Univerzita Karlova / Charles University

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Katedra psychologie / Department of Psychology

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Martin Nejedlý

Psychologické a psychosociální aspekty placebo efektu:
***Status quo* konceptů**

Psychological and Psychosocial Aspects of
the Placebo Effect: *Status Quo* of Concepts

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Vedoucí práce / Supervisor: PhDr. Iva Štětovská, PhD.

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Prohlášení

Prohlašuji, že jsem bakalářskou práci vypracoval samostatně, že jsem řádně citoval všechny použité prameny a literaturu a že práce nebyla využita v rámci jiného vysokoškolského studia či k získání jiného nebo stejného titulu.

V Praze 26. 7. 2020 …….

Martin Nejedlý

Abstrakt

Práce se zabývá současnými psychologickými koncepcemi placebo efektu. Teoretická část začíná popisem vývoje terminologie v placebo výzkumu, která v posledních letech prošla významnou proměnou. Následně diskutuje rozdílné psychologické mechanismy, které se s placebo efektem pojí, a uvádí přehled modelů, jež se snaží tyto mechanismy konceptuálně uchopit. Třetí kapitola zasazuje placebo efekt do širšího psychosociálního kontextu a shrnuje přechod od dispozičního přístupu zdůrazňujícího osobnostní rysy k interakční perspektivě. V poslední kapitole jsou nastíněny vybrané metodologické problémy placebo výzkumu. Na tuto část plynule navazuje návrh výzkumu, který tato úskalí zohledňuje a zaměřuje se na vztah mezi možností volby léčby, osobností a silou placebo efektu.

Klíčová slova

placebo, placebo efekt, farmakologické podmiňování, komunikace s pacientem, randomizované kontrolované studie

Abstract

This thesis focuses on contemporary conceptions of the placebo effect. The beginning of the theoretical part describes the development of terminology in placebo research that has significantly changed in the past few years. Next, it discusses various psychological mechanisms of the placebo effect and provides an overview of models which attempt to conceptually clarify these mechanisms. The third chapter puts the placebo effect into a larger psychosocial context and summarises the shift from a dispositional approach emphasizing the role of personality traits to an interactional perspetive. The last chapter addresses selected methodological issues in placebo research. This part is followed by a research proposal that attempts to account for these challenges and focuses on the relationship between the choice of treatment, personality, and strength of the placebo effect.

Keywords

placebo, placebo effect, pharmacological conditioning, doctor-patient communication, randomised-controlled trials

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Seznam zkratek / Acronyms and Abbreviations

ASCIA	Australian Society of Clinical Immunology and Allergy
BAS	behavioral activation system
BIS	behavioral inhibition system
BPS	British Psychological Society
CS	conditioned stimulus
CsA	cyclosporine A
CR	conditioned response
IBS	irritable bowel syndrome
IL	interleukin
IFN	interferon
mRNA	messenger RNA
RCT	randomised-controlled trial
RNA	ribonucleic acid
SPT	skin-prick test
US	unconditioned stimulus
UR	unconditioned response
VAS	visual analogue scale

Introduction

The placebo effect is a phenomenon that is often discussed as a confounder. And yet, approximately half of American rheumatologists and internists admit to prescribing placebos regularly (Tilburt et al., 2008). Moreover, in clinical settings, the placebo effect is an inseparable part of the outcome on an individual level. Therefore, it is something physicians and patients encounter on a daily basis.

In the past twenty years, the topic has received a considerable amount of interest from the scientific community. For example, the number of publications on PubMed focusing on placebo and nocebo has increased from a few hundred in 2004 to more than 3400 in 2016 (Enck et al., 2017). New possibilities, such as extending the effects of active medicine via placebo conditioning and using placebos without deception, have been discovered.

In science, more attention from researchers often leads to discoveries of some conceptual issues as well. The placebo effect was no exception. Not only were some fundamental assumptions shattered, but the shift in perspective has been so prominent that some sceptics have questioned whether the concept is meaningful at all. It has also been demonstrated with various issues that the topic is extraordinarily demanding on methodological considerations. While the implications are starting to be heavily emphasized, conceptual confusion is one of the largest issues in research on the placebo effect.

In accordance with this shift, **this work aims to describe the placebo effect in its current conceptual perspective and present some of the fundamental questions that have not yet been answered in a sufficient manner**. It is therefore mapping the current macro perspective of the placebo effect. While psychobiological research has contributed greatly to the understanding of some phenomena, this thesis will focus mostly on the psychological and psychosocial aspects of the topic, as the biological research on placebos has some issues of its own and would require a more context-specific perspective. That being said, a few conceptually important biological studies will be mentioned as well.

The first chapter describes the debate on questions such as what the placebo effect is, what it is not, and how it relates to placebos.

The second chapter elaborates further on these concepts and summarizes models which attempt to explain the main mediating psychological variables that are required for the placebo effect to occur.

The third chapter follows two main questions: Who is prone to experience the placebo effect? When do people respond to placebos? In this context, it monitors the recent transition to a more interactional perspective.

And lastly, the final chapter on methodology highlights some challenges associated with placebo research specifically and their implications.

Given the macro perspective approach and the multidisciplinary nature of the topic, it would be easy to diverge from the main line of the thesis. For that reason, where relevant, additional details were disclosed in appendices. The corresponding bibliography can be found in the References section.

The 7th edition of the APA publication manual was selected as the referencing style (APA, 2019).

Theoretical Part

1 Defining Placebo and the Placebo Effect

The first usage of placebo's current meaning occurred in medical terminology in 1772 when used by the Scottish physician William Cullen as a description of a treatment aiming to satisfy his patient's need for medication. At that point, the term referred to a treatment that only had a weak effect with respect to the condition (often low dosage of an otherwise pharmacologically active compound). Later on, physicians started using the term for an inert[1] or sham treatment (Jütte, 2013).

In the 20th century, the first placebo-controlled clinical trials were conducted. Placebo itself received a large amount of interest in 1955 with the publication of Beecher's paper *The Powerful Placebo* which popularised the notion that placebos can have clinically relevant physiological effects (Guijarro, 2015). Although not explicitly providing a rigorous definition of the term, Beecher also refers to placebos as "*inert substances",* following up on the definition which was already widely accepted at the time in the context of placebo-controlled trials (Beecher, 1955). This description of placebos has become the standard reference, as summarised by Miller and Kaptchuk (2008):

Placebos are defined as *"inert interventions or active interventions believed not to have specific efficacy for the patient's condition, with the aim of promoting beneficial outcomes or satisfying the patient's wish to receive treatment"* (p. 1).

Arthur Shapiro (1964), who has proposed that the term placebo be understood via its non-specific effect (see the definition above), defines the **placebo effect** as "*the changes produced by placebos"* (p. 75).

The current literature often refers to this phenomenon in its plural, **placebo effects**, because as we will see in the next chapter, there are multiple mechanisms, and thus there is no single placebo effect (Benedetti, 2008). The terms are, however, often used interchangeably as an umbrella term.

The counterparts of placebo and the placebo effect (when the outcome is a worsening of the symptoms) are often referred to as **nocebo** and **the nocebo effect**. The distinction of nocebo effects is partially supported by their different physiological

[1] Inert in a medical context can be defined as *„not active pharmacologically; serving only as a bulking, binding, or sweetening agent or other excipient in a medication"* (O'Toole, 2013, p. 919).

pathways and possibly a different allele determination (Benedetti et al., 2007; Hall et al., 2015). For this reason, this thesis only focuses on placebo effects.

1.1 Criticism of the Traditional Placebo Terminology

In the past 20 years, the placebo terminology has been subject to an extensive conceptual debate. Moerman and Jonas (2002) pointed out that defining the placebo effect via the effect of inert interventions that do not have any specific effect on the particular condition results in a paradox. If a substance or a procedure is inert, it cannot *cause* anything by itself.

Others have argued that no substance can be truly inert (Howick, 2017; Miller & Kaptchuk, 2008). An often-quoted example are sugar pills, which are by no means inert to a diabetic patient (Sievenpiper et al., 2007). Therefore, a procedure can only be inert with respect to some condition (and as discussed in Howick's conception mentioned later, with respect to some group of patients). The non-specificity of interventions does not hold either. Various physiological pathways have been identified for the mechanisms of the placebo effect (Finniss et al., 2010). An example of that can be placebo hypoalgesia acting via μ-opioid receptors, which can be inactivated by an opioid receptor antagonist (Benedetti, 1996; J. K. Zubieta, 2005). Moreover, since there are observable changes in the outcomes, they must be achieved via some specific process (Miller & Kaptchuk, 2008). These discrepancies might also be the result of a poorly defined concept of "specificity of an intervention", which is generally not elaborated - not even in Shapiro's terminology.

Another set of problems arises with the connection of the placebo effect to placebos. An improvement of symptoms after an empathetic doctor-patient communication does not necessarily require an administration of a placebo. Also, the concept is often used in a manner that is too broad (Moerman & Jonas, 2002). In randomized-controlled trials (RCTs), symptom relief in a placebo group should not be attributed to the placebo effect by itself. Other phenomena such as regression to the mean, natural course of the disease, reporting bias, social desirability, and other effects can be responsible (Finniss et al., 2010). The **placebo-control** should not be confused with the placebo effect. For these reasons, several authors have made alternative proposals that either re-conceptualise the placebo effect and/or replace some of the terminology, or abandon it completely.

1.2 Alternative Concepts of Placebo and the Placebo Effect

In accordance with their criticism focusing mainly on the inertness paradox, Moerman and Jonas (2002) proposed that the term "placebo effect(s)" could instead be replaced by the "**meaning effect(s)**" while keeping the current placebo definition:

> We define the meaning response as **the physiologic or psychological effects of meaning in the origins or treatment of illness**; meaning responses elicited after the use of inert or sham treatment can be called the placebo effect when they are desirable and the nocebo effect when they are undesirable. (p. 471)

Moerman (2013) later also provides 10 studies as support for his model. For example in the case of open/hidden drug experiments, patients are randomly split into two groups with one group receiving the medication knowingly, whereas the other group will be given the medication automatically via a special pump without knowing when exactly the substance will be delivered. In this case, Moerman notes that it would be confusing to call such an effect "the placebo effect" because no placebos are given.

Two main objections have been raised with respect to the meaning model. Firstly, it fails to address a problem that has already been mentioned before – no substance is generally inert. Secondly, the term "meaning" is not defined in any scientifically sound way, that is, it replaces one vague term with another (Annoni & Blease, 2018). While some authors point out (including Moerman himself) that the meaning response has not been scientifically tested (Howick, 2017), others note that it is not falsifiable in the first place (Blease & Annoni, 2019).

One critic, Howick (2017), proposes in his recent comprehensive review **a revised model of Grünbaum** instead. The complexity of the model is, unfortunately, beyond the scope of this work. It defines the placebo and nocebo effects via so-called characteristic and incidental features. A characteristic feature:

> (1) is not expectancy [conscious, or unconscious created by conditioning] *that* a treatment is effective,
> (2) has an incremental benefit on the target disorder over a legitimate placebo control in a well controlled trial. (p. 18)

All of the other features are called incidental. The placebo effect is defined as "*a remedial effect produced by the incidental features of some treatment, or any positive effect of a generic placebo"* (p. 31).

Howick's model has several advantages. It avoids confusion by precisely defining all of its components. The inclusion of expectations allows for restricting the model to more relevant variables. It differentiates between a placebo control, placebo and the placebo effect, relates the terms to each other (placebo effect is indeed an effect of a placebo) and allows for a special case of intentional placebo.

Notwithstanding its positives, Blease and Annoni (2019) point out that in the case of new psychological mechanisms other than expectations and conditioning being discovered, the model would have to be revised (and as seen in the next chapter, there are already some candidates). Other objections from the two authors, such as that the placebo effect in the Howick's model might include subjective reporting and the Hawthorne effect[2], require further clarification as the first one is not necessarily related to the treatment characteristics themselves and the latter is a highly controversial concept in general (McCambridge et al., 2014).

Given all the issues with defining placebo, some authors have suggested that scientists eliminate the term completely from their terminology. Nunn (2009) notes that there might not be any real construct underlying placebo:

"If something cannot be defined and does not make sense no matter how it is viewed, it's time to ask if it's really there at all" (p. 1).

This viewpoint is followed by Turner (2012), who especially advocates for dropping the term placebo comparison because in RCT, the ultimate goal is to compare two groups which are equal except for the part of the intervention that the experimenters are interested in. There is no need for including placebo within the terminology.

Howick (2017) fully rejects these ideas stating that descriptors need not replace terms, whilst Blease and Annoni (2019) respond with a notion that researchers do not consider placebo effects to be operating under one single process and reflect this in their methodology. Although they do not agree with Howick's critique, the common ground is that placebo as an umbrella term can still be useful.

In spite of that, they do support Turner's proposal for RCT. The argument is that the confusion arises partially because an **ontological definition** of placebo and a **methodological** one should be separate. When examining placebo effects for their intrinsic properties (ontological), placebos can be described as inert relative to some condition. In the methodological context, their role is to be equal to the tested treatment

[2] Generally, the distinction between the Hawthorne effect and the placebo effect has not been discussed in most conceptions.

except for the *"hypothesized remedial factor(s)"* (p. 9). Therefore, replacing methodological placebos with the term "control" in and of itself would provide clarification, whereas the ontological context of placebo should be retained. That being said, Blease and Annoni do acknowledge that the definitions are likely to change. However, they find none of the current alternative conceptions sufficient and believe there is a need for more anomalies and further understanding of the mechanisms hidden under the umbrella term in order to develop a more precise and sensible definition. They summarize the *status quo* not as a definition (*what* it is), but rather as a description of *how* the terminology is currently used:

> Placebo effects engage perceptual and cognitive processes to produce salubrious, psychobiological events. Placebo effects are considered amenable to scientific investigation using the methods and techniques of the behavioural and psychological sciences. A growing body of research shows that placebo effects have considerable potential to alleviate many commonly-experienced symptoms and conditions (e.g., pain, depression, anxiety, irritable bowel syndrome). (p. 9)

Similarly, ontological placebos can be described as:

> Interventions that, owing to their intrinsic properties, are ineffective for a particular condition or symptom(s), but which may be intentionally or unintentionally administered in clinical settings or experimental placebo research, to placate patients and/or with the aim of eliciting placebo effects. (p. 9)

This approach will be adopted for the purpose of this thesis that will focus almost exclusively on the ontological concept of placebos and placebo effects.

The term **placebo response** is not used consistently in literature. This thesis will operationalise the term as improvements of symptoms following the administration of a placebo, that is, a term including all contributing phenomena occurring in placebo groups, which is a definition that is congruent with its use in RCTs (Evers et al., 2018).

2 Psychological Models of the Placebo Effect Mechanisms

Researchers usually refer to at least two basic psychological mechanisms of the placebo effect – **the placebo effect elicited by means of expectations** and **the placebo effect elicited via classical conditioning** (Bensing & Verheul, 2010; Blease & Annoni, 2019; Colloca & Howick, 2018). Some authors perceive them as distinct and often support this differentiation with research findings such as those suggesting that they might be involved in different clinical conditions (Benedetti & Amanzio, 2013; Finniss et al., 2010). Others point out that this conceptual dichotomy is unwarranted as conditioning is one of the multiple mechanisms of how expectations are formed (Colloca & Miller, 2011; De Houwer, 2018; Kirsch, 1997).

Currently, most of the psychological models focus on the relation between these two. The polarity of the conditioning vs. expectancy debate can, however, be misleading. Although various authors refer to these concepts as if there were only one model of conditioning and one general model of expectations, this does not accurately reflect the plurality of these concepts. Also, it is worth mentioning that some authors have suggested a third general possible mechanism that is usually not accounted for by the current theories - a **direct regulation of negative emotions and distress** (Bensing & Verheul, 2010; Meissner et al., 2011).

2.1 Conditioning Models

2.1.1 S-R models and the evidence for classical conditioning

Stimulus-response (S-R) models are currently the framework that most authors adopt when describing the placebo effect in terms of classical conditioning (De Houwer, 2018).

In his pioneering book called *Conditioned Reflexes*, Ivan Pavlov (1926) demonstrated how morphine injections can be used as an unconditioned stimulus (US) and paired with various cues (the CS) to produce a CR in dogs (enhanced saliva secretion, nausea and vomiting). In the second half of the 20th century, this was further explored within the context of placebos (Herrnstein, 1962). Cohen and Ader (1975), the founders of the field of psychoneuroimmunology, discovered that by pairing cyclosporine A (CsA) with saccharine solution, they were able to condition the immunosuppressive effect as the CR. Later, they found a similar effect in mice with systemic lupus erythematosus that had

a longer time of survival when conditioned with cyclophosphamide, a drug similar to CsA (Ader & Cohen, 1982).

According to Bąbel (2019), the first author to explicitly formalize the notion that conditioning could be the major mechanism causing the placebo effect was Wickramasekera (1980), the author who formulated the **Conditioning Response Model**. Besides describing the placebo effect within the classical conditioning framework, he also describes two stages of placebo effect formation:

Phase 1 – Acquisition. In this phase, connections between a CS and an US are being formed so that the CS (placebos as well as other environmental cues) can trigger a CR (the placebo effect). The main mediators of this process are arousal and attention via which the author also emphasizes the importance of the cultural meaning of the cues (such as the position of a doctor in the social hierarchy of the specific culture). The properties of the stimuli highly affect the rate of acquisition.

Phase 2 – Consolidation. The placebo effect as the CR has already been established and the connection with the CS can be further intensified or attenuated.

It is important to note that this model does not exclude the relevance of expectations. However, it stresses that the placebo effect is always stronger when the CR becomes less automatic and that the one mechanism is always conditioning. The whole context is seen as a set of previously conditioned stimuli that directly trigger other events, such as emotional responses (Wickramasekera, 1977).

The effect of classical conditioning on various health outcomes that could be labelled as the placebo (and nocebo) effect is currently examined in various research designs:

Goebel et al. (2002) managed to replicate the effect of **pharmacological conditioning** with CsA in humans. In their double-blinded study, healthy volunteers were conditioned in 4 sessions using CsA in its peroral form paired with a distinctly tasting drink (lavender strawberry milk). In the next stage, they were re-exposed to the drink together with placebo capsules. The control group received the placebo capsules instead of CsA in the first phase as well. The experimental group indeed had a significant decrease in measured immunological parameters compared to the control group (both IL-2 and IFN-γ mRNA expression as well as IL-2 and IFN-γ secretion by CD3+CD4+ lymphocytes, reduced T-cell proliferation) and an additional analysis showed that the final observed differences were not a residual effect of CsA itself. A similar design

showed the potential for conditioning the effect of histamine antagonists for the treatment of allergic rhinitis (Goebel et al., 2008).

One specific subtype of pharmacological conditioning research is using **dose-extending placebos**. In this design, the pairing of a placebo with a genuine pharmacological effect of a drug can, in theory, be used to extend its positive effects (Colloca & Howick, 2018). Albring et al. (2014) used the previously mentioned combination of CsA and a novel tasting drink and showed that extinction of the conditioned placebo effect might be prevented using subtherapeutic doses of CsA in healthy men. Just like many other placebo phenomena, the placebo effect using the dose-extended placebo design seems to be promising in the treatment of pain (Colloca et al., 2016). One study has also demonstrated the placebo effect using the dose-extending paradigm in psoriasis. However, it should be noted that its results were only true for one subset of participants (Ader et al., 2010).

In **non-pharmacological conditioning**, the US is not a specific pharmacological agent, but rather the experimenter directly manipulates the person's experience. In one of the first studies of this particular design, Price et al. (1999) used the Peltier thermal probe to apply a nociceptive thermal stimulus to the participants' skin. Each participant received three types of creams, with one representing a "strong placebo", another a "weak placebo" and the last being a control cream. Participants were informed that two of the creams were newly tested analgetics. In the manipulation part of the experiment (after calibrating the painful stimulus), the intensity of the stimuli was manipulated according to the intended placebo strength. In the next part, the stimuli were equalized for all the areas and the pain perception was measured using a VAS. As predicted, the participants reported significantly less pain for the strong placebo cream and experienced the stimulus as most painful on the body parts treated with the control cream. Various authors have managed to obtain similar results with slightly different cues and stimuli (some examples are: Bąbel et al., 2017; Colloca et al., 2010; Colloca & Benedetti, 2006; Reicherts et al., 2016; Schafer et al., 2015). The placebo hypoalgesia in this context has also been observed using physiological measures, namely in skin conductance and evoked potential amplitude (Nakamura et al., 2012).

Colloca et al. (2010) found that the number of learning trials for conditioning influences the response to placebos. It also seems that the conditioned placebo effect can be strongly influenced by previous experience of the efficacy of the treatment as well as by the time lag between the experience of this treatment effect and the placebo

conditioning trial (Colloca & Benedetti, 2006). This has been one of the multiple mentioned phenomena that seem to be in favour of the role of expectancy in the context of conditioning.

2.1.2 S-S models

So far, most of the mentioned examples have been described in terms of S-R models. Nonetheless, this general framework of conditioning has been widely criticized. In his pioneering paper titled *Pavlovian conditioning: It's not what you think it is*, Rescorla (1988) summarizes some of the phenomena that cannot be accommodated by S-R models, including that:

- **contiguity is not sufficient**: The rate of the US occurrence in the absence of the CS changes the efficacy of conditioning even when contiguity (that is, the occurrence of the CS in the presence of the US) is held constant. If a mouse experiences a higher base rate of shocks in the absence of a specific tone (the CS), the tone becomes less informative.
- **contiguity is not necessary**: It is possible to learn a negative relation between the CS and the US (that is, the absence of contiguity).
- **not all stimuli can serve equally well as a CS in various context**

He thus aims to explain the effect of conditioning by means of learning the relations between the representations of the stimuli**,** that is, *"the organism is better seen as an information seeker using logical and perceptual relations among events, along with its own preconceptions, to form a sophisticated representation of its world"* (p. 154).

This view was further adopted by the **stimulus-stimulus models (S-S models).** De Houwer (2018) has identified three distinct features of these models:

1. They view the conditioning as an association between the cognitive representations of the stimuli.
2. The S-S associations require certain favourable conditions.
3. These associations are capable of altering cognitive states (such as expectations), which can account for some of the unexplained phenomena.

The complexity of the S-R and S-S debate itself is, unfortunately, beyond the scope of this work. However, this distinction is conceptually relevant for some of the current placebo models. S-S models are compatible with the idea that various types of learning, including conditioning, contribute to the formation of expectations (Colloca & Miller, 2011).

Apart from S-R and S-S models, a new model of conditioning, the propositional model, has emerged in the past few years. Instead of forming simple associations, the basis of conditioning is the formation of propositions, *"qualified mental links, that is, links that specify how two events are related"* (Mitchell et al., 2009, p. 186). Only one author has attempted to view placebo conditioning in this framework (De Houwer, 2018). Given that the model is highly controversial even with respect to its general explanation of conditioning, only a brief summary was included in appendices (see Appendix A).

2.2 Expectation Models

Expectations of improvement have been repeatedly shown to improve clinical outcomes in various settings, such as in placebo hypoalgesia (Peerdeman et al., 2016), Parkinson's disease (Quattrone et al., 2018), irritable bowel syndrome (Flik et al., 2017), asthma (Busse & Lemanske, 2009), and others (Benedetti & Amanzio, 2013). In such designs, patients are usually instructed that they will (or might) receive an effective treatment, and therefore, they expect an improvement of their state.

Some authors differentiate between expectations and expectancies (Corsi & Colloca, 2017; Peiris et al., 2018), while others use them interchangeably (De Pascalis et al., 2002; Howick, 2017; Meissner et al., 2011). For the purpose of this thesis, expectations will be defined as *"a subset of expectancies, specifically those that are consciously accessible and therefore verbalizable"* (Kirsch, 2018, p. 82). As the concept of introspectively inaccessible expectancies has not been formalised within placebo research, its falsifiability would be questionable.

2.2.1 The Response Expectancy Theory

One of the most cited theories of how the placebo effects are formed is the Response Expectancy Theory. Its author, Irving Kirsch (1997), proposed two main objections to the S-R conditioning placebo models:

1. The effect of conditioning can be modified by changing participants' expectations.
2. Placebo conditioning does not always follow the extinction rule.

Kirsch has also embraced Rescorla's objection to S-R models. However, he does not find S-S models sufficient either as they explain only one way of forming expectancies rather than the mechanisms operating in-between the placebo effect and these expectancies.

According to the response expectancy theory, **response expectancies** are the main mediator of the placebo effect. They can be defined as *"expectancies of the occurrence of nonvolitional responses, either as a function of behavior (R-R expectancies) or as a function of specific stimuli (S-R expectancies)"* (Kirsch, 1985, p. 1189). For example, the expectation that a patient is going to feel less pain after the application of an analgetic cream is a response expectancy that can result in the placebo effect, while the expectation that a researcher will decrease the intensity of a painful stimulus is not a response expectancy. Rather, it is a **stimulus expectancy,** because it is related to an external event and not internal states, and therefore, it is not sufficient by itself for eliciting the placebo effect (Kirsch, 2018).

It should be mentioned that Kirsch (2004) later updated his definition to explicitly mark response expectancies as accessible by consciousness to avoid the unfalsifiability of the definition (although this does not mean that they are always represented by conscious processes[3]). However, he later marks all expectations as a consciously accessible subset of expectancies (Kirsch, 2018). Although not logically false (response expectancies can always be expectations), it does cause some theoretical confusion with regards to how some of the premises of the models are being assessed.

2.2.2 The Learning Model

Colloca and Miller (2011) have elaborated on Kirsch's theory with their learning model. They view the placebo effect in the context of Peirce's theory of signs and state that expectations are formed on the basis of decoding psychosocial signals and learning. These signs are processed and combined with higher cognitive functions via learning mechanisms to form expectations. The learning mechanisms include:

- **instructional learning** (what some other researchers refer to as the mechanism of expectations)
- **conditioning** (S-R or S-S as well as operant conditioning)
- **observational and social learning**

A clear advantage of the learning model is that it relates conditioning and expectations and allows for various processes of learning to be considered.

The idea of placebo effects induced by observational learning has been supported by studies of placebo hypoalgesia where participants observed other people's responses

[3] A good example is when a person is thirsty and takes a glass of water without realizing the action. One can still access the information that they are holding a glass of water, but the process does not necessarily always occur consciously.

to certain stimuli to which they were later exposed under the same conditions (Colloca & Benedetti, 2009; Egorova et al., 2015; Hunter et al., 2014; Świder & Bąbel, 2016). As for the suggested mechanism of operant conditioning in placebo effects, it has been directly examined only recently, and even though it does seem that the placebo effect can be elicited in this context as well, it is unknown what role expectations play in this context (Adamczyk et al., 2019). Also, the issue of subjectively reported outcomes becomes especially relevant to this phenomenon (see the chapter on methodology).

The evidence for the idea that the effect of conditioning is mediated via response expectancies comes from studies in which they were explicitly measured and a mediation analysis was conducted (Colagiuri & Quinn, 2018; Jepma & Wager, 2015), although in one such study, this effect was not convincing given its wide confidence interval after bootstrapping (Kirsch et al., 2014). That being said, mediation does not necessarily imply causality and there are other compelling explanations for such effects, such as the measurement of expectations influencing patients' reports, and others (Wager, 2005).

There is, however, substantial evidence against this hypothesis, or at least against the notion that expectations would always mediate conditioning. In a recent study, conditioning effects persisted even after informing the participants that they had been receiving a placebo (Schafer et al., 2015). It should be noted, however, that this does not eliminate expectations completely. More importantly, recent experiments with hidden conditioning (where participants are not told about the relation between the CS and the US) show that the effect still occurs and is not predicted by expectations (Bąbel et al., 2017, 2018). Other sets of studies show that when the conditioned stimulus is presented subliminally (without the participant consciously noticing it after it has been conditioned in the previous phase), the placebo effect also persists, although the role of expectations in this context needs to be further examined (Egorova et al., 2015, 2017; Jensen et al., 2012, 2015).

2.2.3 The Integrative Heuristic Model

Kirsch, Wampold and Kelley (2016) have recently published a new model that builds upon Kirsch's own theory and extends the learning model. Kirsch (2018) further elaborates on the adjustments that this model has made.

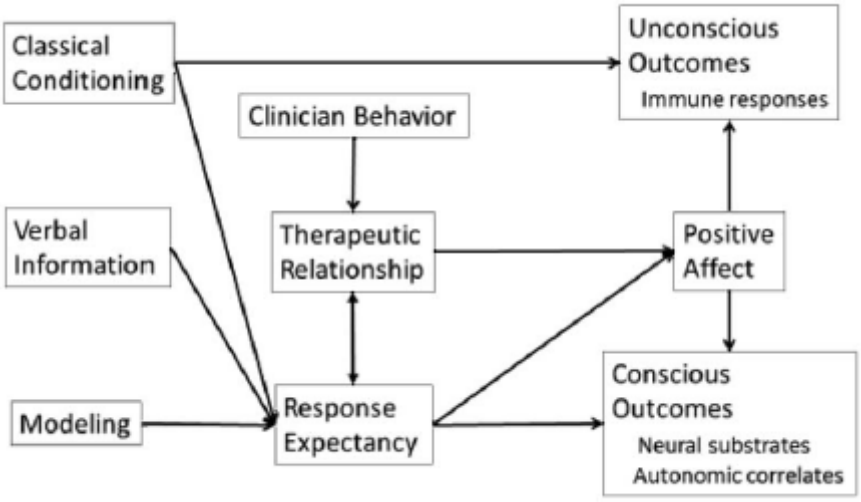

Figure 1: The Integrative Heuristic Model of placebo effects. From "Controlling for the placebo effect in psychotherapy: Noble quest or tilting at windmills?. An empirically derived theoretical model of placebo effects," by I. Kirsch, B. Wampold, and J. M. Kelley, 2016, *Psychology of Consciousness: Theory, Research, and Practice, 3*(2), p. 125. Copyright 2016 by the American Psychological Association.

Firstly, the therapeutic relationship, one of the major psychosocial predictors (see the next chapter) of the placebo effect, has been accounted for. In this model, the therapeutic relationship is influenced mainly by the clinician's behaviour and can affect response expectancies (perceived competence can contribute to the expectation of relief). This relation is reciprocal – beliefs about the treatment efficacy could, for example, contribute to the formation of a good therapeutic alliance.

Secondly, this new model also allows for the direct contribution of positive emotions. Good therapeutic alliance can potentially contribute to a patient's positive affect, either directly, or indirectly via response expectancies.

Thirdly, conscious outcomes have been separated from unconscious outcomes. The author notes that the reason is that the effect of conditioning is probably not mediated by response expectancies in the context of hormonal and immunological changes.

Indeed, this model is supported by some of the evidence on the role of communication and the clinician-patient relationship that will be mentioned in the next chapter. Also, it does seem that the placebo effect influencing hormonal and immunological factors might not be mediated by expectations, which is in accordance with the model, but the evidence is limited (Albring et al., 2012; Benedetti et al., 2003). Further, while there is some support for the role of positive emotions (Koepp et al., 2009), the reduction of negative emotions such as anxiety has been demonstrated more reliably in placebo studies (Flaten et al., 2011) and should be considered when interpreting results

of studies focusing on positive affect. Lastly, the previously mentioned issues with the role of expectations in conditioning-induced placebo effects on conscious outcomes have not been accounted for in this model.

2.3 New Conceptual Frameworks

New conceptual frameworks have recently emerged as well. These do not challenge the previous models, but they view them in the context of some more general psychological, neuroscientific, and computational approaches. As these frameworks have extensive conceptual backgrounds, they will be mentioned only briefly.

2.3.1 The Mindset Framework

The mindset framework has been recently introduced by Zion and Crum (2018). A mindset is defined as *"a lens or frame of mind that orients an individual to a particular set of beliefs, associations, and expectations, and functions to guide attentional and motivational processes"* (p. 141). From the definition, it is clear that mindsets and response expectancies are not identical, yet they are closely related. A mindset is a more general psychological process that orients expectations – for example, a mindset of *"cancer is a catastrophe"* (p. 146) can correspond to multiple specific expectations about the treatment, the disease management, and others. Therefore, some particular expectations are more likely to be triggered by the clinical interaction if they agree with a certain mindset that the patient holds.

This mechanism is supported by studies showing that mindsets can be important mediators of the effects of stress and that mindset-focused interventions can have an impact on objective health outcomes (Crum et al., 2011, 2013; Crum & Langer, 2007). However, the more general viewpoint that mindsets are a distinct concept from expectancies (especially with regards to their mechanisms) and the theoretical implications of this model for the placebo effect need to be further examined.

2.3.2 The Bayesian Brain Framework

The Bayesian coding hypothesis states that perceptual information is processed, interpreted and represented on the basis of conditional probability density functions (Knill & Pouget, 2004; Penny, 2012).

Büchel et al. (2014) have made the first attempt to apply this framework directly to placebo, more specifically using the example of placebo hypoalgesia (the model is expected to generalize to other placebo effects as well):

$$p(pain|sensory\ input) \propto p(pain)p(sensory\ input|pain)$$

(p. 1224)

This expresses that the posterior probability of experiencing pain given a certain stimulus is directly proportional to the product of the prior probability of perceiving certain stimulus when experiencing pain and the expectation of perceiving the pain itself (the *a priori* probability of pain).

In this context, the brain can be seen as generating hypotheses representing bodily processes and the outside world (**top-down predictions**) that shape our perception. It further receives **bottom-up perceptual information** that is interpreted based on these prior probabilities. A mismatch between the prediction and the input alters the probabilities of these hypotheses. When a previously precise prediction of improvement is triggered by placebos, the brain might conform to this highly likely hypothesis by producing physiological changes in accordance with the expected relief to minimize the prediction error (Ongaro & Kaptchuk, 2019). Apart from studies measuring the effect of response expectancies, this is also supported by research showing that different amounts of details in verbal instructions can lead to placebo effects of different effect sizes (Pollo et al., 2001; Vase et al., 2003; Verne et al., 2003).

3 Selected Candidate Psychosocial Predictors of the Placebo Effect

Apart from the controversies concerning the definition of the placebo effect and the psychological models of its functioning, a self-contained debate has arisen about the possibility of predicting who responds to placebos and under what conditions. An overwhelming majority of studies addressing these questions focus on triggering expectations; therefore, they might not generalise to placebo effects underlined with other mechanisms.

Before discussing the main psychosocial predictors of the placebo effect, it is worth noting that they might be culturally dependent (for a more detailed discussion, see Appendix B).

3.1 Trait Perspective

Since the last century, research has attempted to identify what distinguishes **placebo responders** (subjects who respond repeatedly to placebo treatments) from placebo **non-responders**. Kaptchuk et al. (2008) have reviewed the evidence from within-subject placebo studies in asthma and distinguished two perspectives that can be applied when examining the concept. From the perspective of **reliability**, it can be asked: If the placebo effect follows an administration of a particular treatment to a particular person, can the same effect be achieved later via a repeated administration of the same treatment to the same person? From the perspective of **consistency**, researchers would be asking if the same person responds to placebos repeatedly across multiple treatment settings. The authors note that the results are inconclusive, as most of the studies lack control for the natural course of the disease as well as more asthma-specific factors such as diurnal variation influencing the lung capacity.

A recent study found support that challenges the consistency of placebo responding. Placebo pills and electroacupuncture were both found to be effective in increasing pain threshold when compared to a no-treatment condition. However, responding to placebo pills was not associated with responding to electroacupuncture within the same individuals (Kong et al., 2013).

3.1.1 Personality

Although the concept of placebo responders is yet to be examined, researchers have tested if the placebo effect can be predicted using **personality** traits alone. The available literature is highly redundant with conflicting results, and therefore, two systematic

reviews have attempted to synthesize the current evidence. The most recent systematic review has found none of the included personality traits to be consistently supported as independent predictors of the placebo response across studies, including all the Big 5 personality traits. The most promising personality trait seems to be dispositional optimism. Other reported and potentially predictive personality traits included spirituality, absorption, inhibition and activation (activation being negatively associated with the placebo effect), and others. Interestingly, social desirability was not found to be predictive of the placebo response in any of the studies (Kern et al., 2020).

Similarly to the studies focusing on the concept of placebo responders, the review has not considered the importance of controlling for non-placebo phenomena. In this respect, the most methodologically sound piece of evidence might be the second systematic review that excluded such studies and considered other methodological issues. In accordance with the previous results, the authors found support mostly for traits that are more directly related to expectations, namely positive predictors including dispositional optimism, sensation seeking, and negative ones including self-efficacy and internal locus of control (Horing et al., 2014). One of the limitations of the review is that it focused narrowly on medical databases and practically excluded conditioning paradigms. It should also be mentioned that the number of studies for each trait was fairly limited given that only a few studies reflected the important methodological considerations.

3.2 Situational and Interactional Perspective

Currently, the focus has shifted from a dispositional approach to a more interactional approach, where personality traits are being examined within a particular situational context. The interactional nature of the placebo effect has been demonstrated in experiments including the choice of treatment and doctor-patient relationship.

3.2.1 The Role of Treatment Choice by the Recipient

In the context of placebos, it has been hypothesised that when patients are allowed to choose a treatment rather than being assigned one, the placebo effect becomes stronger. Rose et al. (2012) tested this hypothesis using the cold pressor task in which participants immerse their hand in cold water with ice. The study showed that when participants were allowed to choose between two placebo treatments (framed as analgesic pain-relieving ointments), they experienced a stronger placebo hypoalgesia. Interestingly, participants who were allowed to choose did not differ in their expectations about the ointment's

efficacy, but the effect was mediated by reduced anxiety during the task. Brown et al. (2013) present two studies where they extended the previous design. In the first experiment, they included a group with a choice and no expectation (choosing between two hand cleansers) to control for the factor of choice itself (rather than the choice of perceived effective treatment). The placebo effect was higher when both conditions were present, that is, when participants were allowed to choose between two placebos. A second experiment included all four of the previously mentioned conditions and additionally a group that was not presented with two alternatives but given one cream selected for them. This was done in order to control for a potential reduction in the placebo hypoalgesia after being presented with options and not being allowed to choose (no choice – expectation condition). The placebo hypoalgesia difference was not explained by a mere presentation of options. In a subsequent study, the authors also found that prior experience with a painful stimulus can affect the size of the placebo effect when given a choice (Geers et al., 2014).

One study used placebo labelled as beta-blockers in an exam anxiety setting. Parameters such as heart rate were examined after the administration of a placebo and after the completion of a set of examinations. Providing participants with a choice resulted in a decrease in heart rate post-exam as opposed to the group without a choice which showed an increase in heart rate instead. Also, the choice group reported more "medication" side effects. No relation to choice was found for blood pressure, anxiety, and for the number of physical symptoms such as nausea, cold hands, and others (Bartley et al., 2016). Another piece of evidence found a positive effect of providing a choice between cognitive enhancers on tasks measuring memory performance (Weger & Loughnan, 2015).

All of the mentioned studies have examined the role of choice in the placebo response using an immediate task. A recent study focused on a longer period (1 week) and found the placebo treatment to be effective for insomnia and other sleep problems, while the factor of choice was not found to be a significant predictor. It is, therefore, possible that the factor of choice has a more immediate effect that does not last (Yeung et al., 2019). Another explanation could be that the effect of choice in the placebo group has not been established in the sleep setting and might not be present in this particular context.

3.2.2 Doctor-Patient Relationship

Perhaps the most corroborated situational/interactional predictors are related to social interaction. These have been studied most extensively in the context of a **doctor-patient relationship**, although it should be noted that placebo effects are not relevant for clinical interactions only.

Blasi et al. (2001) systematically reviewed studies from the second half of the 20th century and concluded that although there are inconsistencies in the outcomes, adopting a warm communication style and reassuring the patient results in greater clinical improvements. More recent research supports these findings and a recent meta-analysis has found that empathetic communication and promoting positive expectations in healthcare consultations can positively affect health outcomes across multiple conditions, although the size of the effect was rather small (Howick et al., 2018).

However, it is important to establish the relevance of the doctor-patient relationship in placebo studies specifically. Surprisingly, only few studies allow for such inferences. Kaptchuk et al. (2008) randomly assigned patients with irritable bowel syndrome either to a waiting list, a sham acupuncture group, or a group that received sham acupuncture from physicians who followed a protocol that was supposed to increase their perceived warmth, confidence, and to implement active listening. As expected, an augmented doctor-patient relationship resulted in the largest improvement.

In another study of this kind, Howe et al. (2017) used the skin-prick test to exert a local allergic reaction and showed that patients who were expecting a relief had significantly reduced swelling compared to those who were framed with a nocebo cream. The difference between the two groups was further augmented when the creams were administered by a physician demonstrating high warmth and competence. In a high competence/low warmth group, the difference was augmented, but only in the last section of the measurements. The results for the high warmth / low competence condition were not significant. This study suggests that there might be an interaction between perceived warmth and competence, with competence being a necessary condition for the effect of warmth to manifest. That being said, the study performed many pairwise comparisons with no reported alpha level adjustments, and therefore should be considered rather exploratory. Also, other biological samples were collected with no reported results.

Multiple processes might be mediating the effect of a physician's communication style. A study outside the clinical context used a placebo intervention for balance and coordination tasks in healthy subjects. A warm communication style of a trainer resulted

in higher improvements in perceived performance (but not in objective performance) and this effect was fully mediated by expectations of improvement (He et al., 2018). On the other hand, studies simulating doctor-patient interactions show that a warm and empathetic communication style might act more directly on anxiety, while an appraisal of the treatment effectiveness results in positive outcome expectations. A combination of the two might be most effective in clinical settings, as they seem to interact (van Osch et al., 2017; Verheul et al., 2010). That being said, more research is needed to see if such results from simulation studies have ecological validity, and additionally, if they are supported when measuring genuine symptom improvements.

3.2.3 Transactional Model

Darragh et al. (2015) have attempted to systemise the current knowledge on trait and situational predictors in the form of a transactional model. They describe one main trait predictor being **permeability**, defined as *"perviousness to environmental factors such as treatment rituals and suggestion"* (p. 3). This construct has two facets which synthesize some of the current trait predictors and account for their overlaps. An **inward orientation** marks an orientation at internal states and includes traits such as suggestibility or absorption (tendency to become absorbed in one's internal experience). In contrast, an **outward orientation** is responsiveness to external cues and includes extraversion, dispositional optimism, dopamine-related trait, and others. The authors also compare this differentiation to Gray's theory of temperament describing the behavioural inhibition system (BIS) and the behavioural activation system (BAS).

A match between a person's permeability and environmental cues is required for the placebo effect to occur. For example, an externally oriented individual might respond well to positive interaction and novelty, while an internally oriented individual might prefer a non-threatening type of communication, low novelty, and even authoritative instructions.

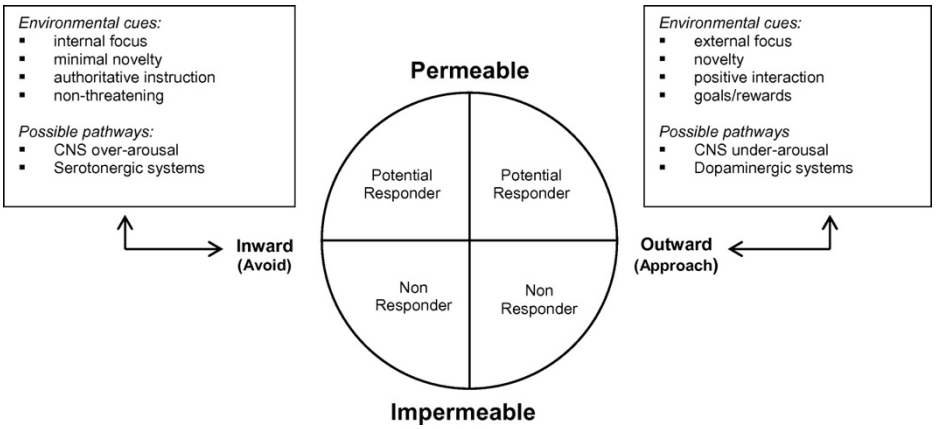

Figure 2: Transactional model of placebo responding. From "Who responds to placebos? Considering the "placebo personality" via a transactional model," by M. Darragh, R. Booth, and N. S. Consedine, 2015, *Psychology, Health & Medicine, 20*(3), p. 291. Copyright 2015 by Taylor & Francis.

One such relation predicted by the model was found in research focusing on persuasion, showing an interaction between optimism and the valence of the message (Geers et al., 2003). Similarly, another study reported extraversion predicting the placebo effect in patients with irritable bowel syndrome (IBS) only in the group with a warm and empathetic communication condition (Kelley et al., 2009).

The authors attempted to test directly whether personality traits predict the placebo response in accordance with the transactional model. They chose ego-resiliency as a trait representing the outward orientation and neuroticism for the inward orientation. The experimenters induced skin itch using histamine. The participants received a control cream in one session and a placebo cream ("antihistamine cream") with suggestions in another. The order of the conditions differed between the two groups. As expected, highly resilient participants responded more strongly when the placebo session happened first. However, the same relationship was found for neuroticism, although only when measured 5 and 7 minutes after exposure, which could be explained by habituation or the reduction of anxiety instead (Darragh et al., 2016b).

Another study conducted again by Darragh et al. (2016a) on healthy volunteers used the BIS/BAS scale. The administered placebo was a nasal spray. The group where the appeal focused on BAS was told that the spray would increase the production of oxytocin and *"regulate the stress response by promoting social engagement"* (p. 11), while participants in the second group (appeal to BIS) were informed that the spray would increase the production of serotonin that *"helps regulate the stress response by suppressing negative stress hormones and generating positive moods"* (p. 11). The study also included an inactive control group. In the oxytocin condition, participants with higher BAS scores experienced a larger reduction in anxiety and depression symptoms than

those with low BAS scores, whilst the results were somewhat mixed for participants with high BIS scores. Contrary to the transactional model, they also experienced a larger reduction in anxiety symptoms. The interaction was not significant for depressive symptoms.

Overall, the evidence seems to support the interaction between an outward orientation and the presence of externally orienting cues, but not the interaction between an internal orientation and its corresponding cues. However, it is unclear whether the selected cues and the measured traits were a suitable representation of these variables.

4 Methodological Issues in Placebo Research

Throughout this thesis, various methodological challenges in placebo research have already been mentioned. This chapter addresses conceptually relevant issues that are specific to placebo studies and that were not discussed in sufficient depth in the previous parts.

4.1 Non-placebo Effects in Placebo Groups

One of the recurring problems is an inadequate discrimination between placebo effects and non-placebo effects, as both of those can occur in control groups receiving a placebo treatment. Horing et al. (2014) have described four ways of filtering the non-placebo effects:

One option is to use **a control group receiving open-label placebos.** Participants assigned to this group would be aware that they are receiving a placebo or a sham intervention. It should, however, be noted that it is not known whether open-label placebos are worse than placebos involving deception. Locher et al. (2017) have reported that an open-label placebo was not significantly different in its effect from placebos involving deception, but it was more important whether participants were told about the effect of placebos. That being said, the authors failed to demonstrate the effect of the placebo compared to a no-treatment control.

Another option would be to determine **the natural progression of symptoms** for a particular condition. For example, when there is a tendency of a symptom worsening, improvements are more likely to reflect a genuine placebo effect. Unfortunately, this solution does not allow for controlling any other potential factors and the natural progression can be practically difficult to reliably predict.

Different levels of placebo manipulations allow for the examination of a relative improvement (for example, comparing a condition using two placebo pills vs. one placebo pill). In this case, it would indeed be possible to establish that there is an effect. In spite of that, it is unclear whether placebo effects are always dose-responding. A recent systematic review has failed to find evidence that greater placebo effects correspond to more intense placebo interventions, although the included settings varied greatly (Fässler et al., 2015).

Involving a **no-treatment control group,** that is, a group that does not receive any interventions (including placebo or sham interventions), is the golden standard method that requires fewer assumptions compared to the other methods and provides control via

the process of randomisation. However, one major disadvantage is that participants in the no-treatment control are well aware that they have not received any active treatment, and therefore, they might reflect their changes more accurately when reporting subjective outcomes without feeling the need to please the experimenter (Hróbjartsson et al., 2011). Therefore, response bias still needs to be addressed.

4.2 Bias in Placebo Studies

Hróbjartsson et al. (2011) have identified nine sources of bias in placebo studies (see Appendix C). For the purpose of this thesis, the response bias will be elaborated on further, as it is especially relevant for conceptual debates and as the authors consider it to be the most prevalent issue.

4.2.1 Response Bias and the Objectivity vs. Subjectivity Debate

In placebo research, it is common to study subjective outcomes, such as pain ratings on a visual analogue scale (VAS). Such reports rely solely on participants' reports and can be biased by multiple confounders.

One of these confounders can be **the social desirability bias,** which can be described as *"the tendency of respondents to provide socially desirable answers"* (Grimm, 2010, p. 105). Another component of the response bias can be the effect of **demand characteristics** of an experiment**.** While the social desirability bias is more related to socially sensitive topics, demand characteristics are present when the responses are affected by the participant's anticipations of the study purpose and can be defined as *"cues that make participants aware of what the experimenter expects to find or how participants are expected to behave*" (Nichols & Maner, 2008, p. 151).

When conducting research aiming to elicit the placebo effect, researchers often use suggestions to trigger expectations and provide information about the purpose of the study (such as "testing a new pain-relieving treatment"). Moreover, the participants often interact with a physician who could be perceived as a medical authority. Also, the no-treatment groups usually do not receive any such instructions. Therefore, controlling specifically for demand characteristics of the experiment is an especially relevant issue for placebo studies.

A Cochrane review has analysed 202 studies that included a no-treatment control group and separately estimated placebo effects for subjectively and objectively reported outcomes. The average SMD across conditions for subjective outcomes was -0.23, while only -0.13 for outcomes that were observed by experimenters. The effects were variable

across conditions and also across studies within one condition. Importantly, the effects were dependent on the form of placebo and also on the purpose of the study. The authors conclude that their analysis has not supported the assumption that the placebo effect can be clinically relevant, although it can affect subjective outcomes, but it is unknown what portion of this effect can be attributed to response bias (Hróbjartsson & Gøtzsche, 2010).

Finnis et al. (2010) respond with an objection that research focusing primarily on placebo effects is more likely to use conditions that are closer to a genuine clinical interaction (such as implementing the effect of suggestions), and therefore, meta-analyses should not focus on other experiments as they would underestimate it.

More importantly, as the number of studies focusing on objective outcomes and implementing new methodologies is increasing, it would be premature to discard the placebo effect as clinically irrelevant. Furthermore, biological measures involved in placebo effects are not easily established. For example, while attempts to link placebo effects to the neurologic pain signature have recently been questioned (Zunhammer et al., 2018), a meta-analysis conducted by Wager and Atlas (2014) found that placebo hypoalgesia is often associated with the activation of areas involved in emotional processing, prediction error, and ascribing value. In addition to this, studies using biological markers can have issues of their own. For example, a recent study showed that interpretations of the same fMRI data can vary greatly (Botvinik-Nezer et al., 2020). As the issue of the placebo effect is highly methodologically problematic on its own and can potentially include multiple psychological mechanisms, proper biological markers should be chosen with extreme caution. Apart from that, Hróbjartsson et al. (2011) also note that although biological measures do offer a compelling option, restricting placebo research to those would be a massive limitation with regards to clinically important questions.

How can researchers address the bias of responding in placebo studies when using self-reported outcomes?

Increasing participants' sense of anonymity could potentially reduce the social desirability bias, but on the other hand might also result in lower accuracy of reporting (Lelkes et al., 2012). That being said, for the purpose of group comparisons, this might be an acceptable compromise. More importantly for placebo research, there is some evidence showing that such precautions may reduce the experimenter demand effect as well (Hoffman et al., 1994).

Appealing to honesty might be another effective strategy to reduce reporting bias as well. Signing a proof of an honest intent prior to being given a chance to cheat has

been shown to significantly reduce cheating (Shu et al., 2012). In a similar context, Bryan et al. (2013) have shown that small differences in the phrasing of similar instructions may matter. While the context of reporting bias is different and these studies might not be relevant, emphasizing the importance of honest reporting at the beginning of the study might be an option worth exploring for reducing the effect of demand characteristics, especially in the case of attempting to please the experimenter.

Another option is to **directly measure responding bias as a tendency of a person.** While there are tools to measure social desirability responding (Crowne & Marlowe, 1960; Paulhus, 1991) and person's awareness of the research hypothesis (Rubin, 2016), a scale measuring the tendency to please the experimenter would be more relevant and is yet to be developed

An interesting option might be the use of the **within-subject design**. While the between-subject design can be better suited for testing the effects of interventions compared to well-designed control groups, such well-designed control groups are often not possible in placebo research. In this case, a within-subject design has the advantage of each participant serving as their own control. De Quidt et al. (2019) describe three strategies that reduce the responding bias in within-subject designs:

1. **a progressive revelation** of the treatments
2. **randomising the order of treatments** for each participant
3. **breaks** in-between treatments

Moreover, the within-subject design can be combined with the between-subject design when the first two conditions are met, as the first task can be analysed using between-subject comparisons as well. Studies assessing the amount of bias in such designs are yet to be conducted.

As can be seen from the brief summary of some potential methods, there are no established guidelines for addressing the responding bias in placebo research. Many of the debates that were outlined in this thesis were based on studies using subjective reporting. New research on these methodological challenges is necessary for the conclusions to be valid.

4.3 Placebo Effects Across Conditions

As was already discussed in the first chapter of this thesis, the terms "placebo effect" and "placebo effects" are used interchangeably as umbrella terms that may mark various phenomena. This seems to be a widely accepted premise. However, only few authors discuss the issue of context specificity.

It is only logical that for different conditions with distinct physiological features, different physiological pathways for the placebo effect would be required (Finniss et al., 2010). While the psychological mediators might be conceptually common to some extent as was outlined in the second chapter, a further combination of formed predictions with sensory inputs and subsequent neurobiological pathways can be more specific (Geuter et al., 2017). Also, there are conditions where the placebo effect seems to be either too weak beyond detection in smaller samples, or not present at all (Pollo-Flores et al., 2015). Furthermore, while there might be differences in the size of placebo effects across conditions, comparing their variability is problematic due to large differences in methodologies (Hróbjartsson & Gøtzsche, 2010). The issue of different conditions becomes especially relevant when comparing conflicting results that were observed in different settings. Studies verifying if such comparability is warranted are another challenge that the placebo research is yet to properly examine.

4.4 Placebo Effects Over Time

While experimental designs using short-term outcomes bring ethical and methodological advantages, such outcomes might not generalise to genuine clinical situations. Little is known about how placebo mechanisms change over time. There is some evidence suggesting that these changes might be important indeed. Tuttle et al. (2015) have analysed data from RCTs in neuropathic pain conducted between 1990 and 2013 and found that improvements in control groups receiving placebos have been increasing. Interestingly, these changes were found only in trials from the US. The improvements were positively correlated with the sample size ($r = 0.42$) and with the study length ($r = 0.34$). Both of these characteristics have been increasing in the US trials, but not in trials from the rest of the world. Similar relations of increasing improvements in control groups were found. In antidepressant trials, a positive association was found between the number of follow-up assessments and the magnitude of placebo responses (Posternak & Zimmerman, 2007). The opposite was found for antipsychotic medication, that is, placebo responses were larger in short-term trials (Agid et al., 2013; Welge & Keck, 2003).

Of course, these improvements cannot be certainly attributed to the placebo effect. A potential condition for examining these effects might be IBS, as a more direct study suggested that the placebo effect might potentially increase over time for this condition (Vase et al., 2005).

Empirical Part

5 Research Proposal

5.1 Theoretical Context and Research Objectives

This research proposal focuses on the interactional perspective of the placebo effect, one of the leading research concepts that have been affected by the shift in definitions and methodologies related to placebo. Unfortunately, this perspective cannot be verified or refuted by a single study. Rather, its specific forms need to be investigated.

This study will address the effects of choice on the placebo effect and its relation to personality. As has been outlined in the theoretical section, there is some support that choice increases the placebo effect. The studies were conducted primarily in the settings of pain, mostly using the cold pressor task. In this context, only subjective self-reports were assessed (Brown et al., 2013; Geers et al., 2014; Rose et al., 2012).

Therefore, the first objective of this study will be to **find support for whether the choice of a treatment can influence the placebo effect.** This study will use a different context and will attempt to reduce the response bias to see if the results replicate. As there are currently no verified methods of reducing the response bias for placebo research without compromising on a no-treatment group, objective measures will be used as well.

Darragh et al. (2015) predict that people with high outward orientation respond better to external cues, such as novel treatments. On the other hand, people with high internal orientation might respond better to *"authoritative instructions in non-threatening contexts"* (p. 5). From this reasoning, it might follow that the factor of providing a choice may serve as an external cue and increase feelings of engagement of the participant, and therefore increase the placebo effect in patients with high outward orientation, while clear instructions about the cream would be predicted to increase the placebo effect in people with high inward orientation. **Therefore, the second objective is to assess whether predictions based on the transactional model of placebo responding will hold in the selected setting and find indirect support for or against the model.**

5.2 Experimental Design

This study will implement a similar task to what Howe et al. (2017) used for examining the effects of perceived warmth and competence of a physician. The authors

used a skin-prick test (SPT) to induce a small allergic skin reaction that was furthermore the intended subject of the placebo effect. SPT is a routine diagnostic method that tests whether a person responds to various allergens. A small lancet is used to introduce the allergen to various areas of skin (often the forearm) and after 15-20 minutes, the size of the wheal (a raised bump) and the redness (flare) can be quantified. As a positive control for the test, 10 mg/ml histamine dihydrochloride is used (Heinzerling et al., 2013). For the purpose of this study, the main outcomes will be the wheal size (objective outcome) and subjective reports of itchiness measured on a continuous VAS scale. The wheal size was selected over the flare as the placebo effect demonstrated in the previous study was larger (Howe et al., 2017).

The combination of a subjective and an objective outcome provides the advantage of comparing the two responses. This is especially important in the context of the issue of subjective self-reports and can contribute to the placebo debate.

The placebo used in this case will be a cream with a neutral smell. For the purpose of testing the effect of choice, a similar design to the one that Brown et al. (2013) applied to the cold pressor task will be used. Participants will be randomised into four groups based on two binary variables – the presence of a placebo (yes/no) and the opportunity to make a choice (yes/no). Table 1 summarizes these conditions that will be discussed later in more detail:

	placebo	no placebo
choice	choosing between two placebo creams	choosing between two creams labelled as disinfectants
no choice	being assigned one of two placebo creams	being assigned one of two creams labelled as disinfectants

Table 1: Summary of the 2x2 design

Participants will also fill out the BIS and BAS scales that represent the inward orientation and outward orientation of individuals in accordance with the transactional model. These tools will be used in a way that is similar to how the authors of the model used these measures in their oxytocin/serotonin spray placebo study (Darragh et al., 2016a). The BAS scale has 3 subscales: *drive* (5 items)*, reward-responsiveness* (4 items), and *fun seeking* (4 items), which will be combined into a composite score. The BIS scale

is not further divided into subscales and is composed of 7 items. The BIS/BAS scores are somewhat independent (Carver & White, 1994).

The analysis will be separated into a confirmatory and an exploratory part. The **confirmatory part** will test research hypotheses that were chosen prior to conducting the research and derived from the theoretical part in accordance with the research objectives. All of these hypotheses will be evaluated separately for the main objective outcome (the wheal size) and the subjective outcome (the VAS itchiness report).

H1	The administration of a placebo cream decreases the wheal size / VAS reports.
H2	The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports more than the sum of the individual effects.
H3	The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports more in participants who score higher on the BAS scale.
H4	The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports less in participants who score higher on the BIS scale.

Table 2: Research hypotheses

The **exploratory part** will not test any specific hypotheses but will attempt to find trends in the data (data-driven approach). The result of the exploratory part will be testable research hypotheses that can be verified in future research.

The study will be comprised of two phases – the preparation phase and the main phase. As part of the preparation phase, a pilot study will be conducted to ensure that the two placebo creams are comparable in their attractiveness. The second step will be the training of physicians administering SPTs in order to at least partially equalise cues influencing their perceived warmth and competence (for details on the preparation phase, see Appendix D).

5.2.1 Main Phase

The main phase of the study is the main experimental procedure that includes SPT. This phase would take place at several medical facilities across England. Participants

would be greeted by a physician who would introduce themselves, ask the patient to read a description of the purpose of the study (*examining your individual response to a new allergen)* and outline a full description of SPT.

First, the participant would be asked to carefully read the whole description. Afterwards, the doctor would ask them to confirm their interest in participation by signing informed consent.

Then, the physician would collect the patient's medical history in order to check for the exclusion criteria (see the Participant Recruitment section) and to simulate a genuine physician-patient interaction. This part is common to all of the groups. From this point, the conditions will differ:

In both of the placebo conditions, participants will be given the cream descriptions that were used and verified in the pilot study together with additional written instructions:

As part of the experiment, we will compare two creams that are expected to soothe the allergic skin reaction. Please read the description and confirm that you agree with its application.

The group having a choice will then be asked to tick which of the creams they want to try. The group without a choice will be randomly assigned one by the physician.

The no placebo conditions will receive leaflets with different instructions:

For the purpose of this experiment, two disinfecting creams have been approved. Please read the description and confirm that you agree with its application.

Similarly to the previous case, participants will either be asked to select one of the disinfectants, or they will be randomly assigned one.

Afterwards, histamine SPT will be introduced. In accordance with the previous study, the cream will be applied 9 minutes after the test. The measures of wheal size, flare, and anonymised VAS scores of itchiness (all of those measured in millimetres) will be taken twice – the first time will be before applying the cream and the second would be 6 minutes after the cream application. Then, a difference between the two time points will be computed and used further for the analysis, which allows the individual variability of the response to be accounted for and for the relative change to be assessed (for a more detailed description of outcome measurements, see Appendix E).

After the procedure, participants will be asked to fill out BIS and BAS scales. Also, at the end, they will be asked to determine what the purpose of the study was.

5.3 Participant Recruitment

Given the extent of this study and its practical requirements, the assumption is that it would be conducted in a multidisciplinary team of physicians, psychologists, and also graphic designers. In the best-case scenario, multiple medical facilities from different parts of the country would be involved. Another assumption is adequate financial support, possibly via a research grant.

Healthy volunteers would be recruited online for participation in an allergy study via the Facebook pages of the medical facilities. Facebook ad targeting would be used in order to optimise the sample in terms of age, sex, and education. If possible, potential participants would be offered a small amount of financial compensation. Potential probands would first be informed via email about the skin-prick test and asked to confirm their interest before receiving an invitation to the study. The sample size obtained from a power analysis is 136 participants (see appendix F).

Apart from the inclusion criteria requiring currently healthy volunteers between the age of 18 - 60, exclusion criteria would include a history of psychiatric diseases, allergies, autoinflammatory diseases, being pregnant, and other conditions described in the ASCIA manual. The study should preferably be conducted some time between November and January outside the major pollen seasons which might influence SPT responses of people with undiagnosed allergies (ASCIA, 2020).

5.4 Data Analysis

Data will be analysed using the R programming language within the RStudio environment. The raw data and the complete R code would be made available for all analyses.

The main phase experiment will be analysed as a 2x2 design with 2 additional continuous predictors and 3 interactions. Two multiple regressions with dummy coded (0/1) variables will be conducted and the Benjamini-Hochberg correction will be used to control the false-discovery rate. The first regression will use the wheal size difference between the time of cream administration (9 minutes post SPT) and the endpoint (15 minutes post SPT, 6 minutes post cream application) as the dependent variable, while the other will use the difference between VAS ratings instead.

The predictors will be the same in both regressions: placebo (0/1), choice (0/1), BAS, BIS, and some of their interactions: placebo x choice, placebo x choice x BAS, placebo x choice x BIS. The formal tests of these predictors are t-tests about their respective population regression coefficients β_i. As the analysis is rather complex, a more

detailed description of the plan was disclosed in appendices, including a table of the null, alternative, and research hypotheses, as well as the pilot study analysis plan (see Appendix F).

The exploratory part of the analysis would attempt to find minimal adequate models and focus on the flare size as well as examining sex and age differences and relations to other variables.

5.5 Ethical Considerations

The Declaration of Helsinki states that apart from the case when no-treatment is available, the use of placebo is acceptable *"for compelling and scientifically sound reasons"* (World Medical Association, 2013, p. 2193).

SPT is a generally safe procedure with rare systemic responses (Heinzerling et al., 2013) that would potentially be handled within the medical facility. Placebo effects are an inseparable part of most treatments. Therefore, the research purpose might justify the use of placebo intervention in this case. A more ethically challenging component of this research is the use of deception. Ethics codes differ in their approach to deception. Given that the study is assumed to take place in England, the British Psychological Society (2014) Code of Human Research Ethics will be used for addressing the issues of this particular study. It states that deception is acceptable where "*the research objective has strong scientific merit and where there is an appropriate risk management and harm alleviation strategy*" (p. 24). A proper cost-benefits analysis and a risk management report should be submitted to an ethical committee.

Is the use of a procedure that causes discomfort justified in this case? Another context without discomfort would be more than welcome, but, unfortunately, measures such as physical performance would be more uncertain given that such studies cannot separate behavioural factors such as stronger effort from a genuine psychobiological response. Another option would be to recruit patients who already suffer from some condition. While this design might also assess the research hypotheses outlined in this thesis and would be worth considering as a follow-up study, the issue is that generally, the conditions may vary with regards to many factors and the required sample size might be difficult to obtain, especially in the context of physically measurable and immediate outcomes.

While SPT is not a procedure that would cause unbearable levels of discomfort in most patients (Tversky et al., 2015), pain is a subjective measure and as part of the risk management of the study, participants would be explicitly offered within the consent form

the choice of terminating their participation at any point and the option of requesting appropriate pain-alleviating medication and other relevant forms of proper medical aftercare (for more details, see ASCIA, 2020).

Another concern might be participants' approach to deception. A recent study has shown that the administration of a placebo involving deception in pain settings was generally well accepted by participants. On the contrary, both deceptive placebo and open-label placebo designs led to an increased willingness to participate in similar research in the future (Mundt et al., 2017). That being said, on an individual level, some patients might experience negative feelings that they have not agreed to the research goal in the first place. For that reason, participants must be explicitly offered the opportunity to withdraw their consent and to not be included in the analyses. If a proband shows signs of distress in relation to any part of the study, free psychological support will be offered.

An alternative to deception might be the option of **authorised deception.** In such cases, participants are told as part of the informed consent protocols that they will be intentionally deceived during some part of the study. Moreover, one study has shown that authorised deception might not decrease the magnitude of the placebo effect in pain (Martin & Katz, 2010). However, it used the placebo conditioning paradigm where expectations might be of lower importance. It is unknown how this methodology would affect the current design. In such a case, a preliminary analysis examining participants' cognitions about the experiment should be conducted. Appropriate adjustments of the design might be necessary in that case.

In accordance with the BPS ethics code, a cost-benefits analysis would be sent for approval to a REC of the National Health Service (NHS). The analysis would emphasize the methodological benefits of full deception in this study compared to its minimal harm risk. The proposal would also include the option of authorised deception as a viable, but not preferred alternative.

In either case, participants will be asked to guess the aim of the experiment at the end, which will be taken into account when interpreting the results. A proper debriefing about the nature of the experiment and the deception involved would follow immediately.

5.6 Discussion

The main line of research on the interaction between choice and the placebo effect used the cold pressor task with subjective outcomes (Brown et al., 2013; Geers et al., 2014; Rose et al., 2012). In this case, differences in potential outcomes might be attributed to two main factors – the possible reduction of response bias by collecting VAS reports

anonymously, and a qualitative difference in outcomes measured (pain ratings in contrast with itchiness reports). In this case, the objective outcome changes might be seen as more important, given that these two explanations cannot be completely differentiated and that it is unclear how well anonymisation reduces responding bias in placebo studies.

Howe et al. (2017) used SPT to compare placebo and nocebo groups, and therefore, the baseline placebo effect in the current study might have a smaller effect size, or might potentially not be established at all, in which case the results of the previous study might be attributed mainly to the nocebo effect. Another difference is in the collected measures - only the difference between the measures taken at the two points will be used for the purpose of the current study in order to keep the analysis economical. In the previous study, endpoint measures 15 minutes after SPT and 6 minutes after the administration of a cream were affected the most. While the natural progression of reactions to SPT is not a question of interest, its description might be important to see its comparability to the previous study.

A major limitation of the current study is the lack of blinding of researchers. While the risk of bias with objective measures is lower and a protocol giving instructions on how to behave will be followed, changes in the behaviour of the physician might be a confounder. That being said, the traditional issue with a doctor knowing which cream is the active treatment would not be of concern in this case, as the whole purpose of the study is to elicit the placebo effect in groups receiving a placebo. Other changes in behaviour might still interfere with the results. Asking each physician about their expectations of the study result prior to conducting it might allow for qualitative exploration of such effects.

The group receiving one of the creams labelled as disinfectant might also be more suspicious of the purpose of the research, as they are presented with a choice which might seem irrelevant. This potential bias might be examined using the qualitative reports of patients' expectations. Also, patients might ask the physician to make a choice for them. In that case, the physician might mask his intentions by saying that the regulations require that the patient chooses. While this option might work, it could potentially raise suspicion in some participants even more. In case a person completely refuses to make a choice, their data must be excluded from the analysis. This might be problematic in terms of excluding indecisive or otherwise specific participants from the choice group while keeping them in the other.

One effect that cannot be completely separated is that the group not being provided with the option to choose might feel disappointed when receiving a different cream knowing that there was another option. Notwithstanding the issue of variable separation in that case, this might more accurately reflect a clinical situation when providing a choice to a patient. Asking participants at the end of the study about their feelings related to the selected option comparatively to the other cream might allow for a qualitative exploration of this potential phenomenon.

The recruitment of participants cannot ensure that those who already participated in the research will not publicly share its research purpose. In this sense, it would be better to debrief the patients when the study is terminated. This option would, however, be ethically problematic. A partial solution is conducting the experiment in a time frame that is as short as possible, which might or might not be a viable option depending on the number of facilities involved and the practical difficulties. Furthermore, self-selection will likely exclude people with high fear of pain.

And lastly, the experiment is quite demanding in terms of methodology, ethics, practical considerations, and team cooperation, all of which might eventually reach their respective limits and the study design might have to be adjusted.

Conclusions

Is the placebo effect a justified concept?

The main psychological mechanisms seem to be similar across conditions as was shown in the second chapter of this thesis. Interestingly, these mechanisms were originally viewed as more separate. With further research, authors have attempted to relate placebo conditioning and expectations to each other. Recently, the distinct approach has emerged yet again to examine new inconsistencies showing that the mechanisms might indeed be connected in some cases, while completely separate in others. Furthermore, models accounting for a reduction of negative emotions and testing new conceptual frameworks might bring more clarity in the future.

Various phenomena falling under the umbrella term are likely to be influenced by similar psychosocial predictors. The placebo personality as a concept has been abandoned. As with many other psychological phenomena, the interactional approach might be more fruitful in explaining the proneness to experience the placebo effect. The outlined research might provide new insights into these interactions. Common factors influencing placebo effects is an important topic for medical practice and for its implementation in personalised health care.

In spite of that, this thesis has shown that there is no straightforward answer to the outlined question. Various relevant subquestions ought to be addressed first:

Is the umbrella term useful?

Are findings from different settings comparable?

Are subjective self-reports truly capturing at least some part of the placebo effect? If not, how much evidence is left?

While the *status quo* of concepts has changed and allowed for a proper theoretical separation of individual variables, it is clear that the *status quo* of placebo methodology is not sufficient to provide answers. In other words, separating the placebo effect from other components of the placebo response is not always possible given the ethical and methodological requirements. In light of this, new methodologies have emerged and present a compelling case for studying the placebo effect. As an example, some of these were implemented in the research proposal. In spite of this, a large portion of these approaches needs to be properly examined before their implementation within placebo research.

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Appendices and Supplemental Materials

Appendix A: The Propositional Model of Conditioning

Mitchell et al. (2009) have proposed a new model of conditioning that sees the formation of propositions as the main mechanism rather than the formation of associations. Propositions are *"qualified mental links, that is, links that specify how two events are related"* (p. 186). An example of this can be a belief that a specific sound precedes an electric shock.

In the context of the placebo effect, the propositional model has not been generally acknowledged by researchers other than De Houwer (2018), one of its founders. According to his view, this model could account for some of the placebo phenomena, such as the role of expectations and prior experience influencing the placebo effect. This advantage is mostly related to one of the model's key assumptions that even though propositional beliefs are accessible to conscious processes, the mechanism of forming propositions is automatic (De Houwer, 2009). This is in accordance with research showing that conditioning placebo effects can be modulated by means of changing expectations (described in the Expectation Models subsection).

The model itself has started an extensive conceptual debate (see the open peer commentaries to Mitchell et al., 2009). For example, Dickinson (2009) has pointed out that the association formation models are compatible with nonautomatic processes as well and that unlike these models, Hower has not sufficiently accounted for the relation between automatic and non-automatic processes. Similarly, a part of the debate has been focusing on the differences between animal and human conditioning with arguments both supporting (Chater, 2009) and questioning (Castro & Wasserman, 2009) the propositional model.

Appendix B: The Role of Culture

Various psychological models incorporate at least partially the idea that the placebo effect can be culturally dependent. They do not reason that the placebo effect would differ among nations in and of itself, but rather that different cues are more likely to trigger the placebo effect in different cultures (Colloca & Miller, 2011; Wickramasekera, 1980).

One such phenomenon might potentially be the effect of placebo colours. In general, it has been suggested that red, orange and yellow placebo pills produce more stimulating effects, while blue and green are more related to tranquilising effects (de Craen et al., 1996). Colour perception might be a culturally dependent symbol. A study examining colour related emotions found that there was little agreement among British and Chinese ratings of colours on the tense-relaxed and like-dislike scales (Ou et al., 2004). While blue seems to be the most preferred colour across different cultures and there is a similar cross-cultural pattern for colour clustering, there are significant cultural discordances in both the proximity clustering and in preferences for colour pairings (Madden et al., 2000). In accordance with previous research, Wan et al. (2015) have found that the colour of pills influenced the participants' perception and response expectancies. Moreover, expectations associated with different colours and shapes of pills slightly varied among Chinese, Colombian, and North American participants. For example, while red pills tended to be perceived as the most alerting and white pills were perceived as the most effective for the treatment for headache across all three of the cultures, only Chinese participants expected red and blue tablets to be harder to swallow.

Moerman (2000) has analysed data from RCTs on medication for ulcer disease, hypertension, and generalised anxiety disorder. The healing rates in placebo control groups varied considerably across the 32 countries. For example, while the average healing rate in control groups for ulcers was 36 %, this number was almost doubled in Germany (59 %) and only 22 % in Denmark and the Netherlands. On the other hand, the data for hypertension showed the opposite trend with Germany having the smallest improvement in control groups. It is not known if these differences are related to genuine placebo effects, or if they are more related to other factors such as participant selection. That being said, it is possible that cultural factors affecting expectations, such as general trust in the healthcare system (and the general attitudes towards various conditions), might lead to placebo effects of different effect sizes. This is in accordance with research showing that trust in a healthcare provider is associated with better treatment outcomes (Murray & McCrone, 2015).

Moreover, culturally specific beliefs have been suggested to influence the proneness to disease. Philips et al. (1993) have examined death records of 28 169 Chinese-Americans compared to the death records of 412 632 controls matched in their age of death, cause of death, and other factors. Chinese-Americans died 1.3 – 4.9 years sooner than their American controls when there was a match between a disease (the cause of death) and a date of birth predicting proneness to the disease according to Chinese astrology. The relationship was stronger among Chinese-Americans whose families refused necropsy to be performed (an indirect measure of adherence to the traditional Chinese culture). Moreover, the relation was more pronounced in acute diseases rather than chronic ones, therefore suggesting that factors such as lower adherence to treatment as a result of negative beliefs were not likely to be the main cause.

Although there is a considerable body of research on the role of culture in health, studies examining placebo effects in relation to culture are scarce and the specific factors remain unknown.

Appendix C: Bias in Placebo Research

Challenges	Characterization	Mechanism	Likely impact
Selection bias	Selection of patients or experimental subjects with different prognosis into compared groups.	Patients included in the compared groups differ at baseline due to either random events or preferred selection of one type of subjects to the experimental group	Overestimation of the effect of the placebo in studies only involving placebo vs. no-treatment. Unclear impact on the estimated effect of placebo in studies involving active vs placebo vs no-treatment.
Response bias	The tendency for patients or experimental subjects to report their symptoms in a way they feel is socially acceptable or desirable.	Patients or experimental subjects in the placebo group may report symptoms more optimistically than in the no-treatment group	Overestimate placebo effects of patient reported outcomes, for example pain and nausea
Co-intervention bias	The tendency for patients or experimental subjects to seek out and get treatment that is not part of the trial or the experiment.	Patients or experimental subjects in the no-treatment group may be more inclined to seek out non-protocolised interventions	Underestimate placebo effects when the non-protocolised intervention has a clinical effect, either due to a placebo effect or a non-placebo effect
Attrition bias	The tendency for patients or experimental subjects to drop out of the trial or the experiment.	Patients or experimental subjects in the no-treatment group may be more inclined to drop out	Unclear. The degree of bias and its direction depend on whether those leaving the no-treatment group had better or worse outcomes than those who stayed.
Outcome reporting bias	The tendency in scientific publications for statistically significant outcomes to be selected for reporting more frequently than outcomes with insignificant results	The authors of scientific publications often report only a subset of the outcomes studied, and tend to select those with statistically significant results	Overestimate placebo effects in articles aimed at studying placebo. Unclear impact on articles aimed at studying an active intervention (typically active vs placebo vs no-treatment)
Publication bias	The tendency for scientific publications with a statistically significant result to be published more frequently than studies with an insignificant result	Published scientific studies often reflect only a subset of the studies conducted, and those published tend to report statistically significant results	Overestimate placebo effects in articles aimed at studying placebo. Unclear impact on articles aimed at studying an active intervention (typically active vs placebo vs no-treatment)

Causal indeterminateness bias	A placebo intervention will often serve as a 'surrogate' causal factor for the largely indetermined true causal factors	The causal factors of the placebo effect are not typically imbedded in the placebo intervention per se, but in the patient-provider interaction	Competing interpretations of which causal factors are most important in a study finding large effects of placebo would typically have very different clinical implications
Nonclinical settings in laboratory experiments	A laboratory experiment will differ from the typical clinical situation in important ways	Non-clinical experimental studies on placebo tend to be of very short duration and may involve healthy volunteers	Provide valuable insight into the neurobiology and mechanisms of placebo effect, but results cannot reliably be extrapolated to a clinical setting
Informed consent and randomization	The trial or experiment may interact with the patients included	Informing patients about being part of a trial or experiment may alter preconceptions and beliefs	May underestimate or overestimate placebo effects. Beliefs in the effect of an interventions may be less pronounced compared with a clinical situation

Adapted from "Placebo effect studies are susceptible to response bias and to other types of biases. Main types of challenges to the reliability and generalizability of randomized trials and experiments assessing the effect of placebo," by A. Hróbjartsson, T. J. Kaptchuk, and F. G. Miller, 2011, *Journal of Clinical Epidemiology*, *64*(11), p. 1126. Copyright 2011 by Elsevier.

Appendix D: The Preparation Phase

The preparation phase will comprise of two steps.

Step 1 – A pilot study. The pilot study is important in order to establish the equivalence of the chosen placebo cream descriptions. First, two descriptions of the intended placebo creams will be developed. These descriptions will contain comparable, but differently stated information (such as general information about the producer, or the appearance of the cream). The difference would be most pronounced in the intended mechanism of action. For example, in one case, the cream might be described as *"creating a protective cooling layer"*, while the other one could be described as *"cooling by desensitising thermoreceptors in the skin"*. One leaflet will be created for each product and both leaflets will be presented together. For each participant, the location (right or left side) of the leaflets relative to each other would be randomised. Participants would be approached by volunteers in public within cities where the study would take place.

Participants will be first asked to imagine they are about to undergo SPT where they develop a small wheal, then presented with the leaflets, and subsequently asked to rate the two creams based on three questions:

1. How attractive is this cream for you?
2. How effective do you expect the cream to be?
3. If you could choose only one of the creams, which one would you prefer?

The first two questions would be rated on a scale of 1 – 10 with 10 being the most attractive/effective. Participants will be told in advance that they might be asked to imagine an uncomfortable scenario involving skin irritation.

Step 2 – Physician Training. In order to better account for the effect of perceived warmth and competence, physicians administering SPT will undergo a short training programme for the purpose of the study. The aim is that the physician is perceived as competent and moderately warm, as high or low warmness might be a confounder for the purpose of BIS/BAS testing. Behavioural and environmental cues described in the original study will be used (Howe et al., 2017). The specific content of the training would have to be constructed based on the number of medical facilities involved and their respective environment.

Appendix E: Measurement Protocol

Obtaining the measures will be performed as follows:

- **wheal size:** a transparent ruler for allergy testing will be used to measure the mean diameter of the wheal in millimetres. In an instance where the wheal takes on an irregular shape, a mean diameter will be computed as an average of the longest and the shortest perpendicular axes from the centre.
- **flare:** an equivalent method will be used for the flare size. In both of these cases, the methods were selected based on the recommendations from the manual of the Australian Society of Clinical Immunology and Allergy (ASCIA, 2020).
- **itchiness:** participants will be asked to mark their itchiness on a continuous VAS scale where the right end of the line represents the worst itch and the left end of the line no itch at all. The VAS measures will be taken anonymously using an electronic device (such as a tablet) in order to reduce responding bias.

When administering the VAS scale, the physician would inform the participant that they will not see the patient's results for the VAS measures and that all of the measures will be evaluated by an independent researcher in order to reduce bias. In line with that, they will emphasise the importance of honest reports so that the study results are conclusive. The physician would step away and allow the participant to fill in the VAS measure. The wheal size ratings and flare would be submitted by the doctor within the same electronic device without the patient seeing the results.

Appendix F: Data Analysis

The two questions from the preparation phase (the attractiveness of the two creams and their expected effectiveness) will be analysed using dependent samples t-tests (one for each question) or their nonparametric or robust counterparts in the event of an assumption violation. The third question (the preference of one cream or the other) will be analysed using a binomial test. The goal is to have equally compelling options to choose from. Of course, absent evidence against the null hypothesis should not be interpreted as evidence of absence. Rather, the statistical tests will be used as a rough guiding principle, but data exploration will be taken into account.

As has already been mentioned in the main section, the main method of analysis will be two multiple regressions[4] using the following variables: placebo (0/1), choice (0/1), BAS, BIS, placebo x choice, placebo x choice x BAS, placebo x choice x BIS. Because the research hypotheses are directional, the alternative statistical hypotheses will also be one-sided in those respective cases. The continuous predictors will be centred prior to their entry. The following table provides an overview of all chosen predictors and their corresponding research and statistical hypotheses. This table serves as a rough overview of the expected effects but using interaction plots will be necessary for an interpretation. A non-significant lower-order interaction or main effects in the presence of a significant higher-order interaction will not be interpreted as a support against the corresponding research hypothesis without considering the plots. To prevent inflation of type I error, a full model analysis will be reported for testing the main hypotheses even if any of the higher-order terms are insignificant. As part of the exploratory analysis, a minimal adequate model will be identified and tested.

Alpha will be set to 0.05 for each test. Because multiple hypotheses tests will be conducted, the Benjamini-Hochberg procedure will be used to control the false-discovery rate. In order to test the research hypotheses, formal tests are needed only for some of the terms and therefore, only those will be corrected. The rest will serve as exploratory parts of the analysis, including a third and equivalent regression analysis using flare size as the dependent variable. For the exploratory part, no multiplicity adjustments will be used.

[4] It might be argued that a multivariate regression or a MANOVA might be more suitable given that two dependent variables are being handled. However, because the research hypotheses should be evaluated separately for each of the measures given the controversies around the subjective and objective measures, conducting separate multiple regressions with multiplicity adjustment is more suitable for this purpose (Grice & Iwasaki, 2009).

predictor	research hypothesis / exploratory	null	alternative
intercept	exploratory	$\beta_1 = 0$	$\beta_1 \neq 0$
placebo	H1: The administration of a placebo cream decreases the wheal size / VAS reports.	$\beta_2 \leq 0$	$\beta_2 > 0$
choice	exploratory	$\beta_3 = 0$	$\beta_3 \neq 0$
BAS	exploratory	$\beta_4 = 0$	$\beta_4 \neq 0$
BIS	exploratory	$\beta_5 = 0$	$\beta_5 \neq 0$
placebo x choice	H2: The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports more than the sum of the individual effects.	$\beta_6 \leq 0$	$\beta_6 > 0$
placebo x choice x BAS	H3: The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports more in participants who score higher on the BAS scale.	$\beta_7 \leq 0$	$\beta_7 > 0$
placebo x choice x BIS	H4: The combined effect of choice and administration of a placebo cream decreases the wheal size / VAS reports less in participants who score higher on the BIS scale[5].	$\beta_8 \geq 0$	$\beta_8 < 0$

Table F1: Summary of the research hypotheses and their respective null hypotheses

Assumptions of the main analyses will be checked using diagnostic plots from base R (function plot()): the assumption of normality of residuals (Q-Q plot of residuals), homoskedasticity (scale-location plot), linearity (residuals vs. fitted values), and absence of great outliers (outliers with Cook's D > 0.5)[6]. If any of these assumptions are violated, respective robust methods, non-linear methods or transformations would be used depending on the nature and severity of assumption violation. In such a case, deviations from the pre-planned analysis would be reported.

[5] This hypothesis could also be stated as: Higher BIS trait reduces the effect of placebo X choice interaction.

[6] While formal tests of assumptions such as the Shapiro-Wilk test of normality would provide a more straightforward and transparent alternative, relying strictly on these tests can be misleading with respect to their power and special cases of data.

Using G*Power (Faul et al., 2007), the required sample size for achieving an appropriate power was computed. The linear multiple regression option under the t-tests family was selected. The previous study found a medium effect on size of the wheal (Howe et al., 2017). Because the previous study compared the placebo group to a nocebo group, the expected effect might be smaller. While small effects might be practically irrelevant, they would still be valuable for the comparison of the effect on subjective and objective measures. Moreover, effect sizes for the interactions are generally smaller. As a compromise between a small effect size and an unrealistic sample size that would be required, f^2 was set to 0.085, that is, between the reference small effect of $f^2 = 0.02$ and a medium effect size of $f^2 = 0.15$ (Cohen, 1988). Power was set to the usual value of 0.8, and the number of predictors to 7. Alpha of 0.00625 was used for the case of the strictest adjustment of $\alpha/8$. The computed sample size is 135 participants. This number was adjusted to 136 as it results in 34 participants per group.