in immunologic processes, we will discuss a large variety of literature that report on placebo effects in immune-related diseases (e.g. arthritis), but also in patient groups where immunological changes were measured (e.g. modulations in cytokine proliferation). Placebo effect rates seem to vary across different types of conditions, which might imply that some conditions are more prone to placebo effects than others. Differences were found in placebo rates in studies with allergies, asthma, gastro-intestinal diseases, arthritis, multiple sclerosis and patients suffering from heart disease. However, due to a broad variety in immunologic outcome measures presented, placebo effects across conditions have to be interpreted with caution. For example, allergic patients in placebo groups from allergen-specific immunotherapy studies (grass, birch and house dust mite allergies)

showed a significant decrease in allergic symptoms after placebo treatment compared to baseline levels [6]. On the other hand, in asthmatic patients lower placebo rates were reported based on clinically relevant improvement in pulmonary function, determined by a 10% increase in forced expiratory volume in 1 second, FEV1 [25]. Furthermore, comparisons between effect size of placebo effects are restrained since changes are not always expressed on both subjective and physiological outcomes. In allergic patients for example, symptom improvement was only demonstrated on a subjective level, but IgG4 antibodies did not change during two years of treatment [6]. However, significant modulations on immunologic outcome measures have been demonstrated in other studies. To demonstrate, less pronounced pro-inflammatory cytokines (reflected by decreased interleukin (IL)-8 and lower IL-6 levels) were measured after a 6 months follow-up in heart patients that received psychological training focusing on optimizing treatment outcomes prior to coronary artery bypass grafting [28]. During this follow-up, significant improvement in disability after six months was also reported [28]. Modulations in immune parameters after placebo treatment have also been reported in other studies, for example in increased natural killer (NK) cell activity in multiple sclerosis patients after receiving placebo treatment instead of IFN therapy [29].

Treatment-related or contextual factors are all situational cues associated with the rituals of clinical context, such as the white coat of the physician or the waiting room in the hospital, and have an important impact on the placebo effect as well. For example, the route of administration has been shown to contribute to higher placebo effects as efficacy was found to much be greater for placebo administration through injections, than placebo's in pill form [6]. These differences were also demonstrated in a meta-analysis of placebo effects in osteoarthritis patients, where more invasive placebo treatments resulted in more pronounced placebo effects. For example, osteoarthritis patients reported higher placebo outcomes for more invasive treatments such as acupuncture, injections and surgical therapies than less invasive treatments such as food supplements, even though all these treatments were 'inactive' in terms of pharmacological properties. [30, 31]. This might indicate that when the physiological system is more employed in the treatment group, this is also reflected in the placebo group. Conversely, route of administration might also play a role in nocebo effects, as patients with juvenile arthritis receiving methotrexate

through an injection had higher odds of experiencing intolerance than patients receiving oral methotrexate [32].

In gastrointestinal diseases, numerous meta-analysis were conducted that report rather high placebo rates in conditions such as Crohn's disease, irritable bowel syndrome, ulcerative colitis and duodenal ulcers [24, 26, 27, 33, 34]. Placebo rates in patients with Crohn's disease were found to be strongly related with longer study duration and a larger number of visits, possibly indicating that the patient-doctor interaction plays an important role in these placebo rates [27]. To elaborate, patients in a study with irritable bowel syndrome (although not a typical inflammatory disease, inflammatory processes have been linked to the pathophysiology of this disease), showed that when a physician adapted a more empathic communication style (the "augmented" condition, focusing their communication style on warmth and confidence) relief rates increased from 44% to 62%, demonstrating the importance of a validating contextual cue in the generation of the placebo effect [35]. In contrast, invalidating contextual cues, for example when a health practitioner gives no or non-understanding feedback, may lead to high levels of arousal and can have detrimental consequences for the development of nocebo effects, again underlining the importance of the patient-doctor interaction [36]. Additionally, by openly administering placebo treatments and educating patients about the importance of treatment expectations (open label studies) it was demonstrated that placebo's can still cause for adequate relief [37]. This has not only been demonstrated in patients with irritable bowel syndrome but in other non-immune related populations as well, such as patients suffering from major depressive disorder [38], chronic lower back pain [39], Attention Deficit Hyperactivity Disorder [41][43][43][43][43] and allergic rhinitis [42].

In sum, these findings show that immunologic processes are susceptible to the learning mechanisms from placebo effects, and although the type of treatment and outcome measures vary greatly among immune-related conditions which allows for only cautious conclusions on comparing placebo rates between conditions, several factors have been demonstrated to play a role that attribute to placebo effects such as the doctor-patient relationship and treatment invasiveness.

The learned immune response

Several studies have shown that it is possible to utilize placebo effects in order to facilitate learned immune responses. In line with the evidence in pain, immune functions can also be altered through classical conditioning. Classical conditioning of immune function has been demonstrated in numerous experimental animal and human studies and shed further light on the mechanisms of the placebo effects. Similar to Ivan Pavlov's experiment in which a contextual cue (i.e., a bell) was paired with food, associations between contextual cues and drug efficacy can be learned as well (see Figure 1) [43]. This holds potential as an innovative therapeutic approach for immune-related disease outcomes. Studies on classical conditioning often incorporate validated conditioning paradigms comprised of a two-phased experiment. First, an association is formed during the acquisition phase, in which two stimuli are repeatedly presented at the same time. In the second phase, the strength of the learned association is subsequently tested during the evocation phase (see Figure 3 for an overview of a conditioning paradigm) [22, 44]. In the acquisition phase, an initial neutral stimulus, like a gustatory or olfactory stimulus (conditioned stimulus, CS), is paired with an unconditioned stimulus (UCS) for example an immunomodulating drug. In order to establish stable conditioning effects, it is important that the CS has strong and salient qualities, such as olfactory or gustatory features, to accommodate associative learning processes. Therefore, a saccharine solution is often used as the CS in animal studies or a green novel tasting drink in human studies. For the UCS, drug agents affecting the immune system such as the immunosuppressant drugs Cyclosporine A (CsA) or cyclophosphamide (CY) are frequently used as the UCS in conditioning paradigms that target immune parameters [45, 46]. After repeated administration of the drink (CS) with the drug (USC), a learned immune response is established in the acquisition phase. In conditioning paradigms, it has shown that after this association has been formed, re-exposure of the CS alone, without the presence of the immunomodulating drug in the evocation phase, can now demonstrate a conditioned response (CR; Figure 3). This conditioned immune response is present on a behavioral level, for example by a conditioned taste aversion and on an immunological level by mimicking the initial drug effect [22, 44]. Most studies examined these learned immune responses with

the immunosuppressant CsA, a drug that induces a response reflected by a reduction in proliferation of cytokine levels [47, 48, 49, 50, 51, 52, 53, 54, 55].

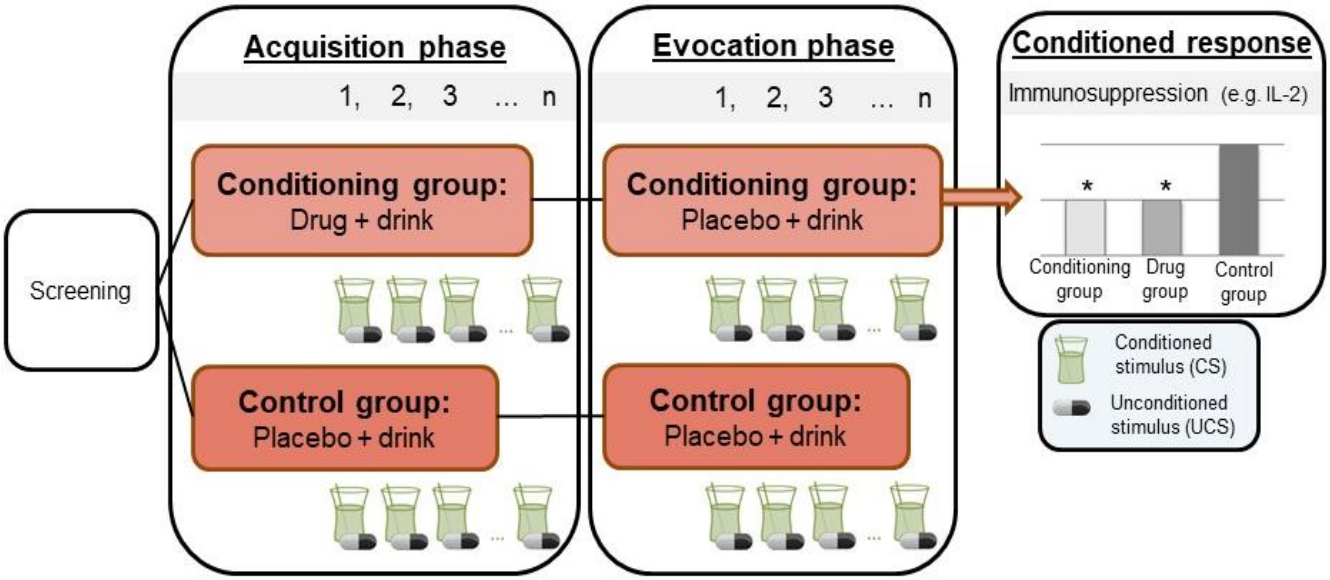

Fig 3. Schematic representation of the frequently used conditioning paradigm. In the acquisition phase a neutral stimulus like a green novel tasting drink is used as the conditioned stimulus (CS) and paired with a pharmacological agent, usually cyclosporine A (CsA) serving as the unconditioned stimulus (UCS). After repeatedly pairing the UCS with the CS an association is established. In the evocation (testing) phase, the conditioned response (CR) is evoked by pairing the CS with identical looking placebo pills. In a successful conditioning paradigm the CR is reflected on a behavioral level by conditioned taste aversion (e.g. avoidance behavior towards the drink) and on an immunological level by significant IL-2 suppression to the same extent as the initial drug effect.

Conditioning of immune responses in animal studies

In one of the first conditioning paradigms in immunosuppression, it was discovered that after a single pairing of CY and saccharine, rats showed significant immunosuppression in antibody titers and had developed a conditioned taste aversion, demonstrated by decreased saccharine consumption [45]. To follow up on these results, a similar conditioning paradigm found that the conditioned immunosuppressant response was also extended to other immunologic parameters (e.g. NK cell cytotoxity) and these responses could be repeatedly evoked later in time, 22 and 26 days after the acquisition phase [46]. However, subsequent studies demonstrated that only a single trial pairing of CsA with saccharine was not sufficient

to elicit a CR. This was supported in a CsA study that compared the magnitude of the CR after 1 versus 3 pairings with saccharine showing that 3 acquisition trials and 3 evocation trials (which will be further referred to as a 3x3 paradigm) showed pronounced inhibition in lymphocytes and caused for significant immunosuppression to the same extent as actual CsA injections [52] whereas a single pairing did not. This is different to CY studies, where a single pairing was sufficient to elicit a CR [45, 46], indicating that the effects of conditioning may depend on the kind of pharmacological agent that is used. Nevertheless, various experimental animal studies have provided further support that more than one acquisition trial (usually up to 3) rather consistently yields a conditioned immune response [49, 52, 54, 56, 57, 58, 59, 60, 61]. In order to elucidate the duration of the learned immune response, the possibility to reproduce the CR was demonstrated by repeating the 3x3 conditioning paradigms over the course of a year. Both the behavioral component of the conditioned response and the immune response were successfully evoked, indicating that immune responses are susceptible to this kind of 'training' when consequently paired and evoked over the course of one year [57]. However, most research demonstrated that these learned immune responses quickly extinct (a process in which a progressive decrease of the learned immune response over time is demonstrated) when pairings between the CS and UCS stop, implying that timely re-introducing the UCS is necessary to maintain the learned response [58, 59]. Some studies postulated interesting hypotheses on how learned immune responses can possibly be prevented from extinction, which is of course important for translating these findings to clinical practice. One possibility may be sub-therapeutic dosing. Results show that administration of sub-therapeutic doses of CsA were effective in maintaining the conditioned immunosuppressant effect up to 10 re-exposures, even though the sub-therapeutic dose that was used in this experiment (2 mg/kg), by itself did not induce immunosuppression [59]. More importantly, a control group that did not receive sub-therapeutic doses did not show this effect of immunosuppression at all. The authors proposed that administration of sub-therapeutic doses strengthened memories of UCS-CS pairings, that could potentially restore the conditioning process [59].

Conditioning of immune responses in humans studies

Human conditioning studies have used paradigms that are very similar to the animal models. Moreover, conditioning designs in humans allow for the possibility to examine the influence of expectations on conditioned immune responses. Conditioning studies have used an immunosuppressant or an immunostimulating approach which will be described separately.

Conditioned immunosuppressant responses

Regarding the human conditioning paradigm, almost all studies employed a design in which a green novel tasting drink (strawberry milk with lavender oil) served as the CS due to its salient taste and unfamiliar color, and CsA mostly served as the UCS. Ultimately, during the evocation phase, the CS was presented together with a placebo [62]. Comparable to animal studies, a conditioned immune response was not established after a single pairing of the green drink and CsA, but mostly after more (e.g. 4) pairings [48, 51, 55]. A successful CR in the evocation phase was reflected by a reduction of IL-2 and IFN-γ production by CD3+CD4+ lymphocytes, mimicking the drug effect of CsA [47, 48, 50, 51, 53, 55]. Moreover, it was demonstrated that mere expectations of taking CsA (verbal suggestions of 25%, 50%, 75%, or 100% probability of receiving CsA injections) however could not evoke a conditioned immune response, indicating that in immune-related processes, classical conditioning processes play a dominant role in steering placebo effects. Like animal studies, conditioning paradigms that studied the time course of extinction are scarce and show incoherent results. For example, one study using CsA as the UCS demonstrated that the conditioned response was extinguished after 14 unreinforced CS exposures [47] while other studies demonstrated earlier effects of extinction [48, 55]. Interestingly, similar to animal studies [59] administration of sub-therapeutic doses (10% of initial CsA dose) did prevent the effects of extinction after 14 exposures, possibly providing new research directions to study the effects of drug extinction in human studies [47].

Conditioned immunostimulating response

Aside from conditioning studies with immunosuppressants (mainly CsA), the potential to condition immunostimulating responses has also been studied in humans. Buske-Kirshbaum et al. found that after 4 pairings of epinephrine injections with a sherbet sweet (a sweet powder that served as the CS), a conditioned response was elicited by a saline injection (placebo) combined with the CS, as reflected by increased NK cell activity which was comparable to the initial epinephrine injection [63]. In contrast, it was found that a single acquisition trial with lipopolysaccharide (LPS) used as the UCS, did not induce changes on a plasma cytokine level, but it did evoke a learned response on a behavioral level, as the smell of the CS was rated significantly less pleasant compared to the control group [64]. A different conditioning paradigm showed that by gradually decreasing the amount of pairings between the CS (sweet drink) and the UCS (recombinant human IFN-γ injections) during the acquisition phase (week 1: 4 times, week 2: 3 times, week 3: 2 times) did not yield a clear conditioned response when the drink was paired with a saline injection in the fourth week, possibly because the decline in pairing of the CS and UCS provided enough time for extinction to occur and learning effects to attenuate [65].

In sum, conditioning paradigms in experimental animal and human studies show that conditioning of immune responses are suited to evoke a conditioned immune response [47, 48, 51, 53, 63], and indicate that extinction occurs after multiple unreinforced pairing in the evocation phase [47, 55]. However, there still remain several uncertainties in translating these findings to clinical practice. First, the exact course of extinction remains unclear. Second, since most studies used similar types of drugs as the UCS, it is unclear if the same conditioning principles apply for different pharmacological agents. Third, as not all conditioning studies have implemented pharmacological control groups, it is not always clear if the conditioned immune response affects immunological parameters to the same extent as the actual drug treatment, which is also an important aspect to elaborate on for future implementation [59]. Conversely, some efforts have been made to counteract the effects of extinction, namely by pairing the CS with a sub-therapeutic dose of a drug during the evocation phase, showing few but promising results in experimental animal and human studies [47].

Conditioning paradigms in clinical practice

So far, studies on conditioning with drug agents have focused primarily on experimental studies on animals and humans. More recently however, several preliminary studies have been initiated where results of these experimental conditioning studies were translated to a clinical framework known as pharmacotherapeutic conditioning, integrating conditioning mechanisms in medication dosing regimens [23, 40, 45]. Even though the amount of studies on this subject is still small, several promising results of pharmacotherapeutic conditioning in immune-related conditions, and other patient populations, have been demonstrated.

First, the principles of pharmacotherapeutic conditioning were utilized in a variable reinforcement schedule applied in psoriasis patients [20]. In such a schedule, the association between the CS and the UCS is intermittently reinforced. The active dose, in this study corticosteroid cream, was administered intermittently with placebo doses, where conditioning effects are assumed to work [20]. Patients who were treated with a 25% standard medication dose showed the same clinical outcomes as patients treated with a 100% dose, but only when the lower dose was received via a variable reinforcement schedule [20]. Subsequently, two patient studies on anti-allergic responses demonstrated the efficacy of pharmacotherapeutic conditioning with desloratadine (a histamine 1 receptor antagonist), by pairings with the frequently used green novel taste drink serving as the CS [66, 67]. Both studies showed that after 5 pairings of desloratadine with the drink, wheal sizes and subjective symptom scores reduced in the evocation phase in the conditioning group where the CS was presented without the drug. Moreover, re-exposure of the CS alone after 9 days showed a similar decrease in basophile activation as desloratadine itself, demonstrating that the conditioning paradigm can successfully be applied in allergy studies and cause for clinically relevant results [66, 67].. More recently, the abovementioned conditioning paradigm with CsA as the UCS and a green novel tasting drink as the CS has been employed in patients after renal organ transplantation in order to find if learned immunosuppressive placebo responses can be used as a supportive strategy to improve therapeutic effects [68]. In line with the experimental conditioning paradigms, the green novel tasting drink was paired with CsA intake for three days. In the evocation phase (2 days later), CsA intake regimens remained the same (twice a day at 9 AM and 9 PM), but now two additional intakes of

placebo pills combined with the CS took place at 1 PM and 5 PM as a supportive regimen to strengthen immunosuppression. Results showed a significant learned inhibition of T cell proliferative capacity, implying that the conditioning paradigm increased the efficacy of medication without increasing the actual dose of CsA [68]. These findings imply that dose reduction may be possible when making use of conditioning principles with variable reinforcement schedules in order to attain treatment effects, which builds upon the findings shown in experimental animal and human studies by the administration of sub-therapeutic doses [47, 59]. Besides studies on allergies, psoriasis and organ transplant patients, pharmacotherapeutic conditioning has also been found to be beneficial in other clinical populations such as irritable bowel syndrome, Attention Deficit Hyperactivity Disorder and in a case study of systemic lupus erythematosus [20, 37, 40, 48, 69, 70]. Currently, the potential of the therapeutic benefit of pharmacotherapeutic conditioning and the possibilities to reduce side effects of methotrexate (MTX) in different immune-related patient groups (i.e., rheumatoid arthritis and juvenile idiopathic arthritis) is being examined [71, 72].

Neurobiological mechanisms of the learned immune response

As mentioned above, placebo effects are mainly driven by the learning mechanisms of expectations and conditioning (see Figure 1). The fact that these components have such a pronounced effect on physiological outcomes can be explained by conditioning paradigms as described above. Findings from these paradigms provide a fascinating example where the bidirectional relationship between the CNS and the immune system is exhibited. Even though the underlying pathways are not completely understood, findings of mimicked drug effects after placebo treatment support the notion of an interplay between the CNS and the peripheral immune system. Based on animal studies, several networks have revealed to play a role in the central, efferent and afferent neurobiological mechanism facilitating the learned immune response.

The sympathetic nervous system has been exposed as one of the major efferent pathways via which the CNS achieves conditioned immunomodulation, since surgical denervation of the spleen completely abrogated the conditioned immunosuppression after a conditioning paradigm [49]. Regarding neurotransmitters,

noradrenaline predominantly seems to regulate the conditioned immune response, as chemical sympathectomy failed to evoke a conditioned response. Also, the administration of the β-adrenoceptor antagonist propranolol showed complete blockage of the conditioned effect of splenocyte proliferation to mitogen and cytokines (IL-2 and IFN-γ), indicating that the conditioned immune response is also regulated by β-adrenoceptors [57, 73].

On a central level, excitotoxic lesions (nerve damage systematically induced by overstimulation) performed before and after acquisition trials demonstrated the involvement of the insular cortex, amygdala and ventromedial nucleus of the hypothalamus (VMH). The insular cortex seems to play an associative role in the acquisition and evocation of learned immune responses and may be responsible for conditioned taste aversion as lesions of the amygdala and VMH did not affect this behavior. Subsequently, the amygdala was found to mediate visceral input necessary for associative learning and the VMH might play a role in communication between the brain and immune system necessary to evoke a learned immune response [61]. On the other hand, the afferent pathways that cause the CNS to detect changes in the peripheral immune system induced by an inert substance are not completely understood, as it is still unclear which messengers activate the brain during the acquisition trials [58].

Practical and clinical implications

Conditioning paradigms in animal, human and clinical populations have shown promising findings and provided a great amount of evidence for future implementation. Eventually, the main objective of pharmacotherapeutic conditioning is to maximize therapeutic efficacy by reduced drug dosing, ultimately resulting in greater therapeutic efficacy and/or less unwanted drug side effect and potentially saving costs. In order to understand the application of placebo effects in treatment, some issues need to be addressed first. From an ethical perspective, it is of utmost importance to be open to patients about the administration of placebo and prevent any form of deceitful information about placebo treatment. Also, it is important to explain to a patient that it is possible to improve due to factors other than the treatment itself, for example by expectations about treatment outcomes. Conversely,

since there is substantial evidence that the way patients are informed by risks and side effects can significantly worsen treatment outcomes, health practitioners should be trained in their communication to minimize nocebo effects. Also, it should be acknowledged that not all patients benefit from being informed in detail about possible risks and side effects in treatment. On that note, future studies on guidelines that focus on different communication styles suitable for different patients are needed [5, 74].

Conclusion

Converging evidence on placebo effects in RCTs demonstrated significant placebo response rates for various immune related diseases. These endogenous placebo-induced immunological changes have the potential of a substantial therapeutic benefit. Studies on conditioning paradigms in animal and human population have greatly contributed to our knowledge concerning learned immune responses and possible applications for clinical practice and have been studied in several preliminary clinical studies. However, a better understanding on whether these learning paradigms can be applied to all (immune-related) conditions needs to be gained and whether the results are generalizable to other pharmacological agents. Also, future research needs to elucidate how these learned immune responses are maintained and when reinforcement is necessary. Ultimately, by answering these questions, patient care may greatly benefit from placebo effects.

Expert commentary

In sum, this review sheds light on the importance of placebo effects in clinical trials and the possible utilization of the learned immune response in clinical practice. First, we reviewed the occurrence of placebo effects in clinical trials that has been extensively documented in various diseases including immune-related conditions. It was shown that the placebo effect is an integrative and important aspect of the overall treatment effects and also explains important variance in the actual drug effect. In order to further elucidate the placebo effect, it has been proposed that an untreated control groups might be included in the classical RCT in conditions that would permit control groups where no treatment is given (i.e. in less severe diseases)

Conditioning paradigms in animal and human studies have greatly contributed to our current knowledge on utilizing placebo effects in immune functions and initial attempts have been made to extent these findings to the clinical practice. A growing body of evidence supports the notion that stable immune responses can be learned in both animal and human studies. These studies furthermore provide us with informative findings on how to employ the placebo mechanisms in clinical treatment. The first important finding for possible clinical implementation is that more acquisition trials may improve the stability of the CR, implicating that it is important that patients start on a stable full dose medication regimen to ultimately establish a CR [47, 49, 50, 51, 54, 55, 56, 57, 59, 60, 61]. Second, learned immune responses are measured with different types of pharmacological agents used as the UCS (e.g. CsA and CY), paving the way for other drugs such as MTX – a drug which is administered in different clinical populations as it is effective and safe but also has substantial side effects and associated conditioned responses - to be exposed to conditioning principles. Third, there have been some findings on the maintenance of the CR, as it was shown that reproducing the acquisition and evocation trials later in time could evoke a CR again [57] which proves that training immune functions may be possible. Also, it was supported that intermittent administration of sub-therapeutic dosages may interfere with the process of extinction which provides useful insights for designing medication regimens [47, 59].

About 40 years of research on conditioning experiments with immune functions in animal, human and clinical populations have introduced sufficient evidence, to possibly capitalize on the conducive effects of placebo mechanisms. By making use of the learning abilities as demonstrated in experimental conditioning paradigms, the first steps that translate these findings to clinical practice have been made. Although recent studies have introduced paradigms suitable for clinical practice, like pharmacotherapeutic conditioning [20, 40], research is still scarce and sample sizes of these studies are generally small. Based on our knowledge of acquisition and evocation trials derived from conditioning paradigms, we therefore emphasize on the ability to train immune functions (i.e., by stable treatment dosages serving as acquisition trials followed by lower dose treatment serving as evocation trials). Other important recommendations for clinical practice is to inform patients about placebo effects and nocebo effects, as they can both substantially modulate the efficacy and

tolerability of active pharmacological agents or other medical treatments. Therefore, we emphasize on the importance of the communication between health practitioners and patients to address these influences and educate health practitioners on communication styles with patients about expectations and enhancing the patient-doctor relationship. Regarding nocebo effects, it is advised that health practitioners inform patients about side effects and risks, for example by making use of reassuring words in order to minimize nocebo effects. Recently, guidelines have been composed among experts in the placebo research field that advise on communication styles to cope with placebo and nocebo effects [5, 74].

To conclude, we brought forth a growing body of evidence on the presence of placebo effects based on findings of RCTs involving immune-related conditions, experimental research designs that demonstrated the ability to learn immune responses and the possibilities to introduce learned placebo responses in clinical practice. Studies implementing these findings in future research designs are urgently needed to further examine the promising results of placebo's integrated in clinical practice.

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