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"Experiencing Pain - The Impact of Variability on Pain Perception and the Placebo Effect"

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Abstract - English

Theoretical background: Pain perception and placebo hypoalgesia are highly subjective and expectancy-driven phenomena. Previous pain studies investigating placebo effects mostly focused on the strength of treatment expectations and experiences. So far, the level of variability within prior treatment expectations has mostly been ignored, despite being a likely modulator of inter-individual variations. Especially, due to the individual subjectiveness of pain, variability is assumed to strongly influence pain perception and may explain the repeatedly observed large differences in the magnitudes of placebo analgesia across individuals as well as studies. Therefore, this dissertation addresses this topic as one of the first approaches to account for individual variability in a pain study investigating placebo analgesia.

Methods: Heat pain was used in four studies to induce acute pain and investigate individual responses to possibly varying pain intensities. Moreover, a Bayesian framework was mathematically implemented, which combines previous treatment expectations (prior) with new incoming sensory information (likelihood) to predict the pain percept and placebo treatment outcomes (posterior). Importantly, for the prior and the likelihood, the framework takes relative variability levels into account weighting the more precise information as more significant and reliable. This was not only tested in a behavioral sample but also via fMRI to investigate the underlying neural mechanisms. Additionally, the model was applied to an independent large sample to examine the reliability of the model fits and model comparisons.

Results: By applying Bayesian model comparisons, the Bayesian framework proved to be feasible describing placebo treatment outcomes when investigating acute pain in two independent studies (**Study 3** and **4**). Placebo effects were less pronounced in subjects with more variable prior treatment expectations, while relating this to increased neural activation in the periaqueductal gray (PAG) and the rostral ventromedial medulla (**Study 3**). However, after repeated exposition to a prior treatment, a strong influence of the mean combined with the variability level of expectations was also observed in the large sample.

Conclusion: Including variability or precision components in the assessment of treatment history and addressing possible non-optimal prior experiences and expectations may highly benefit future clinical interventions of acute pain patients. The Bayesian integration framework in placebo analgesia seems feasible to account for variability differences but needs future clinical research to show transferability to other domains, e.g. chronic pain patients.

Keywords: Placebo analgesia, Bayesian integration, variability, expectation, experience, PAG

Abstract - German

Theoretischer Hintergrund: Schmerzempfindung und Placebo-Hypoalgesie sind sehr subjektive und oftmals von Erwartungen beeinflusste Phänomene. Frühere Schmerzstudien, welche Placebo-Effekte untersuchten, konzentrierten sich dabei hauptsächlich auf die Stärke der Behandlungserwartungen und -erfahrungen. Das Ausmaß der Variabilität früherer Erwartungen wurde bisher größtenteils ignoriert, obwohl sie ein sehr wahrscheinlicher Einflussfaktor inter-individueller Variationen zu sein scheint. Gerade aufgrund der hohen Subjektivität von Schmerz liegt es nahe anzunehmen, dass diese Variabilität die Schmerzwahrnehmung ebenfalls stark beeinflusst. Damit könnten die oft beobachteten großen Unterschiede in Placebo-Effekten sowohl über verschiedene Individuen als auch Studien hinweg erklärt werden. Daher befasst sich diese Dissertation als eine der ersten Forschungsarbeiten mit diesem möglichen Einflussfaktor. Es wird der modulierende Einfluss von Variabilität in mehreren Schmerzstudien zur Untersuchung von Placebo-Analgesie erforscht.

Methode: In vier Studien wurde Hitzeschmerz eingesetzt, um akute Schmerzen zu induzieren und individuelle Reaktionen auf identische und unterschiedlich variierende Schmerzintensitäten zu untersuchen. Hierbei wurde ein theoretisches Bayes'sches Model erstmals mathematisch implementiert, in dem frühere Behandlungserwartungen (prior) mit neuen eingehenden sensorischen Informationen (likelihood) kombiniert werden, um Ergebnisse individueller Schmerzwahrnehmung und Placebo-Behandlungen vorherzusagen (posterior). Wichtig ist, dass die relative Variabilität von prior und likelihood Berücksichtigung findet, wobei die präzisere Information als signifikanter und zuverlässiger gewichtet wurde. Das Modell wurde nicht nur in einer Verhaltensstichprobe, sondern auch mittels fMRI getestet, um zusätzlich die zugrundeliegenden neuronalen Mechanismen zu untersuchen. Außerdem wurde das Bayes'sche Modell auf eine unabhängige große Stichprobe angewendet, um die Zuverlässigkeit des Modells und der einhergehenden Modellvergleiche zu untersuchen.

Ergebnisse: Mittels Bayes'scher Modellvergleiche wurde das Bayes'sche Framework für Placebo-Hypoalgesie bei der Untersuchung akuter Schmerzen in zwei unabhängigen Studien (**Studie 3** und **4**) als plausibel anwendbar beobachtet. Placebo-Effekte waren bei Probanden mit variableren Vorerfahrungen und Erwartungen weniger ausgeprägt, was mit einer erhöhten neuralen Aktivierung im periaquäduktalen Grau (PAG) und der rostralen ventromedialen Medulla (**Studie 3**) einherging. In der großen Stichprobe mit wiederholter Behandlungsanwendung wurde zusätzlich ein wichtiger Einfluss des Mittelwerts in Kombination mit der Variabilität der Erwartungen beobachtet.

Schlussfolgerungen: Der Einbezug von Variabilität bzw. Präzision in der Patientenanamnese bezüglich suboptimaler früherer Erfahrungen und einhergehender Erwartungen könnte akuten Schmerzpatienten für künftige klinische Interventionen große Vorteile bringen. Bayes'sche Integration in einem Placebo-Kontext scheint informativ, da Variabilitätsunterschiede berücksichtigt werden. Es benötigt jedoch zukünftige klinische Forschung, um die Übertragbarkeit auf andere Domänen wie chronische Schmerzpatienten zu bestimmen.

Schlüsselwörter: Placebo-Analgesie, Bayessche Integration, Variabilität, Erwartung, Erfahrung, PAG

List of abbreviations

ANOVA	Analysis of Variance
ACC	Anterior Cingulate Cortex
BDI-II	Beck Depression Inventory II
BF	Bayes Factor
BG	Basal Ganglia
BOLD	Blood-Oxygenation-Level-Dependent
CBT	Cognitive Behavioral Therapy
CDA	Continous Deconvolution Analysis
CT	Computer Tomography
CTE	Constant Treatment Expectation
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
EEG	Electroencephalography
EPI	Echo-Planar Imaging
FKK	Fragebogen zu Kompetenz- & Kontrollüberzeugungen
fMRI	functional Magnetic Resonance Imaging
fMRT	functional Magnetic Resonance Tomography
FWE	Familywise Error Rate
FWHM	Full Width Half Maximum
GLM	General Linear Model
HBM	Health Belief Model
HRF	Hemodynamic Response Function
M	Mean
MCC	Mid-Cingulate Cortex
MDBF	Multidimensional Mood State Questionnaire
MEG	Magnetoencephalography
MI	Primary Motor Cortex
MNI	Montreal Neurological Institute
MR	Magnetic Resonance
PAG	Periaqueductal Gray
PCS	Pain Catastrophizing Scale
PER	Positive Evidence Ratio
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
QST	Quantitative Sensory Testing
rCBF	Regional Cerebral Blood Flow
RFX	Random Effects
ROI	Region of Interest
SCR	Skin Conductance Response
SD	Standard Deviation
SEM	Standard Error of Mean
SI	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SMA	Supplementary Motor Area
SPM	Statistical Parametric Mapping
STAI	State-Trait Anxiety Inventory
SVC	Small Volume Correction
VAS	Visual Analogue Scale
VBM	Voxel-Based Morphometry
VTE	Variable Treatment Expectation

List of publications

Publications specifically prepared and published in the context of the PhD project:

Grahl, A., Onat, S., & Büchel, C. (*2018*). The periaqueductal gray and Bayesian integration in placebo analgesia. *eLife*, 7:e32930. doi: 10.7554/eLife.32930.

Other publications:

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Pfabigan, D.M., Seidel, E.-S., Paul, K., Grahl, A., Sailer, U., A., Lanzenberger, R., Windischberger, C., & Lamm, C. (*2015*). Context-sensitivity of the feedback-related negativity for zero-value feedback outcomes. *Biological Psychology*, 104, 184-192. doi:10.1016/j.biopsycho.2014.12.007.

Pfabigan, D.M., Seidel, E.-S., Sladky, R., Hahn, A., Paul, K., Grahl, A., Küblböck, M., Kraus, C., Hummer, A., Kranz, G.S., Windischberger, C., Lanzenberger, R., & Lamm, C. (*2014*). P300 amplitude variation is related to ventral striatum BOLD response during gain and loss anticipation: An EEG and fMRI experiment. *NeuroImage*, 96, 12-21. doi:10.1016/j.neuroimage.2014.03.077.

Hahn, A., Kranz, G.S., Seidel, E.-S., Sladky, R., Kraus, C., Küblböck, M., Pfabigan, D.M., Hummer, A., Grahl, A., Ganger, S., Windischberger, C., Lamm, C., & Lanzenberger, R. (2013). Comparing neural response to painful electrical stimulation with functional MRI at 3 and 7 Tesla. *NeuroImage*, 82, 336-343. doi: 10.1016/j.neuroimage.2013.06.010.

Grahl, A., Greiner, U., & Walla, P. (2012). Bottle Shape Elicits Gender-Specific Emotion: A Startle Reflex Modulation Study. *Psychology, 3*, 548-554. doi: 10.4236/psych.2012.37081.

1 Introduction

A somatosensory sensation that results in a painful perception is one of the most informative reactions the body is able to present. Human individuals learn the meaning of the word '*pain*' and acquire their intial associated perceptions of pain through injuries in early life (Merskey, 1991). Pain usually functions as a warning signal and is essential for survival as it informs the body of possible tissue damage or harmful behavior which should be avoided in the future. Therefore, pain represents an important and complex mechanism that enables animals, including humans, to protect themselves in a rapidly changing environment. Within such a changing environment, pain can initiate adaptation processes as hurtful experiences are ideally followed by learning of new or updating of existing behavior (Mowrer, 1938; Pavlov, 1927) so as to minimize surprise in a comparable future situation. However, individuals can learn from painful experiences in various ways. Thus, a special characteristic of the perception of pain is its subjectiveness (Coghill & Eisenach, 2003; Fillingim, 2005; Nielsen et al., 2008; Nielsen, Staud, & Price, 2009) which makes this phenomenon particularly challenging to investigate. An identical noxious stimulus is able to evoke very diverse pain responses across individuals. Additionally, the risk for or protection against the development of chronic pain is associated with individual differences in pain sensitivity (Diatchenko et al., 2005; Edwards, 2005). This suggests that the strong influence painful experiences can have, is reflected by the potential severity of the outcomes they result in.

To better understand these effects, research that investigates potential modulators that shape inter-individual differences is needed. As painful experiences and associated treatments may vary widely across individuals, corresponding expectations concerning possible treatment outcomes also differ. Previous research suggests that there is a substantial influence of expectations on clinical interventions, which is best represented by the analgesic effect of a placebo treatment (Atlas, Bolger, Lindquist, & Wager, 2010; Colloca & Benedetti, 2006; De La Fuente-Fernández et al., 2001; Enck, Bingel, Schedlowski, & Rief, 2013; Kirsch, 1999; Klinger, Soost, Flor, & Worm, 2007; Reicherts, Gerdes, Pauli, & Wieser, 2016; Rief, Bingel, Schedlowski, & Enck, 2011; Schenk, Sprenger, Geuter, & Büchel, 2014; Stone, Kerr, Jacobson, Conboy, & Kaptchuk, 2005; Wager et al., 2004). Analgesia in the context of placebo effects is often referred to as a per-

ceptual pain decrease but in general means the absence of pain. Hypoalgesia is the more correct term for a perceptual pain relief. For simplicity reasons within this dissertation, both terms are used equivalently representing decreased pain. The hypoanalgesic effect of placebo treatments is driven by modulators which are not referable to an active treatment. Instead, other factors are inducing and shaping the only psychologically induced analgesic sensation that defines this very powerful phenomenon. Many patients suffer gravely from acute or chronic pain which is a symptom of numerous diseases. Therefore, the effectiveness and success of a treatment is, among other things, specifically evaluated by a reduction in subjective painfulness. This very subjectiveness makes it challenging to assess and measure this physically as well as psychologically demanding sensation, especially in pain related disorders. Moreover, it has also challenged researchers to fully understand the underlying mechanisms of dysfunctional pain perception and lead to a strong focus in pain research on describing individual differences (Cheng, Erpelding, Kucyi, DeSouza, & Davis, 2015; Coghill, 2010; Diatchenko et al., 2005; Edwards, 2005; Nielsen et al., 2009; Wager et al., 2013). By using a multidimensional approach that focuses on the influence of psychophysiological, behavioral, and neural modulators to investigate pain, a much more holistic view of the emergence and treatment of pain as well as related phenomena, such as the placebo effect, is possible.

One important assumption is that not only each placebo treatment, but each clinical interaction is influenced by individual expectations of a patient. This is, among others, well represented in the so-called Health Belief Model, HBM (Green & Murphy, 2014; Janz & Becker, 1984; Skinner, Tiro, & Champion, 2015), developed in the 1950s by the U.S. Public Health Service. This model predicts actions of prevention, detection, or control of illness by subjectively perceived components such as susceptibility, severity, benefits, and barriers or costs concerning the engagement of health related actions. This implies that individual differences in these modulators already influence actions of health care behavior. Moreover, previous research showed a relationship between the treatment outcome of chronic pain patients with post-treatment self-efficacy ratings (Dolce, Crocker, & Doleys, 1986) reflecting that the subjective evaluation of individual functionality predicts treatment outcomes. Such experiences are likely to influence future treatments by shaping prior treatment expectations. Further, the relationship between chronic pain patients' expectations with clinical outcomes was found to be largely mediated by the patients'

global impressions of change (Cormier, Lavigne, Choiniere, & Rainville, 2016). These findings emphasize the importance of expectations before, during, and after clinical treatments as a determinant of outcome.

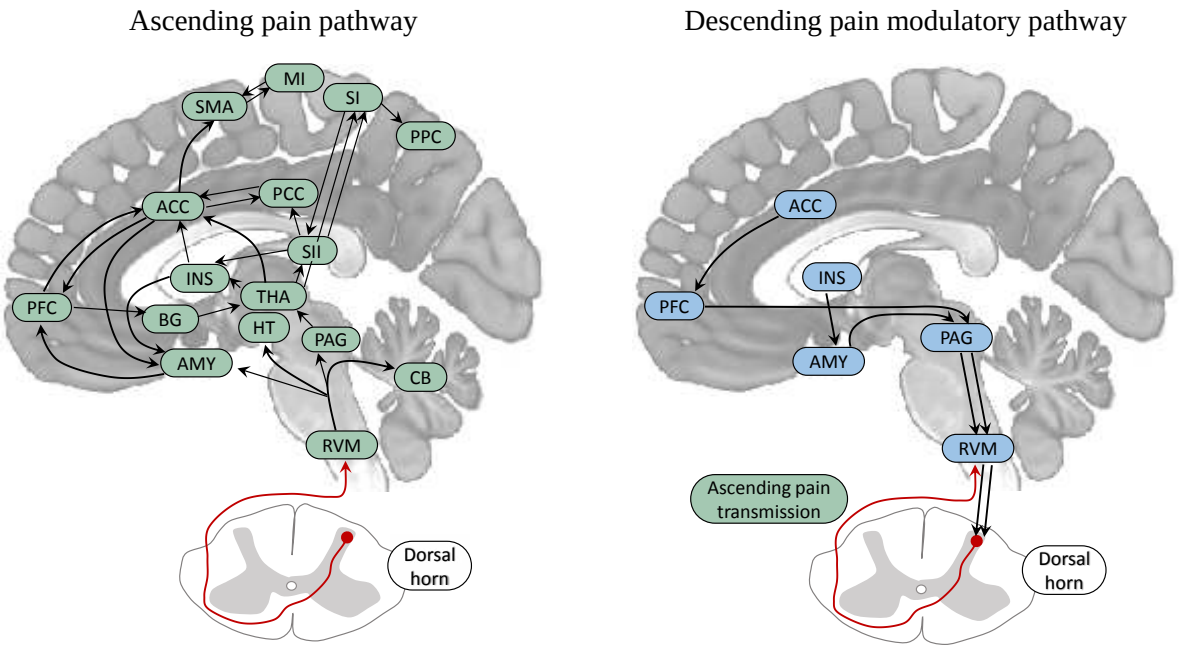
The placebo effect, and resulting analgesic perceptions, is a suitable method to use for exploring this phenomenon as it is mostly driven by treatment expectations. A specific focus lies on the variability of expectations as the aforementioned modulators of treatment outcomes are highly subjective and may be better explained by the inclusion of inter-individual variations. In more detail, this would account for different pain relieving treatment experiences that individuals may have during their clinical intervention history. As previous studies also revealed large differences in the magnitudes of placebo hypoalgesia (Vase, Petersen, Riley, & Price, 2009; Wager, Atlas, Leotti, & Rilling, 2011), the level of variability in prior treatment expectations may likely be a modulator shaping these findings. Approaches which include behavioral as well as neural data are able to account for several factors of treatment expectations. Importantly, by further including not only the strength of treatment expectations (very vs. not effective) but also the variability level (always the same vs. highly fluctuating efficacy) in such analyses may provide new insights into individual differences. Understanding the underlying mechanisms of the influence of variability on pain perception and placebo hypoalgesia will shed more light on possibilities to induce, change, maintain, or reappraise expectation processes to achieve optimal treatment outcomes in clinical interventions.

1.1 Physiology of pain processing

This section provides a brief introduction of the physiology and processing of pain. Unless stated otherwise, the following description of nociception and pain of the current section has been particularly summarized by using Bear, Connors, and Paradiso (2007), Garland (2012), as well as McMahon, Koltzenburg, Tracey, and Turk (2013). First, a differentiation between nociception and pain is important as both do not always co-occur. This means that a noxious stimulus that is potentially harmful does not necessarily induce pain and that a painful sensation can occur without a measurable noxious input being present. This, among others things, again underlines the very subjective perception of nociception and pain - a potentially damaging stimulus may be painful for one individual but non-painful for another. How essential pain as

a warning signal for potential bodily harm can be, is dramatically reflected in the syndrome of congenital insensitivity to pain (Nagasakoa, Oaklanderb, & Dworkin, 2003; Thrush, 1973). Such patients were born without the ability of perceiving pain and often die at a young age due to the failure of noticing injuries and illnesses. This clearly demonstrates the crucial value of pain for survival of an organism and therefore shows the importance of this research topic.

A noxious reaction typically originates from a mechanical, thermal, or chemical input which activates specialized receptors known as nociceptors. When stimulation to these nociceptors is sufficiently intense enough to potentially cause tissue damage, a pain response is initiated by an inflammatory chemical reaction (e.g. release of substance P, bradykinin, prostaglandines) and transmitted via myelinated $A\delta$ (1-5μm diameter) as well as unmyelinated C nerve fibers (0.2-1.5μm diameter). The thicker and more myelinated these nerve fibers are, the faster the noxious information concerning temperature and pain is transmitted. For that reason, $A\delta$ fibers are involved in rapidly transmitting the initial, sharp perception of pain whereas C fibers transmit the subsequent, and often more intensely perceived pain. These so-called primary afferent nerve fibers project and transmit information to the spinal cord via the dorsal horn (Figure 1). After entering the spinal cord and crossing contralaterally to the site of origin of the noxious stimulus, information are relayed up the spinal cord and through the spinothalamic tract. Passing medulla, pons as well as the midbrain, the spinothalamic fibers enter the thalamus, which serves as a relay region for sensory information to the cortex. From here, information is directly transmitted to regions such as the primary (SI) as well as secondary somatosensory (SII), anterior cingulate (ACC), insular, and prefrontal cortex (PFC). Additional regions that are involved in the processing of pain include the supplementary motor area (SMA), primary motor cortex (MI), basal ganglia (BA), amygdala, and the cerebellum. This mechanism of transferring neural information is referred to as the *ascending pain pathway* of the human brain. It conveys the sensory information that underlies conscious perception of pain. Importantly, this is not the only pathway modulating pain perception as the brain does not only passively receive signals from the body. By actively regulating the incoming sensory information via projections back to the dorsal horn, the brain is able to influence the transmission of a painful sensation in a top-down manner. Thereby, a facilitation as well as inhibition of the processing is possible reflecting the modulatory options of anti- as well as pro-nociceptive changes. This top-down modulatory sys-



Adapted from Apkarian et al. (2005) and Schweinhardt and Bushnell (2010)

Figure 1. Ascending and descending pain pathways. Schematic representation of pain processing showing a simplified display of interacting spinal and brain regions. *ACC, anterior cingulate cortex; AMY, amygdala; BG, basal ganglia; MI, primary motor cortex; CB, cerebellum; HT, hypothalamus; INS, insula; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; RVM, rostral ventromedial medulla; SI and SII, primary and secondary somatosensory cortices; SMA, supplementary motor area; THA, thalamus.*

tem is called the *descending pain pathway* (Figure 1). Projections from the cortex arrive at the PAG, transmit through the rostral ventromedial medulla (RVM), and enter the dorsal horn of the spinal cord where the afferent nociceptive transmission is influenced by cortical information of the central nervous system. This descending influence may increase or decrease the intensity of the perception of pain by modulating the afferent transmission accordingly. Additionally, prior studies have found both a relationship between areas of the descending pain pathway, especially the PAG and RVM, and opioid receptors, as well as the secretion of endogenous opioids (Basbaum & Fields, 1984; Hughes et al., 1975; Pert & Snyder, 1973; Reynolds, 1969). Opioids are known for their analgesic properties. Moreover, findings of opioidergic signaling in the dorsal horn, RVM, and PAG lead to the assumption of a descending modulatory system for pain. Nevertheless, these regions are not limited to noxious information transmission as unexpected innocuous stimuli are able to induce modulatory signal changes as well. It is assumed that these regions od the brain may effect homeostatic adaptations which include but are not limited to

harmful incoming stimuli (Mason, 2005). This very complex physical pain system enables the human body to adjust and adapt to different environmental influences. Stimulation resulting in tissue damage can be detected immediately, which induces reactions to counteract against the damaging influence. Additionally, the central nervous system is also able to decrease perceived pain intensities if it is needed. For example, in case of an imminent life threat, which can result in a fight or flight reaction, the organism is able to suppress painful sensations via modulatory mechanisms in order to perform actions needed for survival. Various brain areas are involved in the emergence and modulation of pain (Figure 1), which also process other sensory, cognitive, and motor inputs and mechanisms. Therefore, pain perception is highly influenced by many modulating factors, e.g. attention (Bantick et al., 2002; Frankenstein, Richter, McIntyre, & Rémy, 2001; Tracey et al., 2002), emotion (Apkarian et al., 2005; Hashmi et al., 2013; Phillips et al., 2003; Rhudy & Meagher, 2001), and cognition (Rémy, Frankenstein, Mincic, Tomanek, & Stroman, 2003; Valet et al., 2004; Wiech et al., 2005). For this reason, prior experiences and expectations shape the perception of pain and are likely sources of induced differences between individuals.

1.2 Placebo analgesia and neurobiological correlates

The concept of placebo effects in the clinical context goes back to Henry Beecher, a surgeon during second World War, who ran out of morphine and still observed a pain relief in his patients when replacing infusions with inert saline injections (Beecher, 1945, 1955). Placebo effects are understood as hypoalgesic mechanisms of the body which are characterized by a decreased sensitivity to pain or a pain relief which cannot be attributed to an active substance or medication (Stewart-Williams & Podd, 2004). For this reason, placebo analgesia is very promising for the investigation of the modulatory effects of prior expectations and experiences as well as treatment context independent of the influence of any real medication, injection, surgery, or therapy. Importantly, all these mentioned procedures can be used to induce placebo effects by replacing the active agent with a non-active placebo equivalent (i.e. sugar pill, saline injection, or sham surgery/therapy) to study the influence of expectations on only the bodily induced analgesia. Interestingly, studies have shown that when drug administration is hidden from patients it reduces the effect of the medication. This is believed to be due to the missing influence of patients'

treatment expectations normally presumed to support the efficacy (Atlas et al., 2012; Bingel et al., 2011; Colloca, Lopiano, Lanotte, & Benedetti, 2004; Kam-Hansen et al., 2014). This highlights the importance and critical influence of expectations on clinical treatment, including placebo analgesia (Atlas et al., 2010; Colloca & Benedetti, 2006; De La Fuente-Fernández et al., 2001; Enck et al., 2013; Kirsch, 1999; Klinger et al., 2007; Reicherts et al., 2016; Rief et al., 2011; Schenk et al., 2014; Stone et al., 2005; Wager et al., 2004).

Several studies demonstrated that a combination of verbal suggestion and a conditioning procedure result in the most robust and largest placebo effect magnitudes (Lui et al., 2010; Montgomery & Kirsch, 1997; Schenk et al., 2014; Stewart-Williams & Podd, 2004; Voudouris, Peck, & Coleman, 1990). More specifically, this refers to an experimental design in which participants receive certain information about the efficacy of a treatment prior to receiving it, and, in a subsequent step, experience manipulated pain relief accordingly as an expectation-induction phase. The first-hand experience makes the suggested treatment expectation believable and reinforces the positive efficacy before participants enter a placebo test phase (see section 2.2 for more details).

However, it is important to note that several other factors also contribute to the strength of placebo effects and corresponding physiological responses. Previous research has found relationships between placebo hypoalgesia and modulators such as the medication value (Geuter, Eippert, Hindi Attar, & Büchel, 2013; Waber, Shiv, Carmon, & Ariely, 2008), treatment history (Kessner et al., 2014; Kessner, Wiech, Forkmann, Ploner, & Bingel, 2013; Müller et al., 2016), doctor-patient relationship and beliefs (Baldwin, Wartolowska, & Carr, 2016; Benedetti, 2013; Kampermann, Nestoriuc, & Shedden-Mora, 2017; Kelley et al., 2009), emotion (Petrovic et al., 2005; Zhang & Luo, 2009; Zhang, Guo, Zhang, & Luo, 2013), social influence (Crum, Phillips, Goyer, Akinola, & Higgins, 2016), as well as treatment context effects (Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001). These within-patient and external factors influence every clinical setting.

Importantly, placebo effects can not only be seen in subjective perception reflected by decreased pain intensity ratings, but also have a strong representation in the human brain. Levine, Gordon, and Fields (1978) first showed that the opioid antagonist naloxone was able to remove analgesic effects of a placebo pain treatment suggesting that the biological underpinnings of the

placebo effect are influenced by endogenous opoid release. This finding was later supported by other functional brain imaging studies (Eippert, Bingel, et al., 2009; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). The first placebo imaging study used positron emission tomography (PET) to compare exogenous opioid (μ-opioid agonist remifentanil) vs. endogenous placebo induced analgesia and revealed overlapping neural activation in the rACC, including a covariation with the brainstem area of the PAG (Petrovic, Kalso, Petersson, & Ingvar, 2002). Following this, several studies related signal changes of the ascending and descending pain pathways (Figure 1) to perceived pain relief via placebo treatments (Bingel, Lorenz, Schoell, Weiller, & Büchel, 2006; Eippert, Bingel, et al., 2009; Matre, 2006; Ossipov, Morimura, & Porreca, 2014; Sevel et al., 2015; Scott et al., 2008; Wager et al., 2004). Pain processing regions such as the ACC, insula, as well as thalamus show decreased brain activation after placebo treatment which represented a neural basis of the analgesic effect supporting the reported subjective pain relief (Wager et al., 2004). Moreover, reduced neural activation in regions such as SI, SII, amygdala, and the basal ganglia was also observed (Price, Craggs, Nicholas Verne, Perlstein, & Robinson, 2007; Eippert, Bingel, et al., 2009; Lu et al., 2010). During pain anticipation, lateral and medial prefrontal cortex activation increased after a placebo administration (Wager et al., 2004; Kong et al., 2006; Lui et al., 2010; Atlas & Wager, 2012) likely reflecting preparatory mechanisms. On the spinal level, a very early ascending pain processing prior to cortical modulations, a reduced activation was observed after a placebo treatment (Eippert, Finsterbusch, Bingel, & Büchel, 2009). This was complemeted by studies reporting changed neural activation after placebo treatments in brainstem areas such as the PAG and RVM (Derbyshire & Osborn, 2009; Eippert, Bingel, et al., 2009; Fairhurst, Wiech, Dunckley, & Tracey, 2007; Khan & Stroman, 2015; Vanegas & Schaible, 2004; Zambreanu, Wise, Brooks, Iannetti, & Tracey, 2005). As these regions also play an important modulatory role in pain processing a hint to the importance of subcortical involvement during placebo analgesia processing was presented. The PAG for example is not only known to mediate pain inhibition (Jones & Gebhart, 1988), but is also involved in pain facilitatory processes (Vanegas & Schaible, 2004) which makes it a key structure of anti- as well as pronociceptive effects and a modulator in the pain system. Placebo-induced expectations assuming a pain relief due to a treatment during painful sensations were associated with functional signal increases in brain regions such as the PAG, but also in the OFC, ACC, PFC, ventral striatum,

and thalamus (Atlas & Wager, 2014).

These previous findings provide emerging evidence for several brain regions that are involved in the underlying mechanisms of placebo analgesia. Importantly, growing knowledge about the neural processes of pain and the placebo effect present the opportunity to directly measure and compare findings both in health and disease. These more objective measures nicely complement the subjective pain ratings of individual nociceptive perception preferably providing new information on possible optimization concerning interventions, health, as well as general well-being.

1.3 Bayesian integration in placebo analgesia

Placebo analgesia has been intensively studied over the last decades and several contributing factors have been identified (see 1.2). Despite this, the effect of a bodily induced pain relief is still not fully understood. Multidimensional approaches, parsimoniously accounting for several factors of underlying mechanisms of placebo effects, are highly valuable to better describe such complex phenomena. Some prior research already addressed this issue by explaining behavioral (Anchisi & Zanon, 2015) and neural aspects of pain processing within one model (Büchel, Geuter, Sprenger, & Eippert, 2014; Wager et al., 2013; Wiech et al., 2014). By applying computational modeling methods, better insight concerning individual differences is possible. For example, not only the strength of pain relief provided by a treatment but also the level of variability of prior experiences regarding the outcome can be accounted for in one general framework. Combining such complex behavioral modulators into a single model that corresponds to neural changes in the brain presents a novel and informative approach to better explain the underlying mechanisms of expectations and placebo effects in pain treatments. The Bayesian integration approach for placebo analgesia used in this thesis combines these factors to predict placebo treatment outcomes. Moreover, the model parameters are used to identify neural correlates in the brain which are processing as well as modulating the observed behavioral placebo effects.

1.3.1 The influence of variability

As described before, previous research identified various factors influencing placebo effects which are likely to affect the variance or inverse precision of treatment expectations of individuals. Yet,

no research has accounted for individual variability of treatment expectation and/or experience despite the possibility that it might explain, at least in part, the large differences observed in placebo hypoalgesia studies (Vase et al., 2009; Wager et al., 2011).

Within this dissertation, it is assumed that different variability levels in expectations and prior treatment experience are able to potentially change treatment outcomes. This has already been hypothesized in a theoretical framework (Büchel et al., 2014) but has yet to be investigated via a data-driven neuroimaging study. To exemplify this, believing in the efficacy of a pain treatment as a result of several very effective previous experiences, for instance effective physiotherapy after painful sports injuries, a new treatment will most likely be expected to have similiar pain relieving effects as the treatments before. Contrary to this, if these previous treatment outcomes were less informative due to high variations, i.e. pain-relieving as well as less effective treatment experiences, expectations about a future intervention will probably be based on unreliable highly variable prior information. These different treatment expectations will most likely influence the nociceptive perception in different ways as previous research already showed a strong influence of different verbal/visual suggestion by others (Pollo et al., 2001; Yoshida, Seymour, Koltzenburg, & Dolan, 2013). It is hypothesized that the probability of a certain pain relief due to a treatment is more predictable if it matches learned prior experiences as this makes the prior expectations a reliable source of information for future events. If prior expectations are more variable the future treatment outcome is less predictable and a certain pain relief is expected less likely.

Some research has already hinted in the direction of an influence of variability in treatment expectations showing, for example, that treatment history effects treatment outcomes as well as shows carry-over effects over time and therapeutic approaches (Kessner et al., 2013, 2014; Müller et al., 2016). Previous treatment experiences, and therefore the treatment history, are very likely to modulate expectations. However, this was investigated by mainly differentiating between positive vs. negative treatment expectation irrespective of variability concerning treatment efficacy within one or across different treatments. Another study investigated the influence of different verbal instructions to manipulate patients' treatment response expectancies (Pollo et al., 2001). Their results revealed differences in placebo analgesic effects, based on the precision of prior expectation. Patients who had the placebo introduced as a potent

painkiller showed the largest analgesic effect compared to two other more variable groups being either non-informed or having only a 50% chance of receiving a painkiller. These important findings also hint to an influence but cannot reveal how levels of expectation variability can translate into inter-individual differences in placebo hypoalgesia. This previous study induced uncertainty probabilities in expectations only via verbal suggestion and was therefore not able to refer their findings to variability differences in prior treatment experiences.

Interestingly, pain literature shows that the degree of neural activity in several pain-related brain regions is closely related to the subjective pain intensity ratings of participants (Coghill & Eisenach, 2003; Coghill, 2010; Schulz, Zherdin, Tiemann, Plant, & Ploner, 2012; Tracey et al., 2002). This reflects perceptual intensity coding in pain processing not only in participant's subjective ratings but also on a more objective, neuronal level. Higher reported pain intensities showed increased neural activation in the ACC, SI, insula, and PFC compared to lower reported pain intensities, which were related to decreased activation in these areas. This suggests that ratings as well as neural activation seem to be closely related and should be investigated accordingly. A combination of both types of data will shed more light on the underlying mechanisms instead of exploring them independent of each other.

Accordingly, some imaging study findings suggest, that variability coding also has a neural representation in the brain. One study found a relationship between the processing of vicarious information and the PAG during painful stimulation (Yoshida et al., 2013). Prior to a painful heat stimulus, participants were shown putative pain ratings from other participants regarding the same heat intensity they were about to receive - this priming process included either low variability in rating between the alleged participants, or high variability in the rating of painfulness for the same stimulus. A strong hyperalgesia effect, an increased sensitivity to nociceptive stimulation, was observed in participants who showed high susceptibility to induced variability during this vicarious observation task. This means that the observation of an increased level of variability in vicarious pain ratings also increased the individual's perceived pain. Moreover, the more certain (i.e. less variable) these vicarious pain ratings were, the more shifted the individual's own perception was driven towards the respective direction of the observed pain intensity. The authors related this influence of uncertainty to neural signal changes in the PAG which represents a well-known modulatory pain processing region (Jones & Gebhart, 1988; Vanegas

& Schaible, 2004). An increased susceptibility to uncertainty-induced hyperalgesia was related to higher activation in the PAG reflecting increased signaling in this area.
Supporting this, another study showed that the PAG was involved in the modulation of expected probability of pain in a pain avoidance task investigating prediction error coding (Roy et al., 2014). Prediction errors are phenomena reflecting the amount of a certain mismatch between the expected and actual outcome of an event. Assuming that prediction error and variability level coding in expectations are distinct but share related aspects of modulatory functions, the results of this study also suggest that the PAG is involved in the processing of variability in painful sensations.
In order to begin closing the gap of missing research concerning the important, and as of now mostly neglected, influence of variability in prior treatment expectations on pain and the placebo effect, this dissertation especially focused on this relationship: By combining behavioral, neuroimaging, as well as computational methods using a new theoretical Bayesian framework (Büchel et al., 2014), the complex interplay of pain perception can be parsimoniously accounted for within one mathematical model.

1.3.2 The Bayesian framework

A rising interest in models that are able to account for several modulating factors in order to holistically describe a certain phenomenon, particularly in the field of neuroimaging, lead to the use of Bayesian integration in different research areas such as sensorimotor learning (e.g. Körding & Wolpert, 2004; Körding, Ko, & Wolpert, 2006), visual and auditory perception (e.g. Battaglia, Jacobs, & Aslin, 2003; Butler, Smith, Campos, & Bülthoff, 2010), as well as somatosensory and nociceptive processing (e.g. Anchisi & Zanon, 2015; Büchel et al., 2014). Bayesian integration became a helpful tool to account for the influence of variability and uncertainty, especially used to investigate and better understand perceptual, sensorimotor, and psychophysical mechanisms (Knill & Pouget, 2004; O'Reilly, Jbabdi, & Behrens, 2012). The basic idea is that the brain constantly combines incoming sensory information with previously acquired knowledge, which was built from prior experiences, to generate new expectations about the environment in order to minimize future surprise (Feldman & Friston, 2010; Friston, 2010; Friston et al., 2009). This concept is based on probability theory and aims to predict the likeli-

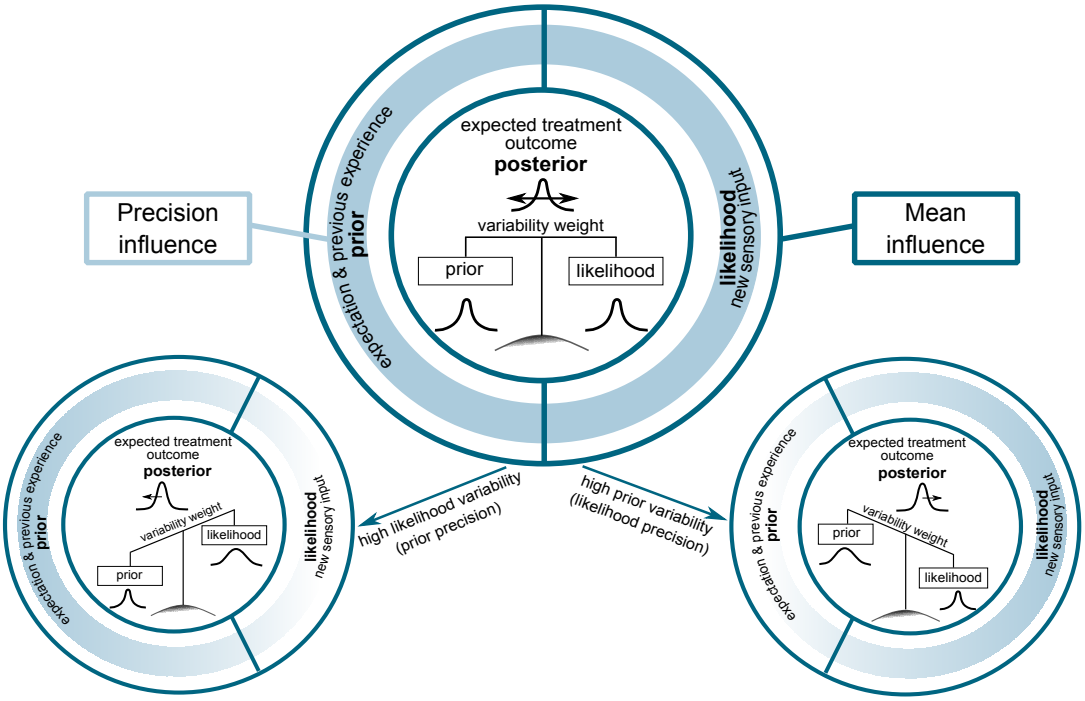


Figure 2. Bayesian integration principle. The large middle circle displays prior and likelihood as identical in terms of variability levels (filled light blue circle). For that reason, the two means (dark blue outer circle) are weighted as equally informative which results in a posterior distribution that lies exactly in the middle of both means. The smaller left circle illustrates a prediction including a more precise prior compared to a highly variable likelihood in which the posterior is drawn into the direction of the prior as the mean is weighted and perceived as more informative. The smaller right circle shows this vice versa for a precise likelihood compared to a variable prior.

hood of the outcome of a certain event using Bayes theorem (Bayes & Price, 1763). Section 2.3 describes the mathematical basis for Bayesian integration in more detail. In general, Bayesian integration optimally integrates previous experiences and expectations, the *prior*, with incoming sensory information, the *likelihood*, and makes a prediction about the outcome of a certain event, the *posterior* (Figure 2). For that reason it is assumed that the posterior is proportional to the product of prior and likelihood. Within this approach, not only the mean of prior and likelihood are combined to predict the posterior, but both are weighted by their respective level of variability. Importantly, the prediction of the posterior will always be driven in the direction of more precise information, which can be either the prior or the likelihood.

Transferring this into the context of pain and placebo analgesia, previous treatment experiences and expectations serve as the prior which is illustrated by a Gaussian probability distribution reflecting the amount of pain relief as well as the level of variability concerning treatment efficacy.

A new incoming untreated pain experience reflects the likelihood distribution. By integrating two Bayesian key components, the prior and the likelihood, this framework (Büchel et al., 2014) offers the opportunity to explain the outcome of a new treatment experience, including the placebo effect, by predicting one's perceived pain as the model posterior. The rationale behind this framework is to present a formal model which incorporates prior treatment expectation (prior) with an untreated pain sensation as reference (likelihood) to predict a certain treatment outcome and the corresponding pain relief (posterior). Figure 2 illustrates this framework in more detail. Depicted are three examples of different Bayesian posterior predictions resulting from varying variability levels of the prior and likelihood. Investigating these different individual model features via model-based fMRI (Gläscher & O'Doherty, 2010) will help to identify possible neural correlates and their underlying processing mechanisms. This makes the Bayesian integration framework of sensory processing and placebo analgesia a promising candidate to parsimoniously account for several modulating factors of these phenomena.

1.4 Principles of functional magnetic resonance imaging (fMRI)

In general, neural imaging techniques aim to visualize the structure and function of the human brain, ideally by non-invasive procedures in order to better understand the biological mechanisms that shape behavior and anatomy in health as well as disease. All imaging methods, for example, electroencephalography (EEG), positron emission tomography (PET), magnetoencephalography (MEG), computer tomography (CT), and functional magnetic resonance imaging (fMRI) offer advantages as well as disadvantages. MRI was used in this dissertation as it provides high spatial as well as reasonable temporal resolution of the structure and function of the human brain. By using strong magnetic fields, electric field gradients, and radio waves, MR signals allow to construct gray-scale images via a readout of the spatial distribution of spinning hydrogen protons reflecting differences in tissue (structural) or hemodynamic properties (functional) of the brain. A structural MRI reflects anatomy including the brain surface as well as deeper brain structures such as the brainstem via different hydrogen proton densities in the several tissue types (e.g. gray matter, white matter, cerebrospinal fluid). Functional MRI is defined as reflecting changes in the regional cerebral blood flow (rCBF) of active brain areas which is thought to be increased due to any information processing. This provides highly oxygenated blood as

well as glucose to brain areas that need energy to process the incoming information (Logothetis, Auguth, Oeltermann, Pauls, & Trinath, 2001). The blood-oxygenation-level-dependent (BOLD) signal reflects the magnetic properties of oxygenated (less magnetic/diamagnetic) and deoxygenated (more magnetic/paramagnetic) hemoglobin in the blood (Ogawa et al., 1992). An increased blood flow due to increased local brain activation causes a proportional decrease of deoxygenated hemoglobin and the so-called hemodynamic response function (HRF) reflecting MR signal increases. The HRF follows a typical physiological cycle after the onset of an event starting with a dip of oxyhemoglobin followed by a rapid increase of the oxygen rate, reaching a maximum after approximately 5-6s. After this, the return to baseline is characterized by a signal decrease and a short overshoot in the end (Fox & Raichle, 1986; Logothetis et al., 2001) resulting in an overall HRF duration of approximately 16-18s.

Commonly, fMRI images are acquired via T2* echo-planar imaging (EPI) measuring the brain slice by slice per excitation pulse and reconstructing a 3D version of it afterwards. Such a reconstructed low-resolution functional image of the whole brain is called a volume, image, or scan and consists of several brain slices being segmented into voxels, small cuboid elements usually with an edge length of 1-3mm. The gray-scale signal changes per voxel from volume to volume over time display the neural activity which is related to the specific information being processed. By using statistical analyses, these changes can be compared with other processes of interest (see section 2.5.4). For more detailed information on the underlying physiological mechanisms and statistical analyses of fMRI see Huettel, Song, and McCarthy (2009).

1.5 General aims

The overall aim of this dissertation is to contribute to a better understanding of the emergence and maintenance of placebo analgesia. This is done by following recent approaches which not only account for one but several modulating factors of pain perception (Anchisi & Zanon, 2015; Büchel et al., 2014; Wager et al., 2013; Wiech et al., 2014). Using optimal Bayesian integration in placebo hypoalgesia, a new framework is tested in healthy participants to present behavioral and neurobiological correlates of treatment variability and placebo effects. This model aims to predict placebo treatment outcomes by not only investigating mean pain intensities but also explicitly accounting for variability of prior treatment information (i.e. expectations and ex-

periences). Variability in treatment expectations may represent one specific modulator driving large differences in placebo effect magnitudes across studies (Vase et al., 2009; Wager et al., 2011).

This dissertation consists of four studies. **Study 1** and **2** are considered as groundwork concerning the main **Studies 3** and **4**. The following objectives are addressed in the respective studies:

- **Study 1** investigated the difference between constant vs. variable painful stimuli on pain perception and how this influences subjective measures such as ratings ($N_1 = 15$).
- **Study 2** aimed to explore placebo effects in two groups comparing the influence of constant vs. variable prior treatment expectation on treatment outcomes using a conditioning procedure to manipulate variability levels ($N_2 = 41$: $N_{2_{CTE}} = 21$, $N_{2_{VTE}} = 20$; constant treatment expectation - CTE, variable treatment expectation - VTE).
- **Study 3** used the optimized experimental design of **Study 2** to investigate the neurobiological correlates of treatment variability in placebo hypoalgesia by combining behavioral data of the Bayesian integration model with functional resonance imaging especially focusing on the modulatory influence of the PAG ($N_3 = 62$: $N_{3_{CTE}} = 31$, $N_{3_{VTE}} = 31$). Moreover, informed by the previous two studies, the mathematical basis of the yet only theoretical Bayesian framework for placebo analgesia (Büchel et al., 2014) was created and implemented within this study.
- **Study 4** explored the validity of the mathematically implemented Bayesian model of **Study 3** in a large placebo sample, which was acquired over years at the Department of Systems Neuroscience (University Medical Center Hamburg-Eppendorf), to investigate whether a translation to other experimental placebo approaches is feasible ($N_4 = 714$).

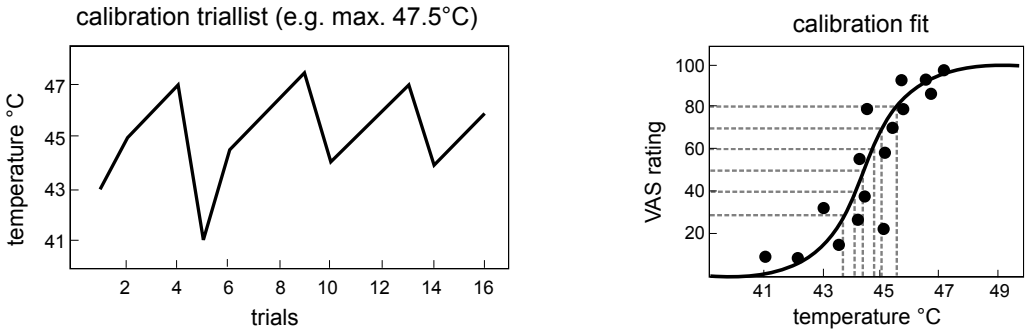
2 General methods - all studies

2.1 Participants

All participants were recruited by online advertisements and had no history of psychiatric or neurological illness. General exclusion criteria in all studies were neurological and/or pain related diseases, psychological disorders, skin afflictions, substance abuse, as well as current medication. All studies were approved by the Ethics Committee of the Medical Board Hamburg (Germany) and conducted in accordance with the Declaration of Helsinki. Every subject was remunerated for participation and gave written informed consent prior to the experiment. All studies used an experimental deception to investigate the effect of interest (e.g. to induce placebo effects). In a post-experimental debriefing, participants were fully informed about the real purpose of the experiment including the option to withdraw their acquired data from the study. Information that were given to boost expectations concerning a used placebo treatment were also revealed at the end of the experiment to fully undeceive every participant.

2.2 Study design and task

All four studies used heat stimulation to investigate pain. **Studies 1-3** were designed, performed, and analyzed specifically for this dissertation. **Study 4** was designed and performed by other experimenters and data collection lasted approximately four to five years in total. The data of **Study 4** was used to test the applicability of the Bayesian integration approach on other experimental placebo designs in a sufficiently large sample. For that reason, **Studies 1-3** used similar experimental tasks that are described below whereas **Study 4** used a slightly different but comparable approach (see 3.4.2). If not stated otherwise, the following general descriptions of the experimental design and task only apply to **Studies 1-3**. To induce pain, thermal heat stimuli were presented in all four studies using so-called *PATHWAY* thermodes by Medoc, Ramat Yishai, Israel (**Studies 1-3**: model *Contact Heat-Evoked Potential Stimulator - CHEPS* with a stimulation diameter of 27 mm, temperature range of 30°C to 55°C, rapid heating rate of up to 70°C per second, cooling rate of 40°C per second; **Study 4**: model *Advanced Thermal Stimulator - ATS* with a stimulation surface of 30 x 30 mm, temperature range of 0°C to 55°C, heating/cooling rate up to 8°C per second). These devices offer very precise



(a) Representative calibration triallist. In total, four different triallists were used dependent on the individual pain threshold of each participant (max. 45.5, 46.5, 47.5 → depicted, 48.5°C).

(b) Schematic representation of sigmoidal fit of calibration ratings. A Weibull function was fitted to the rating data ($N_{\text{trials}} = 16$) offering individual predictions of VAS ratings to corresponding temperatures. Dashed lines display corresponding heat intensities to 30, 40, 50, 60, 70, and 80% of pain tolerance. *VAS, visual analogue scale.*

Figure 3. Heat calibration stimuli and fitting procedure.

temperature deliveries and are therefore optimal to induce different heat pain intensities.

Prior to every experiment, a calibration procedure was performed. This was done to identify the individual's heat pain threshold as well as potential abnormal pain perception and familiarize the subject with the heat stimuli and rating procedure. **Studies 1-3** used identical calibration procedures which are described as follows: First, basic pain thresholds were assessed performing a limits procedure by slowly increasing temperature until the heat was reported as just painful by the participant. This was done three times and the mean of these three threshold measures was used as an anchor point ('*just painful*') for the actual calibration procedure trials. The heat calibration consisted of ten (**Study 2**) or sixteen (**Studies 1** and **3**) different intensity trials delivered in a pseudorandomized order on the right volar forearm (see Figure 3a). One trial consisted of a thermal stimulus with a rapid heating rate of 70°C per second, the same duration as a corresponding experimental trial (**Study 1** 5s, **Studies 2** and **3** 8s), and a cooling rate of 40°C per second. Each heat stimulation was rated concerning its pain intensity using a visual analogue scale (VAS) rating procedure to collect subjective pain perception in the form of explicit ratings. '*No pain*' as the left and '*unbearable pain*' as the right visual anchor points (corresponding to a VAS of 0 to 100) were used. The rating scale was instructed being the range of subjective painfulness of each individual starting at the level of just painful (corresponding to VAS 1). Warm but non-painful stimulation was supposed to be rated as '*no pain*' (correspond-

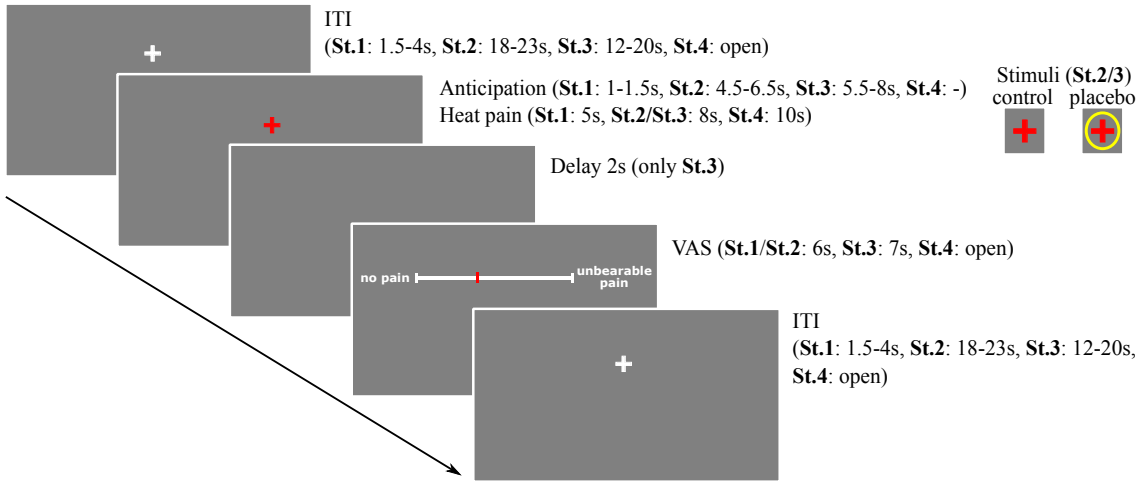


Figure 4. Experimental example trial. Representation of one experimental trial showing each corresponding duration separately for **Studies 1-4**. The two cues used in **Studies 2** and **3** are also depicted. *ITI, inter-trial-interval; St.x - Study number.*

ing to 0). '*Unbearable pain*' was instructed being painful enough that the participant would like to remove the thermode from their skin. This rating procedure was not only used for the calibration but also for all experimental heat trials.

To predict individual temperatures corresponding to different levels of subjective pain intensities in the experiment, a sigmoidal function was fitted to the ratings (see Figure 3b). This was done to ensure that individual pain ratings, despite possible temperature differences, were comparable across subjects. The used heat intensities were defined as percentage of the individual pain threshold: **Study 1** - 40%; **Study 2** and **3** - 30, 50, and 70%; **Study 4** - 40, 60, and 80%. Stimulation sites of **Studies 1-3** were the right volar forearm for the calibration procedure and the left volar forearm for the actual experiment using a velcro strap to attach the thermode to the skin. This was done to avoid strong habituation or sensitization effects. Each trial consisted of an inter-trial-interval (ITI), followed by a short anticipation phase, the painful heat stimulation, and the VAS rating procedure. The ITI was represented by a white fixation cross. For the anticipation cue, the cross' color changed to red. The cue remained on screen during heat stimulation and disappeared after cooling down. **Studies 2** and **3** included an additional cue corresponding to the placebo treatment. Dependent on the condition, the participant either saw the red cross (control) or a red cross surrounded by a yellow circle (placebo). Subsequently, the VAS appeared and subjects rated and confirmed their perceived painfulness. For a detailed

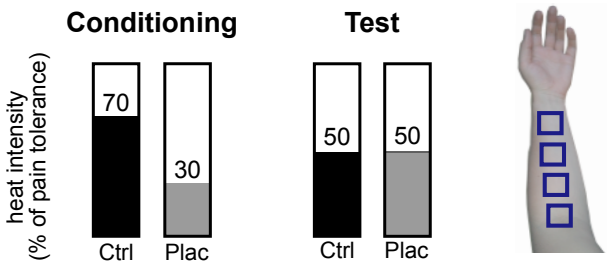


Figure 5. Design of placebo experiment. Displayed is an example with heat intensities corresponding to individual pain tolerance levels of 70% and 30% for the conditioning and 50% for the test phase as well as four skin patch positions for experimental heat stimulation per block. *Ctrl, control condition; Plac - placebo condition.*

depiction of an experimental trial see Figure 4. Note that timings are slightly different across studies.

Studies 2-4 included a placebo block-design. It followed a well-established placebo analgesia paradigm in which both, expectation and conditioning components were used (Colloca & Benedetti, 2006; Eippert, Bingel, et al., 2009; Geuter et al., 2013; Klinger et al., 2007; Montgomery & Kirsch, 1997; Price et al., 1999; Wager et al., 2004). This procedure involved a conditioning as well as a test phase which each consisted of two conditions: a placebo treatment and a non-treated control condition (four blocks in total for the whole experiment). Four different skin patches were used for the experiment. To minimize possible order confounds, the stimulation positions and order of blocks (first placebo or control) were counterbalanced and pseudo-randomized across subjects in all studies. A treatment was always introduced to the participants being described as well-established and known to reduce pain. During the conditioning phase, expectations concerning the respective experimental placebo treatment were induced. Participants expected the same heat intensity across all heat stimuli of the experiment of approximately 70-80% of the individual pain tolerance. Changes of the perceived pain were believed to be caused by the active treatment effect. However, during conditioning, a higher pain intensity for the non-treated control condition compared to the placebo treatment condition was applied (see Figure 5 for an example). This manipulation procedure served to enhance expectations regarding the placebo treatment and its effectiveness concerning heat pain relief. In other words, the pain relief in the placebo compared to the control condition leads to the fact that the treatment is attributed with good efficacy. Importantly, the participants were not aware of the different heat intensities. In the following test phase, the created treatment

expectation was now compared to the non-manipulated control condition. For both conditions, placebo and control, identical heat stimuli were applied. As stimulation was physically the same in both blocks, placebo effects were assessed by directly comparing pain ratings of the two conditions. If there was a placebo effect present, the VAS ratings for the placebo condition would be reduced compared to the control condition. This would reflect a pain relief only due to the generated expectation effect of the treatment experience during the conditioning phase.

2.3 Bayesian integration framework in placebo analgesia

This section describes the mathematical rationale behind the Bayesian integration framework in placebo hypoalgesia. A computational model was used to analyze how individual painfulness of a treatment outcome is shaped by prior treatment expectation and experience (prior) as well as new incoming sensory information (likelihood). It was especially focused on the level of variability of the prior as a modulator for the treatment outcome. Addressing this, Gaussian probability density functions (pdf) were used to predict the painfulness of the test phase placebo condition, i.e. the placebo treatment outcome. Within such an approach, the mean as well as the variance can be inserted in the model prediction. An unconstrained non-linear optimization algorithm (implemented in MATLAB's fminsearch function) was used to fit Gaussian distributions to the rating data of the conditioning placebo (prior) and test phase control condition (likelihood) to predict the test phase placebo ratings (posterior). As both conditions of the test phase are identical in terms of heat intensity, this enables the use of the control condition as the likelihood as the objective painfulness is identical to the sensory input of the placebo condition. Importantly, this allows for the comparison of the model prediction for the posterior distribution with the actual observed data. Bayes' theorem (Bayes & Price, 1763) states that the posterior is proportional to the product of the prior and the likelihood:

$$posterior \propto prior * likelihood \tag{2.1}$$

Translating this into Gaussian distributions, Bayes' theorem can be displayed as:

$$N(\mu_{post}, \sigma^2_{post}) \propto N(\mu_{prior}, \sigma^2_{prior}) * N(\mu_{like}, \sigma^2_{like}) \tag{2.2}$$

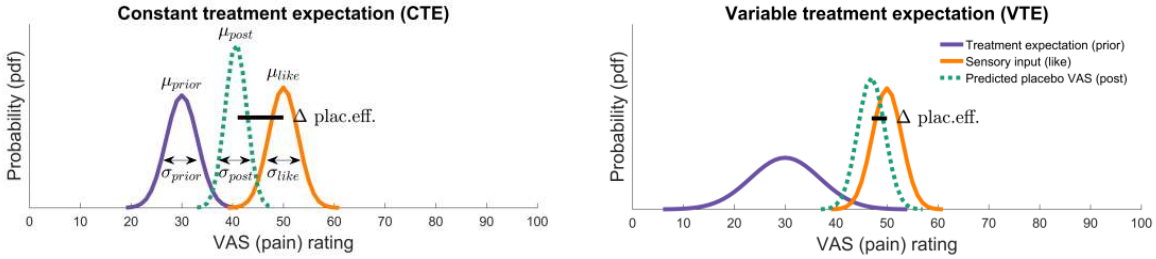


Figure 6. Bayesian integration prediction. Posterior prediction for a constant and variable prior illustrated by Gaussian probability density functions. The different prior distributions (violet) reflect precise (left panel) and variable (right panel) treatment expectations both around a mean of 30 (μ_{prior}) but with different standard deviations (σ_{prior}). The likelihood distribution (orange) is displayed identical for both groups to illustrate the influence of variability differences in the prior expectations. The posterior distribution (dashed green) reflects the model prediction of the perceived pain of a new treatment experience. Prior and likelihood are weighted by their relative variability level which draws the respective prediction into the direction of the more precise distribution. The hypothesized placebo effect ($\Delta = \mu_{like} - \mu_{post}$) is therefore larger for individuals with less (CTE) compared to higher (VTE) variability in treatment expectations. *pdf, probability density function; VAS, visual analogue scale; like, likelihood; post, posterior.*

Based on the parameters of the Gaussians, the posterior was estimated according to Equations 2.5 and 2.6. Figure 6 displays these Gaussian distributions via probability density functions (pdf) including examples for a constant/precise vs. variable/uncertain prior and the respective posterior prediction. As the prediction is always drawn into the direction of the more precise information, the hypothesized magnitude of the placebo effect is predicted larger for more consistent vs. more variable prior expectations. For illustration purpose, the likelihood variance is displayed as constant in both examples. However, the interplay of the variability levels of both, the prior and the likelihood, defines the weighting of the two means for the posterior prediction. Therefore, a so-called *attraction weight* was created (w_{prior}) to account for individual differences in combining the variability levels of prior expectations and new incoming sensory information. This weight reflects the relative influence of prior over likelihood variability displayed via the corresponding precision level of both (i.e. inverse variance $\frac{1}{\sigma^2_{prior}}$ and $\frac{1}{\sigma^2_{like}}$).

$$w_{prior} = \frac{\frac{1}{\sigma^2_{prior}}}{\frac{1}{\sigma^2_{prior}} + \frac{1}{\sigma^2_{like}}};\ 0 \leq w_{prior} \leq 1 \tag{2.3}$$

$$w_{like} = \frac{\frac{1}{\sigma^2_{like}}}{\frac{1}{\sigma^2_{prior}} + \frac{1}{\sigma^2_{like}}};\ 0 \leq w_{like} \leq 1 \tag{2.4}$$

$$\mu_{post} = \mu_{prior} * w_{prior} + \mu_{like} * w_{like};\ w_{prior} + w_{like} = 1 \tag{2.5}$$

$$\sigma_{post} = \sqrt{\frac{\sigma^2_{prior} * \sigma^2_{like}}{\sigma^2_{prior} + \sigma^2_{like}}} \tag{2.6}$$

The *attraction weight* w_{prior} is larger the less variable, and therefore the more precise, the prior is compared to the likelihood contribution is. In other words, the more variable prior treatment expectations and experiences are the less likely the treatment outcome is to be driven into the direction of those expectations. This parameter also includes the assumption that a certain level of treatment variability is necessary to induce placebo effects as absolute predictability of the treatment outcome would not induce expectation processes (De La Fuente-Fernández, Schulzer, & Stoessl, 2004). For a treatment experience that is too far away from the prior expectation would make it unbelievable concerning the individuals subjective environment and would not induce a placebo effect.

2.4 Data acquisition

In the following, data acquisition of **Studies 1-3** is described (if not stated otherwise). For the presentation and triggering of stimuli as well as the recording of pain ratings, Matlab (Mathworks, Natick, MA, USA) and the open-source Matlab based Psychophysics Toolbox 3 was used (Brainard, 1997; Pelli, 1997). **Study 4** was performed using the *Presentation* software (version 11.3; Neurobehavioral Systems Inc, Albany, CA) for visual stimulus presentation and recording of pain ratings. In **Studies 2** and **3** additional skin conductance response (SCR) data was acquired on the distal and proximal hypothenar of the left hand. The two electrodes (Ag/Ag-Cl) were placed on dermatome C8. In **Study 2**, a V-Amp 16 digital DC amplifier (Brainproducts, Gilching, Germany) in combination with a galvanic skin response (GSR) module BP-BM-30 (Becker Meditec, Karlsruhe, Germany) was used to measure SCR. Data were recorded via the software Brainvision Recorder 1.20 (Brainproducts, Gilching, Germany) with a sampling rate of 250Hz. Technical details for SCR data acquisition for **Study 3** differed as

this was an experiment performed in the magnetic resonance scanner. A CED 2502 (Cambridge Electronic Design Limited, Cambridge, UK) was used to amplify and a CED micro 1401 to digitalize skin conductance signal at 1000 Hz. The data was recorded by the CED software Spike 2. Mainly to monitor participant's well-being, respiration and heart rate were recorded during scanning as well using the Expression patient monitoring system (Invivo Corporation, Orlando, FL, USA). Only for **Study 3**, magnetic resonance imaging (MRI) data were acquired using a 3T Magnetom Trio scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. Blood oxygenation level dependent (BOLD) responses were measured using a T2* sensitive echo planar imaging (EPI) sequence. A brain volume consisted of 38 transversal slices with a voxel size of 2x2x2mm^3 and a 1mm gap (repetition time: 2.35s, echo time: 26ms, flip angle: 80°, field of view 224x224mm, GRAPPA PAT-factor: 2, reference lines: 48). Volumes were tilted approximately 30° relative to AC-PC line to allow coverage of most of the brainstem area. Considering T1 saturation, the first 4 volumes of every session were discarded. To account for B0 inhomogeneity, prior to each session, B0 field maps were also acquired (40 slices, voxel size: 3x3x3mm^3 , repetition time: 398ms, short echo time: 4.31ms, long echo time: 6.77ms , flip angle: 40°, field of view 216x216mm). Additionally, a high-resolution anatomical T1-weighted image was acquired for each subject (MPRAGE sequence, voxel size: 1x1x1mm^3).

2.5 Analyses

2.5.1 Behavior

Data analysis for all four studies was performed using Matlab (2014a, Mathworks, Natick, MA, USA) and SPSS 24 (IBM, Armonk, NY, USA). Referring to the statistical analysis, a frequentist approach was applied to test for main and interaction effects of all experiments. A statistical significance threshold of $p \leq 0.05$ was used. The placebo effect was calculated by subtracting both mean pain ratings of the two test phase conditions (control - placebo). The level of variability regarding prior treatment expectations was defined as the variance of the pain ratings in the placebo condition of the conditioning phase. Higher precision concerning a possible treatment outcome would therefore be reflected by a smaller variance within these ratings. Each correlation analysis was estimated by means of the Pearson's product-moment correlation coefficient (r). Two-sample t-tests were used to investigate comparisons between

two independent samples (e.g. group comparisons of prior treatment variability levels).

2.5.2 Bayesian model selection (BMS)

This analysis was performed to investigate how individual painfulness of a treatment outcome is based on prior expectations and experiences and how this is related to treatment variability. To test the proposed Bayesian integration in placebo hypoalgesia, the data was analyzed using Bayesian model comparison. This was only applied in **Studies 3** and **4**. Such an approach compares models of consideration based on a ratio called the Bayes factor. A Bayes factor greater than 3 indicates at least a moderate evidence for one model over another reflecting the winning model to be 3 times more likely to have produced the observed data than the competing model (Kass & Raftery, 1995; Lee & Wagenmakers, 2013). Within this dissertation, two models were designed either assuming an influence of prior treatment expectation and experience on placebo treatment outcomes, the Bayesian integration model, or not, the Null model. The Null model served as a control only differing in terms of the prior. Assuming no influence of the treatment experience during conditioning, as it is presumed for the Null model, participants would expect all stimuli of the conditioning phase to be on a level of 70-80% pain tolerance, irrespective of the condition. This was the intensity that the subjects were told would be used for all trials of the experiment. For that reason, the non-manipulated conditioning control ratings were used as a prior for the Null model. This allowed for the comparison of the Bayesian integration model with the Null model by focusing explicitly on the influence of the prior, including its precision level concerning prior treatment expectations. To compare the two model fits, Bayes factors were computed for each subject individually given the observed data. Bayes factors hereby represent the evidence for favoring one model over another indicated by a ratio calculated from the two model evidences. This is reflected by the following equation for the Bayes factor favoring the Bayesian over the Null model:

$$BF_{10} = \frac{p(D|\mu_{Bay}, \sigma^2_{obs}, \sigma^2_{Bay})}{p(D|\mu_{Null}, \sigma^2_{obs}, \sigma^2_{Null})} \tag{2.7}$$

and the Bayes factor favoring the Null over the Bayesian model

$$BF_{01} = \frac{p(D|\mu_{Null}, \sigma^2_{obs}, \sigma^2_{Null})}{p(D|\mu_{Bay}, \sigma^2_{obs}, \sigma^2_{Bay})}. \tag{2.8}$$

The model evidence which is used to calculate the Bayes factor is referred to as the marginal likelihood representing the probability that the observed data was produced by the model of consideration (Demichelis, Magni, Piergiorgi, Rubin, & Bellazzi, 2006; Murphy, 2007):

$$p(D|\mu_{M_x}, \sigma^2_{obs}, \sigma^2_{M_x}) = \int \left[\prod_{i=1}^{n} N(x_i|\mu_{obs}, \sigma^2_{obs})\right] N(\mu_{obs}|\mu_{M_x}, \sigma^2_{M_x}) d\mu_{obs}$$

$$= \frac{\sqrt{\sigma_{obs}}}{(\sqrt{2\pi}\sigma_{obs})^n \sqrt{n\sigma^2_{M_x} + \sigma^2_{obs}}} exp\left(\left(-\frac{\sum_i x_i^2}{2\sigma^2_{obs}} - \frac{\mu^2_{M_x}}{2\sigma^2_{M_x}}\right) + \left(\frac{\frac{\sigma^2_{M_x} n^2 \mu^2_{obs}}{\sigma^2_{obs}} + \frac{\sigma^2_{obs}\mu^2_{M_x}}{\sigma^2_{M_x}} + 2n\mu_{obs}\mu_{M_x}}{2(n\sigma^2_{M_x} + \sigma^2_{obs})}\right)\right) \tag{2.9}$$

D - observed VAS data of placebo test
μ_{M_x} / $\sigma^2_{M_x}$ - mean/variance of Bayesian integration or Null model
σ^2_{obs} - observation noise
μ_{obs} - observation mean (mean of observed VAS data of placebo test)
n - trials per condition

Therefore, for each of the two models, marginal likelihoods were calculated and then, first, translated into Bayes factors (see Equation 2.7 and 2.8) and second, translated into posterior model probabilities for each subject individually. Assuming that both models of consideration were equally plausible a priori, Bayes factors can be directly translated into posterior model probabilities:

$$p(M_{Bay}|D) = \frac{BF_{10}}{(BF_{10} + 1)} \tag{2.10}$$

$$p(M_{Null}|D) = \frac{BF_{01}}{(BF_{01} + 1)} \tag{2.11}$$

Next, the two models were compared across subjects. In a first step, the positive evidence ratio (PER) was computed. This heuristic serves as an indicator of which model is better at a group level only including subjects that show Bayes factors larger than 3 for either one of the compared models (Stephan & Penny, 2007). The outcome is a ratio of subjects for which the Bayes factor in favor of the Bayesian integration model ($BF10$) is greater than 3, and the respective number of subjects favoring the Null model ($BF01$) with a Bayes factor greater than 3. This ratio reflects a more descriptive analysis of the model comparison. In a second step, single subject log model evidences, i.e. the log marginal likelihoods (see Equation 2.9), were used to calculate

the overall conditional expectations of model probabilities $\langle r_{M_x} \rangle$ as well as the exceedance probabilities φ_{M_x} of the model comparison using a random effects (RFX) approach for group studies (Rigoux, Stephan, Friston, & Daunizeau, 2014; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). This procedure (implemented in SPM's spm_BMS function) assumes that subjects may use different models and thereby allows to control for possible group heterogeneity. The posterior model probability $\langle r_{M_x} \rangle$ reflects the expected probability of a model that the data was generated for a randomly selected subject. The exceedance probability φ_{M_x} represents a measure of belief about the posterior probability that a particular model is more likely than all other models of consideration. Both overall probabilities of $\langle r_{M_x} \rangle$ and φ_{M_x} sum to one over the models of consideration.

$$\begin{aligned} \langle r_{Bay} \rangle + \langle r_{Null} \rangle &= 1 \\ \varphi_{Bay} + \varphi_{Null} &= 1 \end{aligned} \tag{2.12}$$

Further, correlations between the model parameters and the placebo effect were estimated by means of the Pearson's product-moment correlation coefficient (r). Additionally, a multiple linear regression was estimated to describe the relationship between the placebo effect and the *attraction weight* in more detail. To predict the placebo effect magnitude the two *attraction weight* components were inserted into the regression: the variability of treatment expectation (σ^2_{prior}) and new sensory input (σ^2_{like}).

2.5.3 Physiology

SCR data collected in **Studies 2** and **3** was analyzed using the Matlab based toolbox Ledalab, Leipzig electrodermal activity laboratory 3.4.8 (Benedek & Kaernbach, 2010a). SCR served as an additional measure of heat intensity coding as it represents a more objective method to assess pain perception in comparison to subjective ratings (Colloca, Benedetti, & Pollo, 2006; Geuter, Gamer, Onat, & Büchel, 2014). This measure reflects autonomic arousal which is quantified as a post-stimulus increase in skin conductance in relation to the pre-stimulus conductance. Higher arousal is assumed to be observed with higher heat intensities. It cannot serve as a reflection of valence as arousal is associated with both, appetitive as well as negative events without differentiating between them (Rhudy, Williams, McCabe, Russell, & Maynard, 2008).

After downsampling to 100Hz due to data processing methodology, the phasic skin conductance response was computed by applying a continous deconvolution analysis, CDA (Benedek & Kaernbach, 2010b), as implemented in Ledalab. This was used to assess the autonomic arousal associated with the onset of pain at the single subject level. In a following step, the phasic responses were averaged separately for the two conditions per session within a temporal window of interest both within and across subjects. Typically, a reaction onset to a stimulus in skin conductance is expected to start between 900-4000ms. Skin conductance is reported in μSiemens.

2.5.4 Functional magnetic resonance imaging

FMRI data and statistical analyses were performed using statistical parametric mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK). Only **Study 3** included imaging data. The experiment of this study included two sessions (conditioning and test phase) with two conditions each (placebo and control) and was designed as a block experiment resulting in four runs per participant. The first four images of each run were discarded prior to further analyses. Preprocessing consisted of motion correction (realignment and field map correction), coregistration of the anatomical T1 image to the functional scans, segmentation of the anatomical T1 image producing DARTEL-imported native tissue class images and in the next step a flow field of the T1 image in Montreal Neurological Institute (MNI) standard space (IXI555_MNI152 template of VBM12 toolbox) using the DARTEL toolbox as implemented in SPM12. First-level analysis was performed in subject-specific native space. Data were high-pass filtered with a 128s cut-off period and corrected for temporal autocorrelations using a first-order autoregressive model. FMRI data analysis was based on a general linear model (GLM) approach as it is implemented in SPM12. The first-level design matrix of each subject consisted of ten regressors for each session, resulting in a total of forty regressors: anticipation cue onset (5.5-8s), pain onset (8s), VAS rating (7s), six motion regressors obtained during realignment, and one session constant. Each regressor, except the six motion regressors, was modeled using a boxcar function and subsequently convolved with the hemodynamic response function. After model estimation, t statistics for each voxel were calculated. All ensuing output images were then normalized to MNI space using the previously obtained subject-specific DARTEL flow field, smoothed with an

6mm (FWHM) isotropic Gaussian kernel, and then used for second-level analyses. Basic main effects of pain as well as the placebo effect were investigated as a quality check. For this, the two test phase conditions were pooled and compared to baseline to display areas that are typically involved in the processing of pain such as SI, SII, insula, ACC, thalamus, and the PAG.

3 Study methods and results

3.1 Study 1 - Constant vs. variable pain perception

The first study investigated two different variability levels in heat intensities across painful stimuli, constant vs. variable, aiming to detect the influence of these levels on subjective pain ratings in a within-subjects design. A constant level was chosen to observe how subjective pain perception and corresponding ratings vary naturally. Importantly, subjects were not aware of the difference between these two levels presented via two independent sessions. This was done to first focus on perceptual rather than expectancy-driven effects and investigate whether temperature changes are subjectively experienced, reflected in more variable pain ratings in the variable session, but not explicitly recognized. Therefore, the effect on pain ratings was examined via the variables mean pain ratings as well as rating variances across trials within a session. It was hypothesized that mean pain ratings per variability level (or in other words per session) would show comparable magnitudes irrespective of the induced variance across trials. Importantly, a necessary prerequisite for this was that the mean temperature of all delivered heat stimuli had to be identical across trials for both sessions/variability levels. Assuming this, a larger variance was expected for the session with a higher variability level across trials.

3.1.1 Participants

Sixteen healthy subjects participated in this study. One subject had to be excluded due to incomplete data collection. Data analysis was performed on the remaining fifteen participants (N_1 = 15, 13 female) with a mean age of 25.67 years (standard deviation (SD) ± 2.82, range 21-32).

3.1.2 Study design and task

Study 1 was the only experiment in this dissertation that did not include an experimental placebo design. Participants were told that the aim of this study was to investigate the subjective perception of painful heat stimuli and to create a model to better predict inter-individual differences. In the calibration limits procedure, the sample showed a mean '*just painful*'-threshold

of 43.9°C (± SD 2.1). After the calibration procedure (Figure 3), the experiment started consisting of two sessions of painful heat stimuli each including 25 trials. A detailed description of the experimental design including heat stimulation, pain rating procedure, trials and timings as well as visual stimuli for the two conditions was given in section 2.2 (see also Figure 4). The first was the constant session presenting all pain intensities on a level of 40% pain tolerance. No variability between stimuli was induced. The mean temperature across subjects for 40% pain tolerance was 45.0°C (± SD 1.3). Session two was the variable session in which all averaged heat stimulus intensities also corresponded to the respective temperature of 40% pain tolerance. However, in this session, variance across stimuli of 0.22°C was induced to create a more variable pain experience. Participants were not aware of this manipulation and expected a simple repetition of the first session. As it is displayed in Figure 3b, slight changes in temperature can have a large impact on pain ratings depending on the subjective pain perception reflected in the slope of the sigmoidal calibration fit. This was the reason a small variance between stimulus intensities was chosen in order to prevent the trials from being too noticeably different from one another and therefore unbelievable. Figure 7 shows the two variance levels across trials per condition. Each trial consisted of an inter-trial-interval (ITI, 1.5-4s), followed by a short anticipation phase (1-1.5s), the painful heat stimulation (5s), and the VAS rating procedure (6s) as depicted in Figure 4.

3.1.3 Analysis

First, mean and standard deviations were computed for each subject per condition (constant vs. variable). Averaging the single subjects' mean pain ratings and respective SDs represents the overall mean and SD per condition for the entire sample. One-way repeated measures ANOVAs were used to compare the mean pain ratings as well as SDs of all subjects per condition (constant vs. variable). To investigate whether pain ratings follow the temperature variations induced in the variable condition, temperature variations were correlated to the VAS pain ratings. For doing this, each presented single trial temperature was standardized: $x_{i_{diff}} = \frac{x_{i_{temp}} - \mu_{temp}}{SD_{temp}}$, e.g. given a single trial temperature of 45.7°C, a mean temperature of 45.4°C and a variation across trials of 0.22°C would result in $x_{i_{diff}} = \frac{45.7-45.4}{0.22} \approx 1.36$. This was done to account for different mean temperatures presented to subjects due to their differing individual pain thresholds. All

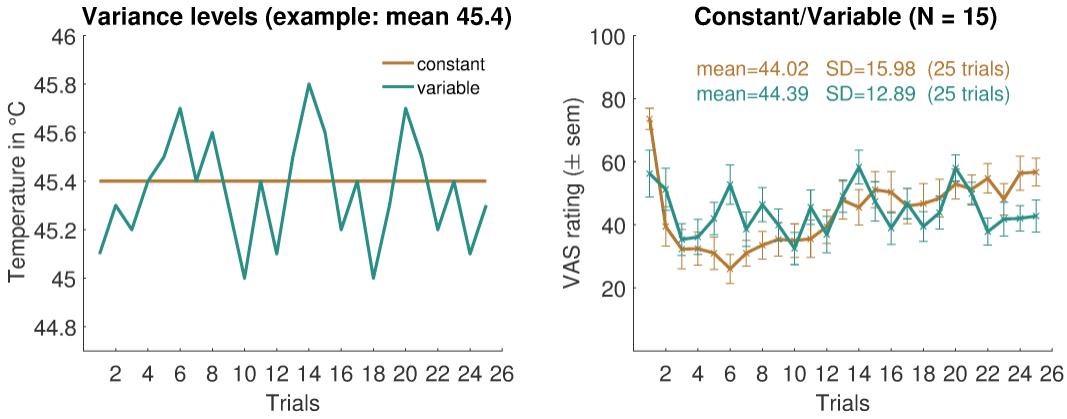


Figure 7. Temperature levels and mean VAS ratings of Study 1 (within-subjects design). *Left panel:* Displayed is the temperature time course across trials for an example mean temperature of 45.4°C per session. This reflects the heat differences that subjects were experiencing during the respective sessions across trials. *Right panel:* Mean pain ratings across trials for constant vs. variable. *VAS, visual analogue scale; sem - standard error of mean.*

difference measures ($x_{i_{diff}}$) as well as corresponding VAS ratings were pooled resulting in two variables with $15 * 25 = 375$ entries ($subjects * trials$). The standardized difference measures were then correlated to the VAS ratings using the Pearson's product-moment correlation.

3.1.4 Results

As expected due to the experimental design, the constant and variable condition showed almost identical mean pain ratings (mean ± SD: constant 44.02 ± 15.98, variable 44.39 ± 12.89), which is statistically reflected as no significant difference in the one-way repeated measures ANOVA ($F(1, 14) = 0.045, p = 0.835$). However, observing an overall smaller SD for the variable compared to the constant condition was unexpected ($F(1, 14) = 9.410, p = 0.008$). By visual inspection of the time course of the VAS ratings, variations across both conditions were observed (Figure 7). The naturally occurring variability in pain perception, displayed via individuals' rating standard deviation across trials in the constant condition, was actually higher compared to the modulated variable condition. Therefore, the induced experimental variability in this study resulted in a more precise pain perception compared to the naturally occurring variability within the individuals. Nevertheless, a clear pattern of corresponding pain rating variation following the presented temperature changes was observed in the variable condition. The correlation of the standardized temperature change ($x_{i_{diff}}$) and corresponding pain ratings

revealed a positive relationship of both ($r = 0.213$, $p < 0.001$). This means that a higher temperature was associated with higher pain ratings and lower temperature was related to lower pain ratings. Referring to this as a proof of concept, the observed positive relationship of subjective pain ratings with delivered different temperature intensities indicates that this procedure captures aspects of perceived as well as induced variability of pain.

3.1.5 Short conclusion

Study 1 revealed that pain ratings do follow different heat intensity changes. However, the naturally occurring variability in pain perception, responding to a repeated identical painful stimulation, shows variability by itself. This reflects the high subjectiveness of pain perception (Coghill & Eisenach, 2003; Fillingim, 2005; Nielsen et al., 2008, 2009) even within a single individual across different identical pain experiences. When only delivering a very small level of variance, corresponding rating variability can be even smaller compared to natural fluctuations in the pain percept. This was observed for slightly varying heat intensities with an SD of 0.22°C. An exploratory hypothesis was formed after investigating the data, assuming that the induced variance in the variable condition was likely to be too small compared to the naturally occurring variability in pain perception to see the expected differences in the VAS ratings SDs. As the study only included a small sample, further investigation with higher levels of variation are needed to induce variability in pain experiences. Therefore, for **Study 2** a higher level of variability across trials was used. Also, the procedure used in **Study 1** testing variability differences in pain perception within individuals revealed important insights into the subjective perception. However, this experimental design is likely to influence expectations as possible carry-over effects of session one to two cannot be ruled out. Another drawback of the experimental design was presenting the sessions in a fixed order always starting with the constant session. This was done to not reveal the variability manipulation of the experiment. As no previous literature about the conscious vs. unconscious perception of small temperature variations was available, this seemed as a good starting point. Participants should perceive the intensity differences reflected in their ratings without explicitly referring it to an actual temperature change. To account for these points, **Study 2** used a between groups design as well as a randomization of the session order to further investigate the influence of variability on pain perception.

3.2 Study 2 - Treatment variability in placebo analgesia

The aim of **Study 2** was to create an experimental procedure which either induces a constant or a variable expectation concerning the effectiveness of a placebo treatment. In a group design, findings from **Study 1** regarding variability levels were used to induce a certain level of variability in one group but not in the other. This was done to generate a sample consisting of two groups to test differences in the levels of variability concerning treatment expectations and how these influence placebo effect magnitudes. As observed in **Study 1**, constant heat stimulation already introduces variation in subjective pain perception and corresponding pain ratings. A difference in terms of variance between constant and slightly variable heat stimulation across trials was not found. It was speculated that inherent intra-individual rating variability was comparable to the variance induced across trials in the variable condition (0.22°C). For that reason, **Study 2** was designed introducing a between-subjects placebo experiment comparing constant vs. variable treatment expectations. A two group approach was chosen to rule out any within-subject design learning and/or carry-over effects. Based on the findings of **Study 1**, the variance across trials in the variable group was increased to ensure a reasonable difference between the two groups. Moreover, the sample sizes per group were increased. In general, a larger placebo effect magnitude was expected in the constant treatment expectation group (CTE) due to more precise treatment expectations and experiences concerning a positive outcome. As the variable treatment expectation group (VTE) resulted in less precision and more uncertainty concerning a positive treatment outcome, a smaller placebo effect magnitude was expected compared to the CTE group.

3.2.1 Participants

Fifty-one healthy male subjects participated in this study. Ten participants were excluded due to incomplete data resulting from technical problems, aborting the experiment by the participant or experimenter, and/or too high pain sensitivity. This resulted in an overall sample of $N_2 = 41$ including $N_{2_{CTE}} = 21$ subjects in the constant and $N_{2_{VTE}} = 20$ in the variable treatment expectation group. The mean age of the entire sample was 24.73 years (SD $\pm$ 3.59, range 19-33).

3.2.2 Study design and task

In the calibration limits procedure, the sample showed a basic pain threshold mean of 44.1°C (SD ± 2.8°C) reflecting a heat intensity just reaching the level of becoming painful. In this study, only the first 10 out of 16 trials were used for the calibration procedure (Figure 3b). The calculated temperatures corresponding to 30, 50, and 70 VAS ratings were used as anchor points to select the actual experimental temperatures. They were slightly adapted as a minimum temperature difference of 0.6°C between 20 VAS point differences (70-50 and 50-30) was chosen to assure a proper distinction between the three intensities without making it unbelievable as a treatment effect. Two skin patch positions, referring to the location of the thermode on the skin, were marked for the experiment. One patch was used for the conditioning and one for the test phase as displayed in Figure 8. SCR was additionally measured in order to obtain a more objective pain perception compared to subjective VAS ratings. Also, SCR was used to boost treatment expectations, as the participants were told that the treatment also has an influence on bodily autonomic responses. As a sham treatment, Transcutaneous Electrical Nerve Stimulation (TENS) was introduced to the subjects, including a brochure explicitly created for the study informing about TENS as an effective pain treatment which is depicted in Appendix A.4. Importantly, all participants received identical information concerning the treatment irrespective of the group. This was done to minimize instruction-related differences in placebo analgesia. The participants were told, that TENS works on a level slightly lower than perceptual threshold. For that reason, a calibration procedure for the TENS stimulation was performed to increase the plausibility of the treatment. During the TENS-calibration, which was never painful, participants experienced very mild electrical stimulation on the right forearm

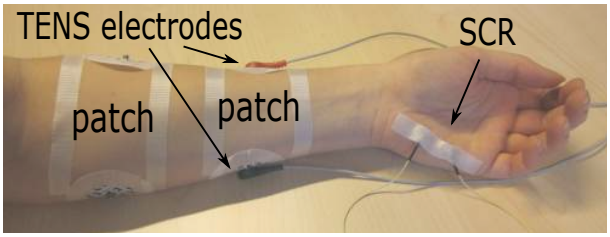


Figure 8. Electrode positions and skin patches for Study 2. One skin patch was used for the conditioning and one for the test phase in randomized order across participants. TENS electrodes were placed on the side of the respective patch. SCR electrodes were placed on the hand. *TENS, Transcutaneous Electrical Nerve Stimulation; SCR, skin conductance response.*

and verbally informed when the intensity reached a perceivable level. Electrical stimulation was presented using a constant current high voltage stimulator (DS7A, Digitimer Ltd, Welwyn Garden City, England) delivering single pulses of 2ms duration until perceptual threshold was reached (mean threshold of 0.42mA). During the experiment TENS was never applied in combination with a heat stimulus. The Digitimer device was immediately switched off after the calibration of TENS prior to the first experimental session. This ensured that during the experiment no electrical input was delivered or perceived.

A detailed information concerning the experimental procedure is given in section 2.2 (see also Figures 4 and 5). Each trial consisted of an inter-trial-interval (ITI, 18-23s), followed by an anticipation phase (4.5-6.5s), the painful heat stimulation (8s), and the VAS rating procedure (6s). A cue depicting a red cross (control) or a yellow circled red cross (placebo) starting with the anticipation phase indicated the respective condition. **Study 2** used heat intensities corresponding to pain tolerance levels of 30% for conditioning placebo, 70% for conditioning control, and 50% for test phase placebo and control condition, respectively. Each condition per experimental phase consisted of 11 trials. The subjects were not aware of this manipulation and always expected a heat intensity of about 70% of their respective pain tolerance for the entire experiment. Importantly, in this study, two different groups were compared to each other, which only differed in respect to their level of variability concerning prior treatment expectations. The aim was to generate two groups that entered the testing phase with different levels of prior treatment variability levels. One group experienced the treatment as consistently building very precise expectations concerning the effectiveness of the treatment (CTE). The second group also perceived the treatment as pain relieving but with much more fluctuation with regard to its level of effectiveness (VTE). This was achieved by manipulating the placebo condition of the conditioning phase. The CTE group experienced the placebo treatment as consistently effective, meaning that they were always presented with the same pain intensity which was 30% of their individual pain tolerance. In contrast, the VTE group received temperatures varying around 30% of their pain tolerance across placebo treatment trials (SD = 0.57°C; mean VAS 30; range around 30 VAS temperature: ±0°C to ±0.8°C). Every subject of the VTE group was presented with the same pseudo-randomized order of manipulated trials during the placebo condition to be able to compare the pain ratings across individuals. Importantly, during the conditioning the

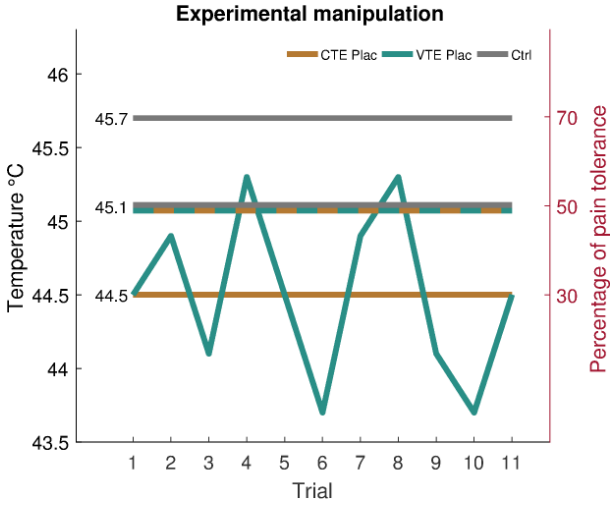


Figure 9. Experimental manipulation example for Study 2. Heat intensities to corresponding pain levels are shown. The depicted example represents temperatures of 44.5°C for 30% (conditioning phase placebo), 45.1°C for 50% (test phase both conditions), and 45.7°C for 70% (conditioning phase control) pain tolerance levels. Note that 50% pain tolerance intensities of the test phase are identical for both, placebo and control condition (different lines only for a better visualization). The placebo condition is always displayed in color (CTE - sepia, VTE - turquoise) whereas the untreated control condition is shown in gray. The mean temperature difference between 30% to 50% as well as 50% to 70% was always 0.6°C. *CTE, constant treatment expectation; VTE, variable treatment expectation; Plac, placebo condition; Ctrl, control condition.*

untreated control stimuli were identical for both groups with a consistent presentation of heat stimulation of 70% pain tolerance intensity without any induced variability across trials. The rationale behind this manipulation was to generate similar mean effects of pain relief in both groups but vary the level of variability in prior treatment expectations to specifically investigate this in placebo effects, i.e. the test phase. The test phase was identical for both groups with a heat intensity of 50% pain tolerance presented for both conditions, placebo and control, resulting in 22 identical pain trials in total. No variability was induced in the test phase. Figure 9 displays an example of the experimental procedure for each group, respectively, corresponding to intensities of 44.5°C for 30%, 45.1°C for 50%, and 45.7°C for 70% pain tolerance levels.

After the experiment, participants were asked to fill out questionnaires and were fully debriefed revealing the placebo context after completion. The German versions of the following questionnaires were used: STAI - State-Trait anxiety inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981), MDBF - Multidimensional Mood State Questionnaire (Steyer, Schwenkmezger, Notz, & Eid, 1997), FKK - Fragebogen zu Kompetenz- und Kontrollüberzeugungen (Krampen,

1991), PCS - Pain Catastrophizing Scale (Sullivan, 1995). This was primarily done to collect descriptive data about the sample. In detail, it indicates the following. A higher score in the specific questionnaire reflects a tendency for:

- **STAI** → *State*: more nervousness, anxiety and tension at the time-point of measurement; *Trait*: evaluating situations more threatening than it seems to be appropriate.
- **MDBF** → *Mood*: being in a positive mood; *Wakefulness*: being awake and rested; *Calmness*: being calm and relaxed.
- **FKK** → *Internality*: a high internal locus of control; *Externality*: a high external locus of control (driven by social interactions); *Chance*: a high destiny-driven locus of control; *Self concept*: a high belief in the own competence and control.
- **PCS** → *Rumination*: concentrating on pain related thoughts without the ability to suppress them; *Magnification*: overstating the threatening character of painful sensations; *Helplessness*: feeling powerless during painful experiences or imminent painful sensations.

3.2.3 Analysis

Within this study, the difference concerning the variability level of prior treatment expectations between these two groups, i.e. the conditioning placebo condition, was the main focus. Two-sample t-tests were used to test whether the experimental temperatures, as determined by the calibration procedure, did not differ between groups as well as to compare the variability levels within prior treatment expectations (SD per subject of conditioning placebo ratings) groups. To investigate the influence in placebo treatment outcomes, the placebo effect was calculated by subtracting the rating means of the two test phase conditions (control minus placebo → $\Delta_{VAS_{test}}$). The individual prior treatment variability level was defined as the subject's standard deviation of the conditioning placebo ratings across all 11 trials. To obtain the group mean level of prior treatment variability, the individual standard deviations were averaged across subjects. Higher variability levels were expected to be visible in the VTE group and, if present, would reflect the experimental manipulation. In general, higher rating variability was assumed to entail low precision concerning the treatment efficacy and lower rating variability was assumed to reflect higher treatment precision. To test the experimentally induced treatment variability and its influence on the placebo effect, linear mixed-effects models were performed for the pain ratings of conditioning and test phase, respectively. This analysis allowed for the control of subject-specific random effects when testing the two main effects (group: CTE vs. VTE; condition: control vs. placebo) and the interaction effect of both for conditioning and test phase.

The level of statistical significance was set to $p < 0.05$. This test was used to reveal whether the experimental manipulation was feasible to induce different variability levels in prior expectations and if this manipulation influenced the placebo effect. Placebo effects were correlated with the level of variability of prior treatment expectations (i.e. SDs of conditioning placebo ratings). Additionally, a multiple linear regression was estimated to describe the relationship between the placebo effect and the prior expectation parameters in more detail. The prediction of the placebo effect magnitude was done by inserting the mean and standard deviation of the conditioning placebo condition into the regression. SCR was analyzed as described in section 2.5.3 using a time-window of 12s after heat stimulus onset. As SCR was not part of the main hypotheses within this thesis and only used to include a less subjective representation of individual heat intensity coding, no further statistical analysis of the SCR data was included.

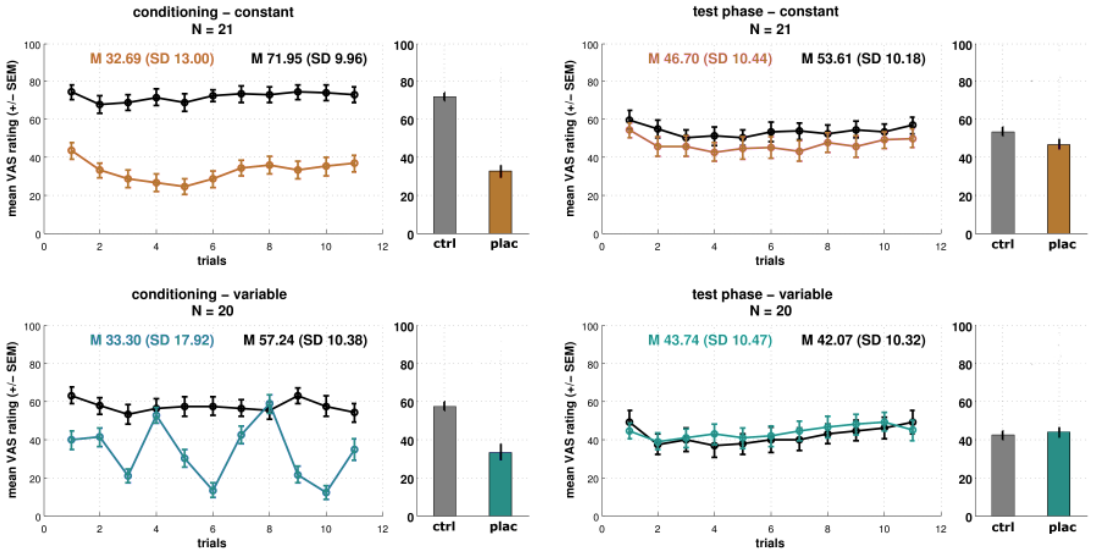
3.2.4 Results

Appendix A.1 shows the single subjects sigmoidal fits of the calibration procedure. The two groups did not differ in terms of experimental heat intensities (30%: $t(39) = 0.615, p = 0.543$; 50%: $t(39) = 0.587, p = 0.562$; 70%: $t(39) = 0.526, p = 0.604$). Table 1 displays a description of the two groups concerning the three heat intensity levels as well as the assessed personality dimensions and mood states. The results of the linear mixed-effects models revealed the following. In the conditioning phase, a main effect of condition was observed reflecting the two distinct temperatures used for creating the treatment experience between the control and placebo conditions ($F(2, 902) = 25.44, p < 0.001$). Unexpectedly, a main effect of group was revealed suggesting that general mean pain ratings, irrespective of the condition, were decreased in the VTE group ($F(2, 902) = 3.21, p = 0.001$). The bar plots of Figure 10a show this difference in the conditioning phase. Also, a significant interaction between condition and group was found ($F(2, 902) = 6.93, p < 0.001$). This means that the CTE group showed a larger conditioning effect (control minus placebo) compared to the VTE group which was not expected due to the experimental manipulation. Only the variability levels within the placebo condition and not the mean intensities were differed between the two groups. This makes it difficult to interpret the data as both main effects as well as the interaction became significant. However, it was also observed that the variability levels of the placebo condition, i.e.

Table 1. Descriptive statistics of heat intensities and personality questionnaires of the two groups for Study 2. Displayed are the calibrated heat intensities and overall sum scores of the questionnaires for the CTE ($N_{2_{CTE}} = 21$) and VTE ($N_{2_{VTE}} = 20$) group, respectively. *M, mean; SD, standard deviation; CTE, constant treatment expectation; VTE, variable treatment expectation.*

	M_{CTE}	SD_{CTE}	M_{VTE}	SD_{VTE}
°C 30%	44.2	0.7	44.4	1.3
°C 50%	44.9	0.7	45.0	1.3
°C 70%	45.5	0.6	45.7	1.3
STAI: Trait	36.00	7.25	30.30	5.55
STAI: State	36.38	9.02	31.80	5.51
MDBF: Mood	18.86	2.63	19.75	1.80
MDBF: Wakefulness	15.52	3.34	16.85	2.81
MDBF: Calmness	17.67	2.67	19.10	2.57
FKK: Internality	32.43	4.24	35.10	1.80
FKK: Externality	24.76	5.64	24.90	3.97
FKK: Chance	24.33	5.36	22.70	5.20
FKK: Self concept	34.05	4.40	34.85	4.63
PCS: Rumination	6.67	3.41	6.95	3.22
PCS: Magnification	4.00	2.41	4.90	2.38
PCS: Helplessness	5.43	3.49	6.30	3.56
PCS: Sum	16.10	8.12	18.15	7.17

the pain ratings SD per subject, were clearly different between the two groups (mean ± SD: CTE 13.00 ±5.20 vs. VTE 17.92 ±8.13, $t(39) = 2.32, p = 0.026$). For the test phase, in which all subjects received identical heat stimuli for both conditions, again, a main effect of condition was found ($F(2, 902) = 5.61, p < 0.001$). No main effect of group was revealed but note that a trend was observed ($F(2, 902) = 1.87, p = 0.062$). Importantly, as hypothesized, the interaction between condition and group also revealed a significant effect in the test phase ($F(2, 902) = 4.87, p < 0.001$). This interaction revealed that the CTE group (mean $\Delta_{VAS_{test}}$ ±SD: 6.90 ±14.30) showed a larger placebo effect than the VTE group (-1.67 ±12.61). Also, a correlation of the placebo effect magnitudes with the variability levels of prior treatment expectations revealed a negative relationship ($r = -0.315, p = 0.045$) of both. This suggests that in subjects with more variable prior treatment expectations (i.e. less precision in treatment efficacy expectations) smaller placebo effect magnitudes were observed. For subjects with more precise prior treatment expectations a larger placebo effect was found. The multiple linear regression revealed no significant effect ($F(2, 38) = 2.32, p = 0.112, R^2 = 0.109, adj.R^2 = 0.062$).



(a) Conditioning phase pain ratings. **(b)** Test phase pain ratings.

Figure 10. Pain ratings per group for Study 2. The upper panel represents the constant treatment expectation group (sepia - placebo condition) and the lower panel represents the variable treatment expectation group (turquoise - placebo condition). The untreated control condition is always depicted in gray scale or black. *VAS, visual analogue scale; SEM, standard error of mean; M, mean; SD, standard deviation; ctrl, control condition; plac, placebo condition*

The corresponding equation for the prediction of subjects' placebo effect magnitude was equal to $9.56 - 0.628 * SD_{expectation} + 0.086 * mean_{expectation}$. However, inspecting the corresponding coefficients statistics, the variability level of prior treatment expectations showed an influence on the prediction of the placebo effect ($\beta = -0.628, t(39) = 2.09, p = 0.043$) whereas the mean of it did not ($\beta = 0.086, t(39) = 0.65, p = 0.523$). A negative regression weight for the SDs of the conditioning placebo ratings indicates that the placebo effect magnitude is expected to decrease for subjects with less precise (more variable) prior treatment expectations. Nevertheless, this analysis was not found to be significant and therefore only the beta statistic of the prior treatment expectations ($\beta = -0.628, p = 0.043$) hint at a possible influence. This, however, underlines the negative relationship of placebo effect magnitudes and the variability levels of prior treatment expectations as seen in the correlation analysis. Appendix A.3 displays the descriptive results for the SCR mean data showing responses to heat onsets of conditioning and test phase per group.

3.2.5 Short conclusion

Study 2 was designed to test whether a manipulation of variability levels of prior treatment expectation was possible using a between-groups design with a temperature manipulation across pain trials. The effect of variability on placebo analgesia was tested. Benefiting from findings of **Study 1**, the sample size was increased for this study. Different variability levels between the two groups were induced in the prior treatment expectations (i.e. SDs of conditioning placebo ratings). A clear reflection of this was observed in the placebo ratings during the conditioning phase (Figure 10a). However, it was not expected to observe a significant main effect of group in the conditioning phase of the experiment. This suggests that the mean painfulness of heat stimulation, irrespective of the conditions, revealed a higher pain for the CTE compared to the VTE group. The manipulation intended to keep the mean pain perception between groups constant and only induce changes in the variance of prior treatment expectations. Nevertheless, the CTE group showed the expected mean pain ratings of approximately 30 for the placebo and 70 for the control condition as calibrated prior to the experiment. This is a similar observation to previous placebo studies which also use identical heat intensities across one condition during a conditioning phase (Eippert, Finsterbusch, et al., 2009; Klinger et al., 2007; Montgomery & Kirsch, 1997; Schenk et al., 2014). For the variable group, it was unclear whether the induced variability manipulation would also produce ratings around the respective calibrated mean VAS ratings as this was never tested before. It is speculated that the induced variability in the VTE group changed the perceived pain as a fixed temperature difference of 0.6°C between mean intensities of 30, 50 and 70 VAS points that were used in every subject. Inspecting the individual sigmoidal calibration fits (see Appendix A.1), various differences in the slopes of the subjects were observed. In other words, the same temperature change may affect pain ratings of individuals differently depending on their subjective range of pain perception. A very steep slope represents a very small temperature range between non- vs. unbearably painful perceptions. In contrast, a more flat slope reflects a larger temperature range. This means that a temperature difference of 0.6°C in one subject might already span the entire non- vs. painful range whereas another individual might rate this difference as only slightly different. Combined with the induced treatment variability within this group, it seemed possible that this might have changed the conditioning ratings as observed. Importantly, the placebo effects ($\Delta_{VAS_{test}}$)

for both groups differed significantly from each other, which is reflected in the interaction effect of the test phase (Figure 10b). A larger placebo effect magnitude was observed for the CTE compared to a smaller magnitude in the VTE group. In other words, the less variable prior treatment expectation group perceived the placebo treatment during the test phase as more pain relieving than the group which previously experienced the placebo treatment as more variable. This finding was likely related to the different treatment experiences the participants of the two groups had during the conditioning phase. Therefore, an influence of variability in prior treatment expectations on placebo analgesia seemed likely but was not clear due to the observed interaction effect during the conditioning phase. It might be possible that the decrease in pain ratings of the VTE group within the control trials of the conditioning phase (Figure 10a) also influenced the placebo analgesia finding of the test phase. For that reason, the experimental design was optimized for the neuroimaging study (**Study 3**) in order to account for this.

3.3 Study 3 - Neural correlates of Bayesian treatment variability

Study 2 revealed that the chosen manipulation procedure to induce variability in prior treatment expectations seemed feasible. Also, a correlative relationship with the placebo effect was found but not clearly ascribable to the variability level differences due to an interaction effect of the conditioning phase. Minor adaptations of the experimental design were needed in order to be able to connect the findings more precisely. The focus of **Study 3** was to first replicate the findings of **Study 2** and, second, investigate the underlying neural processes. Importantly, the Bayesian integration approach (see section 2.3) was applied on the data of **Study 3**. This was done on the entire sample ignoring group allocation, as the Bayesian framework accounts for different variability levels. Therefore, the manipulation in the VTE group was mainly performed to ensure a variety of variability levels in prior treatment expectations as well as to test the relationship of induced variability in treatment expectations and the placebo effect. The main interest of **Study 3**, however, was to investigate the neural correlates underlying the processing of prior treatment variability. It was primarily focused on the brain region associated with the PAG as previous research connected this area with the processing of precision of vicarious information (Yoshida et al., 2013) and pain avoidance prediction error coding (Roy et al., 2014). These findings were hinting at an involvement of this brainstem area in variability processing in a pain context. For that reason, it was tested whether behavioral Bayesian model parameters, reflecting the processing of variability, would predict placebo-induced changes in brain signals of the PAG during the experimental test phase. Yet, no other brain areas have been specifically related to variability level processing which led to a strong a priori hypothesis concerning this region of interest (ROI).

3.3.1 Participants

The sample consisted of 70 healthy male subjects without any history of psychiatric or neurological disorders. Participants were assigned to two groups using a randomized double-blind allocation (performed by a study assistant and not the experimenter). Both groups were matched for age. Due to technical difficulties or incomplete data collection, four subjects per group had to be excluded (eight in total). Data analysis was performed on the remaining

$N_3 = 62$ subjects (mean age ±SD: 24.60 ±3.77 years, range: 19-34 years). The two groups ($N_{3_{CTE}} = 31$, $N_{3_{VTE}} = 31$) did not differ significantly in age (CTE 24.71 ±3.88; VTE 24.48 ±3.71; $t(60) = 0.234, p = 0.816$) or basic pain thresholds (just painful °C: CTE 44.0 ±2.4; VTE 44.0 ±2.3; $t(60) = 0.005, p = 0.996$). All participants gave written informed consent prior to the experiment without revealing the placebo manipulation. After the experiment, all participants were fully debriefed about the placebo manipulation and offered the opportunity to withdraw all acquired data from the study. However, no subject demanded a data deletion and confirmed in a second consent form that they were fully debriefed about the real purpose of the study. In addition to the exclusion criteria previously described (see section 2.1), participants were excluded if they had any contraindications for an fMRI measurement (e.g. metal parts in the body, head surgery, epilepsy, claustrophobia, old tattoos).

3.3.2 Study design and task

Section 2.2 and 3.2.2 describe the experimental placebo design. **Study 3** used a very similar procedure as **Study 2**. Minor changes were made to optimize the manipulation. A double-blind procedure was applied meaning that the experimenter was not aware of the subject's group allocation. The experiment consisted of a 2-day procedure with a break of approximately five days between testing (days ±SD: CTE 4.55 ±3.33; VTE 5.03 ±3.74; $t(60) = 0.593, p = 0.592$). Day 1 was only used to familiarize participants with the heat stimuli and rating method as well as to have the participant's MRI applicability checked by a physician. Additionally, any participants with abnormal pain perceptions would have been able to be detected on the first day, and subsequently excluded from further participation. Each participant performed the calibration procedure (Figure 3a) including 16 instead of the 10 pain trials performed in **Study 2**. This was done to increase the precision of the sigmoidal fit and corresponding temperature predictions per pain intensity level (30, 50, and 70% pain tolerance). Despite different intensities, this ensured that individual pain ratings were comparable across subjects. The entire day 1 procedure lasted approximately one hour and did not include any placebo manipulation or MR scanning.

On day 2, the entire placebo experiment in the MR-scanner was performed including both the conditioning and test phase. Experimental instructions concerning the treatment were identical

again for both groups and also included the same putative TENS information brochure of **Study 2** (Appendix A.4). Four skin patches were marked on the left volar forearm (Figure 5). Also, the two TENS electrodes were attached beside the patches. Identical to *Study 2*, a TENS calibration was performed to boost the impression of a real clinical treatment. The heat pain calibration from day 1 was repeated to update the predicted heat intensities for 30, 50, and 70% pain tolerance levels (see Appendix B.1 for single subject fits). Both the TENS as well as heat calibration were performed in the MR-scanner without acquiring BOLD data to account for possible context effects of the MR environment (Ellerbrock & May, 2015). The two groups did not differ in terms of heat intensities (in °C mean ±SD → 30%: CTE 44.4 ±0.7, VTE 44.3 ±0.6; 50%: CTE 44.9 ±0.6, VTE 45.0 ±0.6; 70%: CTE 45.5 ±0.6, VTE 45.7 ±0.6). Scanning started immediately after pain calibration was finished. Again, for every experimental heat stimulation, all participants expected a constant pain level of approximately 70% individual pain tolerance. As in **Study 2**, the experiment consisted of a conditioning and test phase, each including a placebo and a control condition. The experimental manipulation was identical to the foregoing study except an additional trial per condition was presented, which resulted in 12 trials total. The restriction of using a fixed temperature difference of 0.6°C between the pain intensities of 30 to 50 and 50 to 70% pain tolerance levels was changed. Instead, the slope of the sigmoidal calibration fit was used to determine individual temperature differences between the three intensities. A minimum difference of 0.4°C was chosen as **Study 1** revealed that too small temperature variations were not recognized as different. The conditioning placebo manipulation of the VTE group, introducing a certain level of treatment variability, was identical to **Study 2**, resulting in a total temperature SD of 0.55°C across trials around a mean pain intensity level of 30% (range ±0°C to ±0.8°C). Again, this was done to build treatment expectations regarding the sham TENS treatment's effectiveness concerning heat pain relief. Each trial consisted of an inter-trial-interval (ITI, 12-20s), followed by the anticipation phase (5.5-8s), a delay of 2s showing a blank screen, the painful heat stimulation (8s), and the VAS rating procedure (7s). The timings were slightly adapted to optimize the design for the imaging analysis (Figure 4). The test phase of **Study 3** was identical to **Study 2** and is described in section 3.2.2. Again, identical heat stimuli were presented for both groups and conditions resulting in a total of 24 trials (12 placebo, 12 control) with an intensity of 50% of individual pain tolerance. At the end of each of

the four sessions, participants additionally rated the subjective average painfulness of all trials received during this session. Outside the scanner, subjects completed several questionnaires to assess personality dimensions and mood components. This also included a self-created post-experimental TENS questionnaire assessing the participant's experience during the treatment prior to debriefing (see Appendix B.2). The whole experimental procedure during day 2 lasted approximately 3 hours.

3.3.3 Analysis

Study 3 used the same analysis methods as previously described in **Study 2** (see section 3.2.3). In addition, the Bayesian integration framework as well as the corresponding analysis previously described in section 2.3 and 2.5.2 were applied to the data from **Study 3**.

First, the sample of **Study 2**, which represented independent subjects that underwent the same manipulation procedure, was used to create induced treatment variability cut-off values for **Study 3**. As previously stated, individual treatment variability was defined as the subject-specific standard deviation over all 12 trials of the placebo ratings during conditioning. However, **Study 1** showed that individuals can even perceive constant painful stimulation similarly variable as slightly fluctuating painful sensations. To avoid including participants who showed unrelated rating patterns in comparison to their group assignment, a subset of the sample of **Study 3** was used for the mixed-effects analysis. Since being provided with an independent sample of **Study 2** to control for possible outliers, behavioral data of **Study 3** was used to test whether the intended manipulation of the respective conditioning procedure of low (CTE) vs. high (VTE) prior treatment variability was induced according to the respective group assignment. This provided the opportunity to explicitly compare the two groups in terms of experimentally induced prior treatment variability. It is important to note that the sample of **Study 2** was used as an independent sample to identify cut-off values for subjects in which the experimental manipulation was correctly induced. Subjects of the CTE group ($N_{3_{CTE}} = 31$) which showed lower rating variability (i.e. higher precision) than the average VTE group ($N_{2_{VTE}} = 20$) of the **Study 2** sample (rating variance < 384.08) that were selected. Further, subjects of the VTE group ($N_{3_{VTE}} = 31$) which showed higher rating variability (i.e. lower precision) than the average CTE group ($N_{2_{CTE}} = 21$) of the **Study 2** sample (rating

variance > 194.90) were also selected. This led to a sub-sample for the mixed-effects analysis of $N_{3_{sub}} = 49$ including the two groups with $N_{3_{sub-CTE}} = 23$ and $N_{3_{sub-VTE}} = 26$ subjects. It is important to note that the cut-off criteria were only applied to the conditioning phase data (i.e. the manipulated placebo condition) to determine two groups that show clearly different levels of variability in prior treatment expectations. This is comparable to an experimental independent variable whereas the test phase, or in other words the placebo effect, served as the dependent variable on which these criteria had not been applied. This sub-sample ($N_{3_{sub}} = 49$) was only explicitly used to repeat the mixed-effects model analyses that were already tested on **Study 2** pain rating data to possibly provide a more conclusive interpretation of the results by specifically focusing on the influence of prior treatment variability.

Apart from the mixed-effects model analyses, all other analyses including the Bayesian integration (see section 2.3) and model selection (see section 2.5.2), as well as all corresponding behavioral and imaging data analyses, were performed on the entire sample ($N_3 = 62$). This was done as Bayesian integration accounts for differences in the mean as well as variability levels which led to pooling the two groups ($N_{3_{CTE}} = 31$ and $N_{3_{VTE}} = 31$) to an overall sample in order to test this.

Concerning the imaging data, after preprocessing and first level analysis on a single-subject level (see section 2.5.4), basic pain and placebo main effects were visualized (see Appendix B.5). This was done as a quality check to see if typical pain regions of the brain were activated. Next, additional second level analyses, investigating the imaging data across subjects, were performed. The main focus was on the Bayesian integration parameter *attraction weight* (w_{prior}, see Equation 2.3) as it reflects a ratio of prior and likelihood variability. Again, a high value in the *attraction weight* represents high variability in the likelihood (test phase control) compared to lower variability, i.e. higher precision, in the prior treatment expectation (conditioning placebo). The *attraction weight* was used as a covariate in a one-sample t-test investigating whether variability variations in prior and likelihood would explain changes in BOLD responses. This was done for both test phase conditions as well as the placebo contrast, respectively. To complement information about the relationship between Bayesian integration and possible related BOLD responses concerning prior treatment expectations and experiences, additionally, one-sample t-tests were performed either using μ_{prior}, $log(\sigma_{prior})$, or the posterior

model probability for the Bayesian over the Null model (as in Figure 12, cyan bars) as respective covariates (see Appendix B.6). These additional fMRI analyses were not of special interest for this thesis, but were assumed to offer hypotheses-generating information for future research. For example, including both parameters of the Bayesian prior (μ_{prior}, $log(\sigma_{prior})$) into the imaging analysis presents additional information. Also, brain regions being involved in the coding of a complex model comparison (posterior model probability) are difficult to interpret but may present new ROIs to investigate pain perception and placebo treatment outcomes. To account for multiple comparisons, a correction procedure using a family-wise error rate (FWE) approach with a significance threshold of $p < 0.05$ was used, especially focussing on the PAG. This was done using a small volume correction (SVC) approach with a 6mm sphere around coordinates (MNI: 1 -29 -12) which was obtained from previous PAG studies (Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012). Other brain regions found during the analyses were considered significant on a whole brain corrected level of $p < 0.05$. Activations not surviving whole brain correction but meeting the criteria of $p_{uc} < 0.001$ uncorrected (uc) as well as being located in either pain or placebo relevant areas were considered informative and are reported as well. All statistical maps are presented with a visualization threshold of $p_{uc} < 0.001$, masked with the field of view of data acquisition, and overlaid on the mean structural image of all 62 subjects. For SCR analysis as described in section 2.5.3, a time window of 10s after event onset was used to analyze responses to the anticipation as well as heat onset. This was performed separately for each of the two groups.

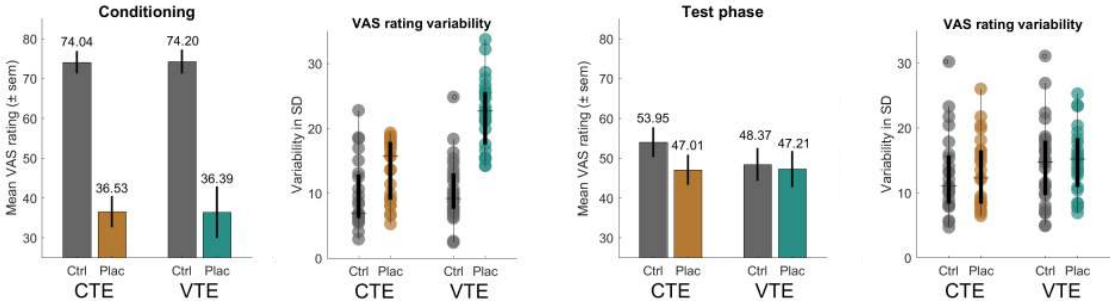
3.3.4 Results

Table 2 shows a descriptive representation of the sample presenting mean sum scores of personality questionnaires already used in **Study 2**. A measure accounting for possible depressive tendencies was added (Beck Depression Inventory II, BDI-II) in which higher sum scores indicate a higher tendency towards a depressive mood (Beck, Steer, & Brown, 1996; Hautzinger, Keller, & Kühner, 2006). The mixed-effects analysis of the VAS pain ratings revealed the following results. For the conditioning phase, a main effect of condition (placebo vs. control) was observed ($F(2, 1172) = 24.55, p < 0.001$). No main effect of group (CTE vs. VTE, $p = 0.963$) or interaction effect of condition by group ($p = 0.885$) was revealed indicating that the two con-

Table 2. Descriptive statistics of personality questionnaires of the two groups for Study 3. Displayed are the overall sum scores of the questionnaires for the CTE ($N_{3_{CTE}} = 31$) and VTE ($N_{3_{VTE}} = 31$) group, respectively. *M, mean; SD, standard deviation; CTE, constant treatment expectation; VTE, variable treatment expectation.*

	M_{CTE}	SD_{CTE}	M_{VTE}	SD_{VTE}
BDI-II	5.19	7.64	4.58	3.32
STAI: Trait	35.74	9.04	32.65	7.09
STAI: State	35.06	9.83	32.74	6.24
MDBF: Mood	19.29	2.57	19.90	1.92
MDBF: Wakefulness	17.55	3.10	18.26	2.18
MDBF: Calmness	18.67	2.48	18.84	2.28
FKK: Internality	32.55	3.49	34.26	3.32
FKK: Externality	26.10	4.02	24.77	4.15
FKK: Chance	24.00	5.50	23.13	4.99
FKK: Self concept	32.65	4.75	33.06	4.06
PCS: Rumination	7.52	4.57	7.00	3.79
PCS: Magnification	4.06	2.41	4.06	3.04
PCS: Helplessness	4.97	4.09	5.13	3.84
PCS: Sum	16.55	9.62	16.19	9.04

ditioning temperatures were perceived differently according to the experimental design without any interfering group or interaction effects (Figure 11a). Importantly, the single subject's SDs of the prior treatment expectations (VAS ratings of placebo condition) were different from each other between the two groups ($t(47) = 6.12, p < 0.001$). As displayed in Figure 11b, the VTE group (mean ±SD: 22.46 ± 5.33) showed a larger variability level in prior treatment expectations than the CTE group (13.63 ± 4.76). These conditioning results reflect the two distinct groups that were created due to a successfully induced respective prior treatment expectation manipulation according to the group allocation ($N_{3_{sub}} = 49$). This means that the two groups only differed in terms of variability levels, which was intended in order to investigate the respective influence on placebo analgesia magnitudes. The difference of the manipulated expectation variability levels between groups, however, was influenced by the selection procedure using cut-off values of **Study 2** for the data analysis of **Study 3**. This can be seen as a proof of concept concerning the experimental manipulation. In the test phase (Figure 11c and d), all heat stimuli were identical for both conditions at a level of 50% individual pain tolerance. A main effect of condition ($F(2, 1172) = 4.49, p < 0.001$) as well as an interaction effect of group and condition



(a) Conditioning phase pain ratings reflecting the two temperatures for the control and placebo condition.

(b) Single subject variability levels of pain ratings of the conditioning phase.

(c) Test phase pain ratings reflecting the analgesic effect of the treatment.

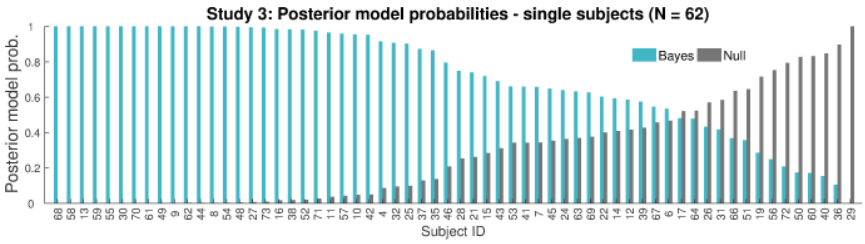
(d) Single subject variability levels of pain ratings of the test phase.

Figure 11. Behavioral results of pain ratings. *CTE, constant treatment expectation ($N_{3_{sub-CTE}} = 23$); VTE, variable treatment expectation ($N_{3_{sub-VTE}} = 26$); Ctrl, control; Plac, placebo; VAS, visual analogue scale; sem, standard error of mean; SD, standard deviation.*

($F(2, 1172) = 2.72, p = 0.007$) were observed. The main effect of condition reflects a significant difference of the perceived painfulness of placebo vs. control in both groups. The interaction effect revealed a significant difference (mean VAS difference control-placebo condition ±SD) between the two groups' placebo effect magnitudes (CTE 6.95 ± 11.31, VTE 1.16 ± 25.43). A main effect of group was not observed ($p = 0.240$). Additionally, the levels of variability between the two groups as well as conditions were not revealing significant differences.

For the Bayesian integration framework, single subject ratings were modeled using Gaussian probability density functions to obtain maximum likelihood estimates for the model parameters of prior and likelihood, respectively (Equation 2.2). Using Equations 2.3, 2.4, 2.5, and 2.6, the prior and likelihood were integrated resulting in a prediction of the test phase treatment outcome (i.e. the ratings of test phase placebo condition). Combining the two distributions of prior and likelihood to predict the treatment outcome offered the possibility of including the mean as well as the variance of treatment expectations and new sensory inputs. This prediction was compared to the prediction of the Null model as described in section 2.3, which assumed no influence of the conditioning experience on the treatment outcome of the test phase. Appendix B.3 shows the single subjects' integration of prior and likelihood including the predictions for the Bayesian and Null model.

A random effects approach (RFX) was used (see section 2.5.2) for the Bayesian model comparison (Rigoux et al., 2014; Stephan et al., 2009). The observed data was better explained by



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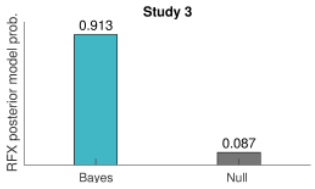
(a) Single subjects posterior model probabilities given the observed data of Study 3. The data is sorted by the Bayesian model posterior probability of each subject ($N_3 = 62$).



(b) Overall random effects posterior model probabilities.

Figure 12. Bayesian model comparison of Bayesian and Null model given the observed data of Study 3. Displayed is the posterior model probability of the Bayesian compared with the Null model. Reflected in a greater model probability, the Bayesian model is more likely having produced the observed data than the Null model. *RFX, random effects; r, correlation coefficient.*

the Bayesian integration model which was reflected as a greater overall posterior model probability across subjects as displayed in Figure 12. The RFX conditional expectations of model probabilities were 0.913 (exceedance probability $\varphi_1 \approx 100\%$) for the Bayes model compared to 0.087 (exceedance probability $\varphi_1 \approx 0\%$) for the Null model. This greater model probability for the Bayesian integration model indicates that the model incorporating the level of variance of prior treatment expectations performed better than the Null model which did not account for this. Looking at individuals, 31 participants (50%: CTE 17, VTE 14) had a Bayes factor greater than three in favor of the Bayesian integration model (BF_{10}) which indicates at least a moderate model evidence (Kass & Raftery, 1995; Lee & Wagenmakers, 2013). Seven subjects (11.3%: CTE 4, VTE 3) showed a greater Bayes factor than three in favor of the Null model (BF_{01}). Following this, the positive evidence ratio in favor of the Bayesian integration model was $PER_{10} = 31/7 \approx 4.43$. For 24 (38.7%) of the participants, none of the two models described the data significantly better than the other model. Importantly, no difference between the groups concerning posterior model probabilities, $p(M_{Bay}|D)$, was observed ($p = 0.872$) meaning that in both groups, a comparable number of model fits favored the Bayesian integration model over the Null model and vice versa. A positive relationship of the predicted placebo effect ($\mu_{like} - \mu_{post}$) with the actually observed placebo effect ($mean_{test_{ctrl}} - mean_{test_{plac}}$) was observed with a correlation coefficient of $r = 0.441, p < 0.001$. Correlating the mean of prior treatment expectations (μ_{prior}) with the observed placebo effect magnitude, no significant relationship was observed

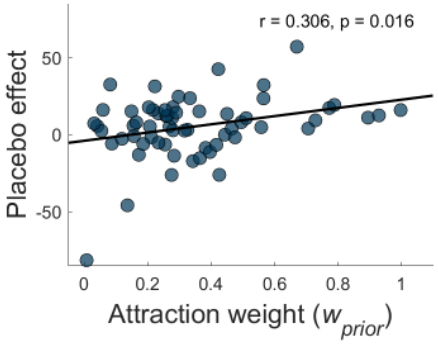


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Figure 13. Positive relationship of attraction weight and placebo effect magnitudes. *Attraction weight*, as described in Equation 2.3, reflects the Bayesian integrated treatment variability (relative variability of prior and likelihood). Larger values in w_{prior} reflect higher precision (less variability) in the prior. A higher variability level in new sensory inputs (likelihood) compared to less variability and more precision in prior treatment expectations (prior) may lead to larger placebo effect magnitudes.

($p = 0.997$). This makes it more likely that the variability level of prior treatment expectation is a possible modulator of placebo treatment outcomes. Next, *attraction weight* (w_{prior}) was used to investigate this variability influence further. This parameter considers the variability level of both, prior and likelihood, irrespective of the influence of the mean parameters of the two. In other words, the *attraction weight* reflects the relative influence of prior and likelihood on the posterior prediction of the treatment outcome. Figure 13 shows the positive relationship with the placebo effect ($r = 0.306, p = 0.016$) meaning that the less variable and therefore more precise prior treatment expectations were compared to the variability of the new sensory input, the larger the placebo effect magnitude was. This significant correlation indicates that the less variable prior treatment expectations were compared to more variability in new sensory inputs, the greater the analgesic effect of the placebo treatment was observed. Participants with higher variability in prior treatment expectations showed smaller placebo effect magnitudes. Additionally, multiple linear regression analysis using both *attraction weight* inputs ($\sigma_{prior}, \sigma_{like}$) revealed a significant effect ($F(2, 59) = 6.83, p = 0.002, R^2 = 0.188, adj.R^2 = 0.161$). The corresponding equation for the prediction of subjects' placebo effect magnitude was equal to $15.005 - 0.883 * \sigma_{prior} + 0.562 * \sigma_{like}$. Inspecting the corresponding coefficients statistics, the variability level of prior treatment expectations showed a significant influence on the prediction of the placebo effect ($\beta = -0.883, t(59) = 3.642, p = 0.001$) whereas the variability of sen-

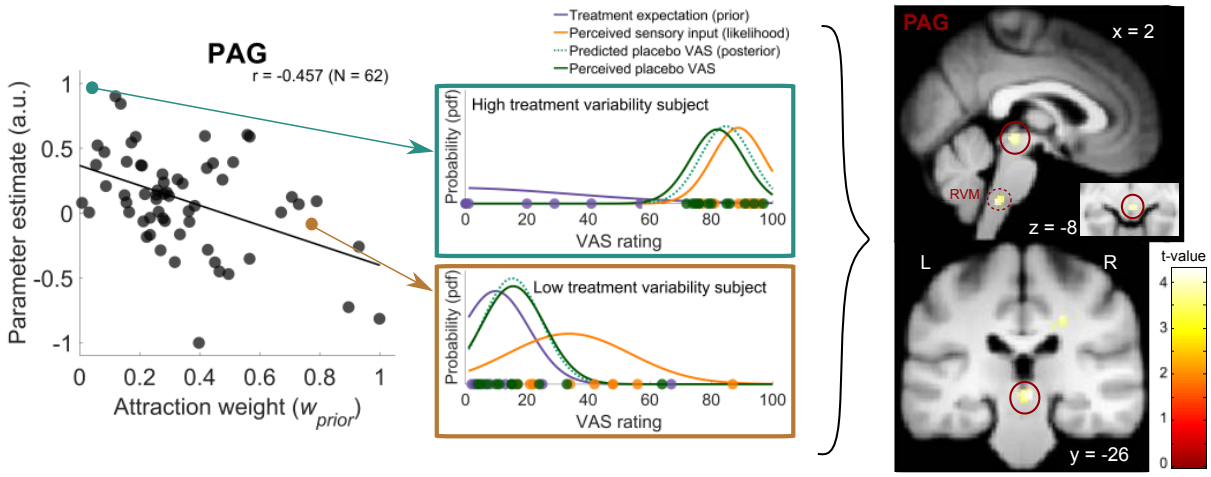

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Figure 14. PAG signal change with Bayesian integrated treatment variability (model-based fMRI). One sample t-test using w_{prior} as a covariate for the test phase placebo condition. An SVC cluster in the PAG and an uncorrected cluster in the RVM was observed reflecting a negative relationship. Increased PAG signal was associated with higher variability in placebo treatment expectations (prior) compared to lower variability in new sensory inputs (likelihood). Corresponding real data modeling examples for Bayesian integration for high and low variability levels in prior treatment expectation are displayed in the middle. fMRI visualization threshold was set to $p_{uc} < 0.001$. *pdf, probability density function; VAS, visual analogue scale; L, left; R, right; a.u., arbitrary units; PAG, periaqueductal gray; RVM, rostral ventromedial medulla*

sory inputs showed a trend effect ($\beta = 0.562, t(59) = 1.842, p = 0.070$). A negative regression weight for σ_{prior} indicates that the placebo effect magnitude is expected to decrease for subjects with less precise (more variable) prior treatment expectations after controlling for the variability level of new perceived sensory inputs (σ_{like}). This underlines the negative relationship of placebo effect magnitudes and the variability levels of prior treatment expectations as seen in the correlation analysis. Appendix B.4 displays the results for the SCR data analysis showing responses to the anticipation cue as well as heat onset for the conditioning and test phase per group, respectively. Similar to **Study 2**, this only served descriptive purpose and no further statistical SCR analyses were included in this thesis.

The neural correlates of treatment variability were investigated with focus on the PAG and the influence of the relative variability of both, the prior and the likelihood (*attraction weight*). This presented the opportunity to test expectations and new incoming sensory inputs as modulators of placebo treatment outcomes without including the influence of simple intensity coding of pain (no involvement of the mean). Figure 14 displays the results. For the analysis of w_{prior}

as a covariate for the test phase placebo condition, an SVC cluster was found in the PAG (coordinates [2 -26 -8], $k_E = 8, t(60) = 4.16, p_{_{FWE}} = 0.001$) as well as an uncorrected cluster in the RVM (coordinates [2 -36 -46], $k_E = 16, t(60) = 4.06, p_{uc} < 0.001$) reflecting a negative relationship between the respective BOLD signal and the *attraction weight*. Complementing imaging analyses can be found in the appendix. Note that all participants of both groups were included in each imaging analysis (high as well as low variability in prior treatment expectation and corresponding placebo effect magnitudes). The main effect of pain, pooling all test phase stimuli (24 trials with identical pain intensity, half control and half placebo), across subjects and comparing it to the baseline activation is displayed in Appendix B.5 which reflects typical brain areas that are associated with the processing of pain. This was done to demonstrate that the participants perceived the test phase stimuli as painful not only in their subjective ratings but also in their corresponding BOLD signal change. Moreover, the neural correlates of the placebo effect across participants is depicted as showing increasing BOLD signal changes for the placebo compared to the control condition of the test phase. Descriptive analyses using the prior treatment expectation's mean (μ_{prior}) as well as the log-transformed variability ($log\ \sigma_{prior}$) are presented in Appendix B.6.

3.3.5 Short conclusion

The results of **Study 3** indicate that a Bayesian framework is able to predict placebo outcomes by incorporating the strength but more importantly the level of variability of prior treatment expectations and new sensory inputs. Importantly, the level of variability did not determine the prediction quality as the framework predicted the different cases, high vs. low prior variability, equally well. Across several studies, placebo effect magnitudes are often observed as highly variable (Vase et al., 2009). Therefore, the results of **Study 3** introduce an important new modulator, level of variability in prior treatment expectations, which may influence different outcomes in placebo effect magnitudes and should be investigated further in the future. As the Bayesian framework is able to account for different variability levels it introduces a useful tool for further investigation of the effect of placebo analgesia and pain perception. Behaviorally, it was shown that placebo effects were smaller in individuals with higher variability in their prior treatment experience and, in comparison, more pronounced for participants who perceived the

treatment as more constant (less variable) relative to the incoming sensory stimuli. Therefore, higher precision in prior treatment expectations seem to facilitate larger placebo effects. Importantly, the same findings were well in line with the observed results in **Study 2** which could not directly been related to the different variability levels of prior treatment expectations due to an interaction effect of group and condition in the conditioning phase. The results of **Study 3** have more clarity, as such an interaction effect was not observed due to an optimized experimental design. Further, a correlation with the mean of prior treatment expectation was not observed in **Study 3**. This means that the strength of prior treatment expectations (μ_{prior}), reflecting the intensity of the previously experienced pain relief, showed no relationship with the placebo effect magnitude, whereas the variability level of the prior (σ_{prior}) did. However, for some subjects the Bayesian integration model was not able to better describe the treatment outcome than the Null model. It is speculated that these subjects were not using optimal Bayesian integration to combine previous with new information. To identify driving modulators that explain this effect of integraters vs. non-integraters further research is needed that explicitly focuses on factors such as environmental, personality, social, genetic, or neural.

Within the non-clinical sample of **Study 3**, a neural modulation was observed at the brainstem level including regions corresponding to the PAG as well as the RVM. This is a first hint that the Bayesian integration approach can not only be used to describe behavior, but can also provide new insights into the mechanisms of pain processing and placebo analgesia. As already described in section 1.2 and 1.3.1, the PAG belongs to both the ascending and descending pain system and is therefore a key region for modulating pain processing (Fairhurst et al., 2007). Previous research has also shown that the PAG is involved in pain avoidance prediction error coding (Roy et al., 2014) and in the processing of precision of vicarious information (Yoshida et al., 2013) which already hinted at an involvement of this area to the coding of variability levels. In line with this, the PAG is involved in both, pain inhibitory (Jones & Gebhart, 1988) as well as pain facilitatory processes (Vanegas & Schaible, 2004) which also hints at a strong modulatory involvement of this brainstem region in pain processing. In **Study 3**, higher PAG BOLD activation was related to higher variability in prior treatment expectations (σ_{prior}) compared to less variability concerning the new sensory input (σ_{like}). It is assumed that less precision evokes more resource-demanding processes to adapt to the uncertain event. Supporting this,

Yoshida et al. (2013) also observed that participants who showed high susceptibility to induced variability were associated with an increased BOLD signal in the PAG. Furthermore, using a delayed conditioning paradigm which presented cues with high and low predictability levels of painful stimuli, Lin, Hsieh, Yeh, and Niddam (2014) again observed an increased PAG BOLD signal for the unpredictable compared to the predictable condition. Complementing this, increased activity in the PAG was also related to the spatial proximity of a threat (Mobbs et al., 2010) which also reflects the importance of this region in processing immanent, possibly harmful information.

Exploiting these findings in a clinical context, by providing precise a priori information concerning a treatment might help to create precise prior expectations in patients. This would present the opportunity to maximize the positive influence of placebo effects which are assumed to be present in every clinical intervention. A fruitful communication between patient and physician might increase these beneficial effects. Finally, as the literature provides growing evidence that a dysregulation of the descending pain modulatory system can be related to the chronification of pain (for a review see Ossipov et al., 2014), the Bayesian integration model presents new insights into the modulatory mechanisms of this system. The following **Study 4** is therefore a first attempt to behaviorally explore this approach in more detail in a larger second sample.

3.4 Study 4 - Bayesian integration in a large placebo sample

As **Study 3** showed that the Bayesian integration framework is able to predict treatment outcomes in a placebo analgesia experiment, testing this on a second, larger sample would be beneficial in order to strengthen the usefulness of this approach. For that reason, a large dataset collected within a 5-year European Research Council funded placebo-nocebo-project was used in order to apply the same Bayesian model to an independent sample in which no variability manipulation was induced.

3.4.1 Participants

The sample which was provided to test the Bayesian model consisted of 720 healthy participants. Due to missing data concerning the VAS ratings, 6 participants were excluded as the model was not applicable in these subjects (N_4 = 714, 426 female, 288 male, mean age (±SD) 24.7±3.7 years, range: 18-35 years). The basic mean±SD heat pain threshold was 42.1°C±3.6. As in the previous studies, all participants gave informed written consent prior to the experiment. Due to a very long data acquisition phase of several years, the debriefing procedure differed between participants. Half of the sample received a full debriefing informing about the placebo/nocebo manipulation after the experiment and the other half was not debriefed. Exclusion criteria were previously described (see section 2.1).

3.4.2 Study design and task

Study 4 was planned and performed completely independently of **Studies 1-3**. This study consistent of an entire day of data collection in the laboratory - approximately 7 hours total. This included several experiments testing placebo as well as nocebo effects. Nocebo, comparable to the placebo effect, is an expectancy-driven phenomenon. Contrary to placebo analgesia in which the pain is decreased due to certain expectations and a putative treatment, the nocebo effect is characterized by an increase in pain perception. However, the nocebo experiments were not of interest for this dissertation as, for now, only a placebo treatment outcome has been expected to be predicted by Bayesian integration. The testing day started with general questionnaires about the participant's demographics and health followed by a saliva sample

as well as drug test via a urine sample. In case of a positive result, the participant was sent home and in some circumstances after a long enough washout phase re-invited. After this, participants were introduced to two ointments. One was described as "Emla" which comprised of the fast acting analgesic agent lidocaine influencing the perception of pressure and pain as well as heat and cold. The aim of the study was described to the participants as investigating changed pain perception using this well-established medical product. The second ointment was introduced as a control which contained no active agent. In reality, both ointments were free of any active agent. All participants were told that the green labeled tube contains the analgesic Emla ointment whereas the blue tube contains the control cream. Figure 15 displays the study design. The ointments were applied to the respective patches and the participants were told that the cream needed a duration of approximately five minutes before the active agents would begin to take effect. During that time, participants either filled out questionnaires or were tested with a Quantitative Sensory Testing (QST) procedure defining warmth and cold detection as well as heat and cold pain thresholds which were relevant for other parts of the experimental assessment. After the QST, the calibration procedure followed using several heat pain trials of 10s duration either increasing or decreasing by 0.5°C due to the pain or no pain rating of the participants until first, it reached 40% (mean±SD 44.8 ± 1.3°C) and second, 80% (46.7 ± 1.1°C) of the individual pain threshold. The level of 60% (45.6 ± 1.1°C) of individual painfulness was determined by the mean of the 40 and 80% heat intensities. These intensities were used for the conditioning and test phase similar to the procedures described before for **Study 2** and **3**. Figure 15 displays the experimental design of the placebo experiment of **Study 4**. A non-conditioned verbally induced expectation-only placebo experiment was performed prior to the placebo experiment. This expectation-only placebo treatment was not primarily of interest for this dissertation as the Bayesian framework was intended to be performed on a large sample as comparable as possible to **Study 3**. It was used to test placebo effect magnitudes by only inducing treatment expectations via verbal suggestion without an additional conditioning procedure. Pain intensities of 60% on the individual painfulness for all trials (16 in total) were delivered in the expectation-only experiment. Eight trials with a duration of 10s of heat stimulation were presented per block (placebo/control). One of the green patches were used for the placebo ointment and one blue patch was used for the control ointment. The

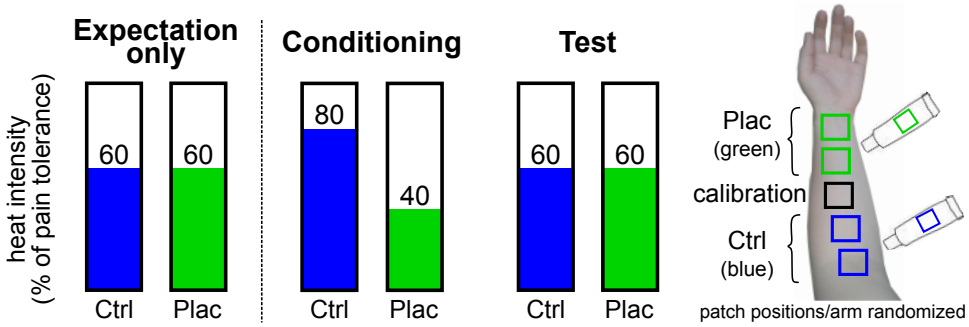


Figure 15. Experimental placebo design of Study 4. Study 4 used heat intensities corresponding to individual pain tolerance levels of 80% and 40% for the conditioning and 60% for the test phase as well as five skin patch positions for the heat stimulation. The two upper and lower positions were randomized and used for the experimental placebo (always green ointment) or control (always blue ointment) blocks, respectively. The stimulated arm was also randomized across subjects. The middle patch was used for the calibration procedure prior to the experiment. An expectation-only placebo treatment, testing the placebo effect solely by inducing it via verbal suggestion, was performed prior to the conditioning phase. *Ctrl, control condition; Plac, placebo condition.*

results were not of main interest as no subjective ratings or other measurements concerning variability levels of prior treatment expectations and experiences were given due to the missing conditioning procedure. Therefore, testing the Bayesian integration model on this data was not possible. However, this might be a possible confound when comparing the results of **Study 3** and **4** as the unconditioned expectation-only procedure might prime specific expectations about the putative effectiveness of the Emla ointment during the conditioning and test phase. Following this, either additional QST procedures or a working-memory-pain task (N-back) were performed. After this, the conditioned placebo experiment followed (Figure 15), which was the main procedure of interest of the entire assessment in order to test the application of the Bayesian integration framework to a large placebo analgesia sample.

This procedure was identical to **Study 2** and **3** only differing in the following (Figure 4 for details). The duration of the painful heat stimulation was 10s with no anticipation phase prior to the heat onset. The ITI as well as VAS rating duration was not defined and dependent on the participants reaction (button presses). The visual stimulus was identical to the other studies showing a white fixation cross for the ITI and a red cross during the painful stimulation. The visual input during heat stimulation was identical for placebo and control trials as the colors of the respective arm patch paired with verbal suggestion gave the necessary information concerning the block condition. Two adjacent skin patches were always used for either placebo

or control blocks as depicted in Figure 15 stimulating one during the conditioning and the other during the test phase. The stimulated arm (left or right) as well as the placebo vs. control patch positions (upper or lower two patches) were randomized across participants. Every block consisted of 8 trials (8 placebo, 8 control per conditioning and test phase, respectively). For the conditioning phase, the same patches were used as for the expectation-only placebo experiment as several minutes fell between these two portions of testing. For the test phase, new, previously unused skin patches were used. After this, all participants underwent additional testing including questionnaires and the nocebo experiments. However, these procedures were not of any interest for this dissertation and will therefore be not described in more detail.

3.4.3 Analysis

Data analysis was performed using the identical procedure as **Study 3** including the calculation of the placebo effect (mean VAS control minus placebo of test phase $\rightarrow \Delta_{VAS_{test}}$), the Bayesian integration (see section 2.3) and model selection (see section 2.5.2), as well as the relationship of the placebo effect with the *attraction weight* (w_{prior}, see Equation 2.3). No group allocation was used as no variability manipulation of the treatment expectations was induced. Only 8 instead of 12 trials per condition were presented in this study and used for analysis. This may be a potential confound in terms of comparing the results of **Study 3** and **4**. Additional comparisons between the sample of **Study 3** and **4** were performed using the Mann-Whitney U-test as the sample sizes differ extremely between the two studies which could have distorted the results. This test represents the non-parametric equivalent to a two sample t-test by comparing the two distributions via focusing on the median instead of the mean.

3.4.4 Results

Table 3 displays a description of the sample presenting mean sum scores and standard deviations of personality questionnaires. In this sample, FKK and MDBF were not acquired. A different measure accounting for possible depressive tendencies was used (Allgemeine Depressionsskala, ADS) in which higher sum scores also indicate a higher tendency towards a depressive mood (Hautzinger, Bailer, Hofmeister, & Keller, 2012). The mixed-effects analysis was performed without group as a fixed effects variable (contrary to **Study 3**). Therefore, only a main effect

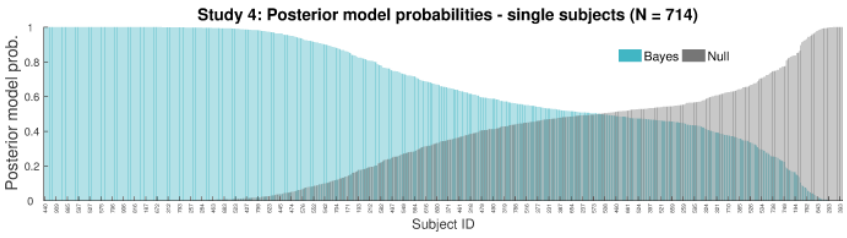
Table 3. Descriptive statistics of personality questionnaires for Study 4. Displayed are the overall sum scores of the questionnaires for the entire sample ($N_4 = 714$). *M, mean; SD, standard deviation.*

	M	SD
ADS	6.98	5.55
STAI: Trait	37.16	8.47
STAI: State	35.91	7.72
PCS: Rumination	2.20	0.99
PCS: Magnification	1.39	0.80
PCS: Helplessness	1.29	0.76

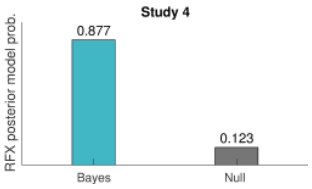
of condition was tested using subject as the random effects variable for conditioning and test phase respectively (identical to **Study 3**). In both experimental phases, a significant condition effect was observed. The conditioning effect reflects the two different temperature intensities presented for placebo vs. control ($F(1, 11422) = 81.30, p < 0.001$) with a mean difference of 28.98 ± 21.02 rating points across subjects. The test phase mean difference of 3.32 ± 12.08 also indicates a significant analgesic placebo effect ($F(1, 11422) = 9.41, p < 0.001$).

The mean variability level of prior treatment expectation (conditioning placebo ratings) reflected by the individual mean SDs across trials was 16.63 ± 7.87. Comparing the variability levels of prior treatment experience of the two samples of **Study 3** ($N_3 = 62$, median SD 18.42 ± 7.15) and **Study 4** ($N_4 = 714$, median SD 15.87 ± 7.15), a Mann-Whitney U-test revealed no significant difference ($U = 19249, p = 0.088$). However, this result needs to be interpreted with caution as it can also be understood as a trend effect near the significance threshold. Also, the placebo effect distributions of the two samples were observed as significantly different comparing them by also using the Mann-Whitney U-test ($median_{Study3} = 6.50 \pm 19.93, median_{Study4} = 2.56 \pm 12.08; U = 18651, p = 0.040$). These two comparisons reflect general differences in the two samples most likely due to different experimental designs and manipulations.

The results of the Bayesian integration model comparison were comparable to the modeling results of **Study 3**. Figure 16a displays the single subject's posterior model probabilities given the observed data. A similar model comparison pattern to **Study 3** in which the Bayesian model is favored over the Null model, was also observed in the large dataset of **Study 4**. Moreover, the overall random effects posterior model probabilities (Figure 16b) revealed that



(a) Single subjects posterior model probabilities given the observed data. The data is sorted by the Bayesian model posterior probability of each subject ($N_4 = 714$). For reasons of clarity, only a few subject IDs are displayed in the x-axis due to the large sample size.



(b) Overall random effects posterior model probabilities.

Figure 16. Bayesian model comparison of Bayesian and Null model given the observed data of Study 4. Displayed is the posterior model probability of the Bayesian compared with the Null model. Reflected in a greater model probability, the Bayesian model is more likely having produced the observed data than the Null model, similar to the results of **Study 3**. *RFX, random effects; r, correlation coefficient.*

the data was better explained by the Bayesian integration model which demonstrated a larger model probability of 0.877 (exceedance probability $\varphi_1 \approx 100\%$) compared to 0.123 (exceedance probability $\varphi_1 \approx 0\%$) in favor of the Null model. Concerning the positive evidence ratio (PER), 311 participants (43.6%) showed a Bayes factor larger than 3 (BF_{10}) which is in favor of the Bayesian integration model. For 60 participants (8.4%), the Null model described the data significantly better than the Bayesian integration model showing a Bayes factor larger than 3 (BF_{01}). This resulted in $PER_{10} = 311/60 \approx 5.18$ in favor of the Bayesian integration model being comparable to the result of **Study 3** ($PER_{10} = 31/7 \approx 4.43$). For 343 of the participants (48.0%), none of the two models described the data significantly better than the other model. Similar to **Study 3**, a positive relationship of the predicted ($\mu_{like} - \mu_{post}$) as well as the observed ($mean_{test_{ctrl}} - mean_{test_{plac}}$) placebo effect was found ($r = 0.304, p < 0.001$). Different to the result of **Study 3**, a small but significant negative relationship between the mean of prior treatment expectations (μ_{prior}) and the placebo effect magnitude was observed ($r = -0.132, p < 0.001$). The less painful the heat intensity or, in other words, the more effective the treatment was perceived to be during the conditioning (irrespective of the variability level), the larger the placebo effect magnitude during the test phase was.

Next, the *attraction weight* (w_{prior}) was used to investigate the variability influence within the larger sample to compare it to the findings of **Study 3**. As described before, this parameter considers the variability level of both, the prior and the likelihood, irrespective of the influence

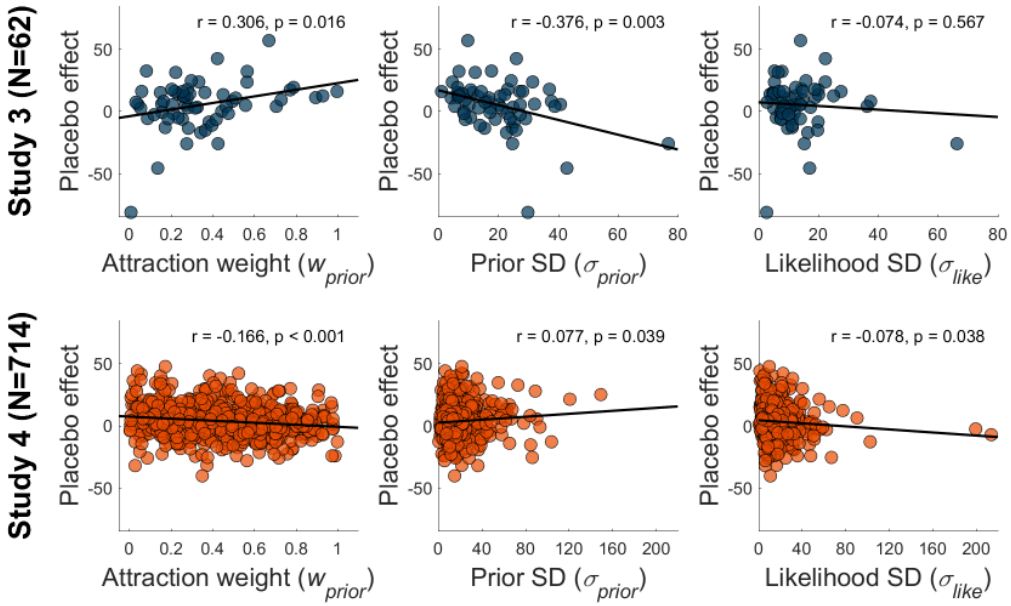


Figure 17. Relationships of attraction weight as well as its two components σ_{prior} and σ_{like} with the corresponding placebo effect magnitudes for Study 3 and 4. Displayed are correlative relationships of the placebo effect with the *attraction weight* and the variability levels of both, prior treatment expectations (σ_{prior}), as well as new incoming sensory information (σ_{like}) for **Study 3** and **4**, respectively. *SD, standard deviation; r, correlation coefficient.*

of the mean parameters of the two. The *attraction weight* reflects the relative influence of prior and likelihood on the posterior prediction of the treatment outcome as described in Equation 2.3. Figure 17 (first in bottom row) shows the negative relationship of the *attraction weight* with the placebo effect ($r = -0.166, p < 0.001$) indicating that the more variable and therefore less precise prior treatment expectations are compared to the variability of the new sensory input, the larger the placebo effect magnitude is. Larger values in w_{prior} reflect higher precision (less variability) in the prior. This *attraction weight* finding is a contrary result to the findings of **Study 3** where higher precision in the prior treatment expectation lead to larger placebo effect magnitudes, as this is also depicted in Figure 17 (first in top row). For this reason, this result was investigated in more detail descriptively. First, the two components of the *attraction weight* (σ_{prior} and σ_{like}) were correlated with the placebo effect individually to see whether a different pattern is observed between the two studies. In both studies (Figure 17), the variability level of prior treatment expectations (σ_{prior}) showed a significant correlative relationship with the placebo effect (middle column). The small negative relationship between

the placebo effect magnitude and the new incoming sensory information (σ_{like}) was observed to be almost identical in both studies (third column). After controlling for the two outliers in the third subplot of **Study 4** for the relationship of σ_{like} with the placebo effect magnitude ($r = -0.071, p = 0.058$), the variability level of the likelihood was observed as being non-significant in both studies. In other words, concerning the *attraction weight*, the influence of the variability level of the prior shapes the relationship of this relative parameter with the placebo effect more than the likelihood variability. However, the correlation of the smaller sample of **Study 3** is more sensitive to outliers which might possibly influence this result. Nevertheless, due to the different experimental protocols of **Study 3** and **4**, the possibility of different underlying correlative relationships must be considered. On the one hand, **Study 3** used an expectation-only placebo test prior to the actual placebo experiment which might have primed the analgesic effect in a certain direction. **Study 4**, on the other hand, induced variability in half of the sample which might have changed the attention towards the different experimental conditions.

To investigate this even further, the relationship of *attraction weight* and the placebo effect magnitudes were considered being dependent on showing a significant Bayesian integration (Bayes winner: $BF_{10} > 3$) or not (Null winner: $BF_{01} > 3$). Figure 18 displays these results in detail. The first row shows again the *attraction weight* and placebo effect relationship which combines all three underlying plots of the second to the fourth row per study. The dashed line in each plot marks the threshold between a positive (pain relief during test phase placebo condition compared to the control) and a negative placebo effect (pain increase during test phase placebo condition compared to the control). In both studies, most of the Bayesian integraters, which were participants showing a Bayes factor of 3 or larger in favor of the Bayesian integration model, had a positive placebo effect (second row). Additionally, a significant negative relationship of these Bayesian integraters with a positive placebo effect was found with the *attraction weight* ($r = -0.213, p < 0.001$) for **Study 4**. In both studies, the non-integraters, characterized by a Bayes factor equal to or larger than 3 in favor of the Null model, were represented mostly by a negative placebo effect (third row). This effect correlated positively with the *attraction weight* in **Study 3** ($r = 0.904, p = 0.005$) as well as in **Study 4** ($r = 0.400, p = 0.002$). However, in **Study 3** only for 7 participants the Null model was favored over the Bayesian model, which represents

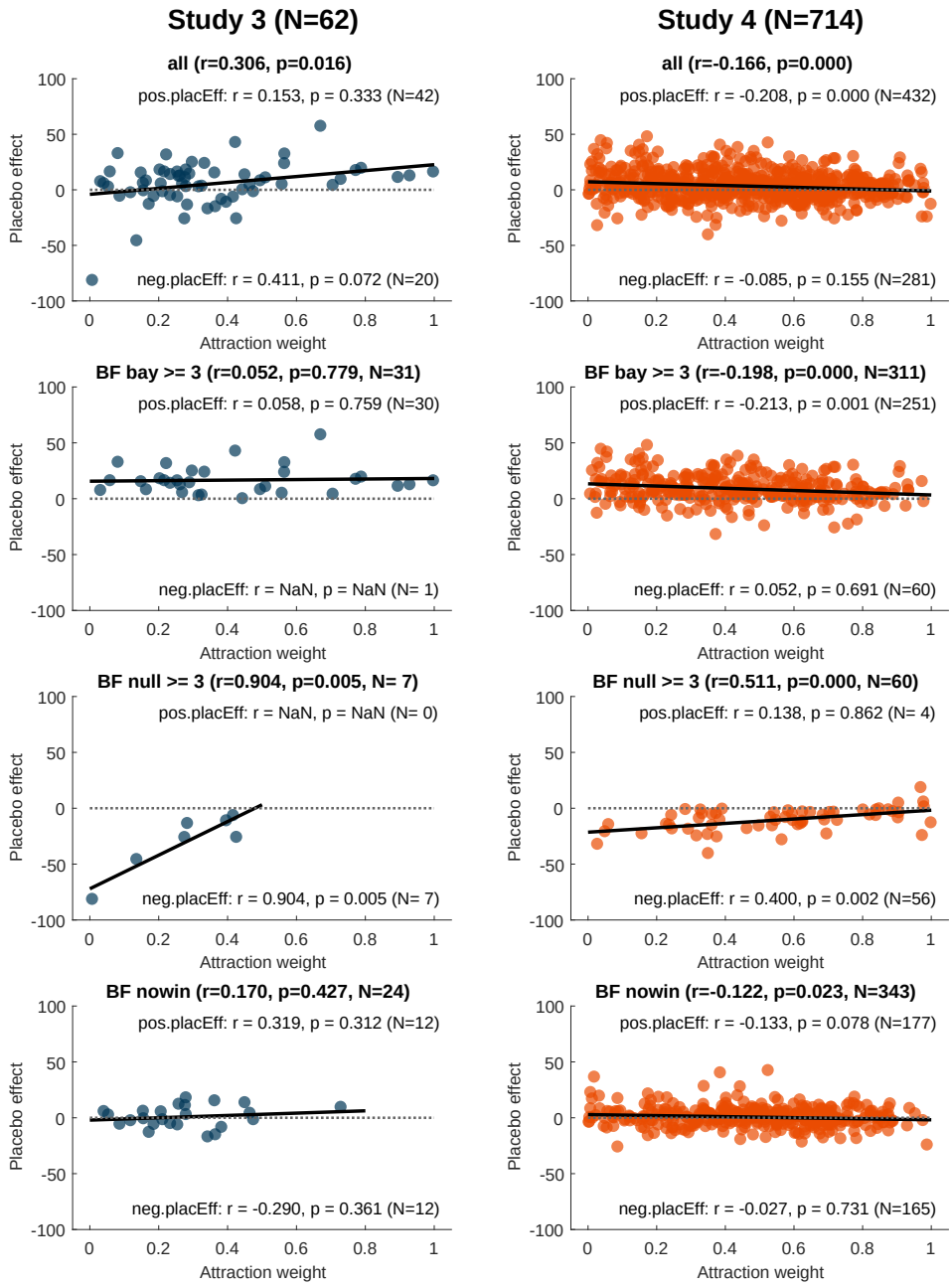


Figure 18. Relationships of attraction weight and placebo effect magnitudes seperated into Bayesian integraters, Null model non-integraters, and non-winners for Study 3 and 4. The dashed line represents the threshold between a positive and a negative placebo effect. The fitted regression line depicts the whole respective sub-sample per subplot irrespective of the direction of the placebo effect magnitude. *pos.plac.Eff, positive placebo effect (pain hypoalgesia - relief in placebo condition); neg.plac.Eff, negative placebo effect (pain hyperalgesia - increase in placebo condition); r, correlation coefficient (Pearson); BF bay, Bayes factor in favor of Bayesian integration; BF null, Bayes factor in favor of Null model; BF nowin, neither model was favored by the data; NaN, not a number (missing value).*

only a small sample and makes it difficult to reliably compare the Null model results of the two studies with each other. Concerning the non-winners, described as participants in which the data neither favored the Bayesian nor the Null model over the other, the results are inconclusive (fourth row). Approximately half of the sample of both studies showed either a positive or a negative placebo effect. A small significant negative relationship between the *attraction weight* and the placebo effect magnitudes was observed in **Study 4**. However, no conclusion can be drawn from this yet, as possible other modulating factors need to be investigated in order to describe this effect in more detail.

As it was performed in **Study 3**, a multiple linear regression was applied entering both *attraction weight* inputs ($\sigma_{prior}, \sigma_{like}$). In the larger sample, this analysis also revealed a significant effect ($F(2, 711) = 7.47, p = 0.001, R^2 = 0.021, adj.R^2 = 0.018$). The corresponding equation for the prediction of subjects' placebo effect magnitude was equal to $3.171 + 0.102 * \sigma_{prior} - 0.105 * \sigma_{like}$. As in **Study 3**, inspecting the corresponding coefficients statistics, both the variability level of prior treatment expectations ($\beta = 0.102, t(711) = 3.247, p = 0.001$) as well as the variability of sensory inputs ($\beta = -0.105, t(711) = 3.255, p = 0.001$), showed a small but significant influence on the prediction of the placebo effect. A positive regression weight for σ_{prior} indicates that the placebo effect magnitude is expected to increase for subjects with less precise (more variable) prior treatment expectations after controlling for the variability level of new perceived sensory inputs (σ_{like}). This, again, depicts a contrary finding to **Study 3** where a negative relationship was observed. To investigate this further, not only the two *attraction weight* components σ_{prior} and σ_{like} were inserted in a more exploratory multiple linear regression analysis, but also the prior mean μ_{prior} was added. This was done as the relationship between the *attraction weight* and the placebo effect depicted in Figure 17 only showed a difference between the two studies in σ_{prior} (variability level of prior treatment expectations) whereas the influence of σ_{like} was comparable in both studies. This more exploratory regression analysis was performed for **Study 3** and **4**, respectively. For **Study 3**, a significant result was observed ($F(3, 58) = 4.70, p = 0.005, R^2 = 0.196, adj.R^2 = 0.154$) showing an influence of σ_{prior} ($\beta = -0.908, t(58) = 3.694, p < 0.001$) but not of σ_{like} ($\beta = 0.515, t(58) = 1.645, p = 0.105$) and μ_{prior} ($\beta = -0.085, t(58) = 0.736, p = 0.465$) when entering all three variables. This reflects that even when controlling not only for σ_{like} but also μ_{prior} a negative relationship between

the level of variability of prior treatment expectations (σ_{prior}) and the placebo effect is still observed. For **Study 4**, a different relationship was found. A significant result was observed ($F(3, 710) = 8.24, p < 0.001, R^2 = 0.034, adj.R^2 = 0.030$) showing an influence of μ_{prior} ($\beta = -0.075, t(710) = 3.097, p = 0.002$) as well as σ_{like} ($\beta = -0.110, t(710) = 3.402, p = 0.001$) but no effect of σ_{prior} ($\beta = 0.018, t(710) = 0.436, p = 0.663$) when entering all three variables in one linear regression. After exploring the data, the two studies showed different effects of the mean (μ_{prior}) and the variability levels (σ_{prior}) of prior experiences as well as different impacts of the variability levels of new incoming sensory information (σ_{like}). This created divergent expectations concerning the placebo treatment and resulted in different relationships of the *attraction weight* and the placebo effect as well as its corresponding components between the two studies.

3.4.5 Short conclusion

The aim of **Study 4** was to use the results of an independent study with a larger sample size to test the validity of a Bayesian framework in placebo analgesia. These findings show that in another experimental placebo design, Bayesian integration is still able to predict treatment outcomes in a sufficient way. Comparing **Study 3** and **4**, again, the Bayesian integration framework predicted placebo treatment outcomes based on various individual prior and likelihood distributions. The model did not favor high over low prior precision and is therefore not only suitable for one specific case as it accounts for the whole variability spectrum of prior treatment expectations. The findings of the two studies add to similar approaches which also propose alternative ways of analyzing perceptual sensory experiences such as pain (Anchisi & Zanon, 2015; Büchel et al., 2014; Wager et al., 2013; Wiech et al., 2014) indicating the usefulness and importance of creating new models which can parsimoniously account for several modulating factors of a phenomenon of interest.

Interestingly, the two studies showed comparable ratios of Bayesian integraters ($N_{3_{10}} = 31 = 50\%$ vs. $N_{4_{10}} = 311 = 43.6\%$), non-integraters ($N_{3_{01}} = 7 = 11.3\%$ vs. $N_{4_{01}} = 60 = 8.4\%$), and non-winners ($N_{3_x} = 24 = 38.7\%$ vs. $N_{4_x} = 343 = 48.0\%$) as depicted in Figure 18. Most Bayesian integraters showed a positive placebo effect and therefore were characterized with a pain relief in the placebo treatment condition compared to the identical control trials. These

individuals probably benefited in terms of pain perception from the optimal integration of prior experiences and expectations with the new incoming sensory information. However, only in the large sample of **Study 4**, a correlative negative relationship of these Bayesian integraters was observed with the *attraction weight*. This means that higher variability levels in the prior compared to less variability in the likelihood were related to larger placebo effects.

The non-integraters, however, favoring the Null over the Bayesian integration model, mostly showed a negative placebo effect and a positive correlation of it with the *attraction weight*. These individuals perceived the control trials as less painful as the identical placebo treatment trials and therefore felt a pain increase instead of a relief for the treatment. The Null model assumed no influence of the prior treatment conditioning on the placebo effect and pain perception. Assuming this, other treatment experiences possibly shaped the placebo response in these participants such as real treatment history or prior knowledge about the respective treatment that was applied during the experiment (TENS or Emla). This observation was identical for both studies. Alternatively, the prior treatment expectations and the test phase analgesic treatment experience were possibly perceived as being too different from one another. Due to this large mismatch between expectations and reality, the placebo effect was unable to form. This is assumed as it was observed that the more variable the prior treatment expectations were, the more negative the placebo effect and therefore the more painful the treatment experience was.

The non-winners most likely represent a group of subjects that cannot be described as Bayesian integraters nor can they be described by a model assuming no learning during placebo treatment conditioning. It was observed that a comparable number of participants in the non-winners showed a positive and a negative placebo effect (each approximately 50%). It is difficult to draw conclusions about this observation as additional descriptive information is missing in the studies performed for this dissertation.

Study 3 and **4** also present interesting new insights concerning different placebo treatments and experimental designs. Dependent on prior treatment manipulations in the different experiments, varying influences concerning the variability level of the prior and the likelihood were observed. In **Study 3**, a conditioning phase prior to the experimental test phase of the placebo effect, paired with verbal suggestion, seemed to cause a higher importance of prior variability levels compared to **Study 4**. This was concluded as in **Study 3**, irrespective of the prior mean,

the prior variability level modulated the placebo effect. Contrary to this, results of **Study 4** showed that the prior mean was the most pronounced in influencing the placebo effect and not the variability level of the prior. In **Study 4**, a non-conditioned verbally induced expectation-only placebo experiment was performed prior to the conditioned placebo experiment. This assumingly induced different expectations in **Study 4** as the first exposure to the treatment was not as pain relieving and effective as it was in **Study 3**. Therefore, it might be possible, that in **Study 4** an additional variability or uncertainty component was presented to the participants due to the non-conditioned only verbally induced placebo in the beginning. This is assumed to have resulted in a higher importance of the prior mean pain relief (μ_{prior}) in the then following conditioned placebo test phase as the subjects were exposed twice to the placebo treatment before entering the test phase. First, the placebo treatment was likely perceived as either just slightly effective, or even not at all effective, based on individual's susceptibility to verbal suggestion (non-conditioned expectation-only treatment: placebo and control condition both 60% individual pain intensity). Second, shortly after an in-between task, a more effective experience of the same treatment followed being characterized by the different heat pain intensities that were presented to the participants (conditioned treatment: placebo 40% and control 80% individual pain intensity). It is assumed that these two treatment experiences were compared to each other and internally averaged in terms of treatment efficacy. Figure 19 in section 4.1 illustrates this assumption in more detail. After this, the participants entered the test phase, which was identical to the expectation-only treatment experience while testing the placebo effect. Such a manipulation can be compared to immediately consecutive clinical interventions that might also vary in their effectiveness over time. On the contrary, in **Study 3**, participants only experienced the treatment once and very effectively before the test phase due to the two different conditioning temperatures (conditioned treatment: placebo 30% and control 70% individual pain intensity).

Therefore, based on the observed results, slight differences in treatment experiences and expectations can modulate factors that influence placebo analgesia. In two experimentally comparable studies, varying importance was identified for prior treatment experience and expectation components. However, up to this point, these findings need future research to further investigate the influence of the Bayesian prior on pain and placebo treatment outcomes. Due to several

open questions, the results only hint at the importance of prior treatment experience and expectations in a Bayesian placebo framework. However, depending on the treatment history of a patient, these findings can be harnessed to optimize individual treatments.

4 Discussion

This dissertation aimed to contribute to a better understanding of the influence of variability on pain perception and the placebo effect. As pain perception varies highly across individuals (Coghill & Eisenach, 2003), the decision to focus on variability as an important driving modulator of somatosensory phenomena seemed promising. It remains a very timely and relevant research question as it is still difficult to predict and fully understand the underlying mechanisms of subjective pain perception. Previous literature provides several studies investigating how this subjective percept can be compared as objectively as possible (Coghill, 2010; Jensen, Karoly, O'Riordan, Bland, & Burns, 1989; Koyama, McHaffie, Laurienti, & Coghill, 2005) to potentially generalize certain findings across individuals. As described before, one of the key components of modulating pain perception and related phenomena are expectations (Benedetti, Arduino, & Amanzio, 1999; Dannecker, Price, & Robinson, 2003; Price, 2000; Robinson, Gagnon, Riley, & Price, 2003; Tracey, 2010; Yoshida et al., 2013). For that reason, finding new insights into how expectations contribute to nociceptive perception and pain processing will not only inform future research, but also contribute to the improvement and development of clinical interventions. The placebo effect is hereby an important phenomenon as it is highly driven by expectations (Atlas et al., 2010; Colloca & Benedetti, 2006; De La Fuente-Fernández et al., 2001; Enck et al., 2013; Kirsch, 1999; Klinger et al., 2007; Reicherts et al., 2016; Rief et al., 2011; Schenk et al., 2014; Stone et al., 2005; Wager et al., 2004) which makes it possible to investigate its modulatory impact on pain perception as well as clinical treatment outcomes. Thus, this dissertation was the first to investigate the influence of different levels of variability in prior treatment expectations on the expectation-driven effect of placebo analgesia during acute pain in healthy individuals.

The brief conclusions described before concerning each of the four studies presented here, already hinted at the promising influence of variability on the processing of pain and placebo analgesia which is mostly ignored in previous research. The variability level of prior treatment expectations might, at least in part, explain the large inter-individual differences which are observed in pain and placebo studies (Coghill & Eisenach, 2003; Vase et al., 2009; Wager et al., 2011). This was assumed as modulators such as medication value (Geuter et al., 2013; Waber

et al., 2008), treatment history (Kessner et al., 2014, 2013; Müller et al., 2016), doctor-patient relationship and beliefs (Benedetti, 2013; Kampermann et al., 2017), emotion (Petrovic et al., 2005; Zhang & Luo, 2009; Zhang et al., 2013), social influence (Crum et al., 2016), as well as treatment context effects (Blasi et al., 2001) were already related to placebo hypoalgesia being likely factors shaping individual expectations differently.

4.1 How Bayesian integration can inform placebo research

In **Study 1** it was shown that a certain level of variability is needed to induce a perceived variation in heat-related painfulness reflected in the differences in subjective pain ratings. As pain ratings are not the most optimal, but yet the most promising method of measuring subjective painfulness (for a review see Williamson & Hoggart, 2005), it was important to test the pain intensity differences which would be needed to observe variability in the ratings of pain percept. This provided the foundations for **Study 2** to create two groups which differed in their levels of variability concerning experienced treatment efficacy. Such a manipulation induction provided the opportunity to compare the influence of variability in prior treatment expectations on the effect of placebo analgesia. These results hinted at the assumption that a higher level of variability in prior treatment expectations and experiences lead to smaller analgesic effects when being treated with a placebo. In other words, participants of the VTE group, which perceived the treatment as more variable prior to the placebo test phase, showed little to no pain relief due to the treatment. As findings of related placebo hypoalgesia studies are still missing, some studies have already reported related results, also observing increased perceived painfulness due to higher levels of uncertainty prior to a painful stimulation (Lin et al., 2014; Yoshida et al., 2013). This is a possible explanation of this finding as the induced variability during the first treatment experience (conditioning phase) created unreliable expectations concerning the treatment efficacy. Therefore, these participants were not benefiting from their expectation as much as those in the CTE group as the perceived prior variability reduced the treatment's prospective placebo effect significantly. In line with this, other research suggested that an invalid match of expected and perceived pain intensity modulates the painfulness in the direction of the expected pain intensity (Lorenz et al., 2005). A high-intensity painful stimulation is perceived as

less painful and a low-intensity stimulation as more painful when followed by mismatching prior cue information. Complementing this, cue information about 'certain' high-intensity stimuli were perceived as more painful, whereas 'certain' expectations about low-intensity stimuli were experienced as less painful (Brown, Seymour, Boyle, El-Deredy, & Jones, 2008). These two studies also contribute to a Bayesian integration understanding of the placebo effect and the findings of **Study 2**. Pain relieving and very precise prior treatment experiences (i.e. CTE group) likely induce higher placebo hypoalgesia effects than pain relieving and quite variable prior treatment experiences (i.e. VTE group). In other words: you always get the pain you expect (Tracey, 2010), especially when you are certain about it.

Study 2 was therefore helpful for informing the procedure of the following study. In **Study 3**, the influence of different variability levels in prior experiences and expectations was tested by introducing a Bayesian integration framework of placebo hypoalgesia (Büchel et al., 2014). The implementation of the mathematical model including the model comparison procedure of this yet only theoretical Bayesian framework and applying it to acquired placebo analgesia data was one of the main aims of this thesis. It was found that, indeed, a Bayesian approach not only focused on the strength (i.e. mean) but also the level of variability of prior treatment expectations, combined with new incoming sensory information is plausible to describe placebo treatment outcomes. Importantly, not only behavioral but also fMRI data showed a modulatory impact of variability on the pain perception and placebo treatment outcomes. The neural data revealed the involvement of the descending modulatory pain system (Figure 1). Specifically, BOLD signal changes were observed in brainstem regions that are associated with the PAG and, at least on the trend level, the RVM. A strong pain modulating association of the PAG has already been observed in previous research (Fairhurst et al., 2007; Jones & Gebhart, 1988; Linnman et al., 2012; Vanegas & Schaible, 2004). Moreover, other studies have also suggested the involvement of this area in the coding of variability related pain phenomena such as pain avoidance prediction error coding (Roy et al., 2014) and the processing of precision of vicarious information (Yoshida et al., 2013). The behavioral data of **Study 2**, **3**, and **4** demonstrates that the pain modulation underlying placebo hypoalgesia is highly dependent on the variability level of prior treatment expectations. Therefore, the results of **Study 3** suggest that the PAG is crucially involved in variability biased integration processes due to its pro- as well as

anti-nociceptive modulatory properties. Moreover, it was found that a lower *attraction weight*, which is characterized by more variable prior treatment expectations compared to more precise new incoming information, was related to an increased BOLD signal in the PAG. This is further in line with the findings of Yoshida et al. (2013) who also observed a signal increase in the PAG due to a subject's high susceptibility to induced variability (see section 1.3.1 for details). It is assumed that the wider range of possibilities concerning the painfulness or efficacy of the treatment leads to less predictability (Fairhurst et al., 2007) and more resource-demanding cognitive processes to optimally adapt to possible future treatments. This is reflected by the signal increase in the PAG. The brain is assumed to modulate the painful input and generates new expectations about the treatment to minimize future surprise (Feldman & Friston, 2010; Friston, 2010; Friston et al., 2009). Moreover, several studies show a relationship of placebo-induced signal increases of the PAG with the strength of the analgesic effect and have connected this to the opioidergic descending modulatory pain system (Eippert, Bingel, et al., 2009; Peciña et al., 2013; Wager et al., 2004). As the findings of **Study 3** revealed that PAG placebo-induced signal increases are also related to higher variability in prior treatment expectations, an influence of opioidergic descending pain modulations is speculated as the same trend-wise activation pattern was also observed in the RVM. In line with this is the finding that the PAG was also found to be responsive to placebo-induced expectations in another study (Scott et al., 2008) which showed a positive correlation of the anticipated analgesic effect with an increased BOLD signal change. Also, since placebo-induced BOLD signals of both brain regions, the PAG and the RVM, were previously related to a reduced activation after the administration of naloxone, an opioid-antagonist known to impair placebo-dependent pain reduction (Amanzio & Benedetti, 1999; Grevert, Albert, & Goldstein, 1983; Levine & Gordon, 1984; Levine et al., 1978), the involvement of the opioidergic descending pain control system seems to also be likely concerning variability processing. To summarize, the use of an optimally integrated Bayesian weight (*attraction weight*) presented the opportunity to explicitly investigate the influence of variability on neural pain processing irrespective of the mean intensity of pain in a placebo analgesia context. Yoshida et al. (2013) were not able to clearly determine whether their observed PAG result was driven by an underlying linear mean effect of pain or the uncertainty level they induced during their vicarious observation task. The results of **Study 3** provide clearer evidence

for this. However, the observations of **Study 3** do not negate the influence of the mean pain intensity as a behavioral main effect of condition during the placebo test phase was also found. This also relates to the findings of **Study 4** in which the Bayesian integration model was tested in a large sample with a different experimental placebo treatment design. It was shown that, in line with **Study 3**, the Bayesian integration framework of placebo analgesia seemed suitable to predict placebo treatment outcomes. However, the relationship of the placebo effect magnitude with the variability level of prior treatment expectations showed a different result compared to **Study 3**. An increased placebo effect magnitude was observed for participants with more variable prior treatment expectations. In **Study 4**, the impact of the mean intensity of prior pain experiences (μ_{prior}) influenced the expectation-driven placebo analgesia more than the prior expectation variability level (σ_{prior}) as observed in **Study 3**. Due to the two studies showing different results concerning the direction of the relationship between variability and placebo effect magnitudes, a more exploratory approach was used to further investigate this variation. First it was noted that in both studies, the Bayesian integration framework predicted placebo treatment outcomes equally well. In other words, comparing the ratios of Bayesian integraters, non-integraters, and non-winners, it was observed that the model produced similar modeling fits across different experimental placebo designs and population samples. Therefore, at least based on the two different studies, a certain robustness of this new Bayesian approach in placebo analgesia can be assumed, given that future research will provide comparable results. This is in line with a previous behavioral study that also noted the usefulness of investigating placebo analgesia via a Bayesian model (Anchisi & Zanon, 2015). Due to these congruent findings concerning the Bayesian model approach, paired with the sound neural observations of **Study 3**, it is assumed that both study results may contribute to a better understanding of the influence of variability on pain perception and the placebo effect. For this reason, the differences between **Study 3** and **4** were compared to find possible modulators for the observed differences in the results. Figure 19 displays the different experimental placebo designs including the two opposing observations of the relationship of placebo effect magnitudes and the *attraction weight* in **Study 3** and **4**.

In more detail, as previously described in section 3.4.5, the main difference between the two studies was in the experimental procedure prior to the placebo test phase. Participants of

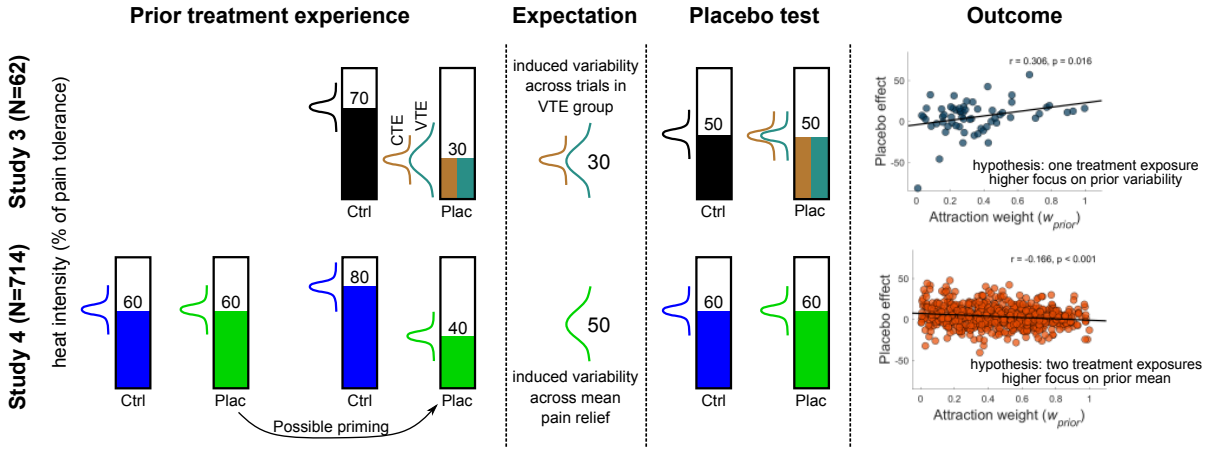


Figure 19. Experimental and outcome differences of Study 3 and 4. Depicted are the experimental differences of the two studies and possible explanations for the opposing observations of the relationship between the placebo effect magnitudes and the *attraction weight*. In the sense of Bayesian integration, experimentally-induced variability is not only assumed being present in the VTE group of the placebo conditioning of **Study 3** but also in **Study 4** via two different mean intensities for the treatment prior to the placebo test phase. A possible explanation for the difference is that one treatment exposure may lead to focus on the variablity level, whereas several exposures may highlight the importance of the treatment's mean pain relief. *Ctrl, control condition; Plac, placebo condition; CTE, constant treatment expectation; VTE, variable treatment expectation; r, correlation coefficient.*

Study 3 experienced the treatment only once compared to those in **Study 4** who were exposed to the treatment twice before entering the test phase. Importantly, the direct experience prior to the placebo test phase was identical for both studies, only differing in the intensity levels of the two conditioned temperatures (30% and 70% vs. 40% and 80% of individual pain tolerance). However, Participants of **Study 4** underwent an additional expectation-only procedure prior to the conditioning phase. Therefore, not the manipulation of the variability across trials (as in **Study 3**), but the variability induction across the mean pain relief of the same treatment was created via the two treatment exposures before entering the test phase (Figure 19). As this presents additional information about possible temporal effects, the different findings of **Study 3** and **4** may not only be considered as a drawback but as a possibility to generate new hypotheses. Certainly, the current findings are not suitable to provide conclusive interpretations, but it highlights the importance of temporal dynamics of treatment experiences and possible differences concerning the frequency of one or several treatment exposures. Also, since previous findings show that the carry-over effects of treatment history on identical and new treatments play a modulating role for treatment outcomes (Kessner et al., 2013, 2014), the different find-

ings of **Study 3** and **4** might be important for future investigations. Additionally, the different study designs may inform future research with regard to optimize the variability manipulation according to the specific hypothesis of interest.

4.2 Clinical implications and future directions

This dissertation offers promising new insight into the important influence of variability on pain and placebo treatment mechanisms. It presents novel neural and behavioral results that support the applicability as well as usefulness of a Bayesian integration framework in the context of placebo hypoalgesia. As these findings provide a new approach for investigating pain perception and related phenomena, such as the placebo effect, future research is needed to further support these results and develop related clinical applications.

Concerning a clinical context, the influence of expectations and therefore placebo effects is assumed to be present in every clinical intervention as it is observed in placebo analgesia studies investigating patient samples (De La Fuente-Fernández et al., 2001; Kaptchuk et al., 2008; Kelley et al., 2009; Marchand et al., 1993). It depends on different modulators how much a patient may benefit from this positive analgesic phenomenon. Addressing this, the results of this dissertation clearly indicate that the level of variability of prior treatment experience and corresponding expectations crucially determine placebo effect outcomes (Grahl et al., 2018). It seems important to explicitly assess prior treatment experiences and expectations to optimally influence the efficacy of future interventions. The Bayesian integration framework of pain perception and placebo analgesia may also be able to inform several pain related research areas. Growing evidence implies that a dysregulation of the descending modulatory pain system may be related to the chronification of pain (for a review see Ossipov et al. (2014)). A novel approach such as Bayesian integration may serve as a method to generate new hypotheses concerning disruptions of the underlying modulatory circuits of pain related mechanisms. It was also previously speculated that the PAG-RVM modulation in pro-nociceptive responses may be involved in the generation and maintenance of uncomfortable and painful functional disorders such as chronic pain, irritable bowel syndrome, and fibromyalgia (Tracey & Dunckley, 2004). Therefore, connecting the PAG-RVM circuit to the coding of variability levels in prior treatment expectations can provide new insights concerning presumably important aspects of these

disorders. It may also generate new assumptions concerning inter-individual differences between such patients. However, as a clinical sample has yet to be tested using the Bayesian integration framework, these interpretations remain highly speculative and need further investigation by future clinical research.

The frequency and corresponding effectiveness concerning the exposure to one specific treatment may also change the influence of certain modulators of the placebo effect. As the results of **Study 3** and **4** only hint at possible implications, further investigation is needed to shed light on these specific relationships. **Study 3** implied that it may be useful to provide precise a priori information concerning a treatment as this likely creates precise prior expectations and therefore increases a possible placebo effect. These findings were supported by neural correlates in the PAG and RVM. However, the results of **Study 4** suggest that two opposing treatment experiences (i.e. expectation-only with no stimulation difference to control followed by conditioned placebo treatment with high and low pain stimulation) prior to a third treatment exposure (i.e. placebo test phase, again identical stimulation) highlight the importance of the mean of prior treatment expectations and experiences. Patients with such a treatment history may even benefit from higher variability levels in prior treatment expectations as it opens the possibility of different more positive treatment outcomes and potentially increases placebo effects. Importantly, treatment history was found to be a crucial modulator of placebo analgesia (Kessner et al., 2013, 2014; Müller et al., 2016) which underlines the importance of testing this hypothesis in future studies.

Furthermore, the experimental design used in **Study 2** and **3**, which modulated different levels of precision of prior treatment expectations in two groups, provided new insight due to an experimentally induced variation of prior treatment expectations. The test phase stimuli, however, were held constant in both groups without inducing any variability concerning the treatment. Therefore, the CTE group experienced the placebo treatment always as constant during both exposures (conditioning and test phase) whereas the VTE group experienced a variability mismatch between the first (conditioning) and the second (test phase) treatment exposure. This was done to investigate the specific effect of variability levels of prior treatment expectations without interfering variability of the test phase stimulation. For that reason, however, the current results cannot answer the question whether and how additional variability induction in the

test phase may also influence pain and placebo treatment processing. A future study investigating both matching as well as mismatching conditioning and test phase variability levels would shed more light on these complex modulatory mechanisms. In line with this, prior research has already emphasized the important differences between valid and invalid expectations and real pain experiences (Lorenz et al., 2005; Tracey, 2010) which validates the need for such a variability focused investigation.

Moreover, in previous research an influence of the medication value on the placebo effect was observed (Geuter et al., 2013). More expensive medication was related to higher placebo effect magnitudes. Additionally, the doctor-patient relationship (Benedetti, 2013) as well as social influence (Crum et al., 2016) seem to also modulate the strength of the placebo effect. These findings emphasize the importance of prior treatment information and interactions. Therefore, a new study not only including a variability manipulation concerning the analgesic pain experience but also introducing a variation of different placebo treatment instructions may also provide new insights regarding the underlying mechanisms of variability coding in the doctor-patient relationship. Dependent on the physician's advice or general information concerning a placebo treatment, a patient may respond differently to more precise vs. more variable/unreliable prior knowledge showing either larger or smaller placebo effects. This could present another research topic which could be easily investigated using the Bayesian integration framework. A simple weight concerning the instruction condition could be applied to the prior parameters (μ_{prior}, σ_{prior}) to investigate this additional influence.

5 Conclusion

Effects of placebo analgesia are highly depend on subjective prior experiences and expectations concerning a treatment and therefore vary extensively across individuals and studies. This dissertation presents promising results for a new multidimensional approach, parsimoniously accounting for several factors of underlying mechanisms of placebo effects. Bayesian integration seems highly valuable for better describing the complex and rather subjective underlying mechanisms of pain perception, treatment outcomes, and placebo-induced analgesia. This was not only shown in several behavioral results but also supported by neural correlates of the processing

of variability of prior treatment expectations via the descending modulatory pain system (PAG and RVM). By integrating both within one model, the strength of a treatment's pain relief, as well as the level of variability of prior experiences concerning a treatment outcome, this dissertation was able to emphasize the importance of the mostly ignored influence of variability on pain perception and placebo analgesia.

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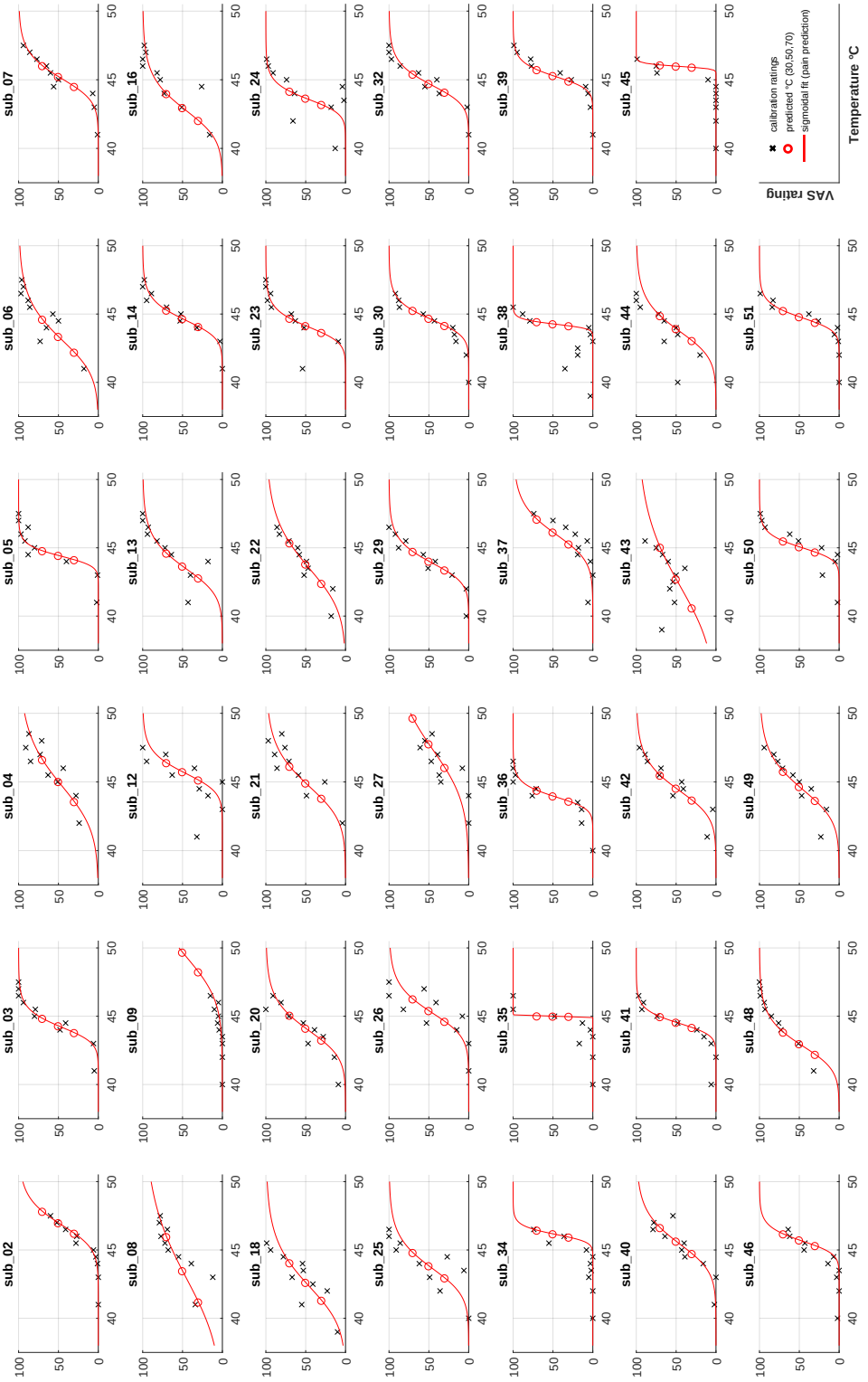
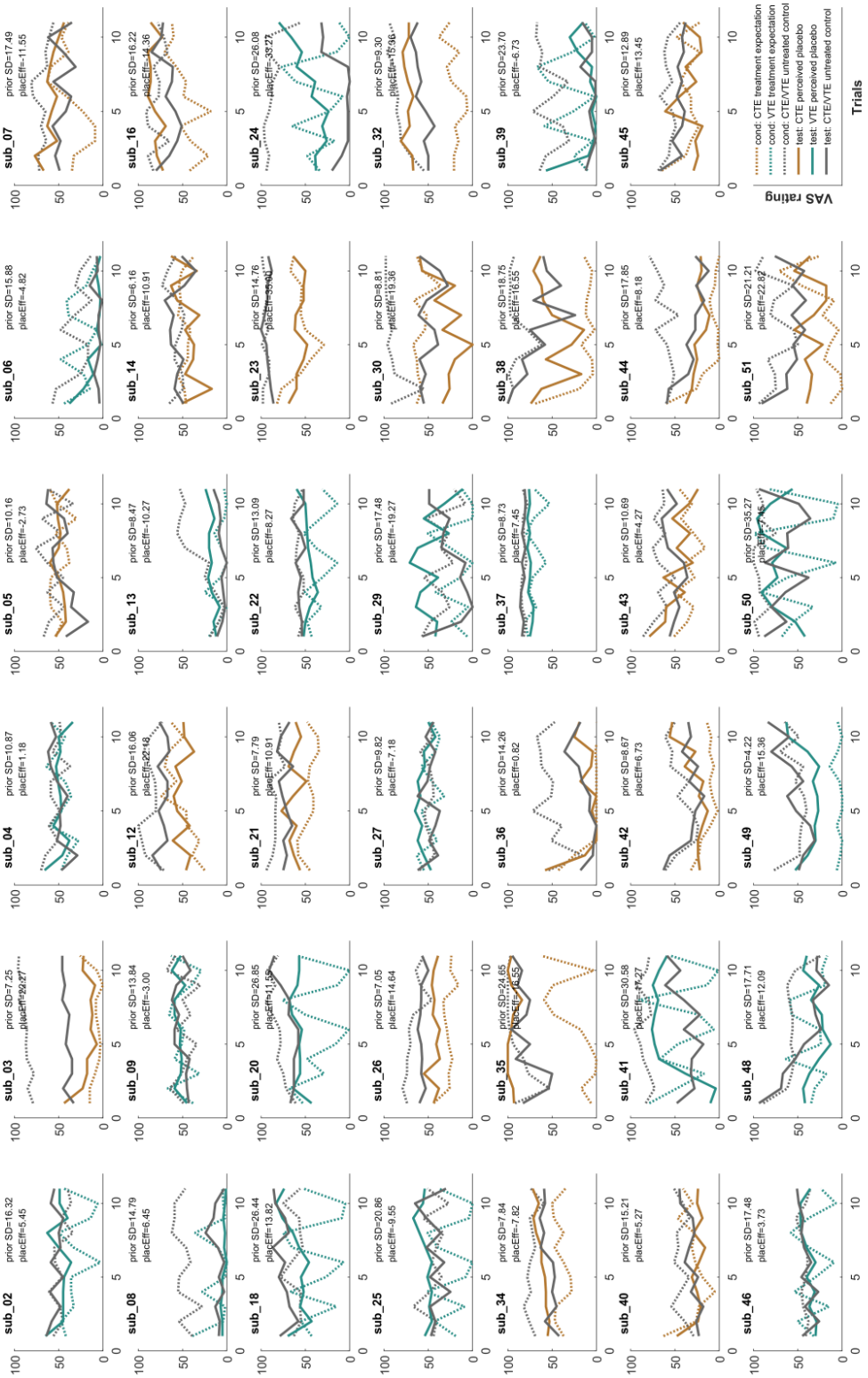
A APPENDIX - Study 2

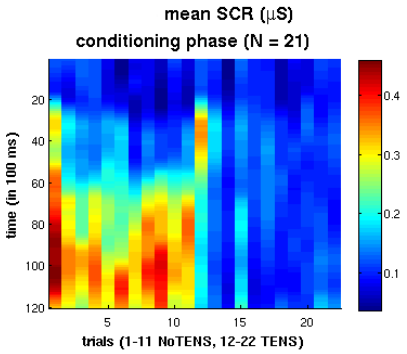
A.1 Sigmoidal fits of calibration data

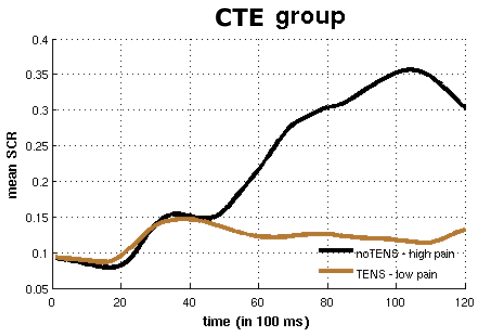


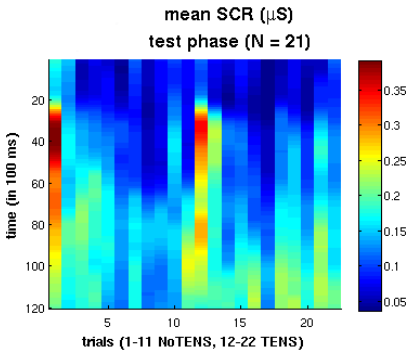
A.2 Experimental VAS pain ratings

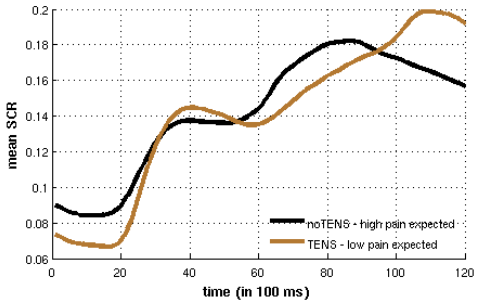


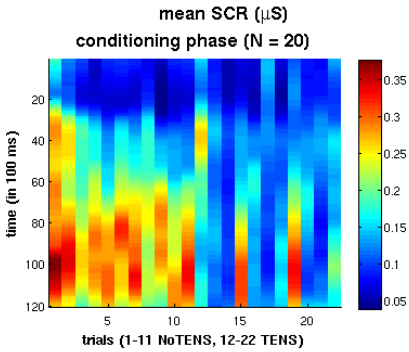
A.3 Mean SCR per group heat onset - conditioning and test phase

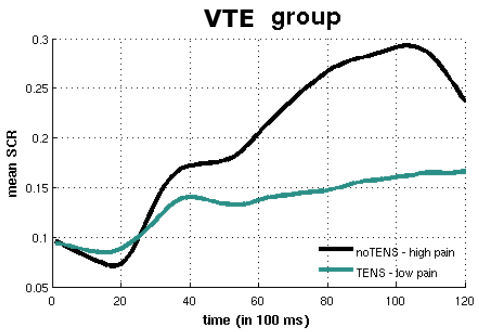


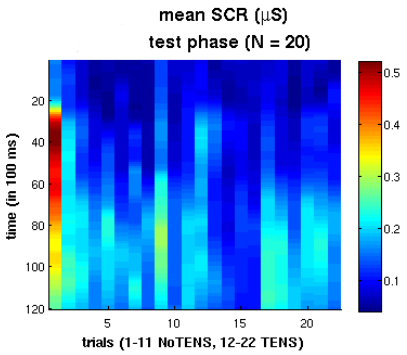


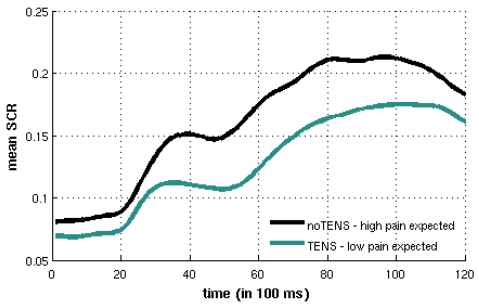












A.4 Putative TENS brochure for Study 2 and 3

Patientenfreundliche Elektroden-fixierung

Um die Platzierung der Elektroden zu vereinfachen und die Behandlung noch patientenfreundlicher zu gestalten, bieten viele Gerätehersteller Fixierungshilfen an, die vom behandelnden Arzt zusätzlich verschrieben werden können.

Fixierung der Elektroden: einfach & patientenfreundlich

Für Fragen oder weitere Informationen:

Deutscher Verband für Physiotherapie

Martin-Walter-Straße 47
70372 Stuttgart
Telefon +49 7553 8925-1
Telefax +49 7553 8925-743
E-Mail info@physio-dtl.de
Web www.physio-deutschland.de

Patienten-Serviceline

0180 6 221 221 (6 Cent pro Gespräch aus dem deutschen Festnetz. Aus Mobilfunknetzen sind abweichende Preise möglich.)

Patienten-Information

Schmerztherapie durch Elektrostimulation

TENS: Medizinische Elektrostimulation

Zur Anwendung bei Schmerzen und Beschwerden an Muskeln, Haut und Gelenken.

Medizinische Elektrostimulation ist ein wissenschaftlich getestetes Verfahren, bei dem elektrische Impulse zur Schmerzreduktion eingesetzt werden.

Wie entstehen Schmerzen & was ist ihr Nutzen?

Sowohl äußere als auch innere Schmerzreize werden von Schmerzrezeptoren (sogenannte Nozizeptoren) aufgenommen. Eine Weiterleitung über das Rückenmark auf weitere Neuronen der Schmerzbahn und schließlich zum Gehirn bewirkt die unangenehme Empfindung. Dabei gilt der Schmerz als Warnhinweis, mit dem der Körper auf potenziell schädliche Einflüsse aufmerksam machen möchte. Unterschieden wird zwischen akutem und chronischem Schmerz. Der akute Schmerz tritt plötzlich auf und dauert nur kurz an. Chronischer Schmerz ist lang andauernd und intensiv und hat seine Funktion als Warnhinweis verloren. Dies belastet betroffene Personen nicht nur körperlich sondern auch psychisch stark.

TENS zur Schmerzlinderung

TENS steht für transkutane elektrische Nervenstimulation und basiert auf der Gate-Control-Theorie. Dabei wirken elektrische Impulse durch Anregung der Schmerzfasern auf die Schmerzpunkte und unterbrechen die Weiterleitung der Signale an das Gehirn. Zusätzlich regt TENS die Bildung körpereigener schmerzlindernder Botenstoffe (Endorphine) an.

Nutzung von TENS

Je nach Schmerzart können nieder- oder hochfrequente Stimulationen angewendet werden. Was für den Einzelfall als Behandlung passend ist, sollte vor einer Nutzung professionell abgeklärt werden. Bei folgenden Indikationen wird TENS u.a. verwendet:

- Akute und chronische Schmerzen
- Postoperative Schmerzen
- Gelenkschmerzen
- Migräne
- Rheumatische Erkrankungen
- Phantomschmerzen
- Muskuläre Dysbalancen

Wann darf TENS nicht genutzt werden?

TENS gilt, bei korrekter Anwendung, als sichere Methode, Schmerzen zu behandeln. Dennoch gibt es einige wenige Kontraindikationen, die dazu führen, dass es nicht verwendet werden sollte:

- Epilepsie
- Schwangerschaft
- Herzschrittmacher
- eingepflanzter Defibrillator
- akute Entzündungen von Gelenken oder Organen

Kostenübernahme durch Krankenkassen?

Bei bestimmten Schmerzzuständen übernehmen gesetzliche Krankenkassen die Miete eines TENS-Geräts. Die Zuzahlung beträgt maximal 10 € für den gesamten Mietzeitraum. Eine erste TENS-Verordnung gilt (je nach Krankenkasse) für bis zu drei Monate. Verlängerungen sind möglich. Privatpatienten sollten die Kostenübernahme mit ihrer Kasse abklären, bevor sie ein Gerät mieten oder sogar kaufen.

Zusammenfassung:

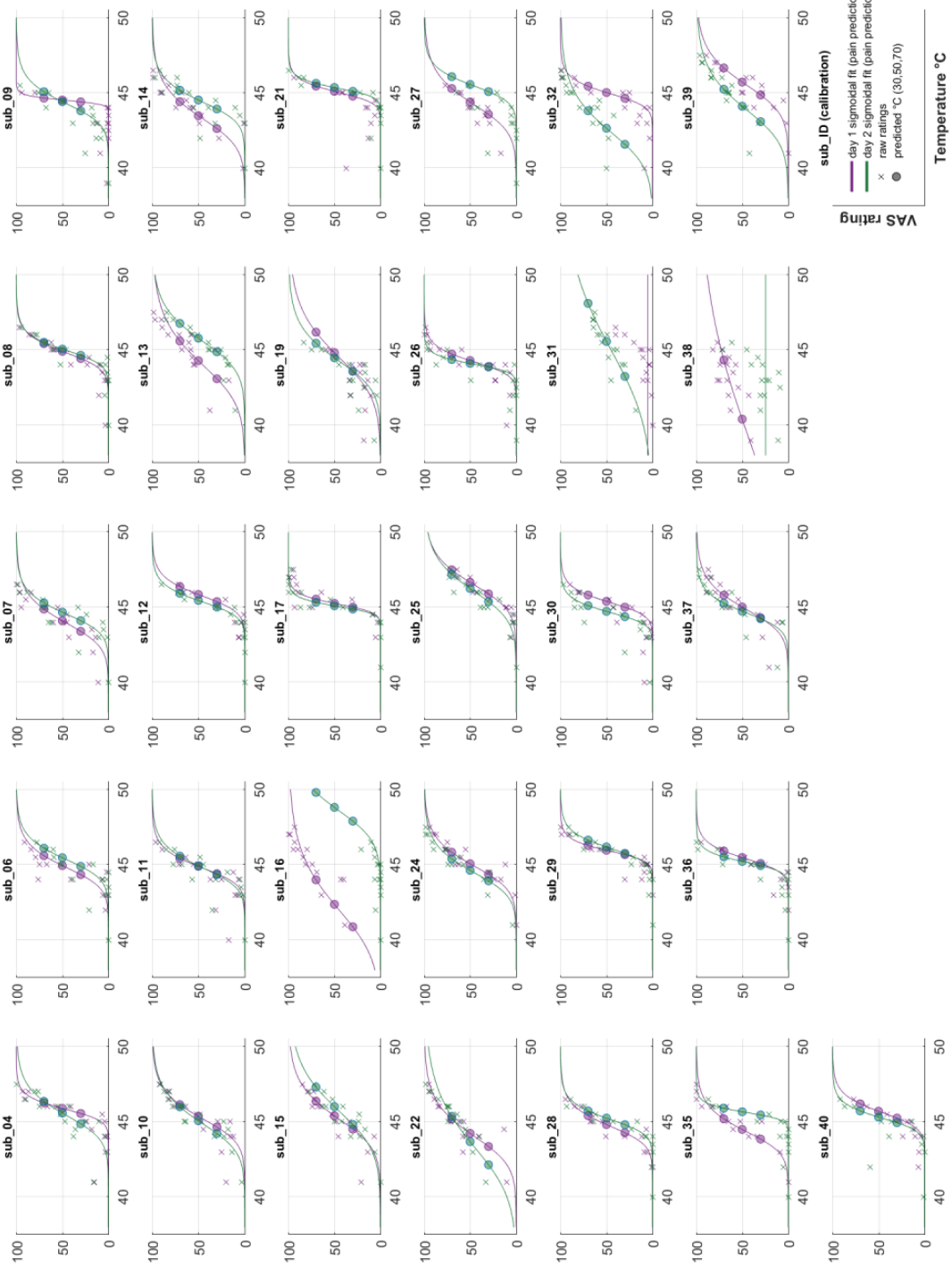
- Einfach in der Anwendung
- Nebenwirkungsfrei
- Kostengünstig (Mietkosten werden i.d.R. durch Krankenkassen übernommen)
- Portabel (Einsatz zu Hause möglich)
- Reduktion des Medikamentenbedarfs möglich
- Therapiemethode ist einfach in den Tagesablauf integrierbar
- Wissenschaftlich getestet
- Möbilitätsfördernd

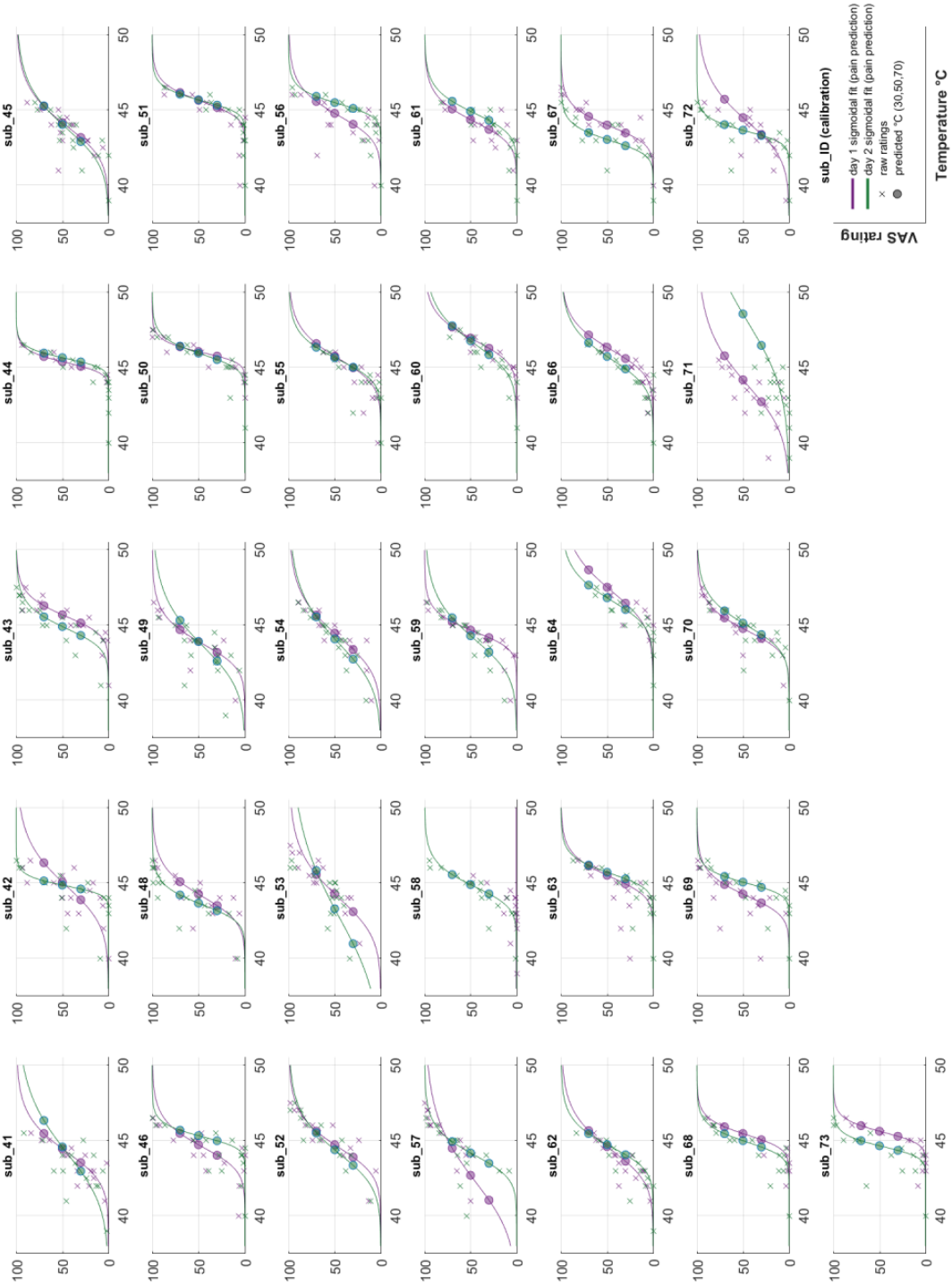
Hinweis:

Beim Kauf eines TENS Geräts sollte auf ein CE-Zeichen oder eine vergleichbare Zertifizierung geachtet werden. Dies stellt sicher, dass es sich dabei um ein hochwertiges und medizinisch getestetes Gerät handelt.

B APPENDIX - Study 3

B.1 Sigmoidal fits of calibration data

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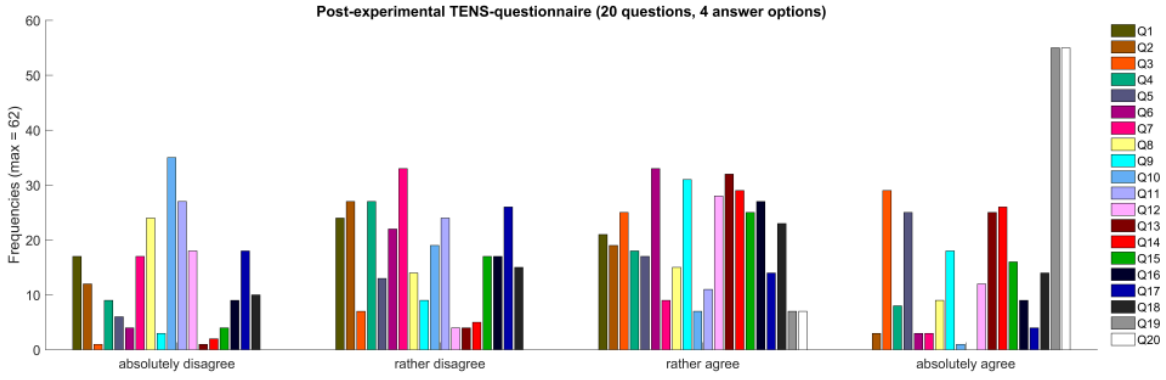
sub_63
sub_69
sub_41
sub_46
sub_52
sub_57
sub_62
sub_68
sub_73
VAS rating
Temperature °C
sub_ID (calibration)
day 1 sigmoidal fit (pain prediction)
day 2 sigmoidal fit (pain prediction)
raw ratings
predicted °C (30,50,70)

B.2 Post-experimental TENS-questionnaire

Post-experimental TENS-exit-questionnaire (prior to debriefing)

	Question (translated from German)	Mean (± SD) N = 62	Correlation (r) with observed placebo effect
1	Heat stimulation paired with TENS (pain intensity) stayed constant over the course of the whole experiment.	2.06 (.787)	-.033
2	Heat stimulation paired with TENS (pain intensity) varied extremely over the course of the whole experiment.	2.21 (.819)#	-.199
3	The heat stimuli were clearly reduced in the TENS condition compared to stimuli not paired with TENS.	3.32 (.742)	.488**
4	The TENS stimulation caused the same pain reduction in the 1st and 2nd half of the experiment.	2.36 (.924)	.331*
5	In the 1st half of the experiment, the difference in painfulness between heat stimuli with and without TENS was clearly larger than in the 2nd half.	3.00 (1.017)#	-.186
6	Over the course of the experiment, heat stimuli paired with TENS became less intense (TENS effectiveness increased over time).	2.56 (.692)	.143
7	Over the course of the experiment, heat stimuli paired with TENS became more intense (TENS effectiveness decreased over time).	1.97 (.789)	-.157
8	During the experiment, I perceived the electrical TENS stimulation as a mild tickling on my skin (ignore the resistance measurement before each run).	2.15 (1.099)	.026
9	The electrical TENS stimulation reduced my perceived pain clearly.	3.04 (.797)#	.381**
10	The electrical TENS stimulation did not seem to have an effect on me.	1.58 (.759)	-.397**
11	Compared to the untreated control condition, the electrical TENS stimulation did not seem to change my perceived pain.	1.74 (.745)	-.222
12	If I am in a painful condition, I would use the electrical TENS stimulation to support a combined drug treatment.	2.55 (1.111)	.024
13	The electrical TENS stimulation seems to be useful to reduce the medical drug intake of pain patients.	3.31 (.667)	.189
14	When I did know that the heat stimulus was paired with TENS, I expected to experience less pain.	3.27 (.750)	.048
15	When I did know that the heat stimulus was paired with TENS, I was much more relaxed before the pain started.	2.85 (.884)	.169
16	When I did know that the heat stimulus was paired with TENS, to compare them, I actively tried to remember how painful the control condition stimuli without TENS felt like.	2.58 (.915)	.102
17	When I did know that the heat stimulus was paired with TENS, I expected the same painfulness of the stimuli as in the control condition without TENS.	2.06 (.885)	.123
18	If I would own a TENS device, based on my experience in this experiment, I would use TENS to reduce my pain.	2.66 (1.007)	-.059
19	I did find the experimenter likable (sympathetic).	3.89 (.319)	-.090
20	The experimenter seemed to be competent (qualified).	3.89 (.319)	-.065

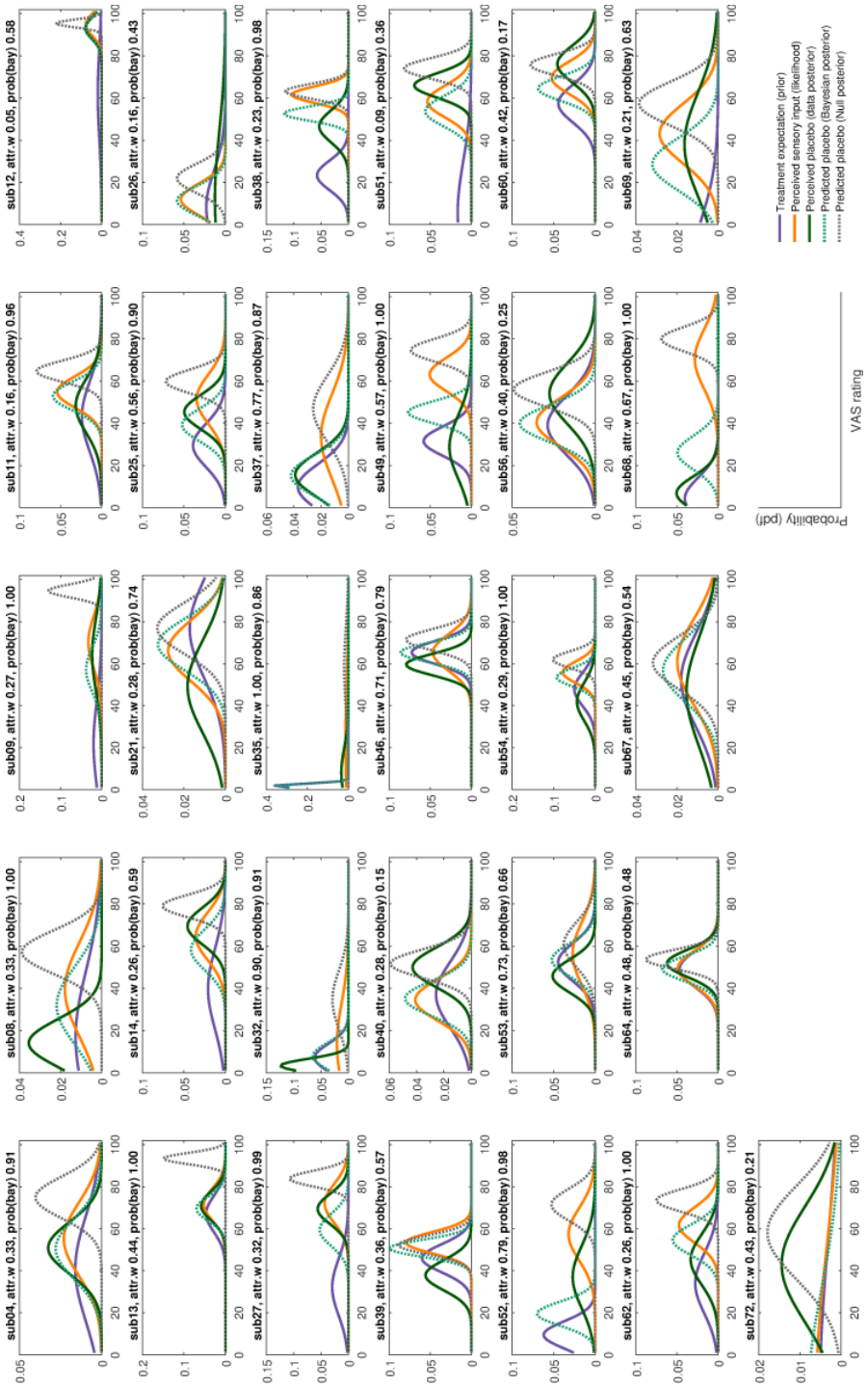
Scale TENS-exit-questionnaire: 1 to 4 (1 – absolutely disagree, 2 – rather disagree, 3 – rather agree, 4 – absolutely agree)
#N = 61, * p<0.01 uncorrected, ** p<0.05 Bonferroni corrected.



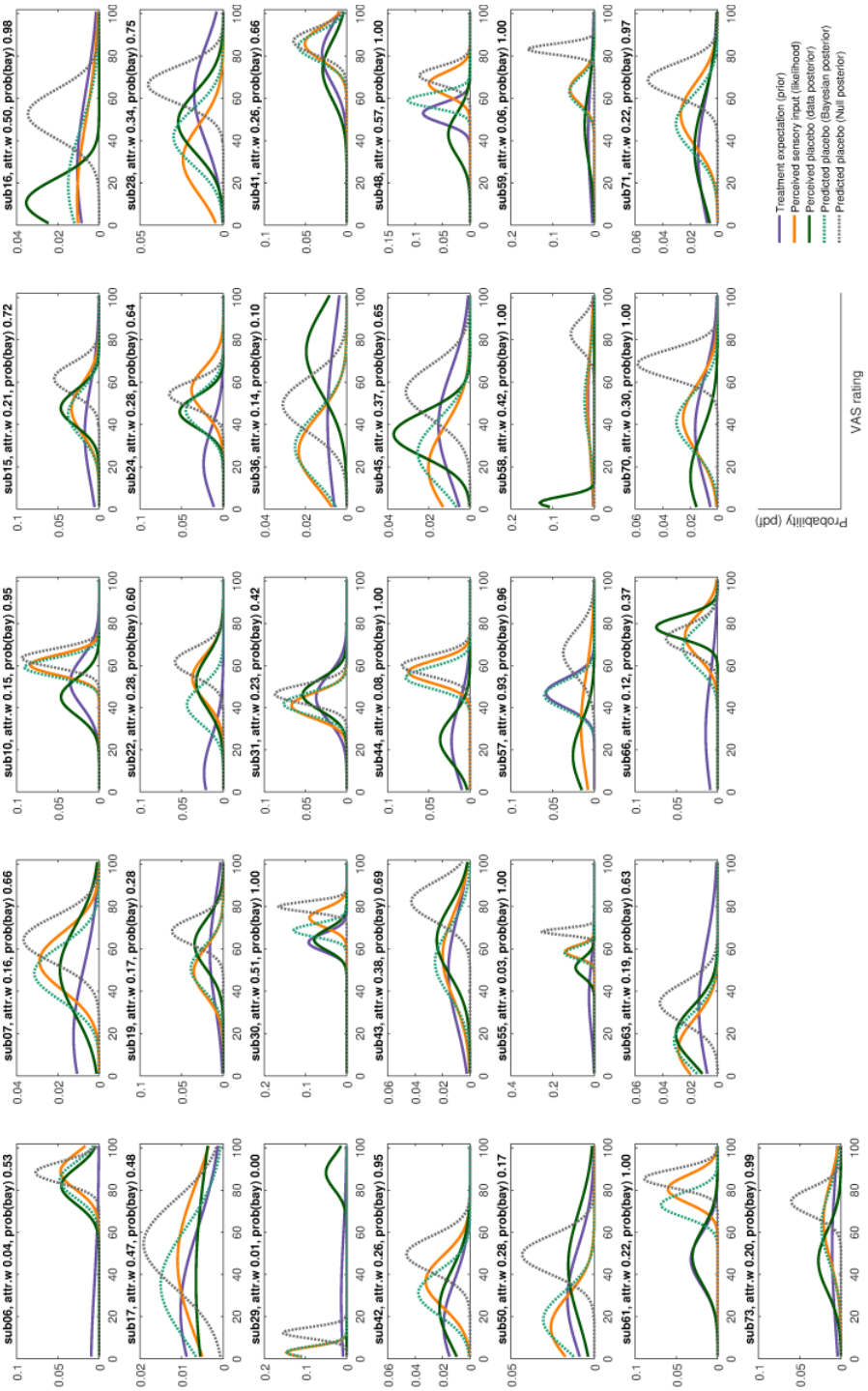
Adapted with permission from eLife (Grahl et al., 2018)

B.3 Bayesian integration model fits (Gaussian probability density functions)

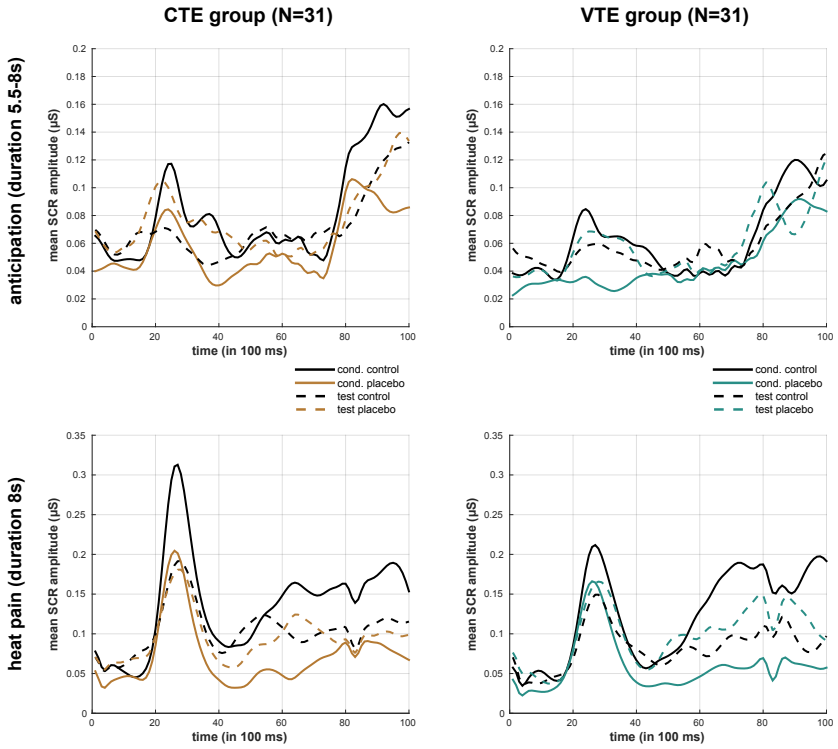
Constant treatment expectation group (CTE) Adapted with permission from eLife (Grahl et al., 2018)



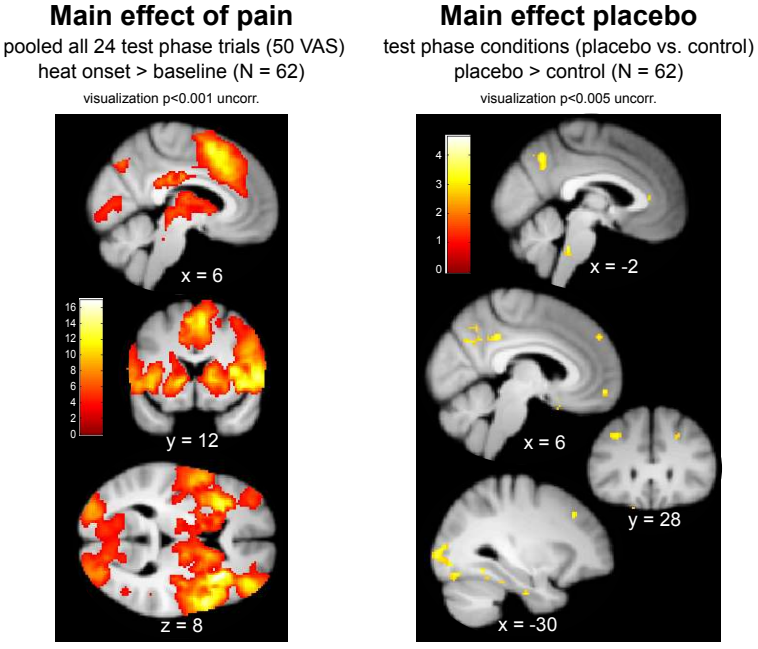
Variable treatment expectation group (VTE) Adapted with permission from eLife (Grahl et al., 2018)



B.4 Mean SCR per group - conditioning and test phase



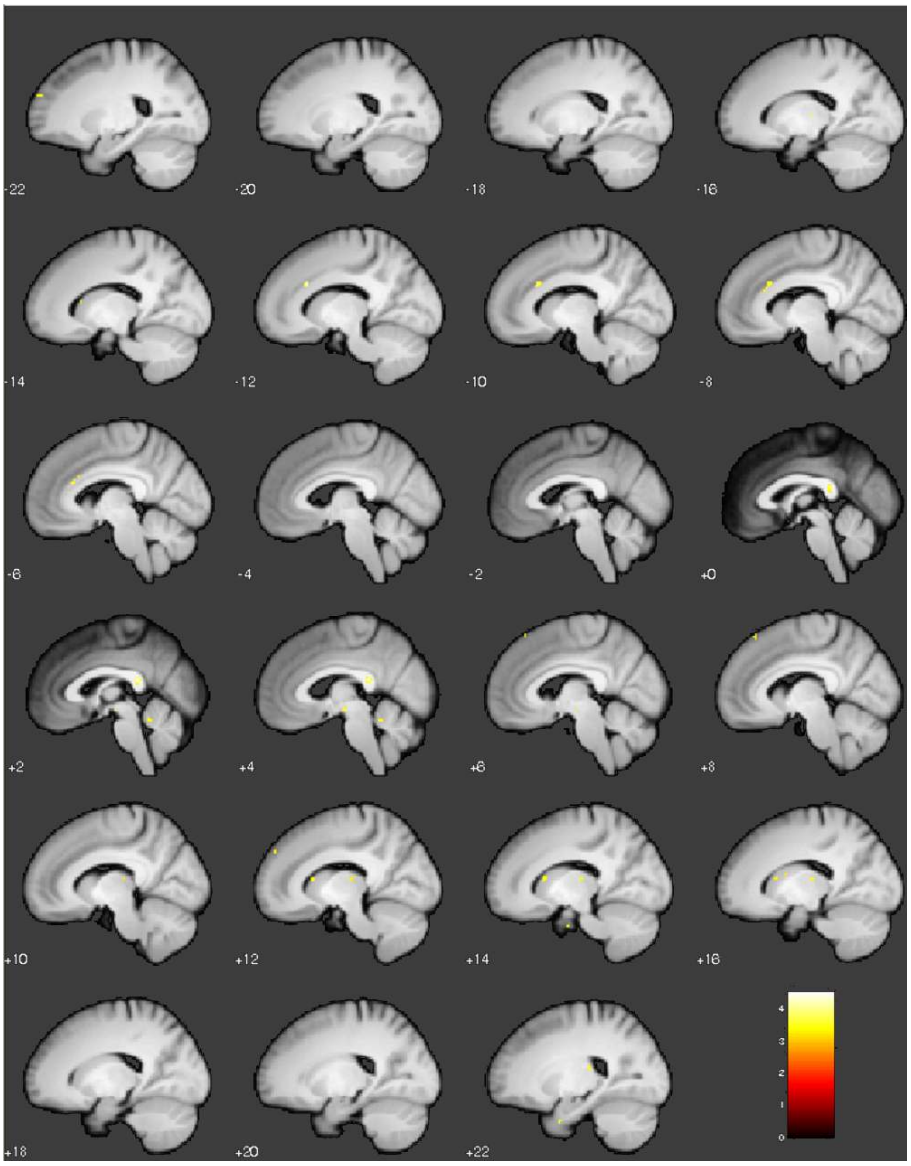
B.5 Main effect of pain and placebo



Adapted with permission from eLife (Grahl et al., 2018)

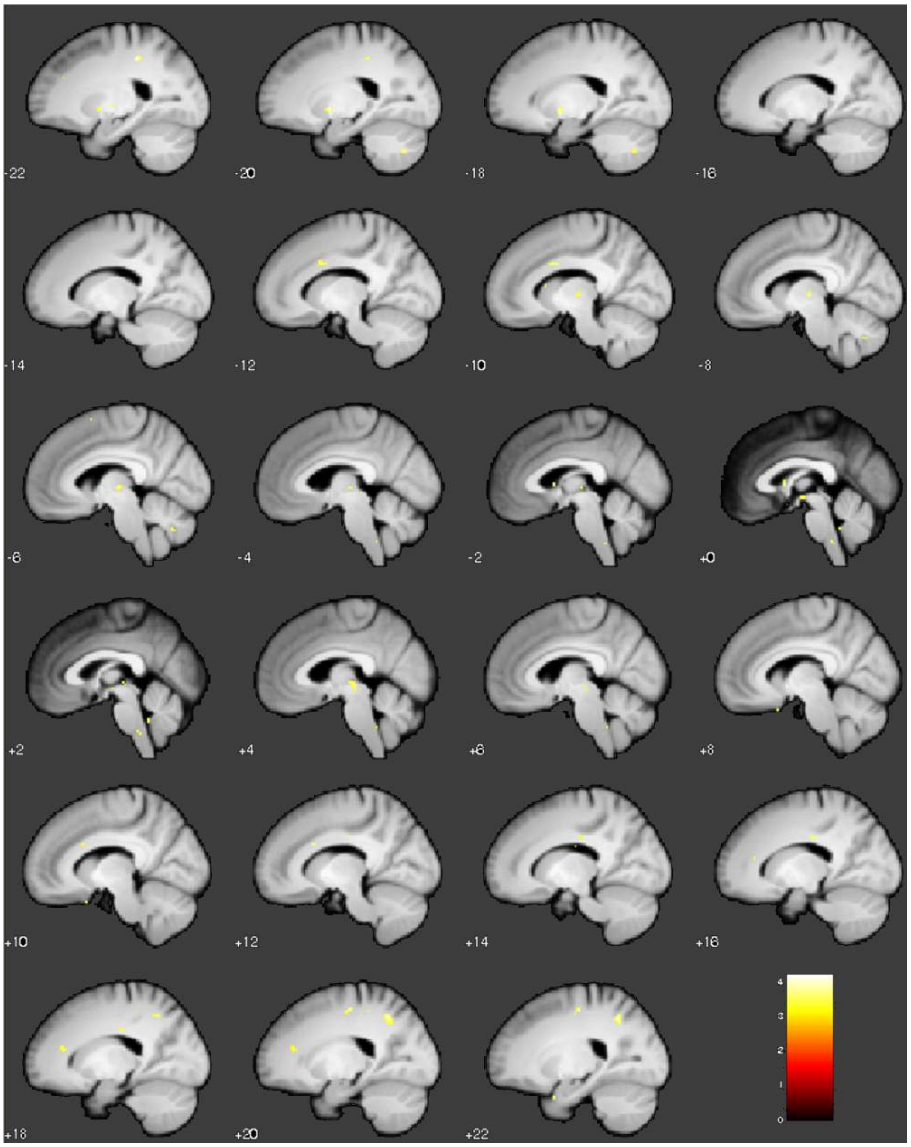
B.6 Complementing imaging analyses of test phase placebo

Covariate: mean of prior treatment expectation (μ_{prior}) $\rightarrow$ positive correlation, visualization of $p_{uc} < 0.001$



Adapted with permission from eLife (Grahl et al., 2018)

Covariate: log SD of prior treatment expectation ($log\ \sigma_{prior}$) $\rightarrow$ positive correlation, visualization of $p_{uc} < 0.001$



Adapted with permission from eLife (Grahl et al., 2018)

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Lebenslauf: Entfällt aus datenschutzrechtlichen Gründen.

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: _____