Between Pain and Math – How Expectations Shape Cognitive Processes from Neural Activity To Behaviour

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"Wenn eine Vorstellung in der Einbildungskraft gewecket wird, so entstehen auch (wie die Physiologie lehret), bestimmte, dieser Vorstellung, und dem Grade ihrer Stärke entsprechende Veränderungen im Gehirne, es werden mehrere andere mit ihr verbundene Vorstellungen gewecket, die dann auch ihre eigenen Reizungen im Gehirne zu Begleiten haben, oder sie anregen. Weil nun die Nerven ihren Ursprung im Gehirne haben, und diese die Werkzeuge der Empfindung und Bewegung in dem ganzen Körper sind, so erhellet, daß überhaupt auch andere von dem Gehirne weiter entfernte Theile von der Einbildungskraft afficiret werden können, und insbesondere, daß merkliche Reizungen der Nerven im Gehirne in die Muskeln, worin diese Nerven hineingehen, geleitet werden, diese in Bewegung versetzen können, die sodann ähnliche Veränderungen in den Gedärmen, in dem Magen, im Herzen, in den Blutadern, und den Röhren der anderen Säfte bewerkstelligen, die durch Einwirkungen äusserer Ursachen, oder auch durch Seelenwirkungen ehedem hervorgebracht waren."

Ferdinand Ueberwasser, 1787 (p. 143f)

„If an image is awakened in the mind, then (as physiology teaches us) specific changes in the brain arise, corresponding to this image and its intensity; other images connected to the first one are roused which then also have to accompany their own excitations in the brain, or spur them. Now, as the nerves originate in the brain and as they are the instruments of sensation and movement in the entire body, it ensues that also other, more remote body parts can be affected by imagination. In particular, it ensues that noticeable excitations of the nerves in the brain are transmitted to the muscles, wherein these nerves terminate, and cause these muscles to move, which, in turn, cause similar changes in the bowel, in the stomach, in the heart, in the blood vessels, and in the tubes of the bodily fluids that originally were brought about by the impact of external accounts or the soul, respectively. "

Ferdinand Ueberwasser, 1787 (p. 143f)

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ZUSAMMENFASSUNG

Erwartungen beeinflussen verschiedenste Arten kognitiver Prozesse, von einfacher Stimulusverarbeitung bis hin zu höheren kognitiven Funktionen. Ihr Einfluss wird häufig nicht bewusst wahrgenommen, auch wenn er merkliche Spuren in unserer Wahrnehmung und unserem Verhalten hinterlässt. Es ist daher die primäre Zielsetzung dieser Dissertation, das grundlegende Verständnis von Erwartungseffekten zu erweitern und verschiedene Wirkungen von Erwartungen wechselseitig zueinander in Bezug zu setzen.

Zunächst werde ich einen Überblick über verschiedene, weitgehend unabhängige Bereiche geben, in denen Erwartungseffekte untersucht und diskutiert wurden. Anschließend werde ich drei Projekte vorstellen, die unser Verständnis von Erwartungseffekten auf kognitive Prozesse erweitern sollen: Das Projekt „*Gender, Pain, and Expectations*“ untersucht den Einfluss von Stereotyp-bezogenen Erwartungen auf die Schmerzverarbeitung und beleuchtet dabei mögliche physiologische Mechanismen, die diesem Phänomen zu Grunde liegen könnten. Dabei bedient es sich verschiedener Maße, wie der Messung von BOLD-Aktivität, Hormonkonzentrationen, und Verhaltensreaktionen auf pharmakologische Interventionen. Das Projekt „*Between Pain*

and Math“ zielt anschließend auf einen Brückenschlag zwischen verschiedenen Forschungssträngen zu sozialen und traditionellen klinischen Erwartungseffekten ab. Dabei untersucht es sowohl den Einfluss von Erwartungen auf Schmerzvariablen als auch auf Maße höher kognitiver Funktionen. Diese Vorgehensweise erlaubt es, die Beeinflussbarkeit verschiedener kognitiver Bereiche zu untersuchen, wenn spezifische Erwartungen induziert werden. Im Projekt „*Expectations and Cognitive Performance*“, habe ich schließlich den Einfluss eines traditionellen Placebo-Paradigmas auf die Leistung in kognitiven Aufgaben untersucht. In diesem Kontext bin ich zudem der Frage nachgegangen, inwiefern objektive und subjektive Maße gleichermaßen von Erwartungsinstruktionen beeinflusst werden.

Die hier vorgestellten Ergebnisse bieten neue Einblicke in kontextuelle Faktoren und Wirkungsweisen von Erwartungseffekten, indem sie zwei große Forschungsfelder zu dieser Fragestellung verbinden: den Einfluss traditioneller Placeboeffekte im klinischen Bereich einerseits sowie den Einfluss sozialer Erwartungseffekte andererseits. Im Laufe der vorgestellten Projekte habe ich physiologische Mechanismen identifiziert, die diesen Phänomenen zu Grunde liegen, und Gemeinsamkeiten wie auch Unterschiede zu aktuellen Modellen von Stereotypen- und Placeboeffekten diskutiert. Die Ergebnisse heben zudem hervor, welche wichtigen methodischen Implikationen Erwartungseffekte für klinische Forschung haben können, und betonen, dass subjektive und objektive Maße unterschiedlich beeinflussbar sein können. Diese Befunde zeigen, dass die Verknüpfung verschiedener Herangehensweisen zur Untersuchung von Erwartungseffekten ein vielversprechender Weg ist, um unser Verständnis von Erwartungseffekten zu erweitern, und um grundsätzliche, globale Mechanismen zu identifizieren, die verschiedenen Formen dieses Phänomens zu Grunde liegen.

SUMMARY

Expectancy effects are a wide-spread phenomenon, influencing cognitive operations from basic stimulus processing to higher cognitive functions. Their influence often goes unnoticed, even though it leaves a lasting fingerprint on perception and behaviour. Providing an improved framework for understanding the impact of expectations is thus the major goal of this dissertation.

I will first give an overview on the many instances in which expectancy effects have been investigated and discussed and then present three projects which seek to expand our knowledge on expectancy effects on cognition: The project *Gender, Pain, and Expectations* studies the impact of stereotype-related expectancies on pain processing, and investigates possible physiological mechanisms underlying this phenomenon including measures of BOLD activity, hormone concentrations, and behavioural responses to pharmacological challenges. The project *Between Pain and Math* then seeks to bridge previous research on social expectancies and traditional clinical settings, while at the same time measuring the impact of expectancies on both, pain variables and variables of higher cognitive functioning. This approach allowed a

direct comparison of the susceptibility to expectancy effects in different cognitive domains. In the project *Expectations and Cognitive Performance*, I finally investigated the influence of a traditional placebo paradigm on performance in cognitive tasks, and studied the question whether objective and subjective measures are affected by expectancy instructions in a similar manner.

The present results provide new insights on the contextual factors of expectancy effects on cognitive processes by fusing two major fields of research on this question: the impact of traditional placebo effects in clinical settings and of social expectancies. In the course of the presented projects, I identified physiological mechanisms underlying the phenomena and discussed similarities and differences to current models of stereotype and placebo effects. Furthermore, the results highlight important methodological implications of expectancy effects for clinical research, as well as a clear dissociation of subjective and objective measures in several settings. These findings show that combining multiple approaches on expectancy effects is a promising path to gain new insights on the effects of expectations on cognition, and to identify basic global mechanisms underlying different forms of the phenomenon.

ABOUT EXPECTATIONS

1 | A Question of Definition

In the 1780s, while revolutionary spirit begins to rise in Europe, Ferdinand Ueberwasser, professor for experimental psychology and logic in Münster, writes a handbook to instruct future students about the regular study in the yet-to-be founded discipline of experimental psychology. Part of this book concerns itself in great detail with the impact of imagination on the body, tells about physiological and behavioural changes evoked by expectations, from the neural beginnings to the affected action (Schwarz & Pfister, under review; Ueberwasser, 1787). Whereas Ferdinand Ueberwasser has been mostly forgotten, maybe due to the political upheavals of his time, his pioneering descriptions and observations in these areas are as valid today as they were 230 years ago.

The influence of expectations on perception, action, and everything in between, in short, cognition, is a wide and active field of research across various disciplines with many aspects still to be uncovered. Reliable effects of one's own expectations or of a

society's preconceived notions, stereotypical ideas, reasonable or unreasonable convictions based on prior experiences have been demonstrated in the fields of medicine, social and cognitive psychology, neuroscience, and behavioural biology. In this thesis, I want to add to our understanding of which roles expectations play in different contexts and which mechanisms might underlie their effects on human perception and behaviour. To this end, I aim at fusing different fields of research that, although asking similar questions, seem to have worked in parallel rather than in conjunction so far. It has been 230 years since Ferdinand Ueberwasser described the impact of the imagination on the body and while we know a lot more now than was known then, we still have quite some way before us.

1.1 Cognition

In order to study the influence of expectations on cognitive processes, it is vital to clarify what exactly cognition entails in the first place. The term *cognition* is widely used, but its definition is not always clear-cut (see, e.g., von Eckardt, 1995). In this thesis, I will use the term cognition in its original sense according to Ulric Neisser (1967): "The term cognition refers to all processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used. (...) Such terms as *sensation, perception, imagery, retention, recall, problem-solving,* and *thinking,* among many others, refer to hypothetical stages or aspects of cognition." (p. 4). In short, cognition is involved in everything human beings do, and, as Neisser specifies, "results in – and is integrated with – the activity of muscles and glands that we call 'behavior'" (p.3). This is obviously a very broad definition, spanning from basic perceptual

mechanisms to higher cognitive functions, but it is this width of meaning that I intend to accommodate in the course of this thesis, to gain a thorough understanding of the susceptibility of cognitive processes to expectations in general. In contrast to this broad definition of cognition, I will therefore use a more confined, operational definition of "expectation" as described in the following section (Figure 1). I adopted this strategy in order to paint a thorough picture of the various effects of a single, well-defined cause.

1.2 Expectations

Before I start to discuss the different fields in which the impact of expectations on cognition has been studied, it is important to explain on which type of expectation I am focusing in this thesis (Figure 1). An expectation, per se, is defined as a "belief that something will happen or is likely to happen" (Merriam-Webster's online dictionary, n.d.). As such, the word "expectation" encloses every belief we develop about the future, be it unconsciously or consciously, be it a belief about a situation, another person, ourselves, or a specific, singular item or event, be it a belief about a certain outcome that we can influence, or be it a belief about a seemingly unchangeable quality of the universe. Because of the width of this definition, it is important to note that my use of the word "expectation" does not necessarily pertain to all possible aspects of this expression. Rather, I will focus specifically on the impact of explicit expectations on perception and performance of human agents. Still, I will give a brief overview over the types of expectations that are not discussed in the empirical part of this thesis, to clarify my use of the word.

First, I will not consider implicit, low-level expectations, i.e., expectations that cannot be articulated or accessed consciously. For instance, humans show a remarkable talent for identifying regular sequences of events, even if these learned relations remain unconscious (Lewicki, 1986; Reber, 1989). This implicitly learned knowledge is then used to adapt own behaviour and can likewise influence future judgments, affect problem solving and decision making (Lewicki, 1986; Reber, 1989). Such expectations also have a direct effect on the processing of sensory information. When an ordered, homogeneous sequence of stimuli is interrupted by a deviant stimulus, this deviant stimulus elicits a distinct electrophysiological response, the mismatch negativity (Näätänen, 1990; Näätänen & Alho, 1995). The mismatch negativity is an automatic process that seems to be independent from attention, and is driven by the mismatch between the *expected* stimulus and the perceived, actual stimulus (Näätänen & Alho, 1995). Implicit expectations based on regularity detection are vital for efficient behaviour (Reber, 1989), but they clearly lie outside of the focus of explicit expectations that I will maintain throughout this thesis.

Second, I will not consider expectations that take the form of schemata, which have been documented to play an important role for action understanding and memory processes (Brewer & Treyens, 1981; Smith, 1998). Schemata are script-like beliefs about prototypical events in certain contexts: When visiting a restaurant, we expect to come in, to be seated, to get a menu, to order food, to eat food, to pay, and to leave later. When having established a schema for a certain context, information will always be processed relative to it by orienting attention to events that are not part of the schema and that therefore come unexpected. Schemata further affect memory retrieval by filling in

blanks with schema-consistent information, irrespective of whether or not these events actually took place. Though such expectations have important consequences for everyday life, they fall out of the present scope because they do not directly affect own performance which will be the focus of the following experiments.

Third, I will not consider expectations in decision making contexts and corresponding behavioural effects of expectations. Decision making has been studied intensively for hundreds of years, historically especially by economists. This influence is noticeable in the language that is used to describe the different components of the decision making process. The process of decision making involves in its simplest form two states, A and B, and an individual who can put himself into either one of those. The individual then chooses the state A over B or the state B over A, i.e., he or she makes a decision as to which state he or she wishes to put himself or herself (Edwards, 1954). Different models have been suggested describing the process of this decision making. Expected Value Theory, for example, postulates that a rational individual computes the likelihood that a particular action might yield a gain or loss, and multiplies the resulting value with the amount of gain or loss that can be expected from that decision (Arnauld & Nichole, 1662; McCoy & Platt, 2005; Vroom, 1964). The result of this computation is called the *expected value* of this particular action, and it is assumed that the action with the highest expected value is chosen. While other models suggest that it is not the expected value that is maximized by any given choice, but the expected utility[1], profit, or reward, it is still a key feature of these models that the agent is using his or her expectations to maximize *something* (Edwards, 1954; Simon, 1959). Therein lies an

[1] The utility of an action or object is in its simplest form defined by its capability to provide pleasure or induce pain. Pleasure is given by positive utility, whereas pain is induced by negative utility. Maximizing utility thus means to maximize pleasure while simultaneously minimizing pain (Edwards, 1954).

important difference between the use of the word “expectation” in this context and in the context of my empirical work. The type of expectation whose impact on behaviour and physiology I have studied is not part of a chain of action that is consciously chosen to gain something. Instead, it is a state of mind that might influence cognition and action without any awareness of the individual. In the following chapters, I will present empirical evidence on the influence of such expectations on various forms of cognition, with special focus on perception (Chapter 2) as well as on higher cognitive functions (Chapter 3).

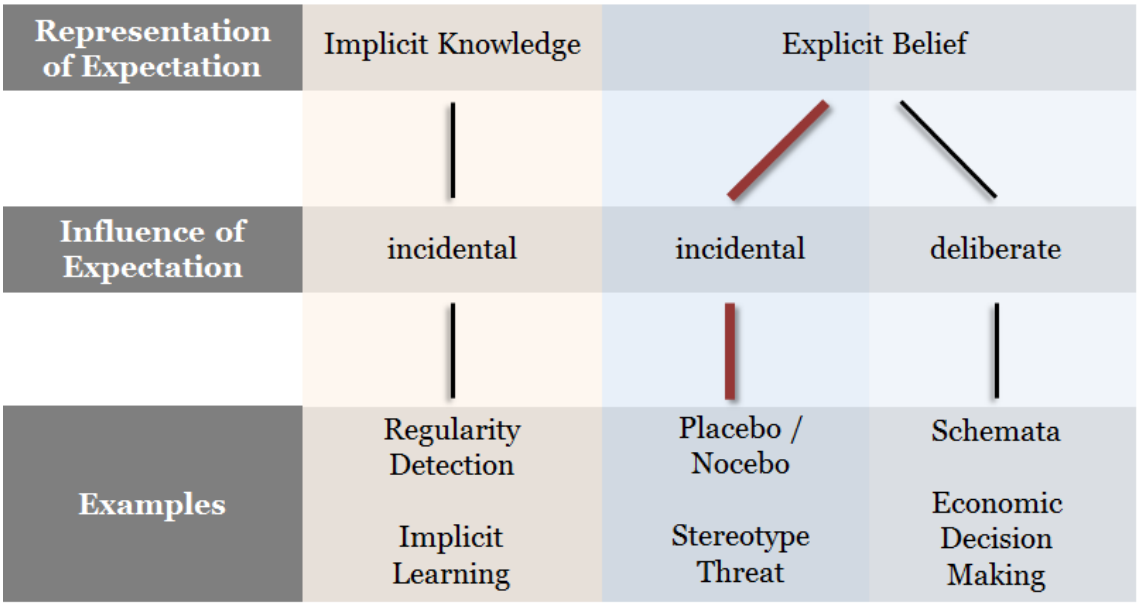

Figure 1. Overview and classification of different types of expectations. In this thesis, I will focus on expectations that are generated by an explicit belief, but whose influence is incidental and not deliberate.

2 | Expectations and Stimulus Processing

This chapter summarizes the impact of expectations on perception and processing of various forms of stimuli. One of the most striking and most extensively studied examples of the influence of expectations on perception is the placebo effect. Because of its relevance to my own empirical studies, as well as the extensive literature on the neurophysiology involved, I will especially focus on this cognitive phenomenon.

2.1 The Placebo Effect

The first descriptions of the placebo effect date back to the 18th century (de Craen et al., 1999). In 1787, Ferdinand Ueberwasser writes: „There are examples that bread crumbs taken in the shape of pills have, by vivid imagination and expectations, yielded the same effects as the medication itself. (...) Furthermore, that vivid imaginations, confident expectations of recovery or relief, and therefore firm trust in the physician, or in the medication alone, even if the medication is without effect by itself, can sometimes lead to real relief, or even recovery, for the invalid." (pp. 141, 146).[2] As this excerpt shows, it has been known and described for several centuries that a sham medication which is in itself ineffective can produce a desired effect simply by engaging strong expectations and prior experience. Especially in the last decades, this line of research has regained its stride, and scientists around the world have produced a wealth of

2 Translated from the German original: „Man hat Beyspiele, daß Brodkrumen in der Gestalt von Pillen genommen, durch lebhafte Vorstellungen, und Erwartungen die nämlichen Wirkungen hervorgebracht haben, wie die Arzeneyen selbst. (...) ferner, daß lebhafte Einbildungen, zuversichtliche Erwartungen der Genesung, oder Erleichterung, und daher festes Zutrauen auf den Arzt, oder nur auf die Arzney, wenn sie gleich an sich unkräftig ist, dem Kranken zuweilen wirkliche Erleichterung, oder gar die Genesung verschaffen können; (...)"

literature on the behavioural and physiological underpinnings of the placebo effect – and lately also on its "evil twin", the nocebo effect. In this paragraph, I will give a short overview over key behavioural findings and the neurophysiology believed to underlie these phenomena.

Placebos have long been regarded as "inert agents or procedures aimed at pleasing the patient rather than exerting a specific effect" (Price, Finniss, & Benedetti, 2008, p. 567). In recent years, this idea has changed to include not only the action of the inert agent, but also the whole psychosocial context that surrounds the patient during a treatment procedure including, but not restricted to, conditioning effects, verbal suggestions, the behaviours of healthcare workers, and finally the application of the sham medication itself (Colloca & Benedetti, 2005; Price et al., 2008). A placebo effect could thus be described as "a genuine psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure" (Stewart-Williams & Podd, 2004, p. 326).

2.1.1 Expectation and Experience

Placebo effects are thought to rest mainly on two components: the expectation of an individual that a treatment is going to bring clinical relief and previous experience with similar treatments that confirms such relief-inducing qualities (Büchel et al., 2014). In the laboratory, this previous experience is often evoked by a conditioning phase, during which a participant learns about the association of symptom-relief and the

respective treatment. These conditioning phases may take different forms dependent on the subject of study and the general study design. In studies investigating placebo hypoalgesia, for example, conditioning phases may simulate a relief of pain as the experimenter lessens stimulus intensity during the treatment unbeknown to the participant, whereas the stimulus intensity remains high during a contrasting control condition (e.g., Eippert et al., 2009a). If real medication is introduced to the paradigm, the experimenter may condition the participant with several sessions of the real pain-relieving drug, followed by the application of a placebo in the same fashion, of course unbeknown to the participant (e.g., Amanzio & Benedetti, 1999).

There has been a long-drawn debate on which aspect – expectation or conditioning – is the major driving force behind the placebo effect and whether or not expectations are really needed for the effect to occur (Stewart-Williams & Podd, 2004). This is a difficult distinction to make, as it assumes that conditioning is a process that happens completely unconsciously and without generating any expectations in itself (Colloca & Benedetti, 2005). Instead, it seems more reasonable to assume that both components may play a role and are not mutually exclusive (Atlas & Wager, 2012; Stewart-Williams & Podd, 2004).

Several studies on this subject support the idea that expectation and conditioning are both important factors in placebo effects that sometimes work in concert, and sometimes work independently of each other, contingent on the dependent variables in question, the study design, and the general experimental conditions. For example, the expectation of pain relief can in itself elicit a placebo response that is even further heightened by a preceding conditioning procedure. However, if an expectation of pain

increase is given after a preceding phase conditioned pain relief, the conditioning effect is abolished (Benedetti et al., 2003). The same general effect was found in motor performance in Parkinson patients (Benedetti et al., 2003). Following the same experimental protocol, the authors also examined the suggestibility of hormone release. Here they found clear conditioning effects (e.g., the release of growth hormone increased after conditioning with sumatriptan), but verbal expectancy did not modulate these effects (Benedetti et al., 2003). This indicates that expectancy and conditioning work in different physiological systems, some of which are sensitive to modulation by expectation whereas others are not.

It still is consistently evident in the literature that, in the domains of pain or motor performance, placebo effects elicited by verbal expectancy alone are usually small and do not always reach statistical significance (Colloca & Benedetti, 2006, 2009). Introducing a conditioning component into the study design increases the modulatory effect (e.g., Colloca & Benedetti, 2009) – an experimental ruse that is used by numerous investigations on this subject (Atlas & Wager, 2012).

It really seems as if there is not one placebo effect, but rather many different ones, a hypothesis that is further supported by a look at the neurotransmitter systems involved in the process.

2.1.2 Neurotransmitters and Neurocircuitry in Placebo

The question of which physiological systems underlie the placebo effect has kept many scientists busy for the last decades. The first of these studies used the opioid

antagonist naloxone to test whether the release of endogenous opioids might play a role in this phenomenon (Levine, Gordon, & Fields, 1978). In this study, participants who responded to the application of a placebo medication with pain relief showed increased pain sensitivity after naloxone was given, i.e., the previous placebo effect was blocked. This was a first indication that the endogenous opioid system might be involved in the generation of placebo analgesia – a hypothesis which is by now supported by many converging findings (e.g., Benedetti, Amanzio, & Maggi, 1995; Benedetti, Arduino, & Amanzio, 1999; Eippert et al., 2009a; for reviews, see Benedetti et al., 2005; Büchel et al., 2014; Colloca & Benedetti, 2005; Tracey, 2010). For example, blocking the endogenous opioid antagonist cholecystokinin (CCK) pharmacologically seems to potentiate the effect of placebo hypoalgesia, suggesting that placebo hypoalgesia effects are dependent on a fine balance between endogenous opioids and CCK (Benedetti et al., 1995). Interestingly, placebo hypoalgesia cannot always be blocked by naloxone (Amanzio & Benedetti, 1999), hinting at non-opioidergic mechanisms which come into play under certain circumstances. If participants are first conditioned with morphine and then given a placebo while still expecting pain-relieving medication (conditioning and expectation), the resulting placebo hypoalgesia effect can be blocked by naloxone – as can effects based on expectations alone or conditioning with morphine alone. However, if not morphine was used as the unconditioned stimulus (US), but the nonsteroidal, anti-inflammatory drug ketorolac, the placebo response after the conditioning procedure alone could not be blocked by naloxone, and if conditioning and expectation cues were both applied, then naloxone only partially reversed the placebo effect (Amanzio & Benedetti, 1999). In fact, instead of endogenous opioids, a recent study implies that the endocannabinoid system, or more precisely the CB1 cannabinoid

receptors, mediate the placebo response evoked by conditioning with ketorolac (Benedetti et al., 2011). These findings invite two conclusions: (1) placebo hypoalgesia which involves verbal expectations seems to – at least partially - depend on the release of endogenous opioids and (2) conditioning-induced placebo responses are mediated by specific subsystems, dependent on the drug and paradigm used for conditioning (Amanzio & Benedetti, 1999).

While research on placebo hypoalgesia has largely focused on the opioidergic mechanisms underlying this effect, placebo effects in Parkinson patients have been partly attributed to the striatal release of dopamine in response to a placebo intervention (de la Fuente-Fernández et al., 2001). Because dopamine and the striatum are both associated with reward processes (Diekhof et al., 2012), this finding has led to the idea that placebo effects could be linked to an expected reward, i.e., the anticipation of therapeutic benefit (de la Fuente-Fernández et al., 2001; de la Fuente-Fernández, 2009). Indeed, further studies have investigated the influence of both, opioids and dopamine, in placebo hypoalgesia and have found that both transmitter systems are activated in specific brain areas when placebo effects are perceived (e.g., opioidergic transmission in the nucleus accumbens [NAc], anterior cingulate cortex [ACC], the insula, and the PAG, and dopaminergic transmission in the ventral caudate, putamen, and NAc; Scott et al., 2008). Furthermore, NAc blood-oxygen-level dependent (BOLD) activity during a monetary reward task has been linked to dopamine release in the NAc during placebo hypoalgesia, finding strong correlations between both incidents (Scott et al., 2007).

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have come a long way in describing a neural circuitry believed to underlie placebo hypoalgesia, the descending pain control system, involving the dorsolateral prefrontal cortex (DLPFC), the ACC, the hypothalamus (HT), the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM), and finally the dorsal horn neurons in the spinal cord (e.g., Eippert et al., 2009a, 2009b; Tracey, 2010). A recent review suggests that placebo hypoalgesia may be implemented through a hierarchical recurrent system including cortical (rostral ACC [rACC], anterior Insula [aI]), subcortical (amygdala [AMY], HT, and thalamus [TAL]), midbrain (PAG), medulla, and spinal sites. (Büchel et al., 2014). Several studies have emphasized a functional coupling between the ACC and the PAG during placebo hypoalgesia (Bingel et al., 2006; Petrovic et al., 2002). Interestingly, this coupling predicted behavioural and neural placebo effects and was inhibited by naloxone, i.e., when the placebo effect was efficiently blocked.

2.1.3 Nocebo

Just as positive expectations and experience can decrease the sensitivity to pain, negative expectations can have the opposite effect and lead to increased pain sensitivity, a phenomenon which is called nocebo hyperalgesia (e.g., Benedetti et al., 2006; Colloca, Sigaudo, & Benedetti, 2008). In fact, hyperalgesia evoked by negative expectations can be strong enough to completely counteract the effect of an effective pain relieving drug (Bingel et al., 2011). Placebo and nocebo effects at first glance seem like two opposite sides of the same coin, and indeed, many similarities in transmitter systems and neural patterns support this intuitive idea. But a few noteworthy differences assure that it is

reasonable to still think of these phenomena as two distinct mechanisms rather than one mechanism ranging from the pain-relieving to the pain-enhancing side of the spectrum.

Several studies have emphasized the involvement of opioidergic transmission also in nocebo hyperalgesia. For example, inhibiting the endogenous opioid antagonist CCK pharmacologically completely blocks nocebo hyperalgesia (Benedetti et al., 2006). Placebo and nocebo effects generally seem to be accompanied by opposite reactions in the same neurotransmitter systems, i.e., in opioidergic and dopaminergic signalling (Scott et al., 2008). Recently, a study also confirmed the involvement of the descending pain control system, by finding hyperalgesic activity modulations in the spinal cord in response to a nocebo protocol (Geuter & Büchel, 2013).

However, it seems as if the emergence of nocebo hyperalgesia is not as dependent on learning and prior experience as the opposite placebo effect. Verbal suggestions alone are enough to provoke reliable changes in pain experience (Bingel et al., 2011; Colloca et al., 2008), with additional conditioning procedures not substantially improving the initial effect based on pure expectations alone (Colloca et al., 2008). Moreover, in contrast to placebo analgesia, anticipatory anxiety mechanisms also seem to play a role in the emergence of nocebo hyperalgesia (Benedetti et al., 2006). These mechanisms were further highlighted by the activation of brain regions involved in anticipatory anxiety as well as the hippocampus, a pattern that was not observed during placebo hypoalgesia which hints at distinct neural correlates separate from placebo effects (Kong et al., 2008; Tracey, 2010).

2.1.4 Placebo Effects in Animals

Placebo effects in animals have been less intensely studied than in humans, but several investigations demonstrate the impact of inert treatments on the animals' behaviour or bodily functions, if those inert treatments had been previously associated with effective medication.

In humans, placebo effects are usually evoked by a mixture of verbal suggestions and conditioning procedures to provide experience with the treatment method. Expectations based on verbal suggestions alone can often elicit placebo effects if on a smaller scale than placebo protocols involving both, suggestions and conditioning processes (see *2.1.1 Expectation and Experience* for more details). In animals, placebo effects based on expectancy alone, without any learning experiences, are difficult to investigate. The studies presented here therefore used classical or operant conditioning mechanisms to evoke placebo effects.

A seminal study addressed placebo effects in immunosuppression. Mice were, for example, conditioned with an immunosuppressive drug (Unconditioned Stimulus, US) associated with an injection of sodium saccharine (Conditioned Stimulus, CS). After a few weeks, mice showed conditioned immunosuppression in response to the sodium saccharine alone (Ader & Cohen, 1982). Similarly, when a gustatory stimulus (CS) was repeatedly paired with immunization with keyhole limpet hemocyanine (KLH; UCS), the production of anti-KLH antibodies was observed in response to the CS alone (Ader et al., 1993).

More recently, scientists have tried to establish a placebo hypoalgesia model in rats and mice, also using conditioning mechanisms to evoke the placebo effects. These studies demonstrate several parallels to placebo hypoalgesia in humans: placebo hypoalgesia in rats or mice seems to depend on opioidergic mechanisms as it is reversible by naloxone, if the US used for conditioning procedure is an opioid agonist (Guo, Wang, & Luo, 2010). If the US is a non-opioid drug, however, other mechanisms seem to mediate the effect (Guo et al., 2010). Moreover, as with human participants, there seems to be a strong interanimal variability in the placebo response with typical placebo responders and non-responders (Nolan et al., 2012). Nevertheless, because placebo effects in animals are purely based on conditioning procedures, direct comparisons to mechanisms in humans have to be considered with caution.

2.2 Expectations, Context, and Face Processing

One of the most thoroughly studied visual stimuli is the human face. Facial expressions have been studied extensively with regard to behavioural and physiological responses to faces or with regard to the neural components responsible for the processing of the stimuli (e.g., Haxby, Hoffman, & Gobbini, 2000). Interestingly, in the last years, the literature on contextual influences on face processing and face perception has also grown steadily, and it is this subcategory of face processing I want to shortly summarize here.

Contextual effects on perception are essentially modulations of perception generated by additional information – and thereby evoked conscious or unconscious

expectations or notions. Contextual information, and thus the resulting expectations or notions, seem to be routinely implemented during stimulus perception (Aviezer et al., 2011; Barrett & Kensinger, 2010; Hayes et al., 2010), and shape the manner in which these stimuli are processed (Righart & de Gelder, 2008a, 2008b; Schwarz et al., 2013; Wieser et al., 2014). Indeed, not only simultaneously presented (e.g., Aviezer et al., 2008; Righart & de Gelder, 2008a, 2008b), but also previously given contextual information changes the interpretation, perception, and processing of stimuli (Carroll & Russell, 1996; Kim et al., 2004; Schwarz et al., 2013, Wieser et al., 2014). Moreover, anticipatory mental imagery has been shown to affect face processing, demonstrating that precise expectations of what a face will express affect how this face is perceived and processed (Diekhof et al., 2011).

Contextual information, for instance, can be provided in terms of verbal information, e.g., in the form of short sentences prior to face presentation. One study to employ this method (Schwarz et al., 2013) used sentences which either conveyed positive or negative evaluations about the observing participant (self-related) or about somebody else (other-related). When participants were later asked to rate how positive or negative they perceived the facial expression, faces presented in positive contexts were rated as significantly more positive than faces in negative contexts, even though all facial expressions were de facto neutral. Faces in self-related contexts were also evaluated as more emotionally arousing than faces in other-related contexts, clearly suggesting that the contextual information influenced the perception and evaluation of these facial expressions. These findings were replicated in a similar study design (Wieser et al., 2014). Moreover, not only the subjective perception, but also the neural

processing of the neutral faces were influenced by the previously presented sentences, modulating BOLD activity in classical face processing areas, such as the fusiform gyrus, or in areas associated with self-referential or self-relevant stimuli, such as the medial prefrontal cortex (Schwarz et al., 2013).

In all these investigations, expectations about specific perceptual changes or behavioural outcomes were not clearly formulated – but the interpretation and processing of various stimuli was manipulated simply by altering the context in which the stimuli were seen. Any contextual information we process can influence our expectation of what we are about to perceive, and these expectations have a distinct influence on the subsequent stimulus perception and processing.

2.3 Expectations and Perception – Further Examples

The previous sections of this thesis make it clear that perception and stimulus processing can be strongly influenced by expectations and higher cognitive processes, but they don't give a complete review of all instances where these phenomena take place. This section will give a short overview over further examples on this matter.

An interesting subject allowing the study of suggestibility in stimulus processing are reversible figures. The primary property of these figures is their multistability, i.e., the fact that they can be seen as a depiction of one specific object, person, or situation, but also – and often just as likely – as something else entirely (for example, a figure depicting either a young, very elegantly dressed woman, or an old woman with a headscarf, depending on one's perception). Interestingly, observers often do not only see

one interpretation of the figures, but revert back and forth between the different interpretational possibilities (for a detailed review, see Long & Toppino, 2004). Different theories have been proposed as to how this figure reversal takes place, which fall largely into two different categories: quite a few experiments support the idea that basic perceptive properties, or *lower order* information, drive this visual occurrence (bottom-up processes), while other experiments confirm the impact of *higher order* processes (top-down processes). Considering the convincing evidence of both sides, it seems reasonable to assume that both, bottom-up and top-down, components play an important role in establishing the visual experience of reverting perceptions (Long & Toppino, 2004).

One aspect of top-down processes influencing figure reversal is the impact of expectancies. For instance, a study highlighting the effects of expectations on stimulus perception (Bruner & Minturn, 1955) confronted participants with a specifically prepared stimulus: a broken B, where the curved part of the figure was separated from the vertical line by one millimetre. The broken B could therefore be seen either as a “B” or as a “13”. When this stimulus was presented for a short time (about 80 ms on average) and participants expected to see a letter, interestingly, most of them did not only report they had seen a letter, they also drew the broken B as a “closed” B when they were asked to copy the stimulus as accurately as possible. However, if they expected to see a number, most of the participants reported to have seen a number and drew an open figure, i.e. a “13” instead of a “B” (Bruner & Minturn, 1955). This finding provides clear evidence that preconceived notions or expectations about a stimulus influence the actual perception.

The influence of expectations on stimulus processing is also obvious in language comprehension. Several studies suggest that predictive context information generate expectancies which are integrated into sentence processing (e.g., DeLong, Urbach, & Kutas, 2005). Eye-tracking as well as electrocortical measurements have been employed to evaluate the time frame of context integration for semantic as well as syntactic features (Altmann & Kamide, 1999; DeLong et al., 2005; Kamide, Scheepers, & Altmann, 2003; Sedivy et al., 1999). These studies show evidence that eye movements are influenced by previous words in a sentence before the actual target word is perceived. Moreover, it seems that stimulus processing is affected by predictive context in a graded fashion, contingent on the probability of any particular sentence continuation. Event-related potentials (ERPs) in response to target words (and previously shown specific articles belonging to the target words, e.g., “a” and “kite” vs. “an” and “airplane”) were altered gradually dependent on how likely it was that this particular word would continue the sentence based on the context (DeLong et al., 2005). This gives evidence that individual words are pre-activated in accordance with the expectancies generated by previous contextual information.

The influence of expectations on perception and stimulus processing can be seen in many examples and while the mechanisms underlying these phenomena have been heavily researched in some instances, they are still speculative at best in others. Perception and stimulus processing is not where cognition ends, though – rather, classical views would argue that it often is where cognition starts. How expectations might influence higher cognitive processes is the topic of the next section.

3 | Expectations and Higher Cognitive Functions

Higher cognitive processes involve many distinct facets, such as memory processes, problem-solving, mental flexibility, verbal reasoning, or mathematical calculations. A particularly relevant research area for the present experiments is the social-psychological field of stereotype threat. Stereotype threat is a phenomenon that has been excessively studied behaviourally and is also characterized on a physiological level. In the following sections, I will therefore focus on this subject in detail, followed by a discussion of the related phenomenon of self-efficacy.

3.1 Stereotype Threat

According to Steele and Aronson (1995), stereotype threat is the predicament that the existence of a widely-known negative stereotype about one's group (i.e., a group with which one identifies) means that "anything one does or any of one's features that conform to it make the stereotype more plausible as a self-characterization in the eyes of others, and perhaps even in one's own eyes" (p. 797). Such stereotype threat can then lead to situational performance decreases in the fields that are relevant to the stereotype at hand. Indeed a multitude of studies describe such effects: For instance, African American participants performed worse than Caucasian participants when a test was labelled as diagnostic of intellectual ability, but both groups performed similarly when it was not (Steele & Aronson, 1995); Caucasian men, by contrast, performed worse than a non-stereotype-threatened control group when they were given math tasks ostensibly designed to investigate the performance superiority of Asians in these tasks (Aronson et

al., 1999); women's performance in a math test decreased substantially when they were informed that the test produced gender differences (Spencer, Steele, & Quinn, 1999); and women's and men's performance in a mental rotation task were influenced by stereotypical information, i.e., if male and female participants were told that women generally perform better than men in the task, female participants showed an improved performance, whereas the performance of male participants deteriorated. Both stereotype groups were compared with respective control groups that did not receive any stereotypical information (Wraga et al., 2006a). Essentially, the stereotype threat effect seems like a specific instance of "choking under pressure" (for an extensive review on paradoxical performance effects, see Baumeister & Showers, 1986), although a few differences between both phenomena have been noted in the literature (Régner et al., 2010). The last decades have produced an enormous amount of literature detailing and analysing stereotype threat effects, asking questions as to when these effects are likely to occur, what drives these effects, what theoretical models may describe the underlying processes, and which physiological basis might be responsible for them. In the next paragraphs, I will give a short overview of this topic.

3.1.1 Stereotype Threat - A Model

Stereotype threat has been described as a cognitive imbalance triggered by individual factors or situational cues (Schmader, Johns, & Forbes, 2008). In this model, environmental signals suggest a negative relation between an individual's group and a specific ability, i.e., the group is pictured as deficient in this ability. At the same time, the individual strongly identifies with the group or situational cues enhance the

individual's group membership. Finally, a positive relation between the individual's self-concept and the specific ability (i.e., the individual associates him- or herself with doing well on the specific task) leads to an imbalance. Although the individual is usually proficient in the ability (and doing well is part of his or her self-concept), the individual is also a member of the group (also part of his or her self-concept) and this group might be generally believed to perform poorly on the respective task. The model then assumes that this state of imbalance results in a higher state of tension that the stigmatized individual will try to resolve through a variety of processes – most of which unfortunately have detrimental effects on performance (Schmader et al., 2008).

Accordingly, higher cognitive tasks which heavily rely on working memory resources are especially susceptible to stereotype threat (Beilock, Rydell, & McConnell, 2007). Further evidence suggests that a reduction of working memory capacity mediates the stereotype threat effect (Schmader & Johns, 2003) and that individuals with lower working memory capacity are particularly likely to show stereotype threat effects (Régner et al., 2010). But which processes lead to a decrease of working memory capacity?

One aspect capable of mediating such an effect is an overly strong tendency to monitor one's actions in circumstances of stereotype threat (Beilock et al., 2007; Schmader et al., 2008). By focusing on the performance itself and becoming more conscious of one's own actions, important attentional and working memory resources are relocated away from task-solving towards a monitoring and constant reappraisal process. Moreover, further evidence suggests that mind-wandering (i.e., task-unrelated thought) increases during stereotype threat, dissociating attentional resources from the

actual task and occupying working memory capacities that could otherwise be used for a successful performance (Mrazek et al., 2011).

A possible factor underlying the stereotype threat effect is a physiological stress response. It is not yet clear whether there is a direct link between an involvement of the hypothalamic-pituitary-adrenal (HPA) axis with subsequent cortisol release and decreased performance in stereotype threat conditions. However, studies suggest that the endocrine stress system is generally involved in social identity threat (Matheson & Cole, 2004; Townsend et al., 2011). Cardiovascular responses in stereotype-threatened individuals also indicate an activation of the physiological stress system in this phenomenon (Derks et al., 2011). While this aspect of the stereotype threat model is not yet sufficiently studied, the current view includes the physiological stress response as an important link between expectation and behavioural outcome (Schmader et al., 2008).

The next section will give details about a few more physiological characteristics associated with stereotype threat, outside the model reviewed here.

3.1.2 A Little Bit More Physiology

The rather lean literature on the physiological stress response in stereotype threat demonstrates that we are still at the very beginning of understanding the physiological underpinnings of the stereotype threat effect. However, a few studies have tried to delve further into this topic, and I will give a brief overview of them here.

The impact of stereotype threat on any participant's cognitive abilities seems to depend partly on the amount of free testosterone present in the individual (Josephs et

al., 2003). When negative stereotypes were primed, high testosterone women performed worse than low testosterone women; vice versa, when positive stereotypes were activated, high testosterone men performed better than low testosterone men. These results suggest that high testosterone levels lead to a higher susceptibility to stereotype threat manipulations, maybe due to status concerns that are more strongly associated with higher testosterone levels (Josephs et al., 2003). Moreover, activating gender-related stereotypes also leads to increased testosterone levels in men which then seem to modulate performance in cognitive tests explicitly characterized as sex-sensitive (Hausmann et al., 2009).

Only a few studies have directly investigated the neurocircuitry that might be involved in stereotype and social identity threat. Still, a common picture seems to emerge from them: under stereotype threat, participants show strong BOLD activity in areas often associated with emotion regulation and control processes, especially the anterior cingulate cortex (ACC), and at the same time less activity in task-related brain areas compared with controls or positively stereotyped individuals (Krendl et al., 2008; Wraga et al. 2006b). These results support the behavioural evidence that stereotype-threatened individuals spend more cognitive resources on emotional regulation and reappraisal processes and less on the task at hand (Derks, Inzlicht, & Kang, 2008). Furthermore, a lesion study also associated the ventromedial prefrontal cortex with general stereotyping. Patients with ventromedial lesions showed lower associations between the stereotypical attributes of men and women and their concepts of gender, i.e., less gender stereotyping, on the implicit association task (IAT) than patients with dorsolateral lesions (Milne & Grafman, 2001).

3.1.3 Stereotype Threat in Other Fields

Although most studies on stereotype threat focus on higher cognitive functions, these are not the only areas in which stereotype threat effects are found. African American participants performed worse than Caucasian participants on a golf task, when the task was described as being diagnostic of "sports intelligence". Likewise, African American participants performed better than their Caucasian counterparts, when they were instructed that the task was diagnostic of "natural athletic ability" (Stone et al., 1999). Similarly, expert male golfers performed worse after they were told that women generally perform better in the experiment's golf task than men compared with controls who did not receive any gender-related information (Beilock et al., 2006). Interestingly, stereotype threat has also been shown to affect everyday activities, such as driving: stereotype-threatened women were more likely to run over jaywalkers in a simulator than women not previously primed by a gender stereotype (Yeung & von Hippel, 2008).

3.2 Self-Efficacy

Expectations about one's abilities can, of course, also be based on one's personal and individual conviction. In these cases, it is not a particular group affiliation that drives a general ability expectation, it is anyone's personal idea about what one can or cannot do. This process is investigated in the field of self-efficacy research. Strong formulations of this theory claimed that "among the mechanisms of personal agency, none is more central or pervasive than people's beliefs in their capability to exercise

some measure of control over their own functioning and over environmental events. Efficacy beliefs are the foundation of human agency. (...) Such beliefs influence whether people think pessimistically or optimistically and in ways that are self-enhancing or self-hindering. Efficacy beliefs play a central role in the self-regulation or motivation through goal challenges and outcome expectations." (Bandura, 2001, p. 10). Indeed, many studies have found a strong correlation between self-efficacy beliefs and ability scores in the respective domain (e.g., Pajares & Miller, 1994; Paunonen & Hong, 2010; for an early review, see Lent & Hackett, 1987) and some even find self-efficacy beliefs to be a better predictor for performance than prior performance in the respective domain (Pajares & Miller, 1994).

Self-efficacy beliefs and outcome expectations differ from stereotype-evoked expectations particularly in two ways: self-efficacy beliefs are generally thought to be more situation- and task-specific than stereotype-related expectations and the general tonus implies a direct positive relationship between self-efficacy beliefs, motivational factors, and subsequent performance in academic domains (Bandura, 2001; Pajares, 1996; Paunonen & Hong, 2010). In other words, efficacy beliefs influence the amount of effort people will expend on an activity and affect perseverance and resilience in the face of adversity (Pajares, 1996). People with low self-efficacy might not be motivated to do their best, might be easily side-tracked, and might generally do worse than would be expected given their ability level alone (Paunonen & Hong, 2010). This stands in stark contrast to the stereotype threat phenomenon, in which especially individuals who strongly identify with the domain in question are affected – and are thus highly motivated to revoke the stereotype (Schmader et al., 2008). In both cases, though, we

can see that specific expectations about one's capabilities strongly influence subsequent performance in the respective domains.

Experience and expectations play a huge role in stimulus perception, processing, and in behaviour. In the next paragraph, I will introduce the goals of my dissertation in broadening our understanding of these phenomena and give a short overview of each project.

4 | Expectations in this Thesis

In the last paragraphs, I have given a detailed, yet certainly incomplete, overview of the fields in which expectancy effects have been investigated so far. Put simply, two main areas of research emerge: studies in traditional medical settings focusing primarily on pain processing or motor performance (placebo/nocebo effects especially well investigated in pain perception and processing) and studies on social expectancy effects (such as stereotype threat) which primarily focus on higher cognitive functions. I have summarized these approaches in Figure 2, detailing what I call the "Context Framework of Expectations". This framework assumes that contextual factors, such as social aspects or specific settings, play an important role in the impact of expectations on cognition and in the mechanisms behind the related phenomena.

The main goal of this dissertation is to broaden our understanding of expectation effects by fusing the previous lines of research. To this end, I investigated the effects of social expectancies such as stereotypical beliefs on pain processing and looked at underlying physiological mechanisms of these phenomena (Project 1: *Gender, Pain, and Expectations*). Moreover, I introduced situational expectancies in a medical context, i.e., traditional placebo and nocebo effects, into an experimental paradigm targeting higher cognitive functions (Project 3: *Expectations and Cognitive Performance*). As a link between both projects, I used social expectancies in a medical context to investigate their effects on both, pain processing and performance in higher cognitive tasks (Project 2: *Between Pain and Math*). Figure 2 summarizes the Context Framework of Expectations including the projects presented in this dissertation.

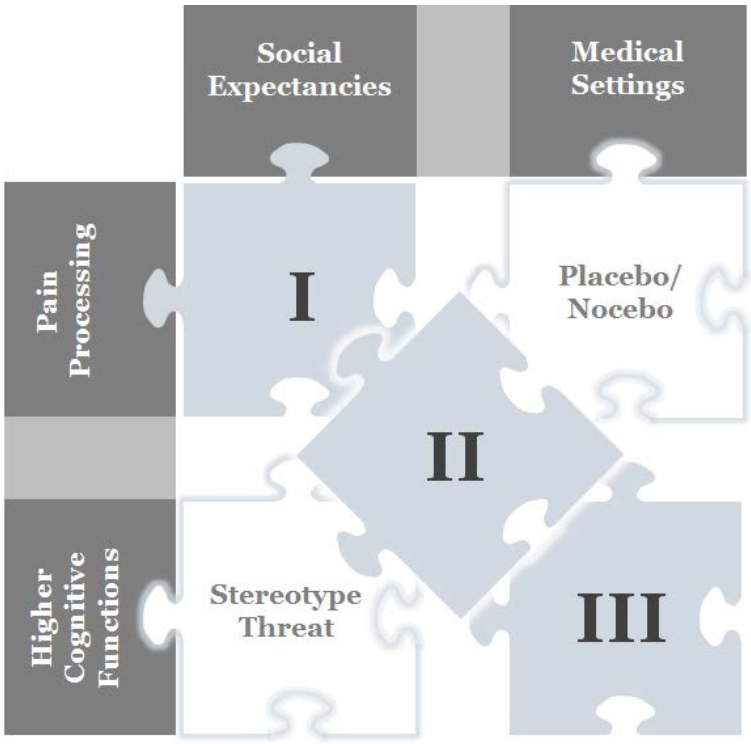

Figure 2. The Context Framework of Expectations: Overview of well-established fields of research and missing pieces on which I will focus in this thesis. Research on stereotype threat is an example of studies focusing on the effects of social expectancies primarily on higher cognitive functions (lower left), whereas traditional placebo and nocebo studies are usually set in a medical context and often focus on pain processing (upper right). In the course of this thesis, I will present a series of experiments investigating the effects of social expectancies in pain processing (**Project I**: *Gender, Pain, and Expectations*). In a second project, I will look at the effects of social expectancies in medical settings on pain processing and higher cognitive functions, both (**Project II**: *Between Pain and Math*). Finally, I will present a third project investigating the effects of situational expectancies in a medical setting (i.e., placebo and nocebo instructions) on higher cognitive functions (**Project III**: *Expectations and Cognitive Performance*).

GENDER, PAIN, AND EXPECTATIONS

In this project, I focused on the effects of stereotypical beliefs on pain perception and investigated possible mechanisms of this phenomenon.[3] Stereotypical beliefs are wide-spread in our society, targeting various aspects, such as race, ethnicity, religion, sexual orientation, or gender. Previous studies investigating the impact of stereotypes on higher cognitive functions often chose common gender-related beliefs to invoke specific expectancies about performance (e.g., Derks et al., 2011; Krendl et al., 2008; Spencer et al., 1999; Wraga et al., 2006a,b; see *3.1 Stereotype Threat*). Moreover, gender-related beliefs about pain perception are also abundant in every-day life (Racine et al., 2012; Robinson et al., 2001). Thus, focusing on gender-related expectancies in pain perception seemed ideal to fuse the fields of the impact of pain-related expectations on the one hand, and social stereotypes on the other.

[3] The chapter *Gender, Pain, and Expectations* is based on the as yet unpublished manuscript (Schwarz et al., under revision):
Schwarz, K. A., Sprenger, C., Hidalgo, P., Pfister, R., Diekhof, E. K., & Büchel, C. (under revision). The tougher sex: How stereotypes affect pain. *Science*.

Authorship Statement

The following chapter describes work with co-authors. The concept of the experiments was developed in collaboration with my supervisor Prof. Dr. Christian Büchel. All experiments were planned, prepared and organized by me. The fMRI experiment was conducted by a student assistant and myself; the Naloxone and Cortisol experiments were conducted by the same student assistant under my supervision. Hormone analysis was performed by a technical assistant and myself under supervision of my co-supervisor Prof. jun. Dr. Esther Diekhof. All statistical analyses were performed by myself, fMRI analysis was performed by myself and by Prof. Dr. Christian Büchel. The first version of the manuscript was written by me.

25. FEB. 2015

Ort, Datum

Unterschrift Prof. Dr. Christian Büchel

5 | General Approach and Core Results

Stereotypes are ubiquitous in our society, detailing specific expectations evoked by gender, ethnicity, nationality, religion, or sexual orientation. Their effects on the stigmatized groups can be detrimental and the effects span such diverse fields as athletics or skilled performance (Beilock et al., 2006; Stone et al., 1999), as well as various cognitive abilities, such as mathematics or verbal skills (Aronson et al., 1999; Beilock et al., 2007; Spencer et al., 1999; Steele & Aronson, 1995).

In essence, stereotypes are a-priori expectations that have little to do with the individual, but rather with the specific role an individual is expected to play. Recent studies on pain perception have investigated whether the irregular and often rather inconsistent gender effects in pain measures might partly depend on such gender role expectations, or, in other words, stereotypes (Racine et al., 2012; Robinson et al., 2004; Sanford et al., 2002; Wise et al., 2002). Indeed, questionnaire measures of these expectations at least partly accounted for observed sex effects in several correlational analyses, pointing to an important field in which stereotypes might have significant consequences. Yet, so far there is no conclusive evidence for a causal relation between gender-specific expectations and observed patterns in pain measures, nor are there any empirical data that would allow speculating about the mechanisms involved.

In a series of behavioural, neurophysiological, and pharmacological experiments, we investigated how gender-related stereotypes affect pain reports and the neurophysiological underpinnings of pain processing as measured by fMRI. We

analysed the data of 105 male participants on two days each[4]. On day 1, we obtained basic heat pain measurements including pain sensitivity and pain threshold measures. On day 2, we manipulated the participants' expectancy regarding their own pain sensitivity by subtly briefing them about alleged evolutionary effects on pain sensitivity. One group was told that, as men used to be hunters and gatherers and therefore more prone to injury, they are generally less sensitive to pain than women (*MLPS* group, n = 34). A second group was told that, as women undergo the painful process of childbirth, women are generally less sensitive to pain than men (*FLPS* group, n = 35). A third group did not receive any further gender-related information (*Control* group, n = 36). After the manipulation, participants underwent the same experimental paradigm as on day 1 (for procedural details, see Figures 8-9).

We hypothesized the *MLPS* group to show decreased pain sensitivity, whereas we expected the *FLPS* group to show increased pain sensitivity (Eippert et al., 2009a; Geuter & Büchel, 2013). Moreover, we expected these effects to be mirrored in the neurophysiological response in pain-related brain areas (Bornhövd et al., 2002).

Our main analysis of interest concerned the difference between the two expectancy manipulation groups, i.e., *MLPS* vs. *FLPS* (Figures 3, 10A). The results show a significant effect of this manipulation on pain reports (interaction Time x Gender Expectancy: $F(1,67) = 5.72$, $p = .020$, $\eta_p^2 = .08$), with a prominent decrease in pain sensitivity for the *MLPS* group (14.7%) in contrast to the *FLPS* group (3.6%). The critical interaction was also significant when expanding the analysis to include the *Control*

[4] Please note that the participants of the Naloxone experiment (n=31) are additional to the 105 participants reported here. The experimental procedure in the Naloxone experiment included an invasive drug application which might influence the participants' behaviour and renders a direct comparison to the behavioural data of the remaining experiments difficult (see *10 | Supplementary Methods* for further information).

group, $F(2,102) = 3.08$, $p = .050$, $\eta_p^2 = .06$. This analysis further yielded a significant linear contrast *MLPS* > *Control* > *FLPS*, $F(1,102) = 6.16$, $p = .015$, $\eta_p^2 = .06$.

The corresponding decrease and increase in pain sensitivity after the expectancy manipulation relative to the *Control* group could be interpreted in analogy to placebo and nocebo effects resulting in hypo- and hyperalgesia, respectively. The effects of the expectancy manipulation were also reflected in pain threshold measures (Figure 10B). Such effects are often observed in response to open medical sham treatments and mostly arise after elaborate instruction and conditioning procedures, of which the latter seem most effective (Eippert et al., 2009a; Geuter & Büchel, 2013; Voudouris, Peck, & Coleman, 1990). It is important to note that we elicited changes in pain sensitivity simply by a subtle briefing on stereotypical gender role expectations, without any conditioning involved.

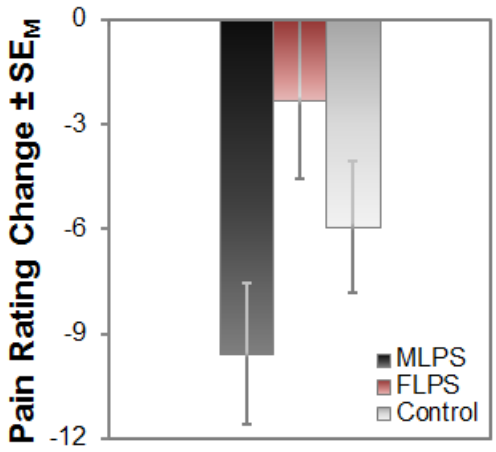

Figure 3. Changes in pain sensitivity ratings (day 2 - day 1) for each group (raw data are shown in Figure 10A).

6 | fMRI Experiment

To ensure that the observed effects mirrored actual changes in pain processing rather than report biases, we obtained fMRI measurements during pain stimulation in 34 participants (n_{MLPS} = 17, n_{FLPS} = 17). We focused on instruction-dependent changes in pain processing on day 2 compared to day 1. As in previous studies in which we used long pain stimulation blocks (Eippert et al., 2009a), we investigated early and late pain periods separately. In the late pain phase, no significant differences were observed. During the early pain phase, however, several brain regions reflected the interaction effect of the behavioural data, including ACC, right insula, bilateral nucleus accumbens and thalamus (Figure 4, Table 1). These regions showed stronger activity on day 2 relative to day 1 in the *FLPS* group compared to the *MLPS* group and have been reported to be sensitive not only to pain in general (Apkarian et al., 2005; Tracey & Mantyh, 2007), but also to pain intensity, i.e., reflecting the participants' pain experience (Bornhövd et al., 2002; Coghill et al., 1999; Oshiro et al., 2009; Zubieta et al., 2003). In particular ventral striatal activation has been linked to emotional reactions to pain (Scott et al., 2006). These results indicate that the behavioural results are not due to report biases or compliance effects, but rather a genuine expression of physiological pain experience.

Because previous studies suggest that testosterone levels might influence stereotype susceptibility and subsequent behaviour (Josephs et al., 2003), we further analysed the participants' saliva testosterone concentration to preclude this confound. The groups did not differ significantly in their testosterone levels (p = .192).

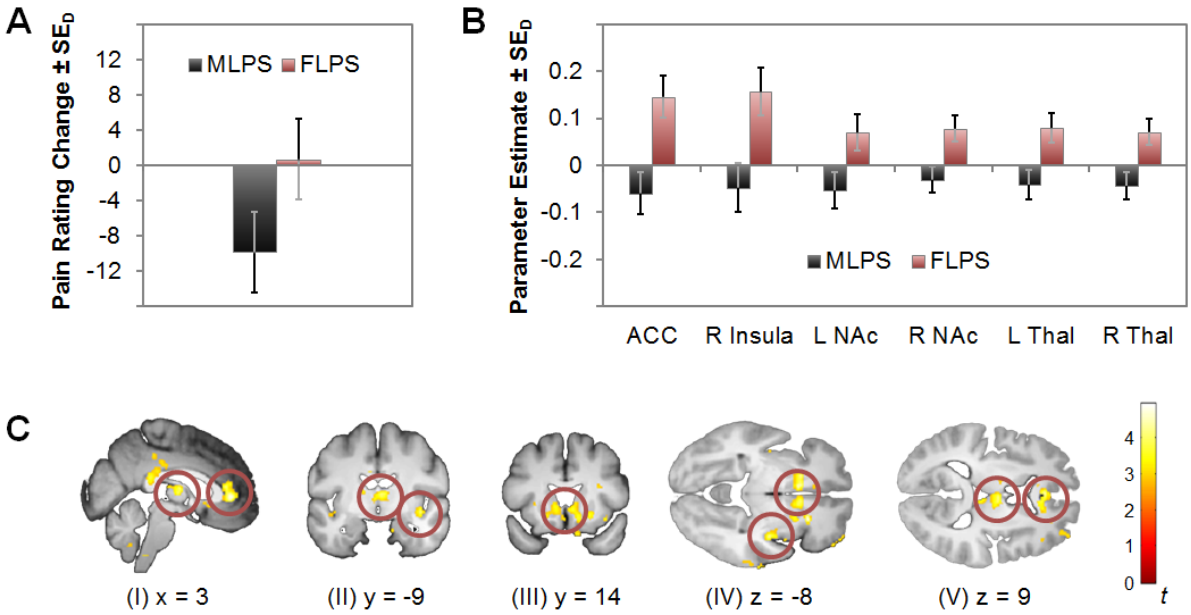

Figure 4. A. Behavioural results of the fMRI experiment in terms of changes in pain sensitivity ratings (day 2 - day 1; scale: 0 - "no pain at all", 100 - "unbearable pain"). Raw scores are plotted in Figure 10C. **B.** Parameter estimates of peak voxels in the early pain phase for the contrast *Pain Day 2 > Pain Day 1* in the anterior cingulate cortex (ACC; 3, 38, 2), right insula (41, -11, -8), bilateral nucleus accumbens (-9, 14, -6 / 12, 8, -12) and bilateral thalamus (0, -14, 6 / 5, -9, 9); *p*s < .05, corrected for multiple comparisons. **C.** BOLD signal in the early pain phase for the contrast *FLPS (Pain Day 2 > Pain Day 1) > MLPS (Pain Day 2 > Pain Day 1)* of the ACC (I, V), the insula (II, IV), nucleus accumbens (III, IV) and thalamus (I, II, V). To better judge the extent of the activations, the display threshold is set to *p* < .005, 10 voxels minimum.

Two distinct mechanisms might mediate the observed effects: The decrease in pain sensitivity in the *MLPS* group might depend on the release of endogenous opioids as in placebo hypoalgesia (Büchel et al., 2014; Eippert et al., 2009a; Levine et al., 1978). Alternatively, differences between the *MLPS* and *FLPS* group could be explained by

differential physiological stress responses to the experimental manipulation. Stress responses mediate the effects of stereotypes on cognitive abilities (in concert with monitoring processes and thought suppression; Schmader et al., 2008). This mediation seems to involve down-regulation of activity in prefrontal circuits which, consequently, impairs working memory processes. Stress responses can also alter pain sensation and reduce pain sensitivity (Butler & Finn, 2009; Flor & Grüsser, 1999; Sorge et al., 2014). This stress-induced hypoalgesia, in turn, can rely on a range of additional non-opioidergic neurotransmitter systems, including monoamines, glutamate and endocannabinoids (Butler & Finn, 2009; Sorge et al., 2014). Stress-related physiological processes are further thought to affect large-scale neural network coupling and especially functional brain connectivity between pain-responsive areas in the anterior mid-cingulate cortex and the brainstem (Hermans et al., 2011; Vachon-Presseau et al., 2013). These findings provide possible pathways for top-down modulation of pain processing during stress.

7 | Naloxone Experiment

The release of endogenous opioids is a well-documented mechanism of placebo hypoalgesia (Büchel et al., 2014; Eippert et al., 2009a), during which the descending opioidergic pain pathway is activated, leading to inhibition of nociceptive processing at the spinal level. This process and subsequent behavioural hypoalgesic effects can be inhibited by the administration of naloxone, an opioid antagonist (Eippert et al., 2009a). Thus, we would expect the hypoalgesic effect observed in our *MLPS* groups to be inhibited by naloxone, if the effect were to depend on the same descending opioidergic pathway.

However, our results indicate that this is not the case. In this experiment, we compared a group receiving naloxone with a group receiving a saline solution (see *10 | Supplementary Methods*). Both groups were instructed according to the *MLPS* expectancy manipulation. The *Naloxone* group did not differ from the *Saline* group in the decrease of pain sensitivity on the second day compared to the first day, neither in pain sensitivity ratings (interaction Time x Opioid State: $F(1,29) = 1.03$, $p = .318$; Figure 5A), nor in pain threshold measures (interaction Time x Opioid State: $F < 1$; Figure 5B). Both groups showed the previously described reduction in pain sensitivity from the first day to the second with an 18.2% decrease for the *Saline* group and a 13.6% decrease for the *Naloxone* group. While there is a descriptively steeper reduction in pain sensitivity in the *Saline* group than in the *Naloxone* group, this change is unlikely to underlie the observed behavioural effects alone, especially regarding the pain threshold measures. We therefore have no evidence suggesting that an opioidergic mechanism is at play in the effects of stereotypes on pain processing.

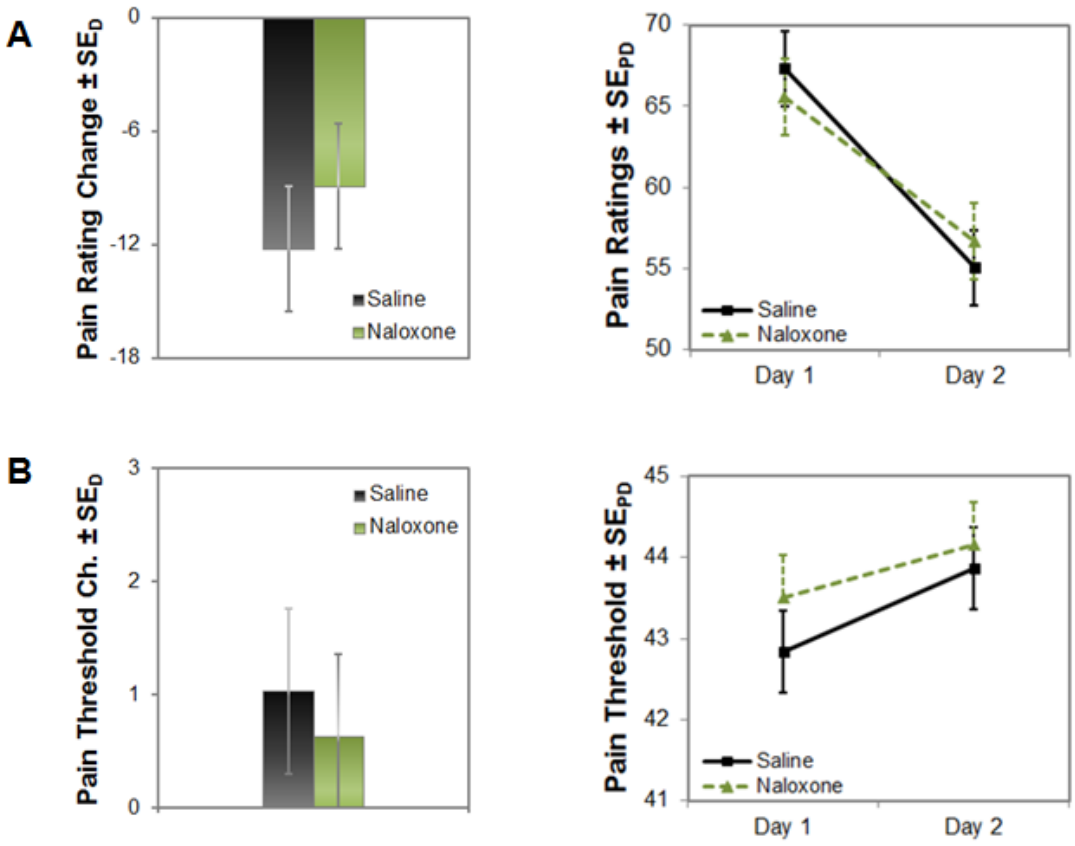

Figure 5. A. Changes in pain sensitivity ratings (day 2 – day 1; left panel) and corresponding raw scores (right panel) of the Naloxone experiment. The expectancy manipulation was the same in both groups ("men are less pain sensitive") and pain ratings were generally higher on the first day than on the second day ($F(1,29) = 41.60$, $p < .001$, $\eta_p^2 = .59$). Subsequent paired *t*-tests for each group indicated the difference between day 1 and day 2 to be significant for both, the *Saline* and the *Naloxone* group (*Saline*: $t(14) = 5.30$, $p < .001$; *Naloxone*: $t(15) = 3.84$, $p = .002$). Even though the difference between day 1 and day 2 was descriptively smaller for the *Naloxone* group (as would be expected according to the *endogenous opioids* hypothesis), the corresponding interaction *Time* x *Opioid State* did not reach significance, $F(1,29) = 1.03$, $p = .318$. The opioid antagonist naloxone therefore does not seem to inhibit the hypoalgesia effect observed in the *MLPS* group in our experiments (Figure 3), even though the corresponding descriptive trend seems to be in accordance with recent findings on naloxone

effects in rodents (Sorge et al., 2014). **B.** Changes in pain threshold temperature (day 2 – day 1; left panel) and corresponding raw scores (right panel). Again, there was no significant interaction *Time* x *Opioid State* ($F < 1$) suggesting that naloxone alone did not inhibit the rise in pain threshold temperature on the second day in the *MLPS* groups in our experiment (Figure 10B). Pain threshold temperatures on the first day were generally lower than on the second day ($F(1,29) = 5.50$, $p = .026$, $\eta_p^2 = .16$), although group-wise paired *t*-tests showed that the difference between day 1 and day 2 was only marginally significant in the *Saline* group ($t(14) = -2.06$, $p = .059$) and not significant in the *Naloxone* group ($t(15) = -1.27$, $p = .224$).

8 | Cortisol Experiment

To test the alternative stress-induced hypoalgesia hypothesis, we measured cortisol concentration in 54 participants on three time points on each experimental day (Figure 8C; n_{MLPS} = 17, n_{FLPS} = 18, $n_{Control}$ = 19). Physiological stress responses engage the hypothalamic-pituitary-adrenocortical (HPA) axis which in turn regulates the release of the glucocorticoid cortisol. Typically, a strong trigger is needed to elicit detectable increases in cortisol levels (Dickerson & Kemeny, 2004), therefore we included another pain-related stressor at the end of day 2: the Cold Pressor Test (CPT). During this test, participants are asked to hold their right hand in ice-water (0°C) and to keep it there until they can no longer bear the pain (see *10 | Supplementary Methods*). After this procedure, participants were asked to rate how painful the test had been perceived. Figure 6 illustrates the effects of the expectancy manipulation on cortisol levels and perceived pain during the CPT (see Figure 11B for CPT duration data). Our main analysis of interest again concerned the difference between the expectancy manipulation groups, i.e., *MLPS* vs. *FLPS*. The *FLPS* group reported significantly higher pain ratings than the *MLPS* group ($t(33) = -2.13$, $p = .041$, d = -0.72). In support of this behavioural effect, the expectancy manipulation groups showed differential physiological stress responses to the CPT with an increase in cortisol levels in the *MLPS* group and no significant change in the *FLPS* group (interaction Time x Measurement x Expectancy Manipulation: $F(2,64) = 3.31$, $p = .043$, $\eta_p^2 = .09$).

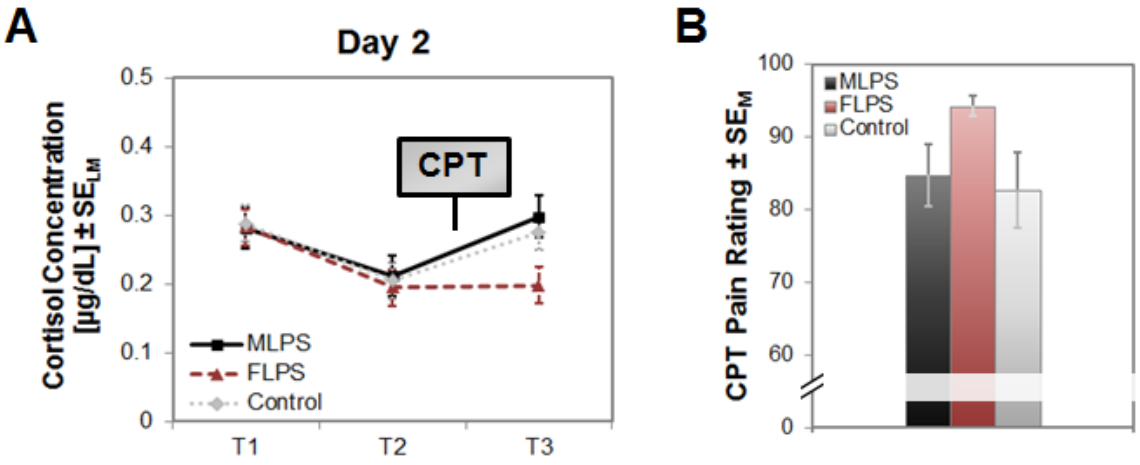

Figure 6. A. Cortisol concentration for each group and measurement (T1-T3) on day 2. See Figure 8C for details on the experimental procedure and Figure 11 for additional data. **B.** Cold Pressor Test (CPT) pain ratings for each group (scale: 0-"no pain at all", 100-"unbearable pain").

To better interpret this effect, we also investigated a *Control* group. Notably, the cortisol concentration of the *Control* group did not lie symmetrically between the *FLPS* and *MLPS* group as is suggested by a non-significant linear contrast (*MLPS* > *Control* > *FLPS*), $F(1,50) = 2.09$, $p = .149$, but was much closer to the concentration change of the *MLPS* group. When comparing the raw cortisol concentration of the last measurement on each day, the *FLPS* group only showed a weak and non-significant stressor-related increase ($|t| < 1$), whereas the *MLPS* and the *Control* group responded with a significant increase in cortisol levels on day 2 as compared to day 1, ($ps < .033$, one-tailed). The *MLPS* and *Control* group also showed similar rating patterns ($|t| < 1$) whereas the *FLPS* and *Control* group differed significantly ($t(34) = 2.11$, $p = .043$, $d = 0.71$), with the *Control* group reporting less perceived pain than the *FLPS* group during the CPT. This

asymmetry is in line with a “default” stereotype which holds that males are less pain sensitive (Robinson et al., 2001). It is therefore not surprising to see a similar pattern in the *Control* and *MLPS* group.

9 | Revisiting the fMRI Experiment

Our results demonstrate that participants in the *FLPS* group – in contrast to both other groups – only showed a negligible activation of the physiological stress response, including the release of cortisol, and simultaneously experienced more pain than participants in the other groups. These results imply that stress-induced hypoalgesia might play an important role in the effects of stereotypes on pain processing.

Stress-induced hypoalgesia has been linked with the dopaminoceptive system including dopaminergic projections to the nucleus accumbens (Altier & Stewart, 1999; Deutch & Roth, 1990; Navratilova & Porreca, 2014). As this system is involved even before pain onset (Jensen et al., 2003), we additionally investigated the anticipation phase of the fMRI experiment. Here we observed a differential activation between both groups in bilateral ventral striatum and anterior insula (Figure 7A-B; Table 2). Importantly, the reduction of ventral striatal activity in the *MLPS* group from day 1 to day 2 was significantly correlated with individual reductions in pain perception, $r = 0.52$, $p = .033$, whereas no such correlation emerged in the *FLPS* group, $r = -0.24$, $p = .351$ (Figure 7C). This observation is in line with previous reports showing that ventral striatal activation is correlated with various components of pain (Baliki et al., 2010) and directly links individual pain reduction in our experimental context with activation differences in the dopaminergic system. Importantly, previous studies (Altier & Stewart, 1999) have implicated activity changes in the dopaminergic system to stress, mediated by a modulation of dopaminergic inputs from the ventral tegmental area by glutamatergic projections from the amygdala (Navratilova & Porreca, 2014).

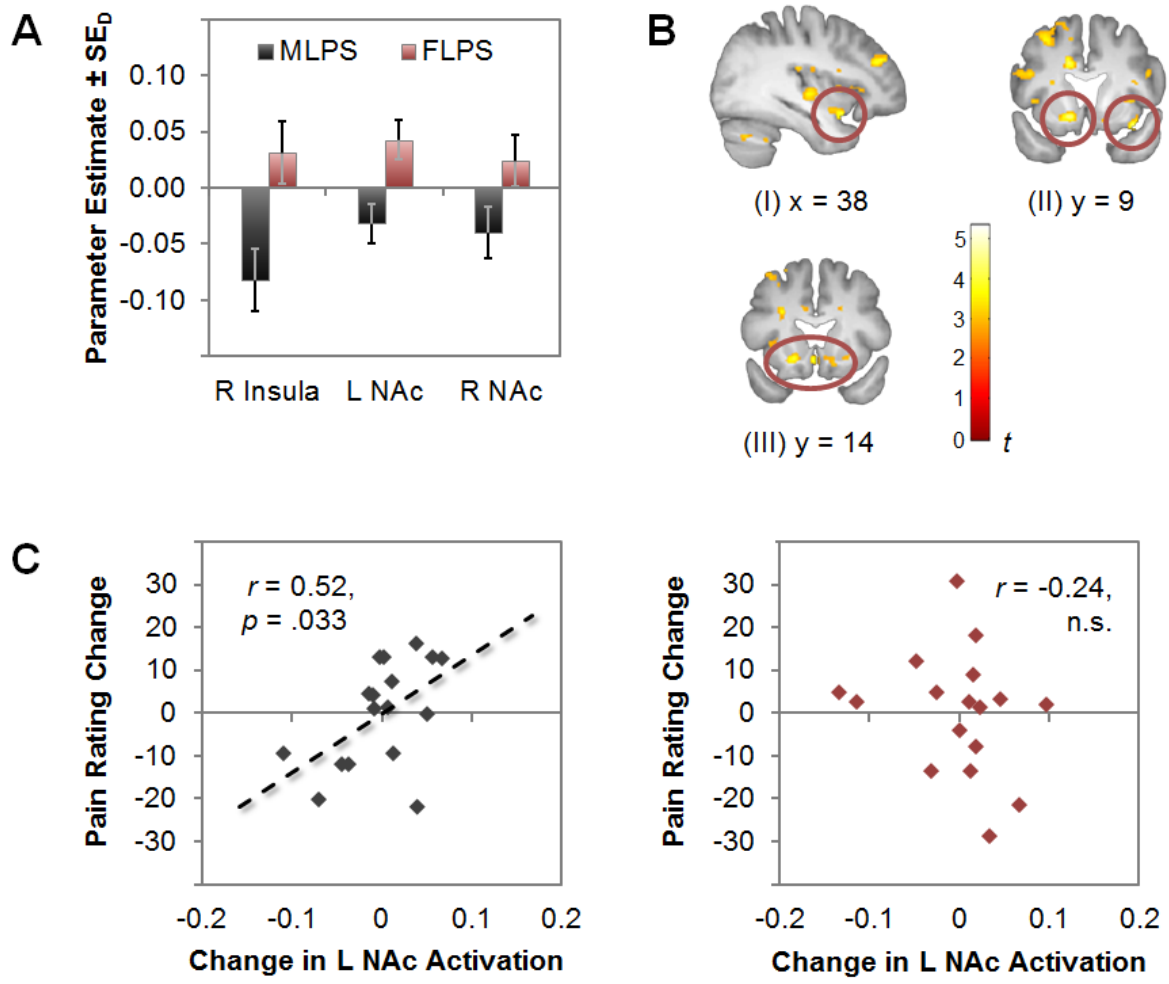

Figure 7. A. Parameter estimates of peak voxels in the anticipation phase for the contrast *Pain Day 2 > Pain Day 1* in the right insula (38, 9, -18) and bilateral nucleus accumbens (-12, 9, -11 / 12, 14, -11). *p*s < .05, corrected for multiple comparisons. **B.** BOLD signal in the anticipation phase for the contrast *FLPS (Pain Day 2 > Pain Day 1) > MLPS (Pain Day 2 > Pain Day 1)* of the insula (I, II) and the nucleus accumbens (II, III). To better judge the extent of the activations, the display threshold is set to $p < .005$, 10 voxels minimum (see also Table 2). **C.** Correlation of changes in nucleus accumbens activation (day 2 – day 1) and corresponding changes in pain ratings, separately for the *MLPS* group (left panel) and for the *FLPS* group (right panel). A direct comparison of the Fisher-*Z*-transformed correlation

coefficients (Z_{MPLS} = 0.57, Z_{FLPS} = -0.25) confirmed the correlations of the two groups to differ significantly, z = 2.17, p = .030, ε = 0.82. Both measures were centred to facilitate visual comparison of the correlations.

Nevertheless, other neurotransmitter systems could also contribute to the phenomenon, such as endocannabinoids. As is the case for dopamine, the endocannabinoid system is a well-established mediator of stress-induced hypoalgesia (Butler & Finn, 2009; Hohmann et al., 2005) and has been shown to interact closely with other transmitter systems, including endogenous opioids (Butler & Finn, 2009; Sorge et al., 2014). This system is thus a promising candidate for further investigation, as are social moderators of the observed effects. These moderators likely include gender-role identification, dyadic male-female relations, and genotype-environment interactions (Martin, Tuttle, & Mogil, 2014; Mogil et al., 2011; Mogil, 2012).

Taken together, our series of experiments demonstrates the substantial effects of stereotype-related expectations on pain processing, giving evidence to a causal link between these two instances. Our expectancy manipulations evoked differential behavioural rating patterns and physiological responses on the neural and hormonal level in response to expectancy-related stimuli. Our results indicate that a differential physiological stress response might play an integral part in gender-related stereotype modulation of pain, possibly mediated by non-opioidergic neural pathways.

10 | Supplementary Methods

10.1 Participants

10.1.1 Main Experiments

We recruited 120 healthy male participants for the behavioural, fMRI and Cortisol experiments in this study, with 40 participants being randomly assigned to either group (*MLPS*, *FLPS*, *Control*). We focused on male participants being tested by a male experimenter to be able to address our main question – the possibility of an impact of gender-related stereotypes on pain – within a homogenous sample to ensure optimal statistical power. Moderating roles of participant gender, male/female interactions between participant and experimenter, and variations of the effects across the menstrual cycle of women certainly seem possible in light of previous research (Kállai, Barke, & Voss, 2004; Martin et al., 2014; Mogil et al., 2011; Mogil, 2012; Riley III et al., 1999; Sorge et al., 2014).

A total of 15 participants did not complete data collection due to technical difficulties or were excluded from data analysis because they either did not understand or did not believe our expectancy manipulation, as was assessed in a questionnaire serving as our experimental manipulation check. Of the remaining 105 male participants, 34 received the instruction that men are less pain sensitive than women on the second day (*MLPS* group, mean age 25.85 years ± 0.78 SE_M), 35 received the instruction that women are less pain sensitive than men (*FLPS* group, 25.54 years ± 0.83), and 36 received no gender-related instruction (*Control* group, 25.53 years ± 0.77). Exclusion criteria involved neurological and neuropsychiatric diseases, current

medication, substance abuse, or skin afflictions on the forearms. The study was approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

10.1.2 Naloxone Experiment

We additionally tested 40 healthy male participants for the Naloxone experiment (these participants are not included in the original count of 120 participants). Nine individuals did not complete data collection due to technical difficulties or were excluded later because they felt uncomfortable for longer than 15 minutes after the intravenous line was inserted. Of the remaining 31 participants, 15 received saline (mean age 25.13 years ± 0.69 SE_M) and 16 received the opioid antagonist naloxone (24.06 years ± 0.84). All participants were given the same stereotype expectation manipulation and were instructed that men are less pain sensitive than women (*MLPS* expectancy manipulation). Exclusion criteria involved neurological diseases, cardiovascular diseases, current medication, substance abuse, illegal drug consumption in the last 4 weeks before the first day of the experiment, or skin afflictions on the forearms. All participants gave written consent and the consent form included information about the experimental procedures, the thermal stimulation, and about the possible adverse effects of naloxone. Participants were not informed about the actual purpose of the study until debriefing at the end of the second experimental day. The study was approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

10.2 Experimental Paradigm

All participants completed the behavioural paradigm as shown in Figure 8A, but the basic paradigm was adapted to the needs of the different physiological measures for subsets of these individuals (see below, Figures 8B-8C). Seventeen participants completed only the behavioural paradigm (Figure 8A, all *Control* group), 34 individuals took part in the fMRI experiment (Figure 8B, n_{MLPS}=17, n_{FLPS}=17), and 54 participants completed the Cortisol experiment (Figure 8C, n_{MLPS}=17, n_{FLPS}=18, $n_{Control}$=19). An additional 31 participants completed the basic behavioural paradigm as shown in Figure 8A for the Naloxone experiment with slight adaptions to the experimental procedure (see *10.2.4 Naloxone Paradigm*).

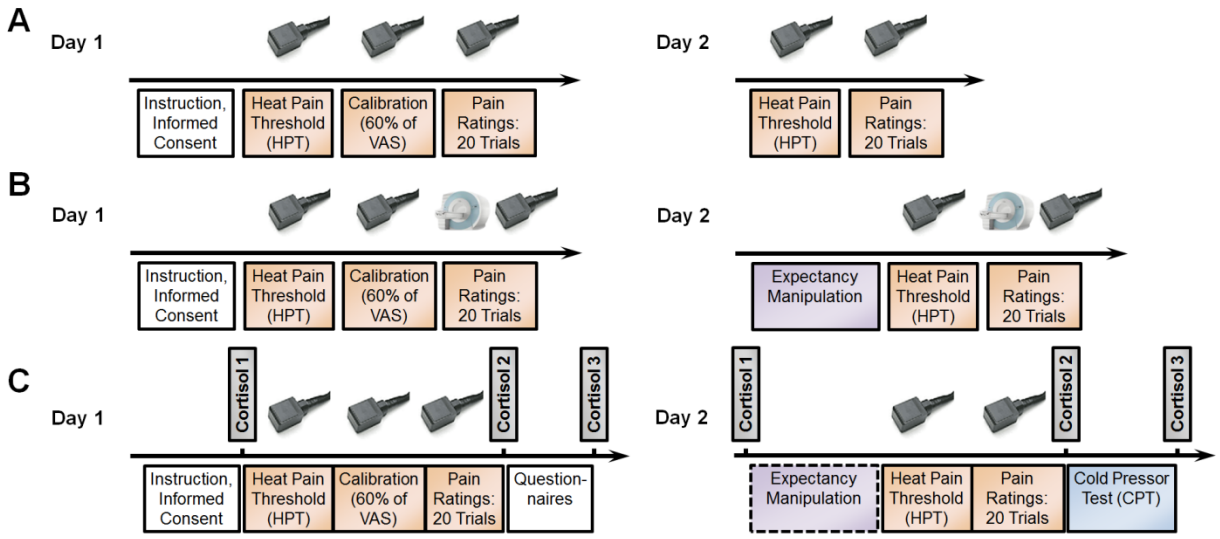

Figure 8. A. Behavioural paradigm. After a general instruction on the first day, we measured the participants' heat pain thresholds, then performed a stimulus calibration to allow for an experimental temperature that elicited 60 to 65 on a visual analogue scale (VAS; 0-100) and used that temperature for 20 consecutive pain stimuli. The participants were asked to rate their pain

experience after each pain stimulus. On the second day, heat pain threshold measures and pain sensitivity ratings (same temperature as on day 1) were assessed anew. Note that no expectancy manipulation took place here, because only participants in the *Control* group were tested in this basic design. **B.** Adaptation for the fMRI experiment. Participants were positioned in the MRI scanner prior to the heat pain threshold measurements on both days to assure a similar experimental environment for all pain measures obtained. However, functional imaging measurements were only acquired for the pain sensitivity ratings (20 consecutive pain stimuli). Note that all participants in the fMRI experiment received a gender-related expectancy manipulation at the beginning of the second day, as all participants were either part of the *MLPS* or the *FLPS* group. **C.** Adaptation for the Cortisol experiment. At six time points over the two experimental days (three time points per day, T1-T3), saliva samples were taken for subsequent cortisol concentration analysis. Additionally, to elicit stronger cortisol responses, a Cold Pressor Test (CPT) was added at the end of the second experimental day.

10.2.1 Basic Behavioural Paradigm

Participants were measured on two experimental days that were scheduled to be one or two days apart (Figure 8A). The experimenter was always male and wore a white coat. On the first day, participants were told that they would take part in a pain study looking to find individual factors of pain experience and were asked to be as honest as possible in their pain ratings. Heat pain stimuli were applied to the left forearm using a Peltier thermode. We measured the heat pain threshold by slowly increasing stimulus temperature at a rate of 0.3°C/s, starting at 30°C. Participants were asked to indicate as soon as they felt the first pain sensation which immediately stopped the temperature

increase. This procedure was repeated four times and the four pain threshold temperatures were averaged. We then calibrated the heat pain temperature to elicit a pain rating of about 60 to 65 on a Visual Analogue Scale (VAS; 0-100), ranging from “no pain at all” to “unbearable pain”. In four blocks of three heat pain stimuli each (13s duration, 10s plateau), pain sensitivity was assessed by asking the participants to rate different pain stimuli on the VAS. The temperature falling within the range of 60 to 65 of the VAS was used for the subsequent experiment. After the calibration procedure, participants received 20 heat pain stimuli at the calibration temperature. To assure an individual rating procedure for each stimulus, participants were not explicitly told that the temperature would be constant for all 20 stimuli. The stimulus was preceded by a cue – a red fixation cross on the screen – five seconds before stimulus onset and the red fixation cross remained on the screen until the pain stimulus terminated (13s duration, 10s plateau) and the temperature had again dropped to baseline (32°C). After the stimulus, the VAS rating scale appeared on the screen, ranging from “no pain at all” to “unbearable pain” and participants were asked to indicate their pain experience with a standard computer mouse. The rating procedure and a subsequent inter-trial interval (ITI) lasted for a total of 55 seconds. This break between pain stimuli was implemented to minimize sensitization or habituation effects due to continuous thermal heat stimulation. Altogether each trial lasted 73 seconds and the whole experimental procedure of 20 trials took 24 minutes.

On the second experimental day, the expectancy manipulation for participants in the *MLPS* and *FLPS* groups was applied by subtly briefing those individuals on evolutionary reasons why men and women, respectively, are less sensitive to pain (see

10.2.2 Expectancy Manipulation below). As part of a questionnaire, they were then asked whether or not they perceived themselves as "masculine" on a 7-point scale ranging from "very feminine" to "very masculine". They were also asked how important it was for them to be perceived as "masculine" by others on a 7-point scale ranging from "not important at all" to "very important". As a manipulation check, participants in the *MLPS* group were also asked if they believed men to be generally less pain sensitive in standardized tests than women on a 5-point scale ranging from "not true at all" to "absolutely true". Participants in the *FLPS* group were asked if they believed women to be generally less pain sensitive in standardized tests than men using the same scale. This was intended to screen participants for understanding the instruction and beliefs in the instruction. Participants who rated the statement as "not true at all" were excluded from further analysis (n=6). Participants in the *Control* group did not receive further gender-related information. After this procedure, the heat pain threshold was assessed as on the first day and afterwards the heat pain stimuli were applied at the same temperature as on the first day. After the experimental procedure on the second day, participants were briefed on the real objective of the study and were informed about the real relationship between sex, gender, and pain experience that is known so far.

10.2.2 Expectancy Manipulation

We manipulated the participants' expectancy regarding their own pain sensitivity by giving participants in the *MLPS* and *FLPS* group an additional information sheet at the beginning of the second day. This information sheet once more reminded the participants of the supposed goal of the study, namely to relate individual factors to pain

experience. Participants were also again asked to rate the pain stimuli as honestly as possible.

Within this information sheet, the following phrases were included for the *MLPS* group (translated from German): “We know by now that various personal factors have a strong and predictable influence on pain perception. For example, pain research shows consistently that men react less strongly to pain in standardized tests than women do, i.e., they seem to be less pain sensitive than women. From an evolutionary point of view, a development of such differences is easy to explain, in this example it is argued that the high risk of painful injuries during hunting or while defending resources which are all actions primarily performed by our male ancestors might be responsible. To improve agility with small injuries, the pain perception in men was probably desensitized over the course of human evolution. Further differences include, e.g., personality traits, age, and hormone levels. (...)”

The information sheet for the *FLPS* group contained the following phrases (translated from German): “We know by now that various personal factors have a strong and predictable influence on pain perception. For example, pain research shows consistently that women react less strongly to pain in standardized tests than men do, i.e., they seem to be less pain sensitive than men. From an evolutionary point of view, a development of such differences is easy to explain, in this example it is argued that the very painful and highly relevant parturition for which the female body is already prepared might be responsible. Further differences include, e.g., personality traits, age, and hormone levels. (...)”

The objective of this gender-related information was to induce the respective expectancy about the participants' own pain sensitivity, while at the same time avoiding to pose an overt challenge to the participants. We suspected that if such a challenge were issued, especially participants in the *FLPS* group would be driven to refute the notion that they might be seen as "inferior" to women regarding pain sensitivity and thus not responding honestly but according to their own agenda. To assure that this latter objective was met, we measured the self-perceived masculinity of the participants by asking them (as mentioned above) whether or not they perceived themselves as "masculine" and how important it was for them to be perceived as "masculine" by others. The summed answers of these two questions ranging from 2 ("very feminine" and "not important at all" to 14 "very masculine" and "very important") were correlated with the participants' rating difference (day 1 – day 2). If a challenge was issued to the participants, we expected a strong positive correlation of the pain rating difference with the self-perceived masculinity score, i.e., the higher the self-perceived masculinity the lower the rating on the second day compared with the first day should be. Figure 9 shows the respective correlations. No correlation for either stereotype group approached significance (*p*s > .482), and as can easily be seen, the *FLPS* group descriptively even showed a negative correlation of the pain rating difference with the self-perceived masculinity score. We interpret these findings as indication that indeed no challenge was perceived by the participants.

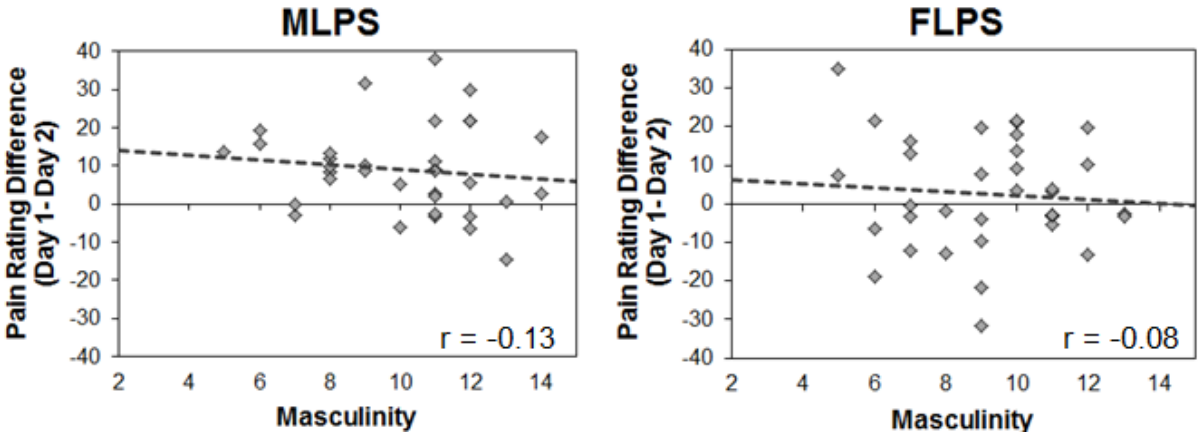

Figure 9. Correlation of the pain rating difference (day 1 – day 2) with the self-perceived masculinity score for either stereotype group. No correlation approached significance and especially the correlation pattern in the *FLPS* group indicates that no challenge was issued due to our expectancy manipulation.

10.2.3 fMRI Paradigm

The experimental design of the fMRI experiment shows slight adaptations to the basic behavioural paradigm described above (Figure 8B). The instructions remained the same, but all pain measurements were obtained while the participants were lying in the MR scanner on both days. No imaging data were acquired during pain threshold measures and during stimulus calibration; however, functional imaging data were obtained during the subsequent pain rating procedure on both days. On the first day, the measurements were concluded with high resolution anatomical T1 scans (see *10.4.1 fMRI parameters*).

The pain rating procedure was slightly altered to adapt the experimental design to the requirements of the changed location and fMRI data analysis. The pain stimulus was again preceded by a red fixation cross on a screen five seconds before stimulus onset, and the red fixation cross (cue) remained on the screen for the duration of the pain stimulus (13s duration, 10s plateau). The pain stimulus was followed by a short jitter period during which the screen turned black, lasting for a randomized time between 2 and 5 seconds with an average of 3.5 seconds. After the jitter, the VAS rating scale appeared on the screen, ranging from “no pain at all” to “unbearable pain” and participants were asked to indicate their pain experience via button presses. The cursor on the rating scale appeared at a random place on the scale and while the left or right button was pressed, it moved continuously along the scale until the button was released. When participants were satisfied with their rating, they confirmed their choice by pressing a third button. Participants were asked to complete their rating within 15 seconds. After they confirmed their rating choice or after the 15 seconds had passed, the screen showed a white fixation cross for 30 seconds, and participants were asked to fixate the cross to reduce head movements. The whole pain rating procedure took 22 minutes.

As an additional measure, we asked our participants in the fMRI experiments to give saliva samples on the morning of the second experimental day for testosterone analysis. Participants were equipped with 2 ml polypropylene Eppendorf tubes and an informational sheet detailing the saliva sample procedure. Saliva collection started in the morning after waking up and before breakfast. All fMRI participants collected five saliva samples in Eppendorf tubes with a time gap of 30 minutes in between, yielding a

total sampling time of 2 hours. This procedure allowed to control for the episodic secretion pattern of steroid hormones and gave a representative sample of the participants' current hormone levels. Participants were instructed not to eat, smoke or drink anything but water during the 2 hours sampling time and they were asked to restrict themselves to a vegan diet for 12 hours before sampling onset. Three participants had to be excluded from this analysis because they failed to comply with the saliva sampling instruction.

10.2.4 Naloxone Paradigm

The experimental design of the Naloxone experiment shows slight adaptations to the basic behavioural paradigm described above. After giving their informed consent on the first day, participants were tested for current drug use (including THC and opiates) using commercially available urine tests. A standard resting electrocardiography was performed to assure that no unknown cardiac arrhythmia existed. Participants then followed the experimental paradigm as detailed in the *10.2.1 Basic Behavioural Paradigm* paragraph. On the second experimental day, participants received either the drug injection or saline solution about 15 minutes before the start of the testing phase (see *10.2.5 Naloxone Administration* below). After the 15 minutes period, the *MLPS* expectancy manipulation was performed and the subsequent testing period precisely followed the basic behavioural experimental design as described above.

10.2.5 Naloxone Administration

About 15 minutes before the start of the testing phase in the Naloxone experiment, we administered a bolus dose of 0.15 mg/kg naloxone or the same amount of saline via an intravenous line inserted in the right forearm in a double-blind study design. We also administered an additional intravenous infusion dose of 0.2 mg/kg/h naloxone or saline, shortly after bolus administration. This dosing regimen leads to stable naloxone plasma concentrations which correlate strongly with the concentration in the central nervous system (Tepperman, Hirst, & Smith, 1983).

10.2.6 Cortisol Paradigm

The basic behavioural design was adapted to the needs of the cortisol measurements in the Cortisol experiment (Figure 8C). One or two days before the start of the experiment, participants were asked to come to the laboratory and were informed about the saliva sampling procedure including diet restrictions (vegan diet for 12 hours before their appointment on the first experimental day, no food or drink but water for two hours before the start of the experiment, no smoking for two hours before the start of the experiment). They were asked to follow a regular sleep-wake cycle over the course of the experiment, i.e., to go to sleep at similar times at night, and to refrain from alcohol use and extensive activity right before sleeping. These instructions were intended to assure that different sleeping and waking patterns did not interfere with comparable cortisol release on both experimental days. We provided the participants with ActiWatches which they were instructed to wear at all times, to enforce compliance

with our sleeping instructions. Participants were also asked to wake up at least three hours before the start of the experiment. Note that all experimental procedures took place in the afternoon to avoid the strong cortisol fluctuations in the first hours after waking up.

On the first experimental day, participants received the same general instruction as described above and gave their consent to the experiment. We then asked them to collect their saliva in two 2 ml polypropylene Eppendorf tubes (first sample). The experimental procedure progressed as described above (see *10.2.1 Basic Behavioural Paradigm*) with pain threshold measures, stimulus calibration, and the pain intensity rating procedure. After the pain stimulation, we waited for 10 minutes and then asked our participants to again collect two saliva samples (second sample). The participants were instructed to fill out questionnaires after this sampling and at the end of the first experimental day collected two more saliva samples (third sample). On the second experimental day, participants collected two saliva samples before the testing phase (fourth sample), and then received the expectancy manipulation in case of the *MLPS* and *FLPS* groups, or no further information in case of the *Control* group. The subsequent pain stimulation followed the experimental design as described above (see *10.2.1 Basic Behavioural Paradigm*). After the testing phase, we waited for 10 minutes and then asked our participants to collect two saliva samples (fifth sample). Because cortisol level increase is primarily detectable after exposure to a strong stressor (Dickerson & Kemeny, 2004), the sampling was followed by a Cold Pressor Test (CPT). This test was surprising for the participants as they were informed about it only right before it took place. During the CPT, participants immersed their right hands into a

bucket of ice-water (0°C). They were instructed to keep their hands in the water until they could not bear the pain anymore. The duration of their stay in the water served as a pain tolerance measure that was recorded by the experimenter with a stop watch. The participants were free to remove their hands and terminate the test at any time, but they were asked to be as honest as they possibly could be about their pain tolerance and not end the test prematurely. If they had not removed their hands after 10 minutes, they were asked to do so, but the participants did not know about this limitation before the test. After the CPT, the participants answered the question "how painful was the test for you on average?" on a scale ranging from "no pain at all" to "unbearable pain" presented to them on a computer screen. We waited for another ten minutes until the participants were asked to give two more saliva samples (sixth sample).

We opted for measuring salivary cortisol rather than blood cortisol for several reasons. First, the repeated collection of blood samples might pose a pain stressor in itself, which would pose a significant confound. Second, the concentration of free bioactive cortisol is considered a reliable indicator of environmental perturbations, i.e., stressors (Inder, Dimeski, & Russell, 2012). Cortisol determined from saliva represents only the free bioactive fraction of cortisol in the system, which in contrast to the bound fraction of cortisol, can pass the membrane of the salivary glands. In contrast, plasma and serum cortisol contain both the free and bound fraction of cortisol (i.e., total cortisol). Following the stressor and the rise of blood cortisol, which takes between 10 and 30 minutes, the transfer from blood to saliva takes place rather rapidly (within 2-3 minutes), thus providing a prompt measure of the stress response. Finally, the analysis of free cortisol in saliva offers a convenient and reliable test with equivalent

performance as the analysis of bioactive cortisol from human blood. The luminescence-enhanced enzyme immunoassay we used shows an excellent analytical and functional sensitivity for the routine determination of cortisol from human saliva (Westermann, Demir, & Herbst, 2004).

10.3 Behavioural Data Analysis

Behavioural data were analysed using SPSS 20. First, mean pain sensitivity ratings of all 20 pain trials were calculated for each participant and each day, separately. Then our main analysis of interest was performed, a 2 x 2 analysis of variance (ANOVA) with the within-subjects factor Time (Day 1 vs. Day 2) and the between-subjects factor Expectancy Manipulation (MLPS vs. FLPS). We then broadened the ANOVA to also include the *Control* group to allow a better interpretation of the expectancy manipulation effect (Time [Day 1 vs. Day 2] x Expectancy Manipulation [MLPS vs. FLPS vs. Control]). Subsequent simple effects ANOVAs looked at the differences between the *MLPS* and *Control* group and the *FLPS* and *Control* group, respectively (Time [Day 1 vs. Day 2] x Expectancy Manipulation [MLPS x Control] and Time [Day 1 vs. Day 2] x Expectancy Manipulation [FLPS x Control]).

Mean pain threshold temperatures were calculated separately for each participant and day. Again, our main analysis of interest was a two-way ANOVA with the within-subjects factor Time (Day 1 vs. Day 2) and the between-subjects factor Expectancy Manipulation (MLPS vs. FLPS). The following analyses were computed as

described for the pain sensitivity ratings. For technical reasons, one participant of the Control group had to be excluded from the pain threshold analysis.

Cold Pressor Test (CPT) pain ratings and pain duration were analysed using separate one-way ANOVAs with the between-subjects factor Expectancy Manipulation (*MLPS* vs. *FLPS* vs. *Control*) and independent-samples *t*-tests for pairwise comparisons between groups. For technical reasons, one participant of the *Control* group had to be excluded from the CPT pain rating analysis.

Note that our results figures employ different error bars dependent on the underlying statistical model of the calculation to optimize the interpretational value of the graphs. The type of the respective error bar is denoted at the y-axis of each figure (SE_M=standard error of the mean; SE_D=standard error of the between-subjects difference between two means, Pfister & Janczyk, 2013; SE_{PD}=standard error of the (within-subjects) paired difference between two means, Pfister & Janczyk, 2013; SE_{LM}=Loftus-Masson within-subjects standard error for repeated-measures ANOVA, Loftus & Masson, 1994).

10.4 fMRI Parameters and Data Analysis

10.4.1 fMRI Parameters

Imaging data were obtained on a 3 Tesla system, equipped with a 32-channel head coil. A T2*-weighted standard gradient echo planar imaging sequence was used to measure BOLD responses (repetition time 2.58s; echo time 26ms; flip angle 80°; field of

view 220 x 220 mm^2; GRAPPA PAT Factor 2). Each volume contained 42 transversal slices (voxel size 2 x 2 x 2 mm^3; 1 mm gap). Volumes were individually tilted by approximately 30° relative to the AC-PC plane to allow whole-brain acquisitions including the brainstem. The first 4 volumes of each session were discarded to account for T1 saturation effects. High resolution T1 scans were acquired using an MPRAGE sequence with a voxel size of 1 x 1 x 1 mm^3.

10.4.2 fMRI Data Analysis

fMRI data were preprocessed and statistically analysed by using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab R2014a. Data preprocessing consisted of motion correction (realignment), coregistration of the individual anatomical T1 image to the functional images, spatial normalization to MNI space using DARTEL based on segmented T1 scans. The DARTEL estimation used templates provided by the VBM 8 toolbox (http://dbm.neuro.uni-jena.de/vbm). All fMR images were smoothed using a 6 mm (FWHM) isotropic Gaussian kernel. We used a high-pass filter to cut off all slow signal drifts with periods longer than 128 seconds and a correction for temporal autocorrelations was performed using a first-order autoregressive model.

fMRI data analysis was based on the general linear model approach as implemented in SPM. For each individual, the design matrix consisted of 10 regressors for each session. Each regressor modelled the activation in a time bin (one TR, i.e., 2.58s) after stimulus onset, where time point zero was defined as the first appearance of

the red fixation cross (cue). The entire set of regressors thus covered a time period of 25.8 seconds after cue presentation. This finite impulse response (FIR) model has the advantage that no a priori assumptions about hemodynamic response patterns have to be made, and at the same time it can test for specific activation patterns at every time period. We focused our analyses on the anticipation phase (i.e., the second bin spanning 2.58s-5.16s after cue onset) and the early (10.32s-15.48s) and late (15.48s-23.22s) pain period. The rigid body transform motion parameters from the realignment stage were included as additional regressors. After model estimation at the first-level comparing parameter estimates between day 1 and day 2 for the anticipation, early pain and late pain phase, the resulting contrast images were used for second-level group analyses. At the second level, a two sample *t*-test was employed comparing the changes from day 1 to day 2 between the *MLPS* and the *FLPS* group.

For all imaging data analyses, results were considered significant at $p < .05$, family-wise error (FWE) corrected for multiple comparisons. For a priori regions of interest (ROIs), correction for multiple comparisons was based on anatomical masks taken from the Harvard-Oxford atlas (normalized to the DARTEL templates as provided by the VBM 8 toolbox), using an initial height threshold of $p < .005$ and an initial extent threshold of 10 voxels. ROIs comprised of bilateral ACC, the insula including the parietal and frontal operculum, the basal ganglia (ventral striatum), the thalamus, and the amygdala (see Figure 12 for ROI locations overlaid on the mean T1 image from all participants). For illustration purposes, statistical maps were thresholded at $p < .005$, uncorrected, with a voxel extent of minimum 10 and overlaid on the mean structural

image of all subjects. All activations are reported using x, y, z coordinates based on the used template, which is in Montreal Neurological Institute (MNI) standard space.

10.5 Testosterone Analysis

Saliva samples were obtained as described above (see *10.2.3 fMRI Paradigm*) and frozen at -20°C until study completion. In preparation for hormone analysis, the samples were thawed and centrifuged at RCF 604 x g for five minutes (i.e., 3000 rpm in a centrifuge) to separate them from mucin and other residuals. The five morning samples were combined to an aliquot by extracting 2ml of clear, colourless supernatant from each of the five Eppendorf tubes. Samples containing traces of blood were excluded. A Testosterone Luminescence Immunoassay was used to determine testosterone concentrations in the aliquot. The sensitivity of the Testosterone Luminescence Immunoassay is denoted as 1.8 pg/mL.

10.6 Cortisol Analysis

Saliva samples were obtained as described above (see *10.2.6 Cortisol Paradigm*). The post-stressor waiting period of 10 minutes was chosen to optimize cortisol increase detection (Dickerson & Kemeny, 2004). The samples were then frozen at -20°C until study completion. In preparation for hormone analysis, the samples were thawed and centrifuged at RCF 604 x g for five minutes (i.e., 3000 rpm in a centrifuge) to separate them from mucin and other residuals. The two saliva samples per time point were

combined to an aliquot by extracting 5ml of clear, colourless supernatant from each of the two Eppendorf tubes, resulting in 6 aliquot samples per participant. Samples containing traces of blood were excluded. A Cortisol Luminescence Immunoassay was used to determine cortisol concentrations in the aliquot. The sensitivity of the Cortisol Luminescence Immunoassay is denoted as 0.005 µg/dL. For technical reasons, one participant of the *FLPS* group had to be excluded from the cortisol concentration analysis. Cortisol concentrations were analysed by a 2 x 3 x 2 ANOVA with the within-subjects factors Time (Day 1 vs. Day 2) and Measurement (T1 vs. T2 vs. T3) and the between-subjects factor Expectancy Manipulation (MLPS vs. FLPS).

11 | Supplementary Figures and Tables

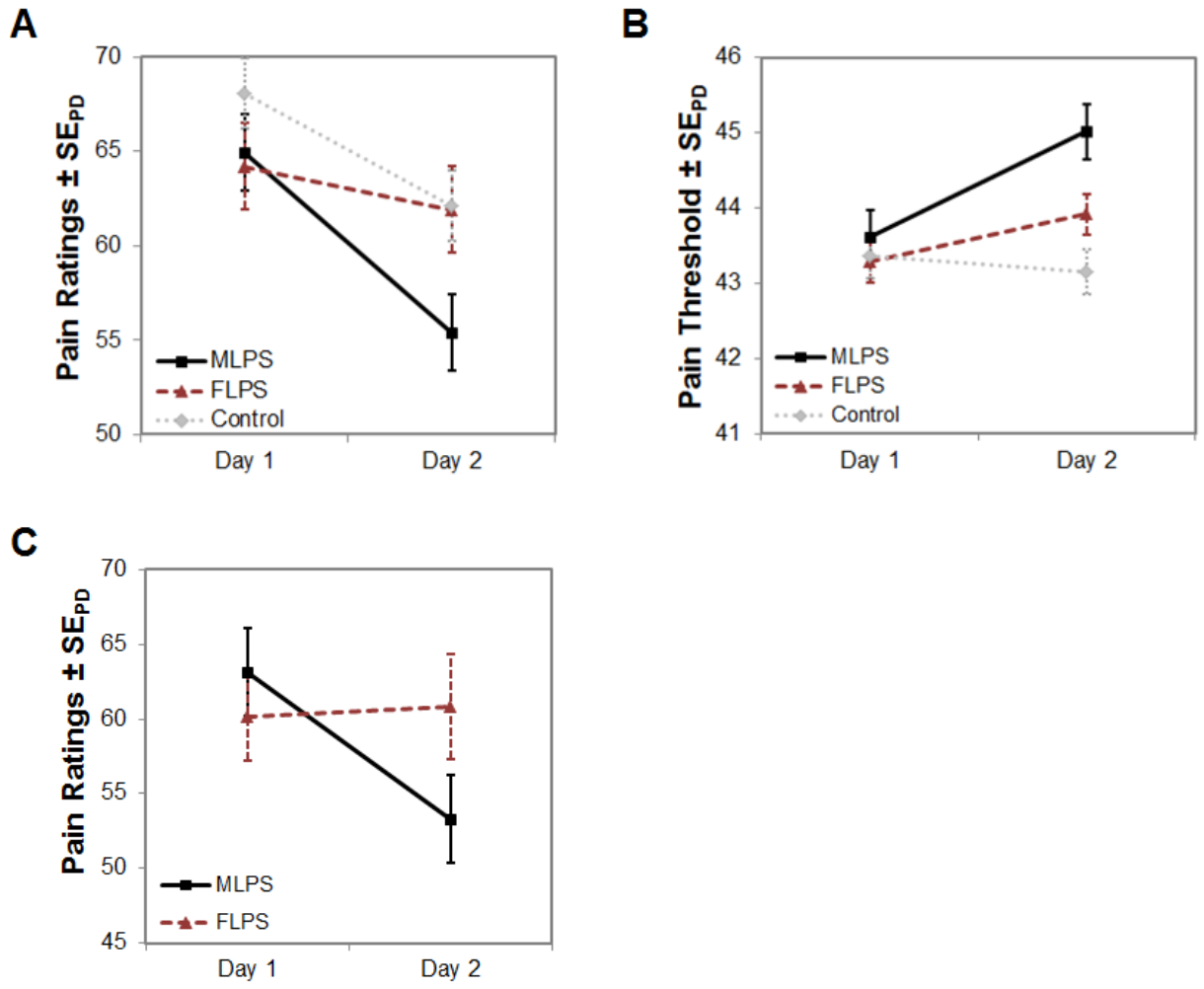

Figure 10. A. Pain sensitivity ratings for each group and each day. The effect of gender-related expectancy manipulation is significant, in our main interest comparison (interaction *Time x Expectancy Manipulation*; *MLPS* vs. *FLPS*) as well as overall (interaction *Time x Expectancy Manipulation*; *MLPS* vs. *FLPS* vs. *Control*). Moreover, the pain ratings on the first day were generally higher than on the second day ($F(1,102) = 24.97$, $p < .001$, $\eta_p^2 = .20$), however group-wise paired *t*-tests reveal only significant differences between day 1 and day 2 in the *MLPS* ($t(33) = 4.75$, $p < .001$) and *Control* ($t(35) = 3.17$, $p = .003$) groups,

not in the *FLPS* group ($t(34) = 1.01$, $p = .319$). The groups did not differ significantly on day 1 ($F < 1$). Scale: 0 - “no pain at all”, 100 - “unbearable pain”. Please note that the *Control* group primarily differed from the expectancy manipulation groups in that their expectancy was not altered from what the participants already believed. Previous literature suggests that the *MLPS* expectancy manipulation likely reflects common stereotypes, possibly accounting for some of the similarities in result patterns between the *MLPS* and the *Control* group (Robinson et al., 2001). **B.** Pain threshold temperatures in °C for each group and each day. The interaction *Time x Expectancy Manipulation* in our main interest ANOVA (*MLPS* vs. *FLPS*) is only marginally significant (interaction *Time x Expectancy Manipulation*; $F(1,67) = 2.83$, $p = .097$, $\eta_p^2 = .04$), but all other interactions (overall and simple effects) show significant differences: the overall interaction including the *Control* group is highly significant ($F(2,101) = 6.51$, $p = .002$, $\eta_p^2 = .11$) and the simple effects ANOVAs reveal significant differences especially between the *MLPS* and *Control* groups ($F(1,67) = 11.55$, $p = .001$, $\eta_p^2 = .15$), but also between the *FLPS* and *Control* groups ($F(1,68) = 4.36$, $p = .041$, $\eta_p^2 = .06$). The general response pattern clearly indicates that the *MLPS* group shows the strongest increase in pain threshold temperature on day 2 compared to day 1. There is again a strong effect of *Time* ($F(1,101) = 11.39$, $p = .001$, $\eta_p^2 = .10$) with a general increase in pain threshold temperature on the second day compared with the first one over all participants. Paired *t*-tests calculated for each group show again that this effect is strongest for the *MLPS* group ($t(33) = -3.79$, $p = .001$). The day 1 vs. day 2 comparison is also significant for the *FLPS* group ($t(34) = -2.35$, $p = .025$), but not for the *Control* group ($|t|<1$). **C.** Raw pain sensitivity ratings for the fMRI experiment; scale: 0 - “no pain at all”, 100 - “unbearable pain”. The critical interaction *Time x Expectancy Manipulation* was significant ($F(1,32) = 5.28$, $p = .028$, $\eta_p^2 = .14$) and the main effect of *Time* showed a non-significant trend ($F(1,32) = 3.91$, $p = .057$, $\eta_p^2 = .11$). The main effect of *Expectancy Manipulation* did not approach significance ($F < 1$). Paired *t*-tests calculated for each group showed a pronounced difference between day 1 and day 2 for the *MLPS* group ($t(33) = -3.34$, $p = .004$) but not for the *FLPS* group ($t(33) = 0.21$, $p = .837$).

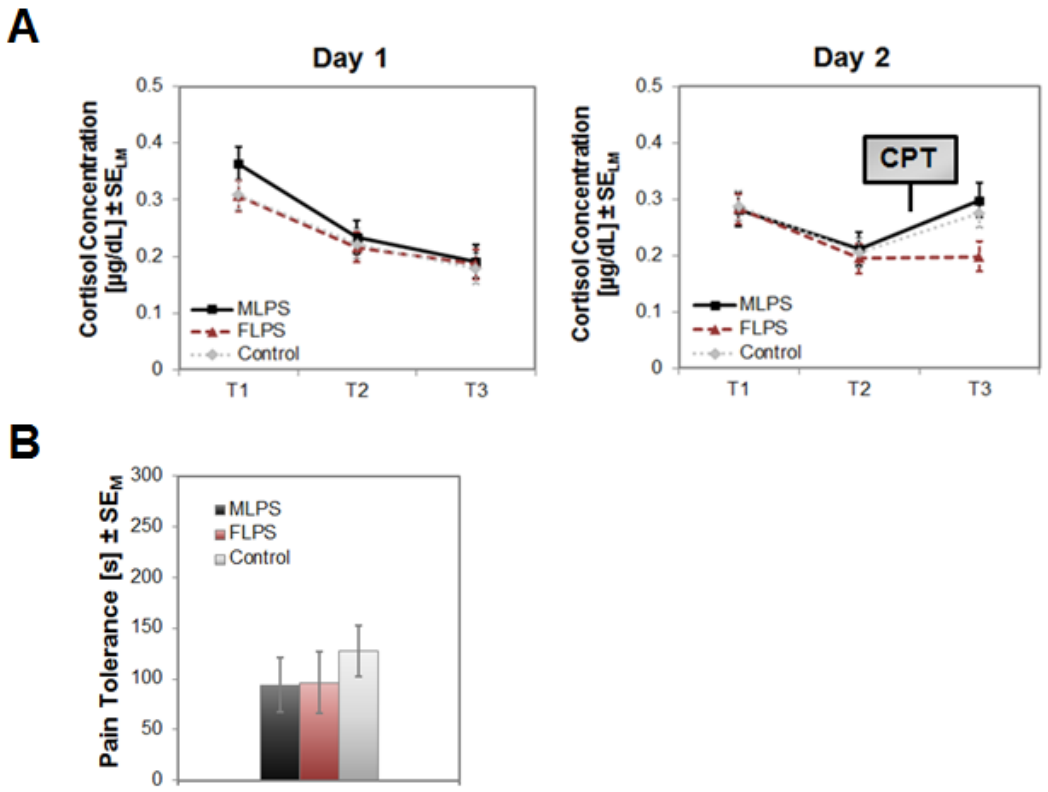

Figure 11. A. Cortisol concentrations for each group and time point (T1-T3) on each experimental day. **B.** Pain tolerance as measured by the Cold Pressor Test (CPT). There were no significant differences between any of the groups ($F < 1$); the effects observed in the rating data are therefore not confounded by differential exposure to the cold pain stimulus.

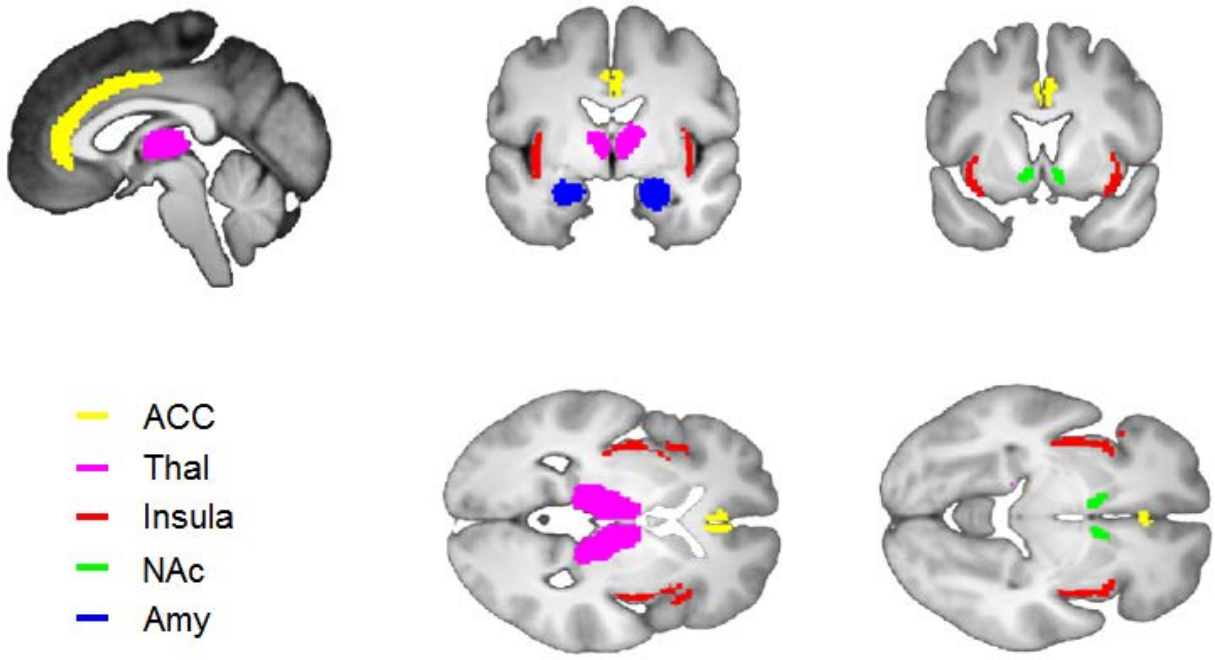

Figure 12. ROI locations for fMRI analysis, overlaid on the mean T1 image from all participants. Coordinates were taken from the Harvard-Oxford atlas, normalized to the DARTEL templates as provided by the VBM 8 toolbox.

Table 1.

BOLD responses for the interaction effect *Time* x *Expectancy Manipulation* for the early pain phase in the FIR analysis; contrast: *FLPS (Pain Day 2 > Pain Day 1) > MLPS (Pain Day 2 > Pain Day 1)*.

Brain Region	***x***	***y***	***z***	***t***	***p***
ACC	3	38	2	4.63	.010
R Insula	41	-11	-8	3.99	.030
L NAc	-9	14	-6	3.21	.020
R NAc	12	8	-12	3.51	.003
L Thal	0	-14	6	3.85	.040
R Thal	5	-9	9	4.07	.027

Coordinates are denoted by x, y, z in mm (MNI-space), and strength of activation is expressed in *t* values (*df* = 32). *P* values are corrected for multiple comparisons.

Table 2.

BOLD responses for the interaction effect *Time* x *Expectancy Manipulation* for the anticipation phase in the FIR analysis; contrast: *FLPS (Pain Day 2 > Pain Day 1) > MLPS (Pain Day 2 > Pain Day 1)*.

Brain Region	***x***	***y***	***z***	***t***	***p***
R Insula	38	9	-18	4.12	.026
L NAc	-12	9	-11	4.33	.002
R NAc	12	14	-11	2.84	.044

Coordinates are denoted by x, y, z in mm (MNI-space), and strength of activation is expressed in *t* values (*df* = 32). *P* values are corrected for multiple comparisons.

BETWEEN PAIN AND MATH

So far we have seen that the induction of specific stereotypical expectancies about pain perception has a significant impact on an individual's own perception of pain and on the manner with which he or she perceives and processes pain stimuli. In this project, I wanted to broaden the research topic by studying social expectancies (such as stereotypical beliefs) within a medical setting. In this setup, I targeted the influence of induced expectations on both, pain perception and higher cognitive functioning.[5]

To this end, I chose to investigate whether the stigma of being a patient, i.e., the negative expectations associated with being a patient such as decreased task performance or higher pain sensitivity, is per se enough to result in decreased performance and heightened pain sensitivity. Such negative beliefs are based on the social component of group identity (patient group vs. control group) within the medical setting of a clinical study and were investigated independent of actual symptom severity in the participants included in the study.

[5] The chapter *Between Pain and Math* is based on the as yet unpublished manuscript (Schwarz et al., submitted):
Schwarz, K. A., Pfister, R., May, A., & Büchel, C. (submitted). The being a patient effect: Group labeling affects patient performance in clinical research.

Authorship Statement

The following chapter describes work with co-authors. The concept of the experiments was developed in collaboration with my supervisor Prof. Dr. Christian Büchel. The experiment was planned, prepared, and organized by me; data collection was performed primarily by me with occasional help of a student assistant under my supervision. All statistical analyses were performed by myself and the first version of the manuscript was written by me.

2 . FEB 20

Ort, Datum

Unterschrift Prof. Dr. Christian Büchel

12 | Introduction

Empirical evidence from controlled patient studies is vital for ensuring progress in all areas of modern medicine and psychotherapy – and studying the effects and mechanisms of diseases and disorders seems a fairly straightforward process in theory. By comparing a patient group with a well-matched healthy control group, the experimenter attempts to pinpoint the disease's effects on a variety of measures, thus describing a detailed clinical picture. Subsequently, this clinical picture informs hypotheses about the physiological mechanisms underlying the disease and allows for improving treatment strategies.

However, psychological findings on the impact of expectations on perception and cognitive function suggest an additional factor: What if the difference between a patient and a healthy control in such domains is not only determined by the effect of the disease, but also by a psychological component that only affects the patient group: the knowledge of being a patient. By default, patients suffering from a variety of diseases will be expected to perform worse on tasks targeting different functions or to feel more pain than the healthy control group (e.g., Dilorio et al., 2004). We hypothesized that these negative expectations might have a substantial effect on patients – the "being a patient" effect (*BP effect*) – possibly leading to a systematic overestimation of the actual disease effect (Figure 13A).

Expectancy-related performance decreases indeed seem likely in light of several well-documented phenomena. For instance, expectancy effects have been repeatedly reported for pain perception (Amanzio & Benedetti, 1999; Atlas & Wager, 2012; Büchel

et al., 2014; Colloca & Benedetti, 2005; Eippert et al., 2009a; Price et al., 2008; Tracey, 2010), such as hyperalgesia induced by nocebo (Benedetti et al., 2006; Geuter & Büchel, 2013) or by a stereotyped group identity (Schwarz et al., under revision). Cognitive functions are likewise susceptible to negative expectations under conditions of poor self-efficacy (Bandura, 1997; Pajares, 1996) or stereotype threat (Aronson et al., 1999; Beilock et al., 2007; Schmader et al., 2008; Spencer et al., 1999; Steele & Aronson, 1995). Negative expectations based on group membership ("I'm a patient, therefore I'm expected to feel more pain / to perform worse than others") could thus cause an actual increase in pain sensitivity or decreased performance in cognitive tasks.

To test this hypothesis, we invited participants with mild seasonal allergic rhinitis and randomly divided them into a "patient" and a "control" group. On the second experimental day, half of the participants were specifically addressed as patients and were instructed before the experiment that their allergies might affect pain perception and cognitive functioning. The other half was addressed as a healthy control group for a clinical study unrelated to allergies. Accordingly, the groups only differed in group labelling and initial instructions, not in actual allergic symptoms or symptom severity. Still, we observed lowered pain thresholds and decreased performance in easy arithmetic tasks in the *patient* group compared to the *control* group (Figure 14).

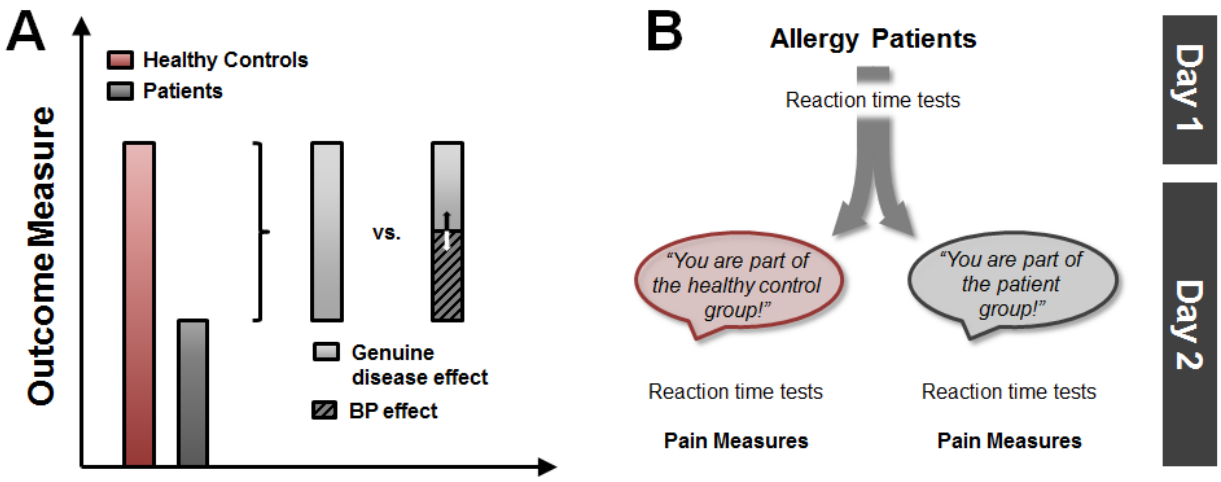

Figure 13. Study rationale and experimental design. **A.** Visualization of how expectancy-related effects of being a patient (BP effect) might inflate typical comparisons of patients with healthy controls. Any performance decrease in patients relative to controls could either result from a genuine disease effect or from a combination of a disease effect and a BP effect of unknown size, thereby leading to a systematic overestimation of the actual disease effect. **B.** Overview of the study design. *Patient* and *control* group only differed in terms of group labelling and initial instruction, not in actual symptom severity.

13 | Methods

13.1 Participants

We recruited participants with mild seasonal allergic rhinitis (N = 48), although they were unaware that they had been invited because of their allergy diagnosis. They were randomly assigned to the *patient* group (n = 27; 7 male) and the *control* group (n = 21; 6 male). Sample size was based on a power analysis that yielded sufficient sensitivity to clinically relevant effects (d = 0.80) with a power of 80%. The groups did not differ in age (25.41 years ± 0.62 SE_M and 26.00 years ± 0.81 SE_M, respectively) or allergy symptom severity (Table 3). None of the participants was currently under medication. One participant of each group had to be excluded because they correctly guessed the purpose of the study; 6 *patients* were excluded from the pain measures for technical reasons and 2 *patients* from the cognitive tasks because they did not believe the respective instructions. Another *patient* had to be excluded for the arithmetic task because she did not understand the task. The study was approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

13.2 Experimental Procedure

Participants were tested on two days (Figure 13B). On the first day, they were asked to perform an arithmetic task (Beilock et al., 2007; Krendl et al., 2008), a mental rotation task (Peters & Battista, 2008; Shepard & Metzler, 1971), and a Stroop colour-

word interference task (MacLeod, 1991), to cover relevant independent domains of cognitive functioning. All tasks were computer-administered reaction time (RT) tests with manual responses and task order was randomized across participants. Before each test, participants rated how well they expected to perform during the respective task. During the arithmetic task, they had to decide whether a displayed equation was true or false within a time span of 7 seconds. Forty-two basic (Krendl et al., 2008) and 42 modular arithmetic equations (Beilock et al., 2007) were created in three difficulty levels (easy, intermediate, or difficult) and appeared in random order (84 trials in total). During the mental rotation task, participants had to indicate whether two three-dimensional Shepard & Metzler-figures presented to them in different angles on the screen were identical or mirror-reversed (144 trials in total, half of them identical, half mirrored; Peters & Battista, 2008). Stroop stimuli were the four words “red”, “green”, “yellow”, and “blue”, randomly displayed in either of the four colours (75% incongruent, 25% congruent; 400 trials in total). Experimental data of day 1 served as baseline for within-subject comparisons.

The critical experimental manipulation was performed about one week later. Participants in the *patient* group were told that they would take part in a study on the effects of allergies on pain perception and higher cognitive functions. Participants in the *control* group were invited as healthy controls in a study on the effects of schizophrenia on pain perception and higher cognitive functions. The experimenter wore a white lab coat in all cases and participants performed the same tasks as on day 1. Afterwards, we measured the critical heat pain thresholds by slowly increasing stimulus temperature at a rate of 0.3°C/s, starting at 30°C, using a Peltier thermode applied to the left forearm

(TSAII, Medoc, Ramat Yishai, Israel). Participants were asked to indicate as soon as they felt the first pain sensation which stopped the trial. This procedure was repeated four times. Both groups were interviewed about their allergy symptoms, the *patients* before and the *controls* after the experimental procedure. In the *patient* group, the interview was followed by a short questionnaire to assess whether participants believed the instructions about the allergies' negative effects.

14 | Results

Figure 14 summarizes our central results. Although the *patient* and the *control* group merely differed in group labelling and initial instructions, patients showed a lower pain threshold than controls (Figure 14A). This clear effect was confirmed by a *t*-test for independent samples, $t(38) = 2.07$, $p = .023$, d = 0.65 (reported as one-tailed due to a directional a priori hypothesis). This finding demonstrates that BP effects can be found even on a physiological level.

BP effects were also present in the cognitive tasks. *Patients* expected to perform worse in the arithmetic task on the second day, whereas the *control* group's expectancy rating did not change. These apparent differences were confirmed by a *t*-test on the difference scores (day 2 – day 1), $t(41) = 2.36$, $p = .012$, d = 0.72 (Figure 14B). This differential effect on the expectancy ratings was mirrored in decreased performance for easy arithmetic equations; omnibus analysis of variance on the difference scores: *Group x Difficulty*: $F(2,82) = 3.95$, $p = .023$, $\eta_p^2 = 0.09$; easy arithmetic equations only: $t(41) = 2.38$, $p = .011$, d = 0.73 (Figure 14B). Mental rotation performance was not affected differentially (Fs < 1), whereas a significant difference occurred for accuracy data of the Stroop task, $t(42) = 2.24$, $p = .015$, d = 0.68 (though partly driven by ceiling effects and therefore not further discussed). All reported changes in task performance and pain perception are significant when correcting for multiple comparisons using the Bonferroni-Holm procedure.

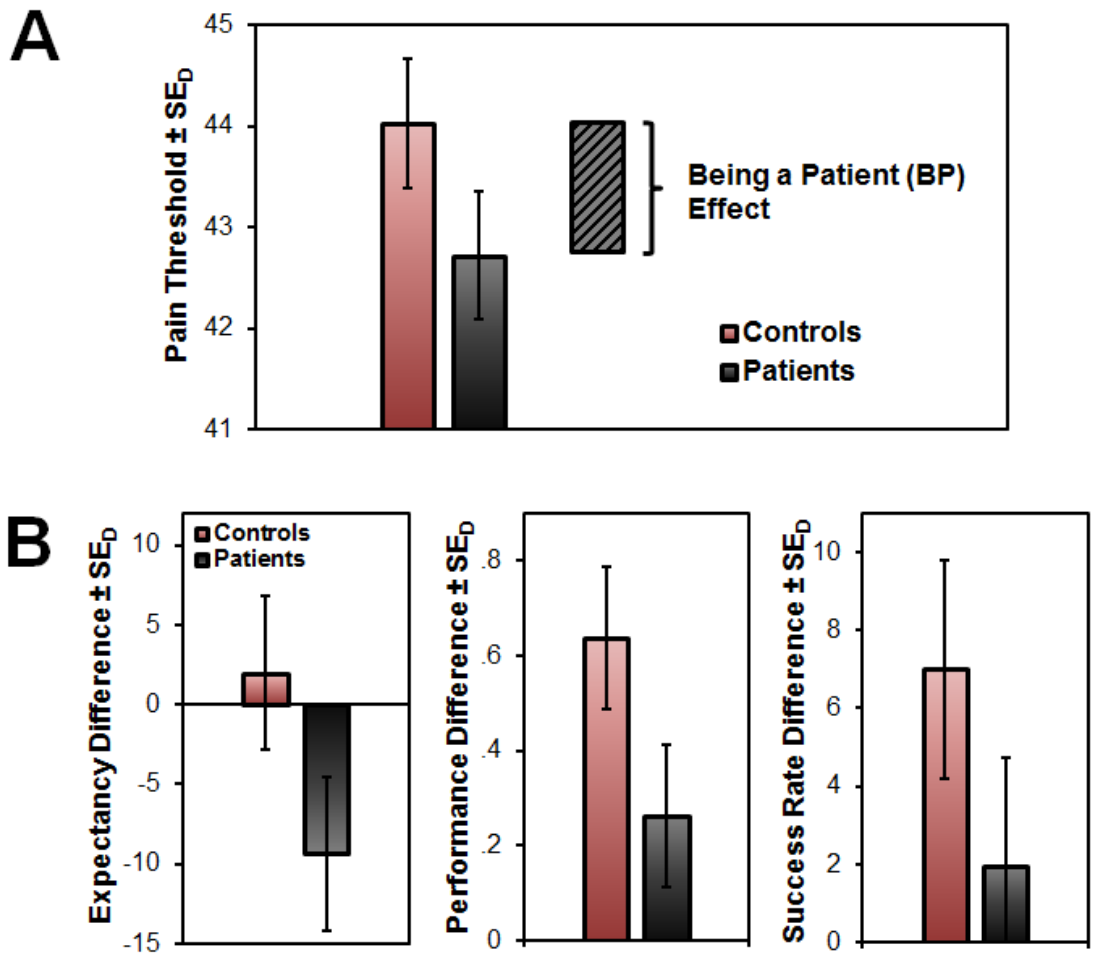

Figure 14. Differences between the *patient* and *control* group signify the Being a Patient (BP) effect. **A.** Difference in the pain threshold temperature (°C) between the *patient* and *control* group, $t(38) = 2.07$, $p = .023$, d = 0.65. **B.** (Left) Performance expectancy difference (day 2 – day 1). The *patient* group expected to perform worse after being treated as patients on the second day, whereas the *control* group's rating pattern remained unchanged, $t(41) = 2.36$, $p = .012$, d = 0.72. (Centre) Performance difference in easy arithmetic equations (day 2 – day 1). Patients performed worse on the second day compared with the controls, $t(41) = 2.38$, $p = .011$, d = 0.73. To facilitate interpretation, performance is displayed as $(1/RT\ [ms])*10^4$, i.e., higher scores indicate faster responses on the second day compared to the first day. (Right) Success rate difference (%) in easy arithmetic equations (day 2 – day

1). The success rate difference showed a similar trend, $t(41) = 1.85$, $p = .036$, $d = 0.55$, indicating that the slower answering pattern in the *patient* group cannot be explained by speed-accuracy trade-offs as *patients* made more mistakes compared with *controls*. Error bars indicate standard errors of the between-group difference.

Table 3. Descriptive data of both groups (2 participants who guessed the true purpose of the study were excluded from these data).

	Patients	**Controls**
Age, mean (SE_M), years	25.19 (0.61)	26.05 (0.84)
Symptom Severity, mean (SE_M)	16.25 (1.03)	15.30 (0.84)
STAI T, mean (SE_M)	38.69 (1.47)	38.55 (2.04)
BDI II, mean (SE_M)	5.97 (0.91)	6.20 (1.08)
LPS 3, mean (SE_M)	9.77 (1.07)	9.35 (1.21)
LPS 4, mean (SE_M)	8.77 (0.95)	8.50 (0.84)

Abbreviations: STAI T = State-Trait Anxiety Inventory Trait; BDI II = Beck Depression Inventory II; LPS 3/4= tests 3 and 4 in the German "Leistungsprüfsystem" (intelligence test).

15 | Conclusions

Our results demonstrate that differences between patients and healthy controls can at least partly be accounted for by the BP effect, i.e., the patients' role and therefore expectations to perform worse than healthy controls. We found differences between two groups of patients with mild allergy that differed only in group labelling and initial instructions, not in symptom severity. While stereotype-related effects on patients are beginning to be realized in clinical settings (Cole et al., 2006; Kit, Tuokko, & Mateer, 2008), the present data indicate that expectancy-based differences might also affect the very process of investigating particular diseases.

Two mechanisms seem likely to explain the BP effect: stereotype threat or, alternatively, poor self-efficacy. Under stereotype threat, the existence of a widely-known negative stereotype about a group with which one identifies (such as gender or ethnicity) can lead to decreased performance in stereotyped fields (e.g., general intellectual ability; Steele & Aronson, 1995). One of the main differences between stereotype threat and self-efficacy effects is the decreased motivation in poor self-efficacy (Pajares, 1996), whereas stereotype threat especially affects individuals who strongly identify with an ability domain and thus are highly motivated to revoke the stereotype (Schmader et al., 2008). Our study was not designed to differentiate between these two theoretical frameworks, but this distinction is an intriguing aspect for future inquiry. Furthermore, patients participating in clinical studies believe themselves to suffer from a certain condition including all limitations associated with it rather than being explicitly informed about these factors by the experimenter. Negative expectations

based on such personal convictions might additionally boost the BP effect in real life settings (Pinel, 2002).

Although a clear BP effect emerged in our results, it was not equally present in all measures. Most susceptible to the expectancy manipulation were the pain threshold measure and the arithmetic task, a test heavily relying on working memory (Beilock et al., 2007). Mental rotation (measuring spatial cognition), by contrast, did not elicit the BP effect. This pattern gives first indications which domains may be especially prone to yield BP effects in clinical research. Interestingly, the effects on pain measures and higher cognitive functions (with the exception of the mental rotation task) are of similar size, indicating that both types of variables were susceptible to expectancy instructions in a comparable manner.

Our results clearly show that the knowledge of being a patient can affect critical measures. Any difference between patients and healthy controls reported even by controlled studies might thus not only indicate genuine disease effects. This psychological component might lead to a systematic overestimation of the actual effects elicited by the disease in question. We propose that future patient studies should take care to avoid or minimize this confound. Possible strategies include a stronger emphasis on within-group comparisons of patients with graded symptom severity or a similar study design as was employed in this study by labelling patients as controls in an allegedly unrelated study. Another possibility would be to avoid solely comparing patient data with healthy controls in favour of inviting patients suffering from other diseases (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Tsuang & Dempsey, 1979) as is already common in certain fields.

EXPECTATIONS AND COGNITIVE PERFORMANCE

The presented results so far indicate that pain perception and specific instances of higher cognitive functions are both susceptible to social expectancies. However, it is still unknown whether higher cognitive functions are equally prone to show placebo or nocebo effects in response to a medical sham treatment. In this final project of my thesis, I studied the impact of a traditional placebo/nocebo treatment on task performance.[6] Moreover, I investigated whether objective and subjective measures are affected alike or whether primarily subjective measures mirror the induction of positive and negative expectations as suggested by several previous studies (e.g., Looby & Earleywine, 2011; Wechsler et al., 2011).

This project fills in the final gap indicated by the context framework depicted in Figure 2 and will thus conclude the empirical part of my thesis.

[6] The chapter *Expectations and Cognitive Performance* is based on the as yet unpublished manuscript (Schwarz & Büchel, under review):
Schwarz, K. A. & Büchel, C. (under review). Cognition and the placebo effect – Dissociating subjective perception and actual performance.

Authorship Statement

The following chapter describes work with a co-author. The concept of the experiments was developed in collaboration with my supervisor Prof. Dr. Christian Büchel. The experiment was planned, prepared, and organized by me; data collection was performed by me and a student assistant under my supervision. All statistical analyses were performed by myself and the first version of the manuscript was written by me.

25. FEB. 2015

Ort, Datum

Unterschrift Prof. Dr. Christian Büchel

16 | General Introduction

Expectancy effects have been extensively investigated in clinical research, especially with regard to placebo hypoalgesia (Colloca & Benedetti, 2005; Tracey, 2010), and with regard to placebo effects in Parkinson's disease (de la Fuente-Fernández et al., 2001) or depression (Mora, Nestoriuc, & Rief, 2011). Originally, these expectation effects on overt behaviour, subjective well-being, and physiological measures, have been regarded as a cumbersome confound and biasing clinical research (Colloca & Benedetti, 2005; Enck et al., 2013). However, in the last years, this view has changed, and more and more clinicians are called to realize the potential benefit of expectation effects when they are deliberately used to the patient's advantage (e.g., in combination with an established therapy; Enck et al., 2013). Research on placebo effects can thus be of genuine clinical interest, as is research on the complementary nocebo effect, i.e., negative effects of expectations on the physical and subjective well-being (Bingel, 2014; Enck et al., 2013; Geuter & Büchel, 2013).

Therapies, however, are not only used as treatment for diseases. In recent years, the use of "cognitive enhancers" by healthy individuals has been subject to controversial debates (Chatterjee, 2009; Harris, 2009; Hyman 2011; Sahakian & Morein-Zamir, 2007, 2011). No matter their ethical conundrums, it seems as if the use of cognitive enhancers to boost cognitive performance in critical situations is already reality on many university campuses (Sahakian & Morein-Zamir, 2007, 2011). However, the mechanisms of action including possible side effects in healthy individuals are often not very well understood (Chatterjee, 2009; Hyman, 2011; Sahakian & Morein-Zamir, 2011). This raises the question if placebo effects could not be part of the picture – and maybe

even part of the solution. Is it possible to elicit performance improvements simply by evoking the expectancy of situational performance improvement? And is it possible to induce the opposite, a cognitive impairment, simply by suggesting that such performance impairment should take place?

Several factors speak in favour of this possibility: For one, this is true of the extensive literature on placebo effects in various domains (Enck et al., 2013), and this is also true for well-established social expectancy effects on higher cognitive functions, such as stereotype threat or self-efficacy effects (Bandura, 1997; Schmader et al., 2008; Steele & Aronson, 1995), suggesting that expectancy effects are a ubiquitous phenomenon. For example, participants who expected to receive methylphenidate, a well-known cognitive enhancer, but received placebos instead, showed altered blood-oxygen-level dependent (BOLD) brain responses and reported higher subjective restlessness and "drug liking" compared to a condition in which they expected and received placebo treatment (Volkow et al., 2006).

However, the most consistent placebo effects have been found in regard to subjective states, not objective measures (Stewart-Williams & Podd, 2004). For example, the expectation to receive methylphenidate affected arousal ratings in participants ("feeling high" and "feeling stimulated"), but it did not improve cognitive performance – actually, it seemed to impair cognitive performance in some instances (Looby & Earleywine, 2011). Similarly, placebo treatment in asthma patients led to no change in actual objective physiological parameters compared with a no-intervention control; in contrast, a large objective drug effect was found when using a real bronchodilator as treatment (Wechsler et al., 2011). Interestingly, the patients'

subjective perception of symptom improvement was similar for the bronchodilator and the placebo treatment, and both conditions significantly differed from the no-intervention control. These findings indicate that placebo effects, while certainly affecting objective measures in some domains (Stewart-Williams & Podd, 2004; Tracey, 2010), might have very little effect on objective measures in others. Furthermore, the subjective experience seems to be largely independent from the objective scores and especially susceptible to expectancy effects.

Whether or not a given domain is susceptible to expectancy effects or not can only be answered by empirical research using both, subjective and objective measures. In this study, we therefore addressed cognitive performance under conditions of positive or negative expectancies (placebo or nocebo conditions). We further investigated whether potential effects would occur for objective and subjective measures alike or whether they would be mainly restricted to the participants' subjective perception. To this end, healthy participants completed a Flanker interference paradigm in a placebo, nocebo, and control condition. As expectancy manipulation, we instructed the participants that special tones (i.e., different sound frequencies) were known to differentially affect brain activity and cognitive performance, a phenomenon allegedly called the "frequency stimulation effect". Before the actual test phase, we induced instruction-congruent experiences by including a conditioning phase adapted from experimental paradigms used in placebo hypoalgesia (Eippert et al., 2009a). This procedure is known to maximize possible expectancy effects, as the literature on placebo hypoalgesia indicates that placebo effects are best elicited when prior experience supports the placebo suggestion (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006).

17 | Main Experiment: Methods

17.1 Participants

We recruited 37 individuals (22 female; mean age 25.19 years ± 0.93 SE_M) for participation in this study. A power analysis suggested a study sample of at least 34 participants to obtain a power of 80% for an expected effect size of d = 0.50 (Stewart-Williams & Podd, 2004), given statistical analyses by means of two-tailed tests. All participants received payment as compensation. Exclusion criteria involved neurological or neuropsychiatric diseases, current medication, or substance abuse. The study was approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

17.2 Expectancy Manipulation

Participants were informed at the beginning of the experiment that they would take part in a study investigating the effects of “frequency stimulation” on cognitive processes. Frequency stimulation was explained as a method to increase or decrease activity in specific brain areas by hearing sounds of specific tone frequencies. Participants were told that, e.g., higher frequencies would stimulate brain activity and thus improve task performance and lower frequencies would inhibit brain activity and thus impair task performance. A third intermediate frequency would be included to serve as a control stimulus that has no effect on brain activity. The instruction was randomized as to which frequencies (high, intermediate, low) were allegedly designed to

increase/decrease brain activity and improve/impair performance or which frequency would have no effect and serve as a control stimulus. All participants were exposed to all sounds to allow for a within-subject comparison between the placebo ("improved performance"), nocebo ("impaired performance"), and control condition. One male participant had to be excluded, because he did not believe our expectancy manipulation.

17.3 Testing Procedure

After informed consent and the expectancy manipulation, participants first were asked to individually adjust the volume of the different sounds to assure that all sounds were easily audible, but not uncomfortably loud, and that all sounds were perceived as equal in volume. The participants then underwent a conditioning procedure similar to common paradigms in research on placebo analgesia (Figure 15A; Eippert et al., 2009a). Such conditioning procedures increase placebo effects by generating personal experience and expectations in line with the expectancy manipulation (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006). To measure the participants cognitive performance, they were asked to complete a Flanker task (Figure 15B) in each expectancy condition (placebo vs. nocebo vs. control) while hearing the respective sound frequencies allegedly designed as cognitive enhancers, disrupters, or controls. The order of the condition blocks were randomized across participants. As a conditioning procedure, success rates were fixed at 75%, 45%, and 60% in the placebo, nocebo, and control condition by means of an adaptive staircase algorithm that allowed more or less time to respond to the presented stimuli. At the end of each block, participants received

feedback about their performance, i.e., their success rates. Blocks were separated by short breaks.

After the conditioning procedure, participants took part in the actual test phase in which we did not manipulate success rates. The test phase consisted of a single, longer block during which the different expectancy conditions and tone frequencies were presented block-wise according to an ABCCBA schema, i.e., if the participants started with the placebo condition (in this example A), they would also end with the placebo condition, whereas the other expectancy conditions (e.g., nocebo as B and control as C) were placed in between. This procedure was applied to assure that changes in motivation or fatigue would not lead to confounding time effects. Which condition served as condition A, B, or C in this schema was randomized across participants. After the test phase, participants were asked to rate how different tone frequencies affected their performance according to their own opinion.

The whole experimental procedure lasted about 2.5 hours per participant. To assure a high motivation throughout the experiment, we increased the amount of money participants received proportionally to their performance across all experimental tests (including the conditioning and the test phase), and informed the participants about this procedure at the very beginning.

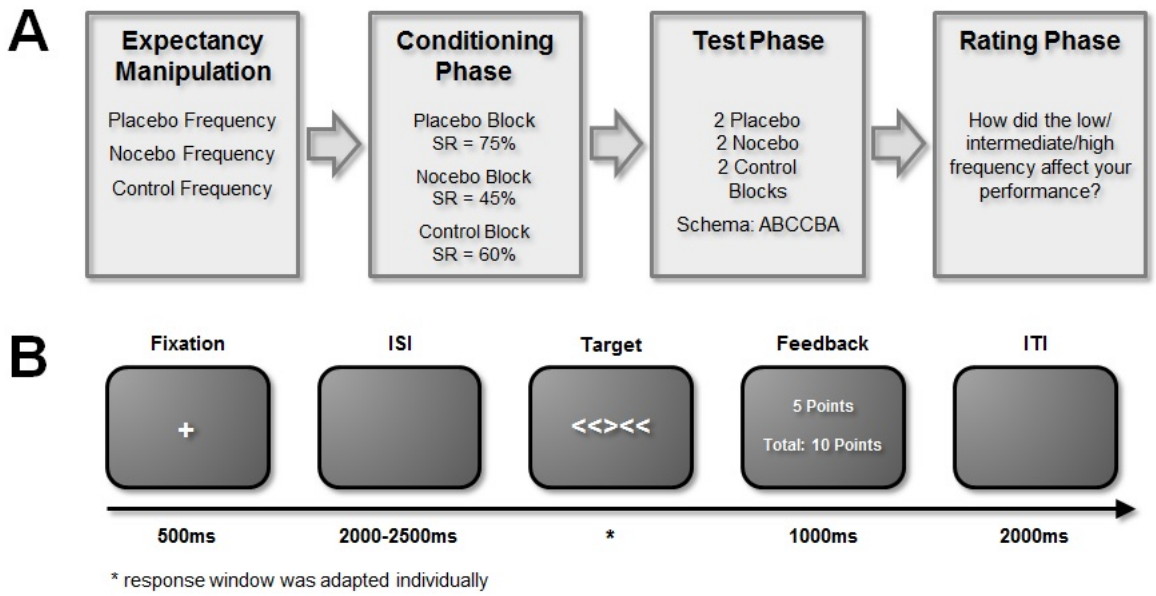

Figure 15. A. Study design. The study started with an expectancy manipulation: Participants were first informed about the effects of "frequency stimulation" and heard three different tone frequencies allegedly designed to either improve, impair, or not affect cognitive functioning (placebo, nocebo, and control frequencies). They then underwent a conditioning phase with fixed success rates to strengthen their expectations, followed by the actual test phase without any additional manipulations pertaining to success rates. In the subsequent rating phase, participants evaluated how the frequencies affected their performance. **B.** Trial procedure of the Flanker task used during conditioning and to assess cognitive performance during test. Participants first saw a fixation cross on the screen followed by a variable inter-stimulus interval (ISI). Then the actual target appeared; participants were asked to respond with a left or right arrow key press when the middle arrowhead pointed to the left or right, respectively. The response window for this task was adapted individually. If participants responded correctly and in time, they gained 5 points per trial, if not they didn't gain any points; this information was presented to them together with the total number of points they had gained during the respective block.

17.3.1 Conditioning Phase

All participants first completed a short introductory block of 10 trials to become acquainted with the task. Control of the experimental timing and the stimulus presentation throughout the experiment was achieved using Presentation 16.4, NeuroBehavioral Systems (Albany, CA, USA). Each trial started with a fixation cross presented on a computer screen for 500ms. After a variable inter-stimulus interval (ISI) of 2000 to 2500ms, five arrowheads (target stimulus) were presented on the screen pointing either to the left or the right. Participants were instructed to respond with the right arrow key on the computer keyboard when the central arrowhead pointed to the right and to respond with the left arrow key when the central arrowhead pointed to the left, irrespective of the other arrowheads presented. The four arrowheads surrounding the centre arrowhead all either pointed in the same direction as the centre arrowhead (compatible condition) or in the opposite direction (incompatible condition). The target stimulus was presented until participants responded with a button press but for a maximum duration of 1000ms. If they answered correctly and in time, a feedback screen told them that they had gained 5 points for the trial; if they did not answer correctly or if they responded too early, i.e., during the ISI, or too late, the feedback screen informed them that they had received 0 points for the trial. The next trial started after an inter-trial interval (ITI) of 2000ms.

During the conditioning procedure, the participants heard the respective tone frequency during the entire expectancy condition block. Each expectancy condition block started with an additional short introductory block of 20 trials. We used these trials to assess for each participant individually which response window he or she

needed to complete 75%, 45% or 60% of the trials successfully in the placebo, nocebo, or control condition, respectively. This information was then fed as the starting point into the staircase algorithm for the actual conditioning phase, i.e., the response window the participants needed during the first 20 trials to complete 60% of the trials successfully was the response window the participants had in the first conditioning trial to respond to the Flanker task target in the control condition. The overall success rate in the actual conditioning block was then calculated after each trial; if the success rate was greater than 75%, 45% or 60% in the respective expectancy conditions, the response window available for the participants to respond to the target was shortened by 10ms, if the success rate was lower than 75%, 45% or 60% in the respective expectancy conditions, the response window was extended by 10ms. This led to a fixed success rate of 75%, 45% or 60%, respectively, after all 80 trials of the expectancy condition block were completed. The success rate and the absolute number of points were then presented as feedback to the participants. This procedure was conducted for each expectancy condition (placebo, nocebo, and control).

17.3.2 Test Phase

After a break, the actual test phase started with an introductory block of 40 trials. The first 20 trials of this block were intended as an opportunity for the participants to get acquainted with the task again, the last 20 trials were used to assess the response window the participants needed to respond to 60% of the trials successfully. This response window then served as the maximum response window the participants had in all testing trials to respond to the Flanker task target. After the introductory block, the

actual test phase started either with the placebo, nocebo, or control condition according to the ABCCBA schema mentioned above. Participants completed six test blocks (two of each condition) à 35 trials each; the blocks were separated by short breaks. The respective tone frequencies were only heard during the test blocks, not during the introductory block before. After all six blocks were completed, the participants again received feedback about the success rate and the absolute number of points they had gained during the test phase. At the end of the experiment, participants were debriefed about the actual study purpose and were asked if they had believed the previous instruction.

17.4 Behavioural Data Analysis

Behavioural data were analysed using SPSS 20 (IBM, Armonk, NY, USA). For the conditioning phase, we calculated the mean reaction time (RT) of all successfully completed trials for each participant separately for each condition. For the test phase, we calculated success rates for each participant and the mean RT of all successfully completed trials for each participant, separately for each condition. The introductory blocks were not included in the calculations. We then performed an analysis of variance (ANOVA) with the within-subjects factors expectancy (placebo vs. nocebo vs. control) and compatibility (compatible vs. incompatible) for the reaction time and success rate data and performed paired *t*-tests as follow-up analyses. The subjective rating data were also analysed with an ANOVA (within-subjects factor expectancy) followed by paired *t*-tests.

18 | Main Experiment: Results

In the conditioning phase, we adapted the response window to fix the success rate (SR) to 75%, 60%, and 45% for the placebo, nocebo, and control condition, respectively. Our data indicate that this manipulation was successful (mean $SR_{placebo}$ = 74.44%, mean SR_{nocebo} = 45.35%, mean $SR_{control}$ = 60.31%), $F(2,70) = 503.18$, $p < .001$, $\eta_p^2 = 0.93$. All follow-up paired *t*-tests showed significant differences between the participants' SRs dependent on the expectancy condition (*p*s < .001). Even though RT was not specifically manipulated during the conditioning phase, we still found a strong main effect of expectancy, $F(2,70) = 14.61$, $p < .001$, $\eta_p^2 = 0.30$. This RT effect counteracted the conditioning, with the participants being the fastest in the nocebo condition (374 ms), the slowest in the placebo condition (400 ms), and intermediate in the control condition (388 ms). Again, all follow-up paired *t*-tests confirmed the RT differences between the conditions to be significant (*p*s < .009). As expected, participants further responded much faster for compatible Flanker stimuli (360 ms) than for incompatible stimuli (433 ms), $F(1,35) = 422.78$, $p < .001$, $\eta_p^2 = 0.92$, whereas the interaction of expectancy and compatibility was not significant, $F(2,70) = 2.43$, $p = .105$, $\varepsilon = .855$ (Greenhouse-Geisser corrected for violations of sphericity).

To pinpoint the actual effects of the expectancy manipulation and the corresponding conditioning on objective measures, we analysed SRs and RTs of the test phase (Figure 16). Our data clearly show that the effects established in the conditioning phase did not carry over to the test phase. More precisely, robust Flanker compatibility effects emerged for SRs, $F(1,35) = 869.85$, $p < .001$, $\eta_p^2 = 0.96$, and RTs, $F(1,35) = 293.82$, $p < .001$, $\eta_p^2 = 0.89$, but the effects were virtually identical in size across the

three expectancy conditions; SRs: $F(2,70) = 0.27$, $p = .766$, $\eta_p^2 = 0.01$; RTs: $F(2,70) = 0.12$, $p = .883$, $\eta_p^2 < 0.01$. Also, neither main effect of expectancy was significant; SRs: $F(2,70) = 0.41$, $p = .664$, $\eta_p^2 = 0.01$; RTs: $F(2,70) = 1.99$, $p = .145$, $\eta_p^2 = 0.05$. To follow up on these analyses, we computed Bayes Factors for the most informative comparison – the difference in compatibility effects between the placebo and the nocebo condition. These tests yielded substantial evidence in favour of the null hypothesis of no effect, $BF_{SR} = 5.42$, $BF_{RT} = 4.93$, indicating that the above findings indeed reflect the absence of a real effect rather than insufficient power (Rouder et al., 2009).

Although no effect of the expectancy manipulation emerged for SRs and RTs, the participants still perceived an effect of frequency on performance as indicated by the subjective rating data (Figure 17), $F(2,70) = 13.13$, $p < .001$, $\eta_p^2 = 0.27$. Indeed, follow-up paired *t*-tests revealed that participants felt a positive effect of the placebo frequency on their performance compared to both, the control frequency, $t(35) = 3.36$, $p = .002$, $d = 0.56$, and the nocebo frequency, $t(35) = 5.93$, $p < .001$, $d = 0.99$. Although the nocebo frequency was descriptively judged to have a worse effect on performance than the control frequency, this difference did not reach significance, $t(35) = 1.42$, $p = .165$. As a control analysis, we also checked if there was a difference in the rating data for the actual tone frequencies (high, intermediate or low), irrespective of their role in the experiment. Participants did not perceive any particular tone frequency as having a more positive or negative effect on their performance as any other ($F < 1$). This finding indicates that the effect in subjective perception depended on the expectancy manipulation, not on the actual frequency of the stimuli.

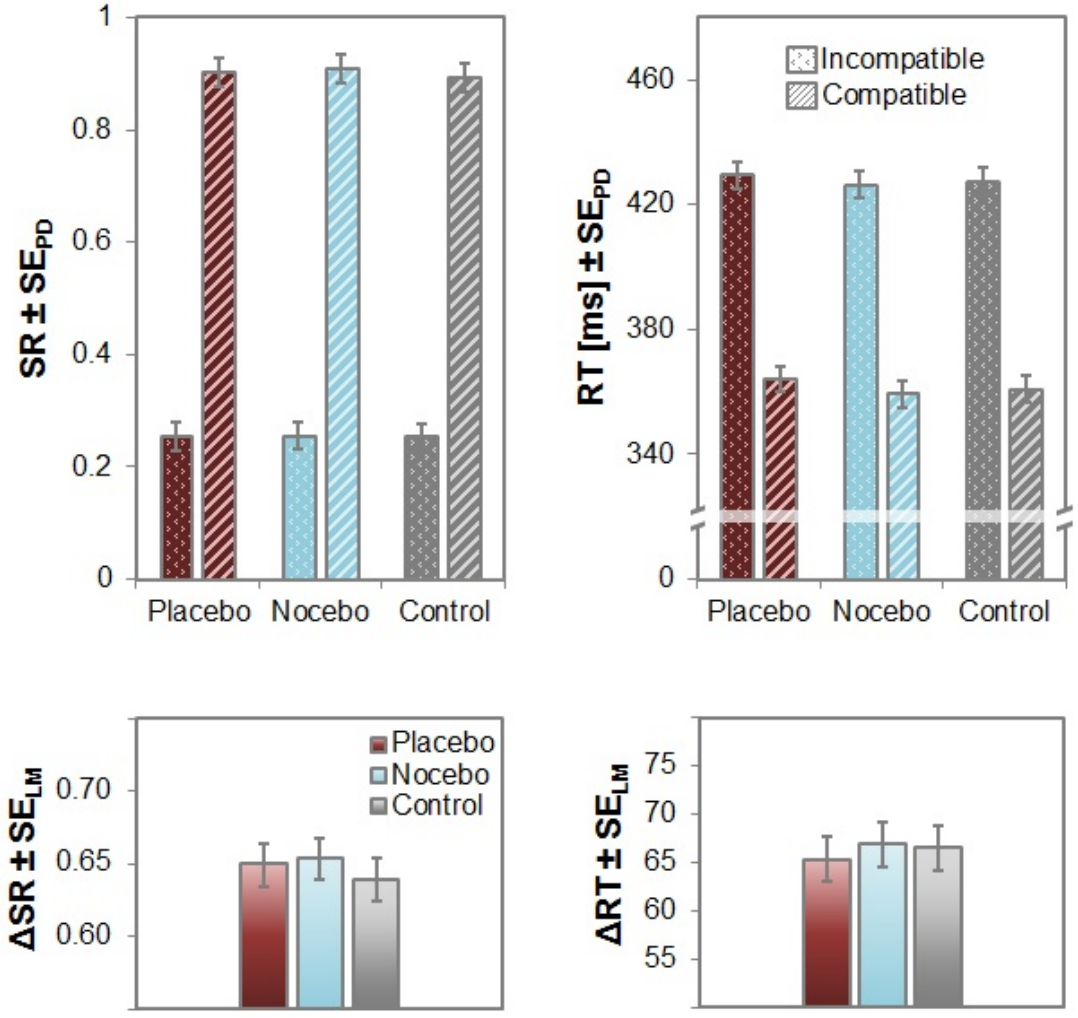

Figure 16. Upper panels. Success rates (SRs) and reaction times (RTs) as a function of expectancy and Flanker compatibility. Error bars indicate standard errors of paired differences (Pfister & Janczyk, 2013), computed separately for each expectancy condition. Lower panels. Compatibility effects for each expectancy condition, computed as $\Delta SR = SR_{compatible} - SR_{incompatible}$ and $\Delta RT = RT_{incompatible} - RT_{compatible}$. Error bars indicate the Loftus-Masson within-subjects standard error for repeated measures ANOVA (Loftus & Masson, 1994).

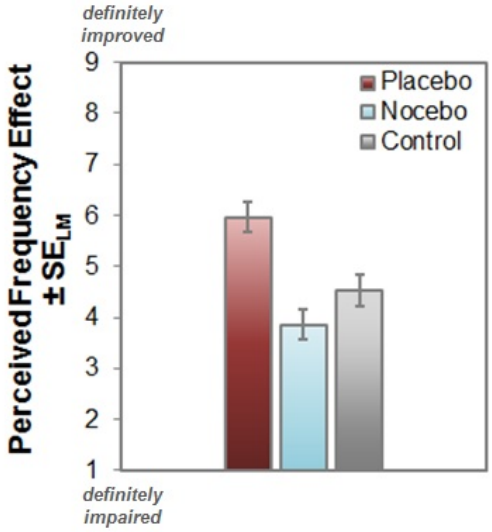

Figure 17. Subjective perception of the frequency effect. Although no frequency effect emerged in objective measures, participants perceived the placebo frequency as having a positive effect on their performance, compared with the control and the nocebo frequency. Error bars indicate the Loftus-Masson within-subjects standard error for repeated measures ANOVA (Loftus & Masson, 1994).

19 | Follow-up Experiments

Two possible explanations for the absence of an expectancy effect in objective measures in our main experiment concern (1) the type of task that was used, i.e., maybe such effects appear only in higher cognitive functions such as tasks based on working memory, instead of simple reaction time tasks, and (2) the expectancy manipulation itself. To pursue these questions, we conducted two follow-up experiments that employed specific arithmetic tasks which heavily rely on working memory capacity and were already successfully introduced in research on stereotype threat (Beilock et al., 2007; Krendl et al., 2008). Moreover, we used two different expectancy manipulations: in the first experiment, we told participants that specific body postures would enhance or impair cognitive performance, respectively, via a body feedback process. In the second experiment, we used a more direct approach by pretending to administer a cognitive enhancer or a saline solution to the participants, when in reality both probes contained saline solution.

19.1 Follow-up Experiment I: Methods

19.1.1 Participants

We recruited 41 individuals (24 female; mean age 26.39 years ± 0.83 SE_M). All participants received payment as compensation. Exclusion criteria involved neurological or neuropsychiatric diseases, current medication, or substance abuse. The study was

approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

19.1.2 Expectancy Manipulation

Participants were informed at the beginning of the experiment that they would take part in a study investigating body posture feedback on cognitive performance. Half of the participants were instructed that a tense body posture would increase cognitive performance (placebo condition), whereas a relaxed body posture would decrease cognitive performance (nocebo condition) via body feedback mechanisms. The other half of the participants were instructed that a relaxed body posture would lead to better cognitive performance (placebo condition), whereas a tense body posture would impair cognitive performance (nocebo condition). Instructions were randomized across participants. Three participants (1 female) had to be excluded, because they did not believe our expectancy manipulation.

19.1.3 Experimental Procedure

As dependent variables, we measured reaction times (RTs) and success rates (SRs) in a modular arithmetic task adapted from the literature on stereotype threat (Beilock et al., 2007). This task was shown to be sensitive to stereotype-relevant instructions and relies heavily on working memory capacity (Beilock et al., 2007). Participants saw equations on the screen and had to decide whether or not the equation was correct. Equations were created in three difficulty levels (easy, medium, hard). To

assure a high motivation throughout the experiment, we instructed the participants at the very beginning that the amount of money they would receive for study compensation would be increased proportionally to their performance across all experimental blocks.

All participants first completed a short introductory block of 12 trials (4 easy, 4 medium, 4 hard; 6 correct, 6 incorrect) to become acquainted with the task. Control of the experimental timing and the stimulus presentation throughout the experiment was achieved using Presentation 16.4, NeuroBehavioral Systems (Albany, CA, USA). Each trial started with a fixation cross presented on a computer screen for 500ms, followed by an equation. The equation was presented until participants responded with a button press. Half of the participants were instructed to respond with the left arrow key on the computer keyboard when the equation was correct and with the right arrow key if the equation was incorrect, whereas the other half was instructed with the opposite mapping. A feedback screen was shown for 1000ms informing them if their answer had been correct or not. The next trial started after an inter-trial interval of 1000ms.

After the introductory block, participants completed two test blocks, one test block in the placebo, one in the nocebo condition. Condition order was randomized across participants. Each test block consisted of 54 trials, 18 easy, 18 medium, and 18 hard; 27 equations were correct, 27 were incorrect. No equations were repeated within a participant.

At the end of the experiment, participants were debriefed about the actual study purpose and were asked if they had believed the previous instruction.

19.1.4 Behavioural Data Analysis

Behavioural data were analysed using SPSS 20 (IBM, Armonk, NY, USA). We calculated SRs for each participant and the mean RT of all successfully completed trials for each participant, separately for the placebo and nocebo conditions. The introductory block was not included in the calculations. We then performed an ANOVA with the within-subjects factors expectancy (placebo vs. nocebo) and difficulty (easy vs. medium vs. hard) for the RT and SR data and performed paired *t*-tests as follow-up analyses.

19.2 Follow-up Experiment I: Results

The expectancy instruction did not have any significant effects on performance in the modular arithmetic task on any measure (SR: $F(1,37) = 2.43$, $p = .128$; RT: $F < 1$; Figure 18). In contrast, the difficulty level had strong effects on both measures, i.e., the higher the difficulty level, the lower the SR and the slower the RT, irrespective of the expectancy condition (SR: $F(2,74) = 44.51$, $p < .001$, $\eta_p^2 = 0.55$; RT: $F(2,74) = 150.71$, $p < .001$, $\eta_p^2 = 0.80$, $\varepsilon = .614$, Greenhouse-Geisser corrected for violations of sphericity; Figure 18). All follow-up paired *t*-tests comparing SRs and RTs in the different difficulty levels were significant (all *p*s < .001). However, no interaction of expectancy and difficulty emerged in either SRs or RTs (SR: $F(2,74) = 2.00$, $p = .143$; RT: $F < 1$), indicating that the expectancy manipulation had no statistically valid effect on any objective measure (Figure 18).

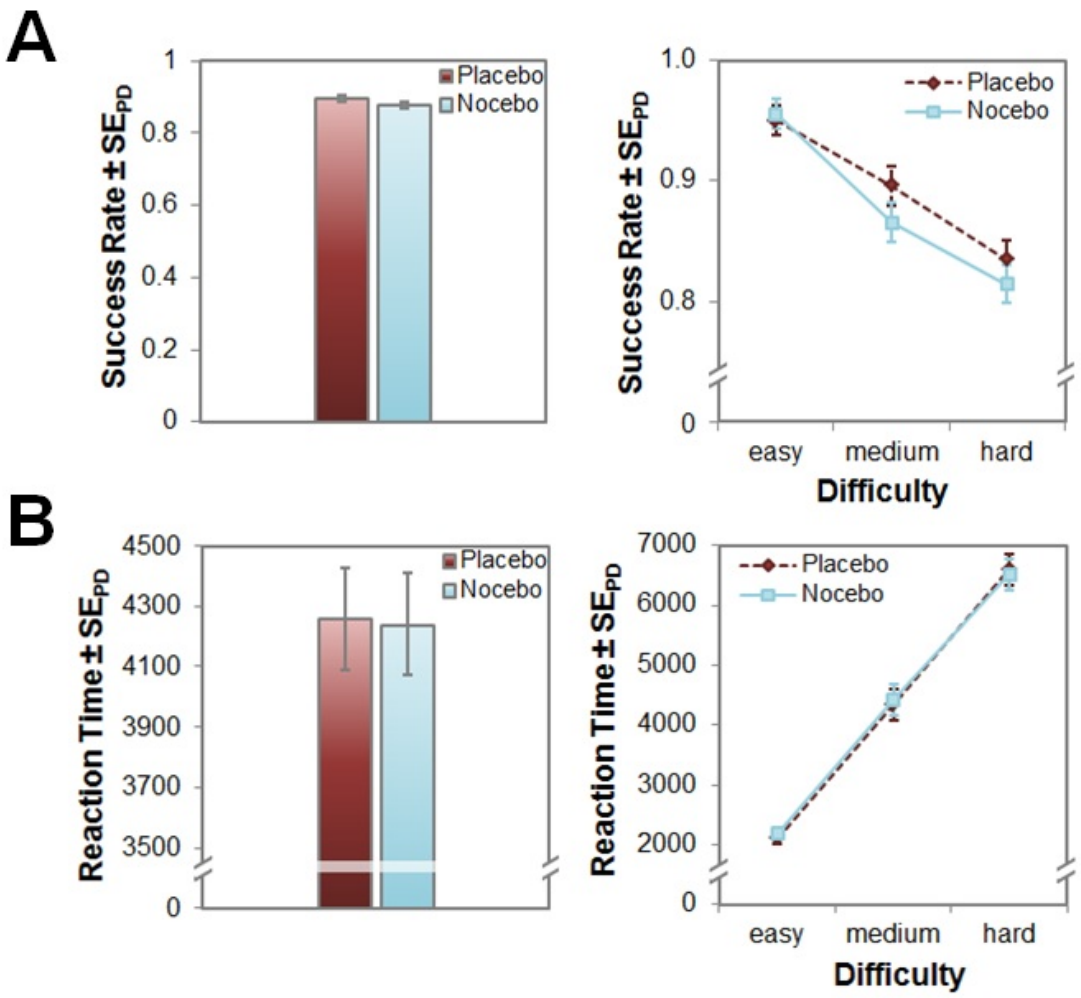

Figure 18. (A) SRs and **(B)** RTs for placebo and nocebo conditions in the modular arithmetics task of Follow-up Experiment I. No effects of expectancy emerged. Error bars indicate standard errors of paired differences (Pfister & Janczyk, 2013).

19.3 Follow-up Experiment II: Methods

19.3.1 Participants

We recruited 37 individuals (17 female; mean age 25.44 years ± 0.85 SE_M). All participants received payment as compensation. Exclusion criteria involved neurological or neuropsychiatric diseases, current medication, or substance abuse. The study was approved by the Ethics Committee of the Medical Council of Hamburg and all participants gave written consent in accordance with the Declaration of Helsinki.

19.3.2 Expectancy Manipulation

Participants were informed at the beginning of the experiment that they would take part in a study in which a cognitive enhancer, oxytocin, was used and applied via nasal sprays. We also informed them about diverse positive effects of oxytocin on cognitive performance. They were told that they would take part in three blocks, at first one short block without any medication, then one block with oxytocin (placebo condition) and one block with an inactive substance (control condition). The order of the expectancy conditions were randomized across participants. The nasal sprays were labelled accordingly, although all nasal sprays contained a saline solution, irrespective of labelling. When using the nasal sprays, all participants were instructed to spray four times, twice in each nostril, and to wait for 10 minutes after application before starting the experimental procedure to allow the “medication to become effective”. At least 40 minutes lay between each nasal spray application to allow the “medication to lose

effectiveness" before applying the next nasal spray. Nine participants (2 female) had to be excluded, because they did not believe our expectancy manipulation.

19.3.3 Experimental Procedure

As dependent variables, we measured reaction times (RTs) and success rates (SRs) in an arithmetic task including modular arithmetic and basic arithmetic tasks adapted from the literature on stereotype threat (Beilock et al., 2007; Krendl et al., 2008). This task was shown to be sensitive to stereotype-relevant instructions and relies heavily on working memory capacity (Beilock et al., 2007; Krendl et al., 2008). Participants saw equations on the screen and had to decide whether or not the equation was correct. Equations were created in three difficulty levels (easy, medium, hard). To assure a high motivation throughout the experiment, we instructed the participants at the very beginning that the amount of money they would receive for study compensation would be increased proportionally to their performance across all experimental blocks.

All participants first completed one experimental phase without any medication application. It started with a short introductory block of 12 trials (4 easy, 4 medium, 4 hard; 6 correct, 6 incorrect), followed by a short training block of 16 trials (4 easy, 8 medium, 4 hard; 8 correct, 8 incorrect), and the actual test phase of 24 trials (8 easy, 8 medium, 8 hard; 12 correct, 12 incorrect). This was intended to get participants acquainted with the task and the block structure. After the training and after the test block, participants were given feedback about their performance.

Control of the experimental timing and the stimulus presentation throughout the experiment was achieved using Presentation 16.4, NeuroBehavioral Systems (Albany, CA, USA). Each trial started with a fixation cross presented on a computer screen for 500ms, followed by an equation. The equation was presented until participants responded with a button press, up to a maximum of 7000ms. Half of the participants were instructed to respond with the left arrow key on the computer keyboard when the equation was correct and with the right arrow key if the equation was incorrect, whereas the other half was instructed with the opposite mapping. The next trial started after an inter-trial interval of 1000ms.

After the first experimental phase, participants either first completed the oxytocin phase (placebo condition) and then the "inactive substance" phase (control condition) or vice versa; condition order was randomized across participants. The oxytocin phase started with a short introductory block of 6 trials (2 easy, 2 medium, 2 hard; 3 correct, 3 incorrect), followed by a training block of 16 trials (8 easy, 4 medium, 4 hard; 8 correct, 8 incorrect). To increase credibility of our previous instruction, we increased the amount of easy equations in this training block, and showed a higher overall performance during feedback after the training block by adding 12.5% to the participants' actual success rate (up to a maximum of 94%). The subsequent test block consisted of 48 trials equally distributed across all difficulty levels (16 easy, 16 medium, 16 hard; 24 correct, 24 incorrect); feedback at the end of the test block, however, was again manipulated to improve the participants' performance by 12.5% (up to a maximum of 96%). The "inactive substance" phase also started with a short introductory block of 6 trials (2 easy, 2 medium, 2 hard; 3 correct, 3 incorrect), followed by a training

block of 16 trials (4 easy, 8 medium, 4 hard; 8 correct, 8 incorrect), and by a test block of 48 trials (16 easy, 16 medium, 16 hard; 24 correct, 24 incorrect). Feedback was again given at the end of the training and at the end of the test block, without any experimental manipulation. No equation in the training or test blocks was repeated within a participant.

At the end of the experiment, participants were debriefed about the actual study purpose and were asked if they had believed the previous instruction.

19.3.4 Behavioural Data Analysis

Behavioural data were analysed using SPSS 20 (IBM, Armonk, NY, USA). We calculated SRs for each participant and the mean RT of all successfully completed trials for each participant, separately for the placebo and nocebo conditions. We only included the test blocks of the oxytocin and the "ineffective substance" blocks in our calculations. We then performed an ANOVA with the within-subjects factors expectancy (placebo vs. nocebo) and difficulty (easy vs. medium vs. hard) for the RT and SR data and performed paired *t*-tests as follow-up analyses.

19.4 Follow-up Experiment II: Results

The results of this experiment precisely mirror the results of Follow-up Experiment I. Again, no expectancy effect emerged in either objective measure (SR: $F < 1$; RT: $F < 1$; Figure 19), but difficulty levels strongly affected SRs and RTs, as expected (SR: $F(2,54) = 68.71$, $p < .001$, $\eta_p^2 = 0.72$; RT: $F(2,54) = 171.99$, $p < .001$, $\eta_p^2 = 0.86$, $\varepsilon =$

.709, Greenhouse-Geisser corrected for violations of sphericity; Figure 19). SRs and RTs were significantly different between all difficulty levels, as follow-up paired *t*-tests indicated (all *p*s < .001). The expectancy x difficulty interaction did not approach significance for either measure (SR: $F < 1$; RT: $F < 1$). These results again indicate that the expectancy manipulation had no effect on any objective measure (Figure 19).

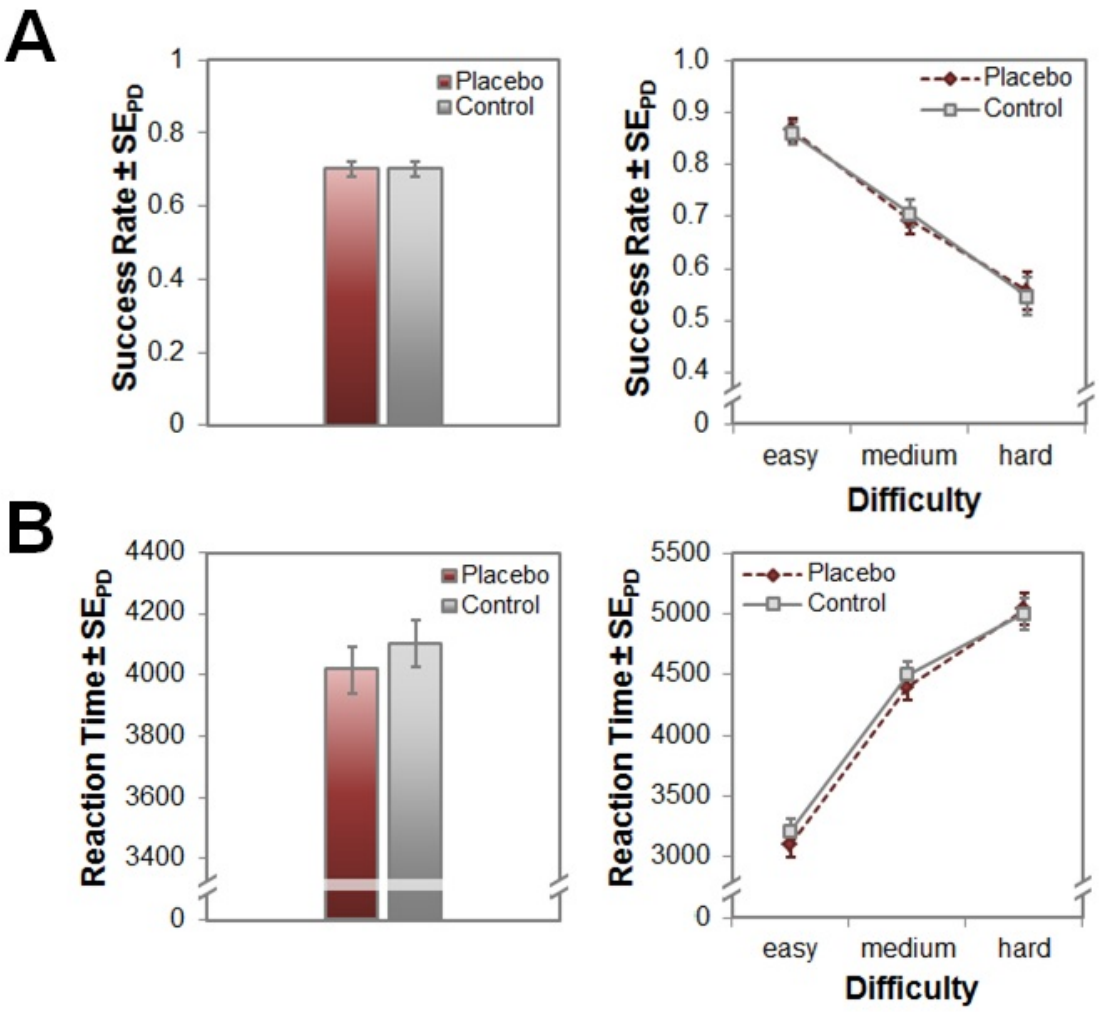

Figure 19. (A) SRs and **(B)** RTs for placebo and control conditions in the arithmetic task of Follow-up Experiment II. No effects of expectancy emerged. Error bars indicate standard errors of the paired differences (Pfister & Janczyk, 2013).

20 | General Discussion

In the present experiments, we investigated whether placebo and nocebo effects in cognitive tasks can be elicited by evoking positive and negative expectations about own task performance. In the main experiment, expectations were manipulated by instructing participants about alleged effects of different sounds ("frequency stimulation") on cognitive performance. To maximize possible effects, we implemented a conditioning paradigm adapted from placebo hypoalgesia research, in which participants experienced either high, medium, or low success rates (SRs) in a choice reaction time (RT) task. The effects of the corresponding positive, neutral, or negative expectations were then assessed in the actual test phase in which participants were confronted with tones that had been paired with different SRs. Interestingly, we found no expectancy effects in objective measures of cognitive performance (SR and RT), but a strong effect on subjective perception. Participants were not more or less successful in the respective conditions in terms of actual performance, but they still felt that the experimental manipulation, i.e., the frequency stimulation, affected their performance in line with the previous verbal suggestion and experience during conditioning.

Previous literature on expectancy effects in, e.g., asthma patients, but also in the cognitive domain documents similar patterns (Looby & Earleywine, 2011; Wechsler et al., 2011). Since expectancy effects clearly affect objective measures and physiological variables in other domains such as pain processing and motor performance (Colloca & Benedetti, 2005; Enck et al., 2013; Schwarz et al., under revision; Stewart-Williams & Podd, 2004; Tracey, 2010), a possible explanation could be that objective measures in cognitive performance are simply not susceptible to any kind of expectancy

manipulation. However, other types of expectancies such as stereotypes and self-efficacy have consistent and well-documented effects on cognitive performance in academic tasks (Bandura, 1997; Beilock et al., 2007; Pajares, 1996; Schmader et al., 2008; Steele & Aronson, 1995) which renders such a general non-susceptibility unlikely.

Another explanation refers to the type of cognitive task that is investigated. Stereotype threat, for example, seems to affect mostly tasks that rely heavily on working memory (Beilock et al., 2007; Schmader et al., 2008). We chose the Flanker task in the main experiment instead because it easily allows the conditioning procedure we sought to implement to maximize possible expectancy effects. However, since the Flanker task is a rather basic interference task targeting cognitive control and flexibility, one could argue that the absence of an expectancy effect is simply due to task choice and that expectancy effects could easily emerge in tasks relying on even higher cognitive functions such as working memory. To pursue this question, we conducted two follow-up experiments using a working memory task that is well-established in research on stereotype threat (Beilock et al., 2007; Krendl et al., 2008) evoking positive or neutral/negative performance expectancy in participants. To further ensure that the experimental manipulation was not responsible for the absence of expectancy effects, we chose two different expectancy inductions for these follow-up experiments: a plausible story on effects of “body posture feedback” as well as a more direct, medical approach during which participants used two nasal sprays either labelled as a cognitive enhancer or as an inactive substance (both nasal sprays contained a saline solution). Despite the change in experimental task and expectancy manipulation, we found no expectancy

effects in either experiment (Figures 18-19), further supporting the results of main experiment.

Which factors could underlie the absence of expectancy effects in objective measures in cognitive performance then? One possibility is that cognitive enhancement is often sought after in situations of high intrinsic motivation, e.g., during exams or for important intellectual challenges (Sahakian & Morein-Zamir, 2007), and that individuals taking them are already highly convinced of their effect. These aspects are difficult to replicate in a laboratory setting. Indeed, previous research suggests that the expectation of cognitive enhancement can even lead to worse results in the laboratory (Looby & Earleywine, 2011), maybe hinting at decreasing motivation in participants to "give their best" in situations of cognitive enhancement. This is unlikely to be a factor in real life situations as intrinsic motivation to perform well is thought to be very high when cognitive enhancers are voluntarily taken of one's own accord. In the present experiments, we tried to keep motivation high across all experimental phases by including monetary compensation as reward for good performance in all conditions. However, especially the RT data during the conditioning phase of the main experiment indicate that participants did not keep their performance stable, but adapted it primarily to the needs of the task, i.e., they were faster when the task became more difficult (nocebo condition) and slower when the task became easier (placebo condition).

Finally, another possible explanation lies in the expectancy manipulation itself. When expectancies about cognitive performance are manipulated, the process of the expectancy manipulation is usually rather subtle. Sometimes, participants are given actual information about the expectancies in form of a short written statement (Wraga

et al., 2006a,b), in other cases the tests were, for example, simply presented as diagnostic of intellectual ability or as known to reveal “gender differences” (Spencer et al., 1999; Steele & Aronson, 1995). In the present experiments, we gave detailed information about the mechanisms and effects of the frequency stimulation and explicitly pointed out which performance effects the participants should expect during which experimental block, similarly to placebo research in the medical domain. However, some researchers argue that conscious awareness of experimental manipulations might attenuate or even reverse effects, for example in social priming (Dijksterhuis, 2014). In this case, a more subtle expectancy manipulation could lead to different results in future studies on this matter.

Irrespective of whether or not cognitive placebo and nocebo effects also exist in objective measures, our results clearly show that the subjective perception of cognitive performance is strongly affected by expectancy effects, i.e., individuals believed their performance was improved even if it actually was not. This is another example of a clear dissociation between actual objective measures and simultaneous subjective perception (Looby & Earleywine, 2011; Wechsler et al., 2011). These results emphasize that cognitive improvements that have been discussed as possible placebo effects such as the positive impact of video gaming on cognitive measures (e.g., Boot et al., 2013, for a review on gaming effects on cognitive measures, see Green & Bavelier, 2012) could very well mirror true effects. Moreover, this finding supports the idea that, while expectancy effects can arise for physiological or objective measures in specific domains (such as pain processing) or under specific environmental circumstances (such as stereotype threat), they primarily affect the participants’ or patients’ subjective perception in other domains.

THE BIGGER PICTURE

The work in the present thesis aimed at fusing different fields of research concerned with the impact of expectations on cognitive processes, such as stimulus processing and higher cognitive functions. To this end, I conceptualized and conducted three different projects intended to fill in the primary gaps in the *Context Framework of Expectations* as detailed in Figure 2 and to interrelate these previously unresolved questions.

Project 1 consisted of a series of behavioural, neurophysiological, and pharmacological experiments which investigated the impact of gender-related stereotypical beliefs on pain processing and the mechanisms behind this phenomenon. I found that manipulating the participants' idea of pain-related gender roles does indeed have an effect on the perception and neuronal processing of pain stimuli. The physiological changes underlying these behavioural effects include alterations in the physiological stress response – a failure to engage with an activation of the HPA axis in response to painful stimulation. Further physiological mechanisms are likely to include differential activation of mesolimbic dopaminergic pathways in anticipation of the pain stimulus. These findings link the impact of gender-related stereotypes on pain

perception to both, placebo and nocebo research which is also associated with changes in dopaminergic brain activity. These findings also link research on pain processing to the literature on social expectancies, which has delineated stress as an important contributor to decreased task performance during stereotype threat.

In Project 2, I then combined the different context variables and outcome measures proposed by the two main fields or research as summarized in the *Context Framework of Expectations*. I introduced social expectancies related to group identification into a medical setting (being invited as a patient vs. being invited as a healthy control participant) and measured the impact of such expectancies on both, pain measures and measures of higher cognitive functioning. This approach allowed me to directly compare the susceptibility of pain perception and intellectual performance to an influence of expectations. In this study, I found that the common stigma of being classified as a patient indeed affects pain perception as well as higher cognitive functioning, and that both types of variables are affected similarly, as indicated by similar effect sizes.

Project 3 finally explored the impact of traditional placebo/nocebo instructions and experimental paradigm on measures of higher cognitive functions. In a series of three behavioural experiments, I found evidence for the susceptibility of subjective appraisal to the evoked expectations, but no changes in actual objective measures across two different intellectual domains. That is, participants believed that they had their performance improved or impaired by placebo or nocebo treatment, but this assessment was not reflected in actual changes in task performance.

In the following chapters, I will discuss these results in relation to biological findings from behavioural ecology, methodological issues relating to expectancy effects, neurophysiological studies on underlying transmitter systems, as well as in light of psychological models on expectancies and stereotype threat.

21 | Nonverbal Expectancies in Non-Human Animals: The Winner/Loser Effect

Experience-based expectations do not only affect human perception or performance. Prominent and surprisingly widespread examples of the influence of experience on subsequent behaviour are winner and loser effects which have been documented and experimentally investigated in such diverse taxa as fish, mammals, birds, reptiles, crustaceans, arachnids, and insects, (Fuxjager & Marler., 2010; Hsu, Earley, & Wolf, 2006; Hsu & Wolf, 1999; Lehner, Rutte, & Taborsky, 2011; Rutte, Taborsky, & Brinkhof, 2006; Whitehouse, 1997).

Winner and loser effects describe the phenomenon that the outcome of previous fighting encounters directly affects the outcome of subsequent encounters, i.e., the probability for a previous winner to win and for a previous loser to lose a subsequent encounter is higher than can be explained by other external features such as size, opponent identity, etc. (Rutte et al., 2006). Interestingly, the losing experience is usually longer lasting than the winning experience and has stronger consequences: the probability of winning a subsequent encounter is almost doubled for previous winners, but is reduced to less than 20% in previous losers, when there are no other asymmetries between opponents (Hsu et al., 2006; Rutte et al., 2006;).

One of the key characteristics of these effects is that they are thought to be a primarily intrinsic phenomenon, resulting from internal changes after a winning or losing experience (Fuxjager & Marler, 2010; Hsu et al., 2006; Rutte et al., 2006). More precisely, evidence suggests that these changes relate to re-assessments of relative

fighting abilities in a contest, especially about the own fighting ability (Hsu et al., 2006; Hsu, Lee, & Lu, 2009; Hsu & Wolf, 1999, 2001; Parker, 1974; Rutte et al., 2006; Whitehouse, 1997). This phenomenon loosely resembles self-efficacy effects in humans: the perceived ability to perform influences performance and performance outcome.

Moreover, evidence suggests that in many species, not objective variables are affected by winner-loser effects, but the subjective perception of the fighting parties. For example, in individuals of *Rivulus mamoratus*, prior fighting experiences influenced non-escalated contests, but not the outcomes of escalated contests, during which the true fighting ability, rather than the perceived fighting ability, is thought to be of greater importance for winning (Hsu & Wolf, 2001). This aspect is particularly interesting in light of the findings of Project 3 (*Expectations and Cognitive Performance*): Here, subjective measures were also affected, whereas objective variables did not mirror the placebo/nocebo expectancy instructions. The evidence thus suggests that, across taxa, subjective measures are most affected by expectancies and experience, whereas objective measures only follow through in rather specific circumstances.

But why do winner-loser effects exist? A possible answer could be that using experience to provide information on fighting ability could lead to decreased costs and risks for winners and losers alike. Indeed, in Norway rats (*Rattus norvegicus*), most rats with a winning experience did not only win a subsequent contest, they did so more quickly than before, saving both time and energy. Rats with a losing experience, in contrast, received less aggression in the subsequent contest, reducing the risk for injury (Lehner et al., 2011). These findings indicate that winner and loser effects have adaptive value for both opponents. Losing a contest incurs especially high costs in terms of time

and energy spent, as well as potential injuries received. Simply retreating without confrontation could be an adaptive strategy to avoid these costs when experience signals that such an outcome is likely to occur (Hsu et al., 2006). It is important to note, however, that winner and loser effects are not the same across all species (Hsu et al., 2006): various factors such as the longevity and general strength of both effects differ greatly between species and are probably dependent on external factors such as territorial behaviour (Fuxjager & Marler, 2010), frequency of social encounters or growth rate (Hsu et al., 2006). If an individual grows very quickly and if size is an important factor in winning or losing an encounter in its species, information from the last fight should quickly lose reliability in predicting the outcome of the next fight. If winner and loser effects are adaptive mechanisms, they are likely to be rather short-lived in such species (Hsu et al., 2006).

The question remains how previous winning and losing experience results in actual changes in behaviour and therefore subsequent contest outcomes. Two somewhat overlapping mechanisms are proposed here: learning processes which include adaptations in specific neuronal pathways, and changes in the individual's endocrinal system. Hormones particularly under investigation in this context are corticosteroids and gonadal hormones, especially testosterone (Fuxjager et al., 2010; Fuxjager & Marler, 2010, Hsu et al., 2006). Interestingly, testosterone seems also responsive to winning or losing situations in humans, although the specific circumstances under which testosterone levels increase are still unclear as some studies observed an increase in response to winning, others to losing (Oliveira, Gouveia, & Oliveira, 2009; Oliveira et al., 2013). Different levels of testosterone were also associated with different reactions to winning and losing, as high testosterone individuals seem to perform especially well on

cognitive tasks after winning and not so well after losing, whereas low testosterone individuals show the opposite pattern (Josephs et al., 2006). Finally, the neurotransmitter serotonin is also a key candidate thought to influence fighting behaviour (Hsu et al., 2006). However, in all cases, relations between physiological changes and subsequent changes in behaviour are not clear-cut and differ greatly across species. Moreover, many studies on the effects of experience on subsequent behaviour use male individuals as subjects and evidence suggests that sex differences in winner and loser effects are not unlikely (Hsu et al., 2006; Huhman et al., 2003). These findings indicate that there doesn't seem to be an unequivocal mechanism explaining winner and loser effect in all species alike – and even within any species, these effects seem to be a complex phenomenon including several physiological changes that might or might not be related to each other.

Winner and loser effects are seen as examples of social competence in animals as individuals learn and adapt from social experiences and use these information to change their behaviour (Taborsky & Oliveira, 2012). A functionally close phenomenon is the generalized reciprocity effect: cooperative behaviour in at least some species is influenced by prior experience with cooperative or uncooperative individuals, irrespective of the identity of the partner. That is, a rat that has received help by a conspecific before is more likely to help a conspecific, even if that conspecific is not familiar (Barta et al., 2011; Pfeiffer et al., 2005; Rutte & Taborsky, 2007). These effects of experience and experience-based expectations (in a most basic sense) are thought to be crucial in allowing individuals to adapt their behaviour to their social environment to minimize costs and thereby increase their Darwinian fitness (Taborsky & Oliveira, 2012).

22 | So, Who Expects What?

As outlined so far, expectations can influence perception and action in many different instances. S0 far, however, I have omitted an interesting distinction between different sources of expectancies: some expectations are generated by internal conviction (such as self-efficacy effects), whereas others are forced upon an individual by societal beliefs (such as stereotype effects) or even by a specific person. An example for the latter case is the Pygmalion effect (Rosenthal & Jacobson, 1966, 1968). In these studies, elementary school pupils took part in an IQ test. Afterwards, their teachers were told that the test also provided reliable information about the pupils' potential for future intellectual blooming. Moreover, the teachers were given information that a specific subset of pupils had shown the best prospects for developing higher IQs during the school year. After the school year was over, all pupils again took part in the IQ test – which resulted in significantly higher scores for those pupils of which the teachers believed that they had the greatest potential for improvement. In reality though, the pupils who allegedly had shown the best prospects for improvement were randomly chosen from the whole sample of pupils, i.e., no systematic, objective reason for a greater improvement was present in them than in their classmates except for the teachers' belief in their potential. Since then, the Pygmalion effect has been the subject of many studies and controversial discussions (Jussim & Harber, 2005; Tenenbaum & Ruck, 2007). Such findings emphasize the effect not only internal conviction, but also external expectancies can have on individuals.

Of course, situations of internally and externally established expectancies are not mutually exclusive and might interact in many real-word settings (Friedrich et al.,

2015). This is especially evident in the second project of this dissertation: In the laboratory setting of evoking the identity of “being a patient”, the negative expectancies associated with the allergy syndromes were primarily generated by the experimenter. However, in real life situations these beliefs are additionally based on the internal convictions of patients themselves which potentially boosts the observed BP effect even more. Moreover, it is possible that already present beliefs about the negative consequences of allergies on perception and performance were simply reinforced by the experimenter, creating a synergy of internal and external expectancies.

23 | Expectancy Effects in the Context of Experimental Design: Avoiding Pitfalls

The Pygmalion effect described in the previous chapter describes in its essence that the expectations of the person charged with supervising and evaluating another person can influence that latter person's performance. It is therefore a prime example of the many pitfalls expectancy effects can cause in any experimental study, if these possible confounds are not controlled for as best as possible.

Indeed, the problems of expectancy effects in the context of experimental design have been discussed for years. Placebo effects, for example, have been (and sometimes are still) regarded as cumbersome confounds which potentially bias clinical research by adding another component to any symptom relief than mere medication efficacy (Colloca & Benedetti, 2005; Enck et al., 2013). Moreover, expectancy effects are known to be highly variable between individuals (Geers et al., 2005; Jensen & Karoly, 1991; Price et al., 1999). And even within an individual, the placebo response to one sham treatment might not predict the placebo response to another (Whalley, Hyland, & Kirsch, 2008). These factors demonstrate how difficult it is to predict and to quantify potential placebo effects in any individual which indeed poses a significant challenge for clinical research that aims at delineating pure medication effects.

Another famous methodological confound relates to expectations of being evaluated. The Hawthorne effect, for instance, describes the phenomenon that whatever contextual change was initiated by the experimenters in a series of field studies (e.g., lighting or pay), it all resulted in a rise in productivity in the factory workers under

observation – including the return to the original state (French, 1953). While still controversial, this effect is mostly attributed to the idea that the knowledge or the expectation of being evaluated and observed per se can lead to changes in performance. No matter the exact mechanisms behind such effects – it is clear that phenomena like the Hawthorne effect emphasize that any experimental inquiry has the potential to alter the study object simply by inquiring.

The Being a Patient effect investigated in Project 2 is another example of undesired expectancy effects in experimental paradigms. Since the BP effect is likely to vary across participants and across measures, it is difficult to quantify its effect size in relation to the true effect of a given disease. It could be virtually nonexistent, but in some instances it could also make up a considerable proportion of the observed disease effect, an unpredictability which renders data interpretation very difficult. In Project 2 (*Between Math and Pain*), I propose possible strategies to avoid such a confound including stronger emphasis on within-group comparisons of patients with graded symptom severity, a control group consisting of patients suffering from a different disease than the one studied, or choosing a study design similar to the one I employed. Methodological pitfalls dependent on expectancy effects can pose serious problems if they are not taken into account. Knowledge of these pitfalls allows the development of methodological countermeasures which can only improve data validity and significance.

24 | Dopamine, Opioids, and Endocannabinoids: Re-evaluating the Transmitter Systems Involved in Expectancy Effects

Expectancy effects are a widespread phenomenon, as outlined in the introduction and the three projects of this dissertation, and they possibly affect most of our cognitive processes. Especially with regard to placebo/nocebo effects in pain processing, I have also discussed findings on the neurophysiology possibly underpinning these effects. Following up on the results of Project 1 (*Gender, Pain, and Expectations*) a more detailed look at the transmitter systems involved in the effects of expectancies on cognition seems to be in order.

The most prominent transmitter system in the focus of research on placebo hypoalgesia is the opioidergic system. To investigate its involvement in placebo hypoalgesia, the opioid antagonist naloxone as well as the antagonist of the opioid antagonist CCK have been used to block or to potentiate the hypoalgesic effect of placebo expectancies (Amanzio & Benedetti, 1999; Benedetti et al., 1995, 1999; Eippert et al., 2009a; Levine et al., 1978). These studies provide conclusive evidence that the release of endogenous opioids plays a major role in placebo hypoalgesia. However, they also indicate that the opioidergic system is not the sole mediator of pain-related expectancies.

Indeed, if a placebo response was triggered by previous conditioning with the non-opioid drug ketorolac, the pain-relieving effect was partly or even completely insensitive to naloxone, indicating that a non-opioidergic pathway is involved in this

particular instance of placebo effects (Amanzio & Benedetti, 1999). This non-opioidergic pathway has been further specified in a recent study: After conditioning with ketorolac, the CB1 cannabinoid receptor antagonist rimonabant blocked placebo effects. In case of preceding conditioning with the opioid analgesic drug morphine, however, the placebo response was insensitive to rimonabant (Benedetti et al., 2011). This indicates that both, endogenous opioids and (endo-)cannabinoids can mediate pain-related expectancy responses, dependent on the specific circumstances of their occurrence.

The results of Project 1 show that stereotypical beliefs and expectations influence pain perception and processing mainly by a non-opioidergic pathway. The participants' saliva concentrations of the stress hormone cortisol, however, suggested that physiological stress responses play a role in mediating the effects of gender-related stereotypes on pain processing, hinting at a specific form of stress-induced hypoalgesia. Stress-induced hypoalgesia is a phenomenon based on a variety of transmitter systems working in concert, including endogenous opioids, endocannabinoids, and monoamines such as dopamine (Butler & Finn, 2009). Several studies provide evidence for a close interaction of endogenous opioids and endocannabinoids during stress-induced hypoalgesia (Butler & Finn, 2009; Sorge et al., 2014), but there are also instances in which stress-induced hypoalgesia, mediated by CB1 receptors, is independent of opioidergic pathways (Hohmann et al., 2005). Although the results of Project 1 revealed that gender-related stereotypes clearly do not affect pain processing through opioidergic pathways alone, they do not preclude that an interaction of endocannabinoids and opioids might mediate the observed effects.

However, the fMRI data from Project 1 suggest the involvement of another transmitter: the dopaminoceptive system. The ventral striatum is part of the mesocorticolimbic dopamine system and heavily associated with the processing of reward information (e.g., Schultz, 1998). Previous studies report the mesocorticolimbic system to be active in response to acute stress, and to be involved in stress-induced pain suppression (Altier & Stewart, 1999; Navratilova & Porreca, 2014). Moreover, the ventral striatum was shown to be active not only during stress but also in anticipation of aversive stimuli (Jensen et al., 2003). Striatal activity further predicted pain relief at the offset of experimental pain stimuli (Baliki et al., 2010), and dopaminergic activity in the ventral striatum predicted placebo responses, possibly triggering further downward signalling pathways (Scott et al., 2008; Tracey, 2010). In line with these findings, differential striatal activation in Project 1 occurred not only during pain stimulation, but also in anticipation of the pain stimuli, dependent on the instructed stereotype. Striatal activity during anticipation was further correlated with individual pain ratings in the *MLPS* group, but not in the *FLPS* group. This finding indicates that dopaminergic signalling in the ventral striatum is linked to the pain reduction mediated by physiological stress.

Several studies directly link the dopaminergic reward system to placebo responses. For example, BOLD activity in the nucleus accumbens (a prominent part of the ventral striatum) during reward expectation correlated with placebo-induced dopamine release in the nucleus accumbens as well as actual placebo response (Scott et al., 2007). Moreover, in Parkinson patients, endogenous dopamine is released in the striatum in response to placebo treatments (de la Fuente-Fernández et al., 2001). These

findings inspired the idea that the reward system could generally be involved in placebo effects, i.e., the expectation of therapeutic relief could activate the reward system in all manners of clinical placebo responses (de la Fuente-Fernández et al., 2001; de la Fuente-Fernández, 2009).

The results from Project 1 go beyond these findings by indicating that the reward system might also be involved when pain-related expectancies are induced outside medical conditions or clinical settings. Indeed, nucleus accumbens activity was also reported when participants expected to receive the cognitive enhancer methylphenidate, but received placebo instead (Volkow et al., 2006). The involvement of the reward system could thus present a general mechanism during which dopaminergic neurons trigger specific subsystems of expectancy-related transmitters which then realize the observed changes in behaviour and perception. Of course, this hypothesis is purely speculative at this point and further research is needed to elaborate these speculations.

25 | Implications for Stereotype Threat

From a psychological view, the effects of stereotypical beliefs on pain processing (see Project 1 and 2) also shed new light onto current models of stereotype threat which I detailed in the introduction (see *3.1 Stereotype Threat*). Such a model established by Schmader and colleagues (2008) covers the influence of stereotype threat on performance on higher cognitive and social tasks – which has been the main focus of previous research – as well as performance on sensorimotor tasks. However, it does not entail any specific assumptions on the influence of stereotypes on stimulus processing (e.g., pain processing), a phenomenon which I studied in the course of this dissertation. In this chapter, I would thus like to update the current model to account for the findings from my thesis (Figure 20). The corresponding extensions also open up further questions regarding the generality of the assumed mechanisms. Therefore, my proposed updates on the model are still speculative. However, the evidence I presented suggests that stereotype effects on stimulus processing already provide important extensions of the models.

The current model emphasizes the influence of physiological stress on the effects of stereotype threat on performance in higher cognitive tasks. Interestingly, the physiological stress response also seems to play a role in the effects of stereotypes on pain processing. This stress response thus seems to be a common denominator for both processes. The results of Project 1 further implicate the dopaminergic reward system to be involved in the phenomenon, possibly initiating the physiological downward processing necessary to result in the observed changes in pain processing. Since the recruitment of the HPA axis is a rather tonic change in the physiological system during

the whole experimental procedure, the differential BOLD activity in the striatum on the other hand a seemingly phasic occurrence evident in the anticipation phase of the various pain stimuli, I hypothesize that the physiological stress response might influence activity in the reward system. Elaborating the precise mechanisms mediating the interplay of physiological stress response, reward system, and the downward brain signalling response certainly seems to be a fruitful avenue for future studies.

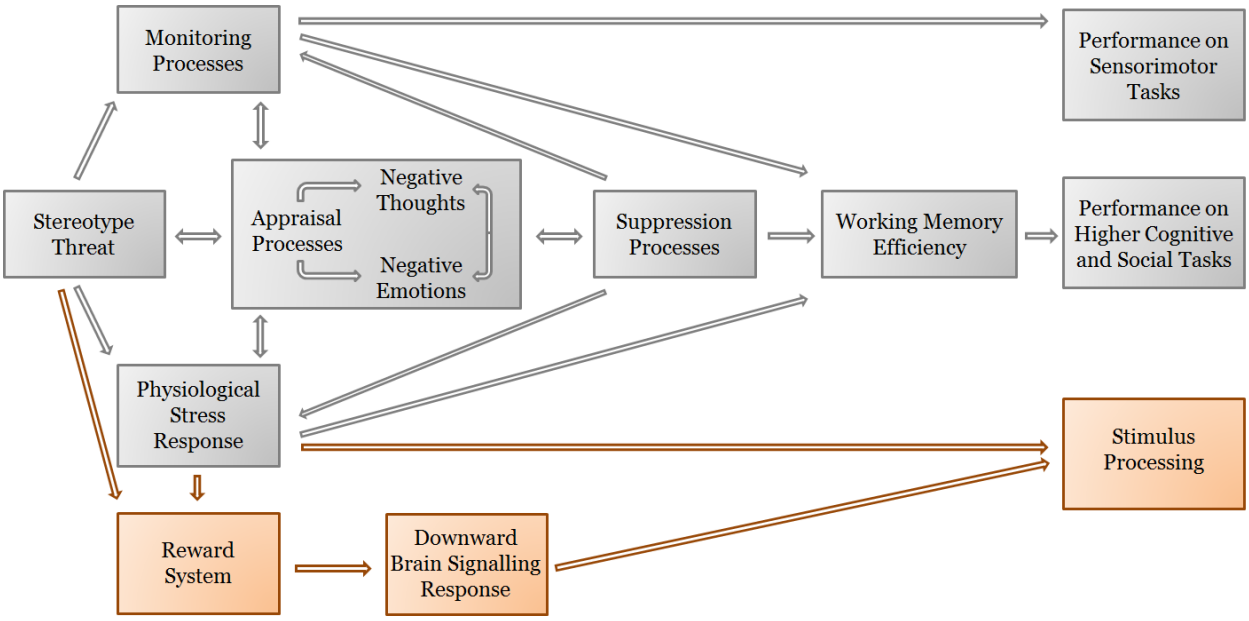

Figure 20. The updated stereotype model, adapted with modifications from Schmader et al. (2008). Based on the results from the projects of this dissertation, I propose to include a pathway realizing the observed effects in pain processing, thus extending the model space to a third outcome variable.

26 | Concluding Remarks

In the course of this dissertation, I sought to fuse several lines of research regarding the effects of social or clinical expectancies on higher cognitive functions and pain processing. To this end, I investigated possible physiological mechanisms behind the phenomena in Project 1, probed for an impact of expectancies on different measures in a clinical setting in Project 2, and studied the effects of traditional placebo and nocebo expectancies on cognitive task performance in Project 3. The results of these projects have substantial implications for a range of fields and complement the current understanding of expectancy-related pain modulation and stereotype-based effects on cognition.

The effects of expectancies on cognition are diverse and span a multitude of different cognitive domains. Their influence on our perception and behaviour is considerable, and yet often goes unnoticed. The study of their effects is thus crucial for our understanding of our own actions. There are still many open questions regarding these effects: precise physiological mechanism underlying the phenomena detailing common pathways and module-specific subsystems are yet elusive, although research of the last decades, including the results of this dissertation, gives a first idea of how such a model could look. It is still not clear which kinds of stimuli are especially susceptible to the influence of expectancies and how the different aspects I presented fit together in detail. However, I believe that by fusing different fields of research that have so far mostly worked in parallel instead of in conjunction, my dissertation has provided an important step into a holistic understanding of the effects of expectancies on human perception and behaviour.

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Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe.

Hamburg, den 24.03.2015

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