Chapter 1

Introduction

The golden scientific standard to check treatment efficacy is to compare it to a control treatment that is similar to the initial treatment but does not have its active ingredients. We term this control treatment the placebo treatment. Applying this design enables scientists to distinguish the effects of the treatment from the nonspecific effects, i.e. the placebo effects. An important reason for this design is that a significant improvement is often also found in the placebo groups without an active treatment component. Placebo effects are defined as positive treatment outcomes due to mechanisms such as expectancies of the patients that cannot be attributed to the treatment's actions (1). Nocebo effects, to the contrary, are negative treatment outcomes that cannot be explained by treatment's specific mechanisms (2). Multiple meta-analyses demonstrated that a large body of evidence exists that the placebo effect improves chronic physical complaints such as pain (3), symptoms of chronic dermatological conditions, such as itch and skin lesions (4, 5), symptoms of mental disorders such as major depression (6) and alcohol use disorders (7), Parkinson's disease (8), irritable bowel syndrome (9), and many more. Previous research also focused on the link between placebo effects and the immune system and demonstrated that placebo effects can affect immune responses of the body (10). To the contrary, far less is known about the link between placebo effects and the endocrine system (11).

The endocrine system is an important regulatory system that maintains a wide range of physiological functions. The main function of the endocrine system is producing hormones, which are chemical elements that are released into the circularly system of the body and regulate functions of organs. Importantly, hormones produced in the periphery are able to reach the brain by penetrating the brain blood barrier or via regions that lack a brain blood barrier such as regions around the ventricles (12). At the same time, hormones that get released in the brain are spread through the whole body via the circulatory system (13). Being a part of a very complex system, hormones regulate various aspects of homeostasis: from blood pressure, digestion, sexual functions (14) to complex social behaviors (15). A dysfunction of the endocrine system is present in approximately 5% of the population (16). These disorders are mostly due to the underproduction of a certain hormones, such as insulin in diabetes type-1, or in contrast the excessive release of hormones, such as thyroid hormone in hyperthyroidism. Moreover,

hormones influence symptoms of mental health disorders, such as mood disorders (17), schizophrenia (18), borderline personality disorder (19) and post-traumatic stress disorder (20). Considering this major role of hormones in all aspects of human health, a better understanding of the physiological mechanisms that influence the production of hormones, and on the other hand, the effects of hormones on different health-related processes, is essential for finding new ways to treat various diseases.

However, despite the accumulating evidence on the importance of placebo effects for health outcomes and the major role of hormones in maintaining health, the interrelationship between these factors has not been studied extensively. Almost no studies have been done on how placebo effects can affect the endocrine system. Moreover, not much is known about possible effects of hormones on the placebo and nocebo effect. In this dissertation, we address this gap in knowledge and consider the bidirectional link between placebo effects and the endocrine system with a focus on the hormone oxytocin. The theoretical model that connects the aims of this dissertation is presented in Figure 1. As reflected in Figure 1, we distinguish two perspectives in this approach: 1) the possibility to trigger placebo effects in the endocrine system and specifically in oxytocin (upper part of the figure), and 2) the potential moderating role of oxytocin in placebo and nocebo effects (bottom part of the figure).

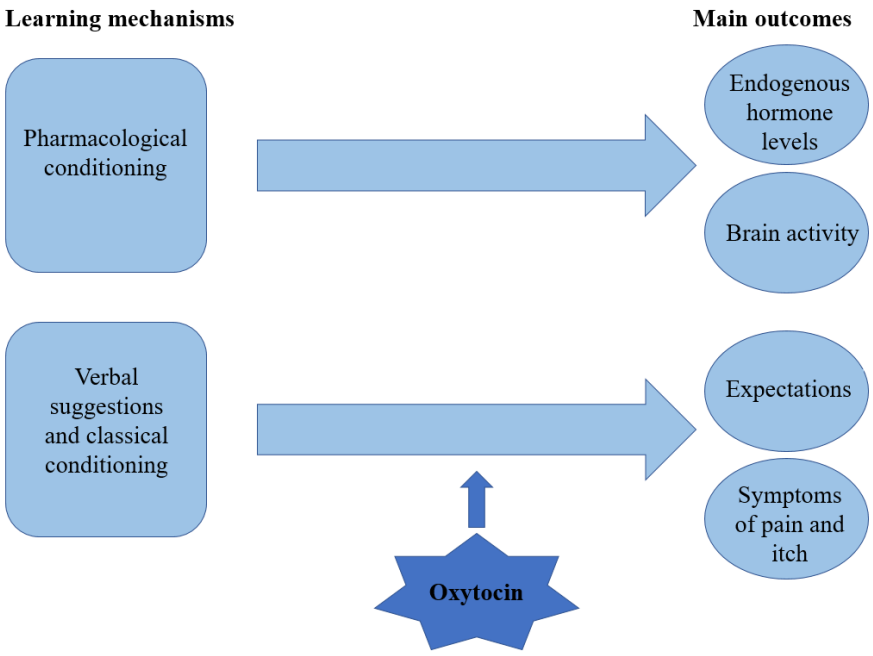

Figure 1. The working model of the dissertation.

Learning mechanisms of the placebo effect

The placebo effect is most commonly described from a learning perspective (21-23). Colloca and Miller (21) have proposed a learning theory of the placebo effect that states that placebo effects are triggered by expectations that in turn are being formed on the basis of how the brain interprets stimuli coming from the environment. The authors have described three mechanisms that link environmental stimuli with expectations: 1) classical conditioning (associative learning), 2) communication or verbal suggestions (instructional learning), and 3) social observational learning. In the following sections we will discuss the first two mechanisms and their role in eliciting placebo responses in the hormonal system, as the link between observational learning and the endocrine system has not been studies so far.

Classical conditioning

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Classical or Pavlovian conditioning is a learning process in which an association is established between an initially neutral stimulus and a physiologically relevant unconditioned stimulus (US) leading to an unconditioned response (UR). After repeated pairings, the neutral stimulus becomes a conditioned stimulus (CS) and triggers a response similar to the US; the conditioned response (CR). Two broad but separate areas can be identified in which the principle of classical conditioning of placebo effects is applied: 1) pharmacological conditioning (conditioning of drug effects) and 2) conditioning by means of manipulation of stimulus intensities (conditioning of somatosensory sensations such as pain). Pharmacological conditioning is frequently investigated by applying a two-phase conditioning design consisting of an acquisition phase (in which learning takes place) and an evocation phase (in which the learned association is tested). In the acquisition phase, an active pharmacological drug (US) is coupled with an initially neutral stimulus (e.g., a drink, CS). In the evocation phase, the drug is replaced with placebo and presented together with the CS. Physiological or psychological responses to the placebo are usually measured in the evocation phase (e.g., 24, 25, 26). In case of successful conditioning, the CS triggers a conditioned response similar to the drug effect even if the active medication is replaced by placebo. The placebo effect thus mimics the response to the medication in this paradigm. Convincing evidence exists that pharmacological conditioning can affect several immune parameters (10), such as interleukin-2 (27, 28), histamine (29), T-cell proliferative capacity (30), and interferon-gamma (28, 31). Placebo effects triggered by classical conditioning in the endocrine system are far less investigated. A number of animal studies have demonstrated that secretion of corticosterone (32, 33), insulin (34), and sex hormones (35), among others, can be classically conditioned. Far less human research focused on this topic, with only a few studies that investigated pharmacological conditioning of cortisol (36, 37), growth hormone (36) and insulin (38, 39). Because of the important role of hormonal responses in the majority of physiological functions and the prevalence of endocrine diseases, the possibility to induce placebo effects in the endocrine system (i.e., by means of pharmacological conditioning) holds great promise for clinical purposes.

Another frequently used application of conditioning is the manipulation of stimulus intensities in order to induce placebo (or nocebo) effects. Most of the research with the manipulation of stimulus intensities has been done in the field of pain (e.g., 40, 41-44). In such studies, placebo analgesia (i.e., placebo-induced pain relief) and nocebo hyperalgesia (i.e., nocebo-induced worsening of pain) are investigated by employing the same two-phase conditioning design as described above. However, in this type of research, the unconditioned response is triggered not by a pharmacological drug but by manipulating the intensities of the stimuli presented to a participant. In case of pain conditioning, in the acquisition phase, different levels of pain stimulation are coupled with the presentation of different visual stimuli (CS). For instance, low intensity pain stimuli are coupled with a green computer screen, and high pain intensity stimuli are coupled with a red computer screen. During this phase, an association between the color and the pain is established. In the evocation phase, participants receive the same levels of medium pain intensity with green and red cues. A decrease in reported pain in response to green trials in the evocation phase is considered indicative of placebo analgesia, while the increase in pain in response to red trials is considered indicative of nocebo hyperalgesia. Various conditioned stimuli have been used in these paradigm such as colors (40, 45), geometrical shapes (46), and photos of faces (47). Overall, a large body of evidence demonstrates that this conditioning procedure is effective in inducing placebo (see meta-analyses 3, 48) and nocebo effects (49, 50) for pain.

Verbal suggestions

Verbal suggestions are another well-investigated method to induce placebo effects in a laboratory setting. Giving information about positive effects of the treatment triggers response expectancies that are defined as anticipations of nonvolitional, subjective, and behavioral responses to particular cues (22). These expectancies are directly linked to the placebo response: if a patient is told that a sugar pill is a strong analgesic that should decrease his/her pain, most probably he/she will feel an actual pain decrease. A large body of evidence exists that giving mere verbal suggestions regarding symptom-reducing effects of a sham treatment can significantly reduce symptoms of, among others, pain (3), fatigue (51), headache

(52), and itch (53). At the same time, suggestions that a sham treatment would exacerbate symptoms have been shown to increase pain (50), nausea (54), and itch (53), and worsen physical performance (55). Almost no research has been done on the possibility to induce placebo effects in the endocrine system by giving verbal suggestions. To our knowledge, only one study attempted to elicit placebo cortisol and growth hormone release and decrease by influencing conscious expectations of participants by giving verbal suggestions (36). Participants in this study were told that the medication they would receive (a placebo) would decrease or increase, depending on the group allocation, their cortisol and growth hormone levels. No effects of verbal suggestions on these hormones were found. Possibly, as changes in hormonal levels are automatic processes that are mostly unnoticeable by people, changing their conscious expectations might not be enough to induce physiological placebo effects. The existing evidence indicates that conditioning is necessary to trigger physiological changes. However, more research employing various types of verbal suggestions and focusing on different hormonal systems is needed to draw any conclusions about the effects of verbal suggestions on hormonal secretion.

Hormonal mechanisms of the placebo effect

The suggestion that the endocrine system may possibly be involved in the placebo effect as a mediator and/or a moderator is intriguing. A lot of attention in placebo research has been given to neurotransmitters and peptide hormones of the endogenous opioid and cannabinoid systems as possible mediators of placebo. It has been demonstrated that positive verbal suggestions and conditioning activate the release of endogenous opioids and cannabinoids, which in turn induce analgesic effects (56, 57). Moreover, it was shown in a series of studies that naloxone, a blocker of opioid receptors, prevents the development of the placebo effect for pain (58-60) and the opioids released during placebo treatment cause side effects similar to the opioid medication (61).

Some studies looked at possible effects of baseline hormonal levels on the response to placebo manipulations. Evidence from these studies remains mixed. For example, Johansen and colleagues (62) did not find a correlation of baseline cortisol and beta-endorphin levels with placebo and nocebo pain responses induced by verbal suggestions. However, baseline cortisol levels have been shown to be related

to the responsiveness to classical conditioning of cortisol (24): participants with higher baseline cortisol levels demonstrated a conditioned cortisol release, whereas participants with lower baseline cortisol levels did not. Furthermore, Ober and colleagues (63) showed that conditioned placebo immunosuppression was related to baseline noradrenaline levels. Baseline hormonal levels might indicate how successful pharmacological conditioning can be, however, this question needs to be further investigated. In general, more research is needed to identify the hormonal factors that can influence the placebo and nocebo effects and the pathways of their action.

Finally, administration of hormones and hormone-stimulating medication can be used to enhance or inhibit placebo and nocebo effects. Again, this area remains underexplored and only a few hormones were investigated in this context. Colloca and colleagues (64) found that administration of vasopressin, a peptide hormone that also regulates social and stress behaviors, enhances placebo analgesia induced by verbal suggestions, but only in women and not men. These findings correspond to behavioral effects of vasopressin, which has shown to increase cooperation and friendliness in women only (65, 66). Benedetti and colleagues (67) found that nocebo effects can be influenced by cholecystokinin, a peptide hormone of the gastrointestinal system that also has anxiogenic effects. The nocebo effect, induced by verbal suggestions, was abolished when patients received proglumide, the cholecystokinin agonist (67).

A hormone that has both anxiogenic and social effects and might have a potential for influencing placebo and nocebo effects is oxytocin. Oxytocin has been shown to reduce stress (68) and increase trust (69, 70) and both of these factors might play a role in the placebo effect. Additionally, there is some evidence that oxytocin facilitates learning in a classical conditioning paradigms (71) and accelerates extinction of the conditioned response (72). Despite this potential, oxytocin has not been sufficiently investigated in the context of enhancing placebo and decreasing nocebo effects, with the exception of two studies that demonstrated conflicting results (64, 73). Colloca and colleagues (64) have used oxytocin to boost placebo analgesia induced by verbal suggestions and found no effect of this hormone on the placebo effect neither in men nor in women. However, Kessner and colleagues (73) have demonstrated that oxytocin increases placebo analgesia also induced by verbal suggestions. At this moment there is no clear

evidence about whether oxytocin can increase the placebo effect induced by verbal suggestions, and moreover, no studies looked at the possible effects of oxytocin on placebo and nocebo effects induced by classical conditioning.

Oxytocin

Oxytocin is a hormone and neuropeptide produced primarily in the hypothalamus. The first oxytocin research was focused primarily on its functions in labor regulation (74), lactation (75) and mother-infant bonding (76). Prosocial effects of oxytocin recently have drawn a lot of attention in social psychology (77). Oxytocin has been demonstrated to regulate emotion recognition (78) and emotional contact (79), decrease stress (68), and increase trust (69), empathy (80), and generosity (81). Neuroimaging studies have demonstrated that oxytocin affects the areas of the brain mostly linked to the perception of social stimuli, the amygdala, the area underlying stress responses and recognition of emotions (82, 83); the insula, the area that plays a role in emotional responses and empathy (84, 85); and the superior temporal gyrus, the area involved in the perception of emotions in faces (86). A two-part model has described the effects of oxytocin on the human brain: bottom-up effects of oxytocin reduce anxiety and facilitate approach behavior; and top-down effects of oxytocin increase reward from social interactions (86). Because of its prosocial effects, oxytocin has been intensively investigated as a treatment for mental disorders related to emotional deficits. Positive effects of oxytocin were found on symptoms of autism (87), schizophrenia (88), and borderline personality disorder (89). Moreover, oxytocin has beneficial metabolic and immune effects. Treatment with oxytocin, for example, increases insulin sensitivity and decreases weight in obese adults (90), reduces inflammation (91, 92), and increases healing processes (93) in animals.

Considering the potential beneficial effects of oxytocin for somatic and mental disorders, the possibility to induce placebo oxytocin release might have various clinical implications. However, no studies so far looked at whether it is possible to classically condition oxytocin release. Very little research has been done on classical conditioning of endocrine responses in general. On the other hand, oxytocin seems to

influence core mechanisms of placebo responding: trust (70), stress reactivity (68), and learning (71), which makes oxytocin interesting as a hormone that potentially can enhance the placebo effect.

Factors influencing the placebo and nocebo effect

In addition to the mechanisms mentioned above that are predominantly based on learning theory, there are numerous other factors that can influence placebo and nocebo effects. For example, the affective state, such as anxiety seems to play a possible role in placebo and nocebo effects. Colloca and colleagues for example showed that baseline dispositional anxiety levels are negatively related to placebo analgesia (64). Moreover, Benedetti and colleagues (94) demonstrated that diazepam, an anxiety-reducing drug, blocks nocebo hyperalgesia. Next to affective states, other factors, such as personality characteristics of extraversion (95), neuroticism (96), and suggestibility (97) have been incidentally found to affect the effects of placebo and nocebo responses. Interestingly enough, Pecina and colleagues (96) found that personality traits were related to a placebo-induced decrease of cortisol levels. This points at a possible role of stress hormones in the relationship between personality and the placebo effect.

Also, a link between genetic factors and placebo effects has been described in the literature (23, 98). Genetic polymorphisms in the catechol-O-methyltransferase (COMT) gene, rs4680, has been repeatedly shown to be associated with predicting placebo responses in chronic pain (99, 100), irritable bowel syndrome (99), and depression (101). Moreover, it has been demonstrated to be related to nocebo effects (102). The COMT gene is responsible for creating an enzyme that metabolizes catecholamines. This enzyme helps to control, among other things, the levels of the hormones adrenaline and noradrenaline. Possibly, therefore, these hormones might play a role in the placebo effect. However, this link has not been systematically investigated in the literature yet.

The current dissertation

In this dissertation, we address the link between endocrine parameters with a specific focus on oxytocin and placebo effects from two perspectives: eliciting endocrine/oxytocin responses by means of classical conditioning (Part I, Chapters 2, 3 ,4), and influencing placebo effects with oxytocin (Part II, Chapters 5

and 6). Additionally, we explore the role of other factors, such as expectations, personality factors, affect and anxiety in these two main research questions.

Part I is dedicated to exploring the possibility to pharmacologically condition endocrine responses, in particular oxytocin. In **Chapter 2** we introduce the topic of classical conditioning of endocrine responses and systematically review studies on this topic done in animals and humans. This is the first systematic review on the topic of endocrine conditioning that includes both animal and human research. We summarize evidence from this field, give an elaborate overview of similarities and differences between animal and human research, describe the study designs used to condition hormonal responses and discuss possible benefits of applying classical conditioning in clinical practice.

In **Chapter 3** we address the topic introduced in Chapter 2 from an experimental perspective and present the results of a randomized controlled trial in which we investigated the possibility to elicit classically conditioned oxytocin responses. This is the first experiment on classical conditioning of oxytocin in humans and one of the few studies on classical conditioning of endocrine responses in general. We investigate oxytocin conditioning using a commonly used two-phase conditioning paradigm with three acquisition days and three evocation days, and explore conditioned oxytocin responses and their extinction process. Next to the measurement of conditioned changes in endogenous oxytocin levels, we also study possible effects of conditioning of oxytocin on a social task and pain sensitivity. Moreover, we explore the role of personality and affect in the classical conditioning of oxytocin responses.

Chapter 4 presents the results of an fMRI experiment that was a part of the trial described in Chapter 3. In this chapter, we compare the effects of endogenous conditioned oxytocin responses and exogenous oxytocin administration on brain activity in response to several tasks commonly used in oxytocin research. In this chapter, we aim to unravel possible brain mechanisms underlying oxytocin conditioning in relation to oxytocin administration.

Part II is dedicated to exploring the influence of oxytocin on the placebo effect. In **Chapter 5**, we describe the results of a randomized controlled trial in which we investigate whether oxytocin influences expectations of participants and enhances placebo effects for pain and itch. In this experiment, we aimed

to induce placebo effects by giving positive verbal suggestions in healthy women and use a standard dose (24 IU) of oxytocin to enhance these effects.

Chapter 6 presents the results of another randomized controlled trial that was performed as a follow-up for the trial described in Chapter 5 and addresses this question from a slightly different perspective. In this trial, we explore whether oxytocin could enhance placebo analgesia, reduce nocebo hyperalgesia, and influence the extinction of both. To induce placebo and nocebo effects, we used a classical conditioning procedure together with verbal suggestions. Moreover, we included a male sample and use a higher dose of oxytocin (40 IU) than in the study described in Chapter 5. Overall, these two experiments investigate the effect of oxytocin on placebo effect in both female and male samples, with different dosages of oxytocin and different methods of placebo induction.

Chapter 7 is the general discussion of the dissertation. This chapter summarizes the results of the conducted studies, connects them to the aims and hypotheses that we initially had and discusses them in the light of possible clinical implications.

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