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Neural Bases of Subjective Control in Pain Processing

Dissertation

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List of Abbreviations

ACC	anterior cingulate cortex.
ANOVA	analysis of variance.
BAS	Behavioral Activation Scale.
BDI	Beck's Depression Inventory.
BIS	Behavioral Inhibition Scale.
BOLD	blood-oxygen-level dependent.
dACC	dorsal anterior cingulate cortex.
dlPFC	dorsolateral prefrontal cortex.
DPMS	descending pain modulatory system.
ELPD	expected log-pointwise predictive density.
EPI	echo-planar imaging.
FIR	finite impulse response.
fMRI	functional magnetic resonance imaging.
FWE	family-wise error.
FWHM	full-width half maximum.
GLM	general linear models.
HMC	Hamilton Monte Carlo.
HPDI	highest posterior density intervals.
IQR	interquartile range.
ITI	inter-trial interval.
LC	locus of control.
LMM	linear mixed effects model.
PAG	periaqueductal gray.

PANAS	Positive and Negative Affect Schedule.
PCS	Pain Catastrophizing Scale.
PFC	prefrontal cortex.
pre-SMA	pre-supplementary motor area.
rACC	rostral anterior cingulate cortex.
RT	reaction times.
RVM	rostral ventromedial medulla.
S1	primary somatosensory cortex.
S2	secondary somatosensory cortex.
SMA	supplementary motor area.
STAI	State-Trait-Anxiety Inventory.
STAXI	State-Trait Anger Expression Inventory.
UCIT	uncontrollability induction task.
vmPFC	ventromedial prefrontal cortex.

1. Introduction

> *We are open systems in exchange with the environment; the environment acts on us to produce sensory impressions and we act on the environment to change its states.*
>
> Friston, 2009

The ultimate and permanent task of a living organism is to ensure its integrity, by protecting its physiological boundaries. This process requires the interpretation of the world with the limited sensory abilities that it has and adequate reactions to response to changes of this interpretation. Traditionally, the interpretation of the world is what we call perception, and the reactions to it actions. Because the human perceptual system can only cover a small part of qualities of our surroundings, it relies on inference. This inference process is not passive, but active, thereby blurring the boundaries of action and perception. Active inference has the goal to minimize surprise elicited by sensory events, a perspective put forward by the normative free-energy principle. Besides the update of predictions, it also entails the recruitment of endogenous bodily sources to map the expected state of the body to the sensory processes (Friston, 2009, 2010). One of endogenous systems is the descending pain modulatory system (Fields, 2004). Similar to other endogenous signals, pain guides the organism away from stimuli that threaten its physiological bounds, thereby reducing surprise. Pain has an interesting intermediate status between sensation and emotion. While there is a clear connection to specific nerve fibers transmitting nociception, pain also has a strong affective component, placing it somewhere in between sensations like vision and audition and emotions of negative valence like fear or disgust (Poublan-Couzardot & Talmi, 2024). This intermediate status might be highly relevant to understand why the adaptive danger signal of pain might become persistent, without an externally perceivable

reason. This is the case in conditions of chronic pain, which are highly prevalent. For example, in the 2019 National Health Interview Survey in U.S. adults, 20.5% reported to be in pain most days or even every day (Yong et al., 2022).

To better understand the effects of the constructive nature of pain, it is crucial to investigate the neural basis of this process and to understand under what circumstances it is modulated. For example, does the experience of contingencies between actions and pain influence the endogenous perceptual processes and attenuate pain? Experiencing contingencies between actions and outcomes is what naturally creates our subjective feeling of controllability. To be able to influence one's surroundings, to be *in control* constitutes a inherently rewarding state for humans (Leotti & Delgado, 2011; Ly et al., 2019). It influences how self-efficient we feel, or if there is a perceived lack of control, how helpless we might be. Helplessness can be interpreted as an emotional outcome of a lack of control. Observational studies found that patients with chronic pain conditions who report higher levels of helplessness and lower self-efficacy also report higher levels of pain severity and interference (Samwel et al., 2006; Craner et al., 2016). While obviously the causality here remains unclear, it suggests an interesting research question, namely, can an increase in subjective control also directly attenuate pain. Thus, the original aim of the projects conducted in the context of this thesis was to investigate the relationship between the subjective feeling of control and pain perception. We thought that this might provide relevant findings for shaping psychologically supported pain management therapies. Furthermore, it would contribute to understand the basic function that pain has for the organisms by investigating environmental factors, which recruit the endogenous modulation system of pain.

The central hypothesis when I started this PhD was that a higher level of perceived control should cause attenuation of experienced pain. Also, this modulatory effect should become visible in brain regions that are part of the descending pain modulatory systems during a controllable painful stimulation. However, when I started the project and reviewed literature on empirical studies on the topic, it became more obvious that such a simple hypothesis neglected the complexity of pain and control. Especially studying control specifi-

cally presented itself less trivial than one could intuitively expect. As outlined above, there is by now overwhelming evidence that pain relies on predictive processing (Büchel et al., 2014). Studies on placebo effects, for example, nicely illustrate how strong expectation effects can be on pain. This matters significantly when studying effects of control over pain, because when something is controllable it naturally is also more predictable (Cramer & Perreault, 2006; Ligneul, 2021).

Because this became apparent during the design of the first empirical study, it resulted in a more methodological approach by including a novel control condition, separating effects of predictability and controllability on pain processing in the brain. I expected to detect a relevant overlap of effects of both. While this does not discredit findings in the domain of control in general, because this overlap is ecologically valid, it is relevant to assess this to know precisely where pain modulating effects originate from. This first project was followed by a second project, that aimed to target the consequences of a lack of control over pain rather than the immediate perception. This was motivated mainly by the reports of helplessness in chronic pain and the possible ensuing motivational and cognitive consequences of the experience of helplessness (Yessick & Salomons, 2022).

In the following chapters, I will provide a theoretical introduction to motivate the interpretation of pain as a not purely sensational experience by separately defining nociception and pain, discuss physiological mechanisms, the behavioral function of pain and the influence of expectations. Then I will review the literature on control and discuss it in the context of empirical investigations of effects of control over pain. The major part of the thesis is two empirical studies, of which I will describe the methodological requirements and results. Finally, I will conclude this work by presenting a synthesis of the results, implications for the field and providing a perspective on how those results potentially could inform future studies.

1.1 Pain

When trying to carry a very hot cup of coffee to your desk, the burning painful sensation that builds up over time typically results in the decision to put the cup down and let it cool before your next attempt to bring it to its destination. This example highlights two relevant aspects of pain that this chapter will address: first, the transmission of the burning, painful sensation from the heat of the cup to the hand and then to the brain in terms of the neurophysiology of nociception and secondly, the behavioral function of pain, that is, that you would put the cup down in order to prevent an injury. Linked to the behavioral function of pain, I will also outline how central neural pathways contribute to endogenous pain modulation in response to environmental and psychological factors.

Importantly, pain is not equivalent to the pure processing of sensory inputs, i.e. nociception, even though both typically co-occur. Nociception refers to the activation of specific nerve fibers (*nociceptors*) when encountering mechanical, thermal, or chemical stimuli that exceed a certain threshold (Basbaum et al., 2009). However, the conscious experience of pain encompasses more than the activation of these sensory neurons and can also be present without their activation (Raja et al., 2020). Pain thresholds can deviate from the typical activation thresholds of nociceptors (Coghill, 2010) and can even emerge in the complete absence of nociceptive input (Tracey, 2005). The pain percept is an interpretation of the nociceptive signal, which is influenced by cognitive and affective factors (Tracey & Mantyh, 2007). The differentiation of pain and nociception is important in context of endogenous pain modulation, because it explains why an individual perceives different levels of pain in response to the same stimulus intensity when it is applied under different internal or external conditions.

1.1.1 Physiological mechanisms of nociception and pain

Nerve fibers that convey nociceptive input after thermal, mechanical or chemical stimulation can be grouped into two main classes. Myelinated A δ fibers mediate well localized, sharp

and fast pain, and unmyelinated C fibers mediate slower but enduring pain (Basbaum et al., 2009; Middleton et al., 2021). Stimuli above a certain temperature threshold (for heat around 43°C) recruit both fiber types (Basbaum et al., 2009). From the periphery, the signal is then transmitted to dorsal horn neurons in the spinal cord (Julius & Basbaum, 2001). There, nociceptive reflexes are initiated through connections with ventral horn neurons (Todd, 2010) and projections from the dorsal horn convey the nociceptive signal to the brain stem, thalamic nuclei and from there to several cortical key areas: the primary (S1) and secondary (S2) somatosensory cortices, the insula and the anterior cingulate cortex (ACC) (Fields, 2004; Todd, 2010; Mouraux & Iannetti, 2018). These cortical key regions for pain perception are not specific for pain processing, but also respond to other salient events (Mouraux & Iannetti, 2018). However, the dorsal posterior insula is a candidate region for the specific processing pain, because it encodes changes in heat pain intensity, but not changes in warmth and is not typically activated in response to other aversive and salient stimuli (Segerdahl et al., 2015; Horing & Büchel, 2022).

Alongside this ascending processing of nociceptive input, excitatory and inhibitory neurons that descend from cortical, subcortical and brain stem regions modulate the nociceptive signal (Fields, 2004). Important hubs of this descending pain modulatory system (DPMS) are the periaqueductal gray (PAG), locus coeruleus, rostral ventromedial medulla (RVM), pontine nuclei, ACC, dorsolateral prefrontal cortex (dlPFC) and limbic system (Fields, 2004; Eippert et al., 2009; Bannister & Hughes, 2023; Neyama et al., 2025). Endogenous pain modulation involves different neurotransmitter systems, including GABAergic neurons, that are sensitive to opioids and project from frontal cortical regions (ACC, dlPFC) to the brain stem and the spinal cord (Fields, 2004; Bannister, 2019; Chen et al., 2024; Neyama et al., 2025) as well as noradrenergic connections of the locus coeruleus (Bannister & Hughes, 2023). These pathways don't have purely pain facilitatory or inhibitory properties but allow context dependent calibration of pain perception by distinct activation of different cell classes (Fields, 2004; Bannister & Hughes, 2023). In sum, the presence of these complex interconnected pathways enables endogenous top-down modulation of

pain and influences an individuals perception of pain beyond the intensity of the physical stimulus that activates nociceptors.

1.1.2 Behavioral function of pain

Fundamentally, the behavioral function of pain is the protection of the physical integrity of an organism (Seymour, 2019). It is a learning signal that prevents or stops the performance of actions that could potentially result in injuries. On a longer temporal dimension, pain signals the body to rest in order to allow recovery and restore bodily resources. This function places pain alongside other homeostatic drives like hunger, itch, need for air, thermo-sensation and thirst, that maintain the physiological functioning of the body (Craig, 2003). Pain is integrated with other internal and external signals and goals, for example other homeostatic drives or external rewards. Relative to other signals, it can become more or less relevant to attend to the pain signal. Studies show that pain is perceived as less intense, when winning in a game of chance, because of a shift in focus towards the acquisition of the reward (Becker et al., 2013, 2017). This effect can be described by the motivation-decision perspective on pain that argues that an organism weighs the pain signal against other goals that the organism needs to pursue. If this weighing leads to prioritizing of the motivation to get the reward, pain is perceived as less intense (Fields, 2018). Additionally, other factors, like the attentional demands of the environment (Torta et al., 2017) or extreme emotional states (Butler & Finn, 2009) can divert focus away from pain and modulate pain processing already at the spinal cord (Sprenger et al., 2012).

1.1.3 The role of expectations in pain modulation

Besides reward, attention and emotions, expectations play a major role in pain modulation (Fields, 2018). The phenomenon of *placebo analgesia*, the reduction in pain perception after receiving an inert treatment along with a positive outcome expectations, or *nocebo hyperalgesia*, the increase in pain after receiving a treatment along with negative outcome expectations, showcases how strongly pain can be influenced by expectations (Atlas, 2021).

Pain modulatory effects of expectations have correlates in the brain (Zunhammer et al., 2021) including key regions of the DPMS, like the insular cortex, ACC and thalamus (Atlas & Wager, 2012) and the spinal cord (Tinnermann et al., 2017).

Pain modulation by expectation arises from the requirement to react as quickly and accurately as possible to a painful stimulus, due to its relevance for physical integrity and survival. This is enabled by integrating prediction and sensation by a mechanism that has been called *predictive processing* (Poublan-Couzardot & Talmi, 2024). The most probable ”true” state of the world is inferred and this prediction is continuously updated with actual sensory input, processing primarily unexpected events to enable efficient use of neuronal resources (Huang & Rao, 2011). Originally developed in context of studies on visual perception, which showed that unpredicted elements of sensory inputs (prediction errors) are conveyed from lower to higher-level processing areas with priority (Rao & Ballard, 1999), the predictive coding model has also been put forward to explain the effect of placebo analgesia (Büchel et al., 2014). Empirical studies confirmed the model predictions regarding pain processing by physiological measures and changes in functional brain activity (Geuter, Boll, et al., 2017).

1.1.4 The Bayesian approach to pain perception

The predictive coding model relies on *Bayesian integration*, a principle drawn from Bayes' theorem, a mathematical rule, which describes how the probability of an event can be optimally inferred by integrating its prior probability with the probability of observations (McElreath, 2020, p. 37). Evidence for Bayesian mechanisms stems not only from studies on visual perception (Huang & Rao, 2011) but also from research on temporal and spatial magnitude estimation, which indicates that a similar pattern is present in many cognitive domains (Petzschner et al., 2015). Translated to theoretical accounts of pain, the term *likelihood* is mostly used to describe the somatosensory or sometimes nociceptive processing, while the *prior* refers to the expected painfulness (Habermann et al., 2024). The integration of the prior and the likelihood results in the pain percept (*posterior*), which can be

assessed by intensity ratings. Typically, the prior and the likelihood are formalized as two normal distributions, with their variance representing uncertainty in expectation and noise in the sensory processing. This formalization allows an analytical mathematical solution for Bayes' theorem (Gelman, 2014), with another normal distribution resulting for the posterior probability of perceived pain (Büchel et al., 2014). The mean of the posterior distribution, i.e. the peak of the pain percept, depends on precision weighted means of the prior and the likelihood distributions and will be biased to the more precise distribution.

An advantage of a formal model definition is that it allows to derive testable predictions. For example, a placebo effect should be stronger when very precise expectations have been established, for example, when given a pill by a very trustworthy physician. In contrast, a placebo effect should be weak when the expectation is vague, for example, when study participants remain uninformed whether they received an allegedly effective treatment or not (Büchel et al., 2014). And indeed a study that manipulated expectation precision through high or low consistency during a placebo conditioning phase could show that lower expectation precision resulted in smaller placebo effects (Grahl et al., 2018). Bayesian models have also been informative for the formalization of pain modulatory effects arising from the interaction of expectations and other factors (Habermann et al., 2024). For example, the beneficial effects of agency, i.e. when self-administering a placebo treatment, may be better explained by a shift in expectations than by a change in sensory precision (Strube et al., 2023). Finally, also the major topic of this thesis - pain modulation by perceived control - is tightly interwoven with the matter of expectation.

1.2 Control

When confronted with a painful experience, a crucial aspect of assessing the risk of the situation is the level of control that the organism has over the cause of the pain. If control is given, a pain-free state can be reached and future painful states can be avoided. Estimating control also allows resource-efficient behavior, because some actions should ideally only

be performed if they are expected to lead to better, pain-free states (Gandhi et al., 2017). Consequently, the estimation of the controllability of outcomes determines which behavioral strategy is selected when confronted with a threat, e.g., a pain-eliciting stimulus (Moscarello & Hartley, 2017). Without control, the metabolic costs of performing defensive pro-active actions can be saved, and alternative coping behavior can be initiated. Similar behavioral strategies emerge in the appetitive domain, where different levels of control signal how much effort should be invested in a potentially rewarding task (Frömer et al., 2021; Grahek et al., 2023). In addition to environmental features, control perception also depends on general beliefs about control (Lefcourt, 1976; Ly et al., 2019). This broader feeling of being in control of personal and societal events, has an important influence on the well-being of a person (Bandura, 1982) and influences reactivity to situations with different levels of controllability. General control beliefs can change the evaluation of outcomes and learning: a high subjective level of uncontrollable stress impairs learning about rewards (Guitart-Masip et al., 2023) and perceived helplessness, or lack of control, is associated with an increase in perceived pain severity in chronic conditions (Samwel et al., 2006; Craner et al., 2016). High perceived self-efficacy on the other hand leads to reinforcement of reward processing (Blain & Sharot, 2021). Before presenting data on the influence of control on pain perception in depth, the following paragraphs will introduce relevant conceptual aspects of control and potential brain mechanisms underlying control estimation.

1.2.1 Definition of control

There are different levels of control that matter for cognitive science. The main focus of this thesis is the effect of *environmental control* on pain perception and related changes in behavior and cognition. With environmental control, I refer to the influence an organism can exert on its surroundings that is given by the design of the environment, for example, when a painful stimulus can be terminated by a button press. This is directly related but not equivalent to *behavioral control*, or the ability to perform movements in a coordinated way and with predictable results, e.g. being able to self-initiate the button press (Haggard,

2017). Finally, *cognitive control* refers to control over internal processes as switching attentional focus or coordinating executive functions (Shenhav et al., 2013), also relevant for coordinated behavior. The different levels of control interact with each other: without behavioral or cognitive control, an organism cannot profit environmental control. Hence, the estimate of environmental control immediately influences how behavior and cognition are coordinated, that is, only when outcomes are controllable, cognitive resources should be focused on the execution of a difficult task (Grahek et al., 2023). Furthermore, control can be exerted over different features of a stimulus, for example, in some cases it might be possible to change the intensity of a painful stimulus, in other cases control can be exerted over the onset or offset of pain (Habermann et al., 2024).

Theoretical notions of control in cognitive science evolve around the fact that organisms estimate the control by performing actions (A) and observing statistics of ensuing outcomes (O) (Huys & Dayan, 2009). If outcomes can be reliably achieved or avoided by performing specific actions, control is given; conversely, no control is perceived, if outcomes occur independently of actions. In an early account (Maier & Seligman, 1976), perceived control was defined as the difference in conditional outcome probabilities. For example, if a shock is less probable after a button press has been performed, the perceived control is high: $p(O|A) < p(O|\neg A)$. Accordingly, animals should keep track of both conditional probabilities and mentally compare them to determine the degree of environmental control. In the controllable environment, the conditional action-outcome probabilities differ, while in an uncontrollable environment the outcome probability is the same regardless of action execution: $p(O|A) = p(O|\neg A)$. Both conditional probabilities can be high or low, but control is only perceived if they are unequal. This formalization provided a good initial solution to quantify control levels in psychological experiments, but some relevant aspects are missing (Huys & Dayan, 2009; Ligneul, 2021).

First, the original definition does not implement changes in control estimation if an action is not only predictive of one, but multiple outcomes. In order to extend the definition of control to more than one action, it can be reformulated in terms of outcome entropy (Huys &

Dayan, 2009). Entropy is defined as the average uncertainty or surprise of an event defined through its average log-probability (McElreath, 2020). Lower entropy reflects decreases in outcome uncertainty and an increase in control, whereas entropy is necessarily high in uncontrollable environments. With this generalizable measure, control can be elegantly parametrized as one value in more complex scenarios, by $H(p) = -\sum_{i=1}^{n} p_i log(p_i)$. For example, there is higher perceived control, when one action only leads to one outcome with a certain probability (low entropy) compared to the case where one action produces multiple different outcomes with the same probability (high entropy; Huys and Dayan, 2009).

Secondly, the basic definition does not take into account the valence of outcomes that are or are not controllable. It might not matter to an individual if a *neutral* outcome can reliably be obtained, but control over highly rewarding or very aversive outcomes should be correctly inferred. Consequently, when estimating control, outcomes of higher positive or negative valence should be weighted in the most, and control can be formulated as the *fraction of achievable rewards* (Huys & Dayan, 2009) or the *fraction of avoidable pain*.

Especially if positive reinforcers are present, the subjective assessment of control can deviate from the factual level of control provided by the environment (Alloy and Abramson, 1979, but see Teodorescu and Erev, 2014). This *illusion of control*, the tendency of individuals to judge the likelihood of success to be higher than what is objectively reasonable (Langer, 1975), can lead them to behave as if they have control over events that are actually governed by chance. The relationships between actions and outcomes are often perceived as causal, despite the absence of contingencies, especially if the outcome is frequent and rewarding (Alloy & Abramson, 1979). While formal definitions of control are crucial for the design of experiments and for the discussion of basic processes, the effect of illusory control has to be kept in mind, when designing and analyzing study results. Ideally, subjective estimates of control should be compared to the levels of factual control provided in the experiment.

1.2.2 Controllability and predictability

A more conceptual critique of the original definition of control argues that it is insufficient because it confounds control with outcome predictability (Ligneul, 2021). While this critique is not per se new (Cramer & Perreault, 2006), it did not lead to a formal redefinition of control until now. The proposed alternative definition of control also relies on the conditional relationship of actions and outcomes, but crucially it also takes the additional dependence on states into account. The factual causal influence over state transitions and not their correct prediction should matter for control estimation (Ligneul, 2021). The formal variable measuring control in this approach is *transfer entropy* (I). Transfer entropy is the difference between entropy of outcomes conditioned on states alone and entropy of outcomes conditioned on states *and* actions $I(O; A|S) = H(O|S) - H(O|A, S)$. If an environment is not controllable, both entropy values should be equal and thus the transfer entropy would tend to zero. In a controllable system, transfer entropy would be positive, because the outcome entropy (i.e. surprise), when conditioned on states and actions, is lower than outcome entropy conditioned on the state alone. A recent study elegantly applied this definition in a computational model and shows that the internal control estimate can be described by comparing the likelihood of two internal learning models: the first one tracking outcomes conditioned on states alone, and a second one taking into account states and actions (Ligneul et al., 2022). The differentiation of predictability and controllability is important, when specific effects of control on behavior and brain activity are under investigation. Especially with regard to pain modulation, the differentiation of expectation and perceived control is crucial, because perceived pain can strongly be influenced by (the precision of) expectations. Hence, if interested in the effects of control and not expectation precision on pain, a sensible control condition has to be implemented in the experimental design.

1.2.3 Generalization of control beliefs

Control beliefs are not generated for each situation in isolation, but previously learned contingencies regarding actions and outcomes influence subsequent selection behavioral strategy and updating of control beliefs. This was first observed in studies, performed by Maier and Seligman, 1976, where dogs subjected to inescapable electrical shocks in a first experimental phase failed to escape in a subsequent shuttle-box task, while another group of dogs that learned to terminate shocks by their own behavior successfully escaped in the second task. Critically, the groups were matched for stimulus intensity and duration, only differing in terms of controllability of the shock duration during the first phase. The authors concluded that experiencing uncontrollable aversive events results in the subsequent selection of passive behavioral strategies, because they learned that proactive escape responses would be a waste of resources. They coined the term ”learned helplessness” for this effect and it has been replicated in multiple rodent studies (for a review see Baratta et al., 2023) showing that experiencing uncontrollable stress leads to slower learning (Amat et al., 2008) and reduced exploration behavior (Kubala et al., 2012). Likewise, early studies with human participants report slowing down in learning after having been confronted with unsolvable anagrams or inescapable shocks (Hiroto & Seligman, 1975). A more recent study tried to translate the original study design as a computerized version and utilized aversive sounds and electrical shocks as stressors (Meine et al., 2020). Contrary to what would be expected, participants in the uncontrollable condition explored more in the second phase of the study. One potential explanation for this result could be that the perceived risk for survival induced in the first phase is relatively low in humans compared to animals that are forced endure electrical shocks in a cage. This could change the behavior following experience of low control. For example, it could lead to compensatory behavior in the second phase to make up for perceived performance difficulties.

Learned helplessness relies on the generalization of the perceived level of control from one situation to future situations (Huys & Dayan, 2009; Lieder et al., 2013). Generalization on the perceptual level is a general property of the nervous system and describes the

effect that after a behavioral response to a stimulus has been established, novel stimuli that resemble the first evoke a similar response (Ghirlanda & Enquist, 2003). For example, after being bitten by a poodle, an individual is likely to act more careful around other types of dogs, but not cats, because the estimated probability of getting bitten again is higher. Generalization takes place across similar looking stimuli (Onat & Büchel, 2015) and contexts (De Voogd et al., 2020; Esser et al., 2021) and generalized responses include genetically prepared and learned behavior (Ghirlanda & Enquist, 2003). Control beliefs rely on higher-order cognition and are more abstract than the reflexive responses, which are typically investigated in fear generalization studies (e.g. differences in skin conductance responses; Dymond et al., 2015). However, putting forward the notion of generalization as a *universal* law with respect to psychological spaces (Shepard, 1987), more sophisticated cognitive responses should align with it as well. Evidence for generalization of cognitive responses comes, for example, from studies on value-generalization in the financial domain, showing similar generalization patterns as physically evoked responses measured by reaction times and expectancy ratings (Norbury et al., 2018). In addition, studies investigating cognitive spaces effectively illustrate how mental representations of abstract concepts resemble the representations of perceptual stimuli, or physical space (Bottini & Doeller, 2020). Therefore, it is conceivable that also control estimates generalize at least partly based on perceptual and conceptual similarities between contexts. Yet, the strength of control belief generalization does not merely rely on perceptual or conceptual similarity between situations, but might additionally depend on personality traits (Huys & Dayan, 2009). This idea is inherent in the concept of the *locus of control* (Lefcourt, 1992) or Bandura's concept of *self-efficiency* (Bandura, 1982). It assumes that the person's inherent control belief influences learning about contingencies and controllability in a new context. In addition, these trait variables might interact with the perceptual level of generalization, as in the case of fear generalization where patients with anxiety disorders or people scoring high on intrusive anxiety show broader generalization patterns (Dymond et al., 2015; Norbury et al., 2018). Other accounts propose the inverse mechanism, suggesting that it is

not the personality trait that leads to differences in the strength of generalization, but rather that the accurately perceived lack of control over repeated uncontrollable stress results in changes in the personality trait, as assessed by depression or helplessness questionnaires (Pizzagalli, 2014; Yessick & Salomons, 2022) or behavioral readouts (Lieder et al., 2013). However, as is often the case with correlation, the direction of causality in this instance remains ambiguous and the directionality of the effects difficult to assess as trait variables and state estimates might also reinforce each other, resulting in a vicious cycle of increasing lack of perceived control and symptom severity (Büchel, 2023). Hence, controlled experimental studies are needed to provide insights in how perceived controllability of pain influences behavior in a subsequent situation, if personality variables interact with this effect and how control affects perception of acute pain.

1.2.4 Locus of control and depression

The locus of control is defined as a general belief regarding the causality of one's own actions and consequences or effects on the world (Rotter, 1966). An external locus of control has been associated with depressive symptoms (Hovenkamp-Hermelink et al., 2019), but sometimes also with a fewer number of depressive symptoms (Yu & Fan, 2016). This depends on what types of events are externalized (Abramson et al., 1978). If failures are attributed to external events, outside of personal influence, this can indeed conserve self-esteem (Yu & Fan, 2016). If positive events on the other hand are exclusively believed to result by chance or the influence of powerful others, this might lower self-efficacy and contribute to anxiety and depression. A lack of perceived control is therefore usually associated with a higher level of anxiety and depression (Dan et al., 2024). The allocation of the locus of control is stable over time and can be considered a personality trait (Hovenkamp-Hermelink et al., 2019).

1.2.5 Neural bases of control estimation

Different brain regions have received attention in the context of control estimation, depending on the domain of investigation. The domains include general learning and contingency estimation (Ligneul et al., 2022), inference about the cause of rewarding outcomes (Dorfman et al., 2021) or state changes (Ligneul et al., 2022), agency over movements (Haggard, 2017), and, coming from the learned helplessness literature, effects of stressor controllability (Maier & Seligman, 2016). Due to this diversity, it is not surprising that many different brain regions have been associated with perceived control, but some brain regions have been repeatedly reported to be relevant to multiple types of perceived control.

One of these regions is the anterior insula. Activity in the insula follows the estimated causal influence of actions over state changes that did (Dorfman et al., 2021) or did not (Ligneul et al., 2022) entail rewards. On the other hand, a study on threat controllability reported lower activity in the anterior insula, when (non-painful) electrical shocks were perceived as controllable than if they were uncontrollable (Limbachia et al., 2021; Meine et al., 2021). These divergent results could be partly explained for different levels of salience of either contingent neutral, or contingent aversive environments. Salience is higher for uncontrollable (non-contingent) stress (Wanke & Schwabe, 2020), as it leads to higher prediction errors. The anterior insula is strongly associated of processing of prediction errors, i.e., salient events (Wiech et al., 2010; Horing & Büchel, 2022; Kim et al., 2025; Willems et al., 2025). Interestingly, patterns of activity in the anterior insula during exposure to uncontrollable stress also differ between participants that were previously exposed to uncontrollable stress and a second group that was able to control the stress induced by aversive sounds in a prior task (Cohodes et al., 2023). However, salience in the sense of attention (Parr & Friston, 2019) could also be increased when experiencing contingencies that are neutral or positive, because it helps processing of these positive events, possibly explaining the higher activation of the anterior insula with control in some studies.

More consistently, activity in the prefrontal cortical regions has been related to higher levels of inferred control. This was the case in non-reinforced scenarios (Ligneul et al.,

2022), as well as in response to higher control over aversive outcomes (Meine et al., 2021). Especially the ventromedial prefrontal cortex (vmPFC), has received a lot of attention in the context of controllable stress. Rodent studies found that stress responses were inhibited by neurons in the paralimbic cortex, the rodent homologue of the human vmPFC, when stressors were controllable (Amat et al., 2005). This process is mediated by the serotonergic pathways connecting dorsal raphe nucleus with the PAG and the amygdala (Maier & Seligman, 2016; Ligneul & Mainen, 2023). Furthermore, fMRI studies in humans report that BOLD signal in the vmPFC increased during non-painful electrical stimulation if its offset was controllable (Meine et al., 2021), as well as during the anticipation of avoidable aversive videos (Kerr et al., 2012) or controllable aversive sounds (Wade-Bohleber et al., 2021).

The dorsal part of the frontal cortex, namely the dorsal anterior cingulate cortex (dACC) is mostly associated with the regulation of cognitive control (Shenhav et al., 2013) and the neighboring pre-supplementary motor area (pre-SMA) has been associated with the cognitive aspects of behavioral control and put forward as a region encoding conscious intention (Lau et al., 2004).

Moving along this frontal to parietal gradient of abstractness of control processes, the region that is primarily associated with perceived control over body movements (agency) is the supplementary motor area (SMA; Moore et al., 2010). SMA activity increases when actions were perceived as voluntary (Kühn et al., 2013) and is thought to arise from the comparison of a neural efference copy with the actual sensory feedback in sensorimotor regions (Haggard, 2017; Wen & Imamizu, 2022). If both match, agency is perceived, whereas if movement plans and sensory feedback are incongruent, the sense of agency is diminished. Theories of sensory attenuation relate agency also to differences in perception, which is crucial when thinking about the effects of self-inflicted or self-controlled painful stimulation compared to externally controlled pain (Strube et al., 2023).

In sum, the vmPFC, the anterior insula and SMA appear consistently in neuroimaging studies on perceived control employing different tasks and types of control. Moreover,

regarding the combined study of control and pain, these regions deserve attention, because to their known role for pain modulation by cognitive and environmental factors (Kragel et al., 2018; Zunhammer et al., 2021; Horing & Büchel, 2022). The next chapter will discuss results of studies that investigated pain modulation by subjective control.

1.3 The Effects of Control on Pain

Pain can be modulated by external and internal factors that lead to the recruitment of the endogenous pain modulatory system. One instance of this modulation are the effects of expectations on pain processing. Subjective control is tightly linked to the precision of expectations, because it results from perceiving reliable contingencies between environmental cues, actions and outcomes. This chapter will converge the topics pain, subjective control and expectations and discuss how control influences pain perception. Special emphasis will be placed on the overlap of control and predictability.

1.3.1 Behavioral mechanisms

As discussed above, pain can be understood as a behavioral learning signal that guides the organism away from experiences that threaten its physical integrity (Seymour, 2019). An interesting question arises, if the organism can't react to this internal learning signal. Such a loss of control occurs, for instance, in chronic pain conditions, where the strategy to alleviate or prevent pain might not be known, and, in fact, in most laboratory experiments investigating pain perception, where participants are asked to endure pain.

Theoretical accounts came up with different hypotheses regarding the effects of control over pain. The first and most intuitive hypothesis on this matter is that if pain falls under individual control, it is perceived as less intense, because it is evaluated to be less threatening (Wiech et al., 2006). Conversely, pain should be perceived as more intense if it is uncontrollable, as no reappraisal in terms of safety can be initiated. This hypothesis also aligns with the idea that perceiving control is related to dopaminergic reward processing

(Leotti et al., 2010; Ly et al., 2019) and may trigger a mechanism similar to reward-induced hypoalgesia (Becker et al., 2021). Support for control induced hypoalgesic effects comes from surveys with chronic pain patients, showing that helplessness, the perceived lack of control and low perceived self-efficacy are predictors of increased pain severity (Samwel et al., 2006; Craner et al., 2016; Yessick & Salomons, 2022). Furthermore, if pain treatment can be self-administered after surgery, patients consume less medication (Ballantyne et al., 1993), but see Macintyre, 2001 for a more in-depth discussion. This indicates lower perceived pain or higher perceived treatment potency, if treatment is under individual control. Also, multiple studies that experimentally investigated effects of control on acute pain found evidence for a hypoalgetic effect of control. The results emerged in context of different experimental designs and across different pain modalities, like electrical shocks (Müller, 2012; González-Roldán et al., 2021), thermal heat pain (Wiech et al., 2006; Bräscher et al., 2016; Strube et al., 2023) and mechanical pain (Lee et al., 2021).

Other accounts propose that control might actually increase perceived pain intensity. The hypothesis of control-induced hyperalgesia can be derived straightforwardly, when framing pain as a learning signal (Seymour, 2019). If pain's function is to convey information about how and when to act, i.e. when to set down the hot coffee mug, then it should be modulated according to the environmental need and opportunity to learn (Zhang et al., 2018). As a result, controllability might increase acute pain, as it allows the organism to react to it and profit from the informational value it provides. In contrast, if no control over pain can be exerted, there is no need for a strong internal learning signal, because nothing can result from it behaviorally. Notably, the theory predicts also an increase in pain relief (i.e. lower pain), if control is provided over the offset of a tonic painful stimulus. It suggests that in this case the relief signal should be increased, because it can be exploited (Desch et al., 2023). Indeed, there are some studies that report hyperalgesic effects, when control over pain was given (Salomons et al., 2015; González-Roldán et al., 2016) and hypoalgesic effects of control, when control over pain relief was given (Zhang et al., 2018; Strube et al., 2023). Another argument for hyperalgesic effect of control over pain is re-

lated to effects of stress on pain: high stress can have hypo- or analgesic effects (Butler & Finn, 2009), because this enables the execution of a defensive action. When facing uncontrollable pain, an individual might be more stressed than if it has control over pain. Thus, reducing stress levels by providing control could result in relatively higher perceived pain, because no stress-induced hypoalgesic mechanisms are triggered. A similar hypothesis has been put forward to explain higher perceived pain when stimuli were predictable, because unpredictability may have led to stress-induced hypoalgesia in the compared experimental condition (Quelhas Martins et al., 2015). However, the results from studies on how stress influences pain perception, particularly when the stress is relatively mild, are ambiguous, as some studies have also shown increases in pain sensitivity under stress (Reinhardt et al., 2013; Löffler et al., 2023), while other studies report a decrease in perceived pain (Timmers et al., 2018), possibly depending on the duration, chronicity and severity of stress.

Finally, when considering that controllability of pain entails a higher expectation precision (Cramer & Perreault, 2006; Ligneul, 2021) regarding its intensity and/or duration, studies investigating effects of (un-)predictability on pain perception can be indicative (Pavy et al., 2024), especially when considering scenarios where a controllable condition has not been compared to a condition in which pain was equally predictable (Müller, 2012). A recent meta-analysis reports that predictability neither generally decreases or increases pain perception, but interacts with stimulus intensity (Pavy et al., 2024). In the context of the Bayesian pain model, it is not surprising that a precise expectation of high pain, in predictable circumstances, should lead to a more accurate perception of its intensity, just as precise expectations of mild pain would do. This may lead to an interaction effect if compared to an unpredictable condition, where percepts of both intensities are biased toward an expected average pain (Zaman et al., 2021), resulting in lower perceived high pain and higher perceived mild pain, if unpredictable. In fact, studies on magnitude estimation show that under uncertainty, participants expect stimulus intensity at the mean of the possible outcomes (Petzschner et al., 2015) and multiple studies report exact this result pattern

when investigating effects of predictability on pain perception (C. A. Brown et al., 2008; Zaman et al., 2017; Pavy et al., 2023).

Because the role of predictability has been considered only rarely (e.g. Wood et al., 2015) when designing experiments on control effects on pain, its interactive influence might explain inconsistencies in behavioral findings and null effects that were reported in some studies (Salomons, 2004; Mohr et al., 2005; Kissi et al., 2021; Mosch et al., 2023). The hypothesis that higher predictability of controllable pain affects its perception depending on the intensity level is further corroborated by a couple of studies on effects of instrumental choice on placebo and nocebo effects. Placebo effects were enhanced, when participants had control over a sham treatment device, resulting in lower perceived pain, i.e. increased placebo effect, compared to a passive placebo condition, that did not provide control (Tang et al., 2019). Inversely, when framing the effect of the device negatively and inducing nocebo effects, also nocebo effects were enhanced in the control condition resulting in higher perceived pain in following active choice compared to the passive nocebo condition (Tang et al., 2024). These results show that increased expectation precision by control can lead to increases or decreases in perceived pain depending on the controlled (and predicted) outcome.

1.3.2 Neural mechanisms

The description of neurobiological mechanisms of control over pain in following section has been summarized by referring to the literature review conducted in the context of this PhD thesis, see Habermann et al., 2024. Studies investigating changes in functional brain activity in response to controllable compared to uncontrollable pain naturally focus on typical pain processing regions. Accordingly, an influential early study reported attenuated activity in the ACC, anterior insula, and somatosensory cortices in response to controllable pain (Salomons, 2004). The results were later replicated by the same authors and complemented by the finding that controllable pain decreased activation in the amygdala and increased activation in the nucleus accumbens (Salomons et al., 2015). The authors inter-

preted these signal changes as resulting from the positive emotional impact of perceived control, which attenuates the affective and motivational response to pain. However, they did not find an effect on subjective pain ratings in response to the control manipulation, but only a decrease in state anxiety during controllable pain in one study (Salomons et al., 2015). Prefrontal brain areas, including lateral PFC, vmPFC and rACC are hypothesized to mediate this emotion-regulatory effect of control (Limbachia et al., 2021) and the affective aspects of pain modulation (Kragel et al., 2018). Indeed, the relative increase in prefrontal cortex (lateral, dACC) activity during controllable pain was replicated and accompanied by lower anxiety ratings and decreased pain ratings (Wiech et al., 2006; Mosch et al., 2023). In addition, a multivariate activation pattern, which primarily predicts psychological aspects of pain (not pain intensity) and includes the nucleus accumbens and PFC, mediated the effect of control on the attenuation of reported pain (Woo et al., 2017).

Other studies point to an influence of control on early sensory processes, as they show a decrease in primary and secondary sensory cortex activity, when control over pain was possible (Helmchen et al., 2006; Lee et al., 2021). Yet, not all results regarding neural processes triggered by control over pain are consistent. Self-applied pain has also been associated with steeper intensity-related increases in posterior insula activity (Helmchen et al., 2006; Mohr et al., 2008), a region that usually scales with increased pain intensity and reflecting rather the sensory than the modulatory aspect of pain (Segerdahl et al., 2015). The same study reported steeper increases in S1, prefrontal cortex activity and cerebellum in the externally applied pain condition (uncontrollable). In addition, increased positive connectivity between the anterior insula and the medial PFC were reported when pain was uncontrollable, alongside with increased pain perception, while negative connectivity between the insula and the dorsolateral PFC in the controllable condition (Bräscher et al., 2016). The authors suggest that different subparts of the PFC either facilitate or inhibit pain via the anterior insula. Finally, studies on pain-avoidance (which could be framed as control over pain occurrence), showed that surprising pain was encoded in PFC, ACC and insula; whereas surprising successful avoidance changed brain activity in S1 (Jepma

et al., 2022; Le et al., 2024). However, these activations were not compared with a condition, where pain could not be avoided at all (uncontrollable condition), so these pain-related brain activation patterns can not be directly related to the opportunity to avoid.

As for the behavioral results, the mixed results in neuroimaging studies can also partly be explained by the fact that no adequate control for predictability effects has been installed, making it difficult to attribute the effects to control and not to decreased salience or surprise. Compared to a condition where outcomes are unpredictable and therefore more salient, control and precise prediction render events less surprising and decrease the need for attentional focus. The (anterior) insula and the ACC represent central regions of the salience network (Uddin et al., 2019; Molnar-Szakacs & Uddin, 2022). Thus, activity changes in these regions were equally likely to result from changes in predictability and not controllability, when both environmental factors were confounded. The same applies to the PFC, which is recruited during focused attention (Uddin et al., 2019), but also has pain-modulatory properties (Peyron et al., 2019) and responds to changes in contingency (Ligneul et al., 2022). Although seemingly difficult to disentangle those factors, it might be that the unspecific role of those brain regions in fact reflects how the (hypoalgesic) effects of control are mediated.

1.4 Contribution of this thesis

This thesis discusses how perceived control over pain influences its perception, specifically whether feeling in control reduces pain. Besides an extensive literature review that investigated control-induced effects on experimental acute pain and brain activity (published as Habermann et al., 2024), I conducted two empirical studies for which I designed novel experimental tasks to first, disentangle controllability and predictability, particularly also as influences on brain activity in response to pain; and secondly test generalization effects of a lack of control over pain. The fMRI-experiment revealed overlapping and specific effects of predictability and controllability on reported pain intensity and neural responses and

pinpoints these effects to changes in the expectation precision. The second, purely behavioral project tested in a typical learned helplessness design, that, also assessed changes in pain perception, how learning is affected by uncontrollable pain. It tested if a causal chain of effects can be created in the laboratory setting, where a lack of control over pain leads to alterations in perception and results in behavioral changes. Results showed that different personality traits influence the response to the experience of uncontrollable pain: dependent on the locus of control and depressive symptoms participants, showed either compensatory or random behavior after experiencing a lower level of control over pain. In the next chapter, I will outline the methods that are relevant to understand the design and statistical analysis of the empirical results. In chapters 3 and 4, I will provide the detailed descriptions of the empirical studies, before merging the findings and interpreting them as a whole in the general discussion in chapter 5, where I evaluate the implications of the results, potential limitations, and provide a perspective on how the results can inform future studies.

2. General methods

The central objective of the empirical studies was to explore the relationship of subjective control and pain on the behavioral and neural level. In a first study, the shared and specific mechanisms by which controllability and predictability modulate pain were investigated by collecting behavioral data (pain ratings) and functional brain activity in two distinct samples. This more conceptual approach of disentangling control and expectation effects is relevant, because expectation effects play a major role in sensory processes related to control and pain. To detect how this effects are mediated, predictions from different mechanistic models of pain perception were applied to the behavioral data. The second study examined how a perceived lack of control might shape learning behavior and pain perception. Before presenting both studies in detail, some general methods are described in this section. These encompass the methods for applying cognitive models to behavioral data, as well as shared methods of both studies, concerning participants, thermal stimulation, statistical models, questionnaires and the software used.

2.1 Participants

Participants for the behavioral and the fMRI samples were recruited through a local online platform (https://www.stellenwerk.de/hamburg) and included when they met none of the following exclusion criteria: acute or chronic disease, drug or medication intake (except for contraceptive or allergy medication), chronic or acute pain conditions, acute condition or injury on the stimulation sites (lower forearm (study 1), lower leg (study 2)). The sample undergoing fMRI scanning, was additionally screened for specific contraindications (pregnancy, metal implants, claustrophobia, etc.) and the participants of study 2 for allergy to capsaicin. Participants were informed about the study procedures and screened for exclu-

sion criteria during a phone call before participation. Upon arrival, all participants provided informed consent and received financial compensation (and in some cases additional study credits) for their participation afterwards. The local ethics committee (*Ethikkommission der Ärztekammer Hamburg*) approved the studies.

2.2 Thermal stimulation and calibration

The pain modality in both studies was thermal heat pain. Thermal stimulation was performed using 30x30mm^2 Peltier element thermode (Pathway model in the behavioral studies and TSA2 model in the MR scanner, with CHEPS probes in the first studies and ATS probe for study 2, all made by Medoc, Israel). The thermode settings were adjusted slightly to accommodate the different safety requirements of the studies, based on the differing durations of the applied stimuli (see Methods sections 3.1 and 4.1). Prior to the main tasks in all studies, individual stimulus intensities (in °C) were derived by a calibration procedure. After the application of pre-exposure stimuli, pain thresholds were determined by binary ratings of the participants classifying a stimulation temperature as either painful or non-painful. Following this threshold determination, stimuli with varying temperatures were applied in order to derive the range of temperatures that would be rated between pain threshold (minimally painful) and pain tolerance (unbearable pain). Individual regression lines were iteratively fitted to the provided rating and temperature relationship and validated in a further step to establish a fit of stimulus intensity to VAS ratings. In study 2, stimuli were administered on skin that was pretreated with capsaicin cream and had different lengths in parts of the experiment. Therefore, different settings and limits for baseline temperature, rise time and maximal allowed temperature were applied, which are described in detail in the methods sections of the empirical studies.

2.3 Locus of control questionnaire

In both studies the locus of control (LC) of the participants was determined. Because there are different ways to assess the locus of control, the instrument used in the empirical part of this thesis is shortly described here. The locus of control questionnaire developed by Krampen, 1991 collects answers to four different subscales that reflect different types of control beliefs: self-concept of own skills, internality, social externality (usually framed as ”powerful others”) and fatal externality (”chance”). From those scales, the subscales internality and externality can be computed by respectively summing up both scores of self-concept of skills and internality and social and fatal externality. Example items from the self-concept and internality subscales are: ”In an unclear or dangerous situation, I always know what I can do.” or ”I can determine many things that happen in my life myself.”. The two other subscales (powerful others and chance) together constitute the externality score. Example items for the externality subscales are: ”My well-being depends to a large extent on the behavior of other people.” (powerful others) and ”It is not good for me to plan far in advance, as fate often intervenes.” (chance). Answers to the items are collected on a scale ranging from 1 (very wrong) to 6 (very correct). The externality and internality scales have a minimum value of 16 and a maximal value of 96. For the other questionnaires utilized in the studies, I kindly refer the reader to the referenced manuals or papers describing the instrument development.

2.4 Visual analogue scales

Pain ratings were collected on a computerized visual analogue scale (VAS) ranging from 0 to 100 that was depicted in white on a dark grey background. Participants were instructed that a rating at the lower anchor indicated a minimally painful experience, while a rating at the upper anchor represented unbearable pain. They were always instructed that ”unbearable pain” was to be understood in the context of study participation and not necessarily

to the most excruciating pain imaginable. Participants were verbally instructed about the meaning of the different sections of the scale, but ticks and descriptive labels were only shown at the scale start and end during the experiments. Participants could move a red rating bar and confirm their rating by button presses. The starting position of the rating bar was randomized to prevent systematic anchoring effects. In study 2, additional pain relief pleasantness, perceived control and helplessness were rated on similar VAS, described in more detail in the methods section of study 2.

2.5 Statistics

2.5.1 Linear mixed effects models

Effects in both studies were quantified with linear mixed effects model (LMM). Linear mixed effects models include explicit predictors of the outcome variable (fixed effects) and, additionally to a random error term, include a structured error term related to other predictive variables. This structured error term is called the random effect term and can be included to control for example, for repeated measurements or a paired design. Main and interaction effects are be defined in the design matrix. Importantly, the effects are always estimated as deviations from an implicit reference category. This reference category is the intercept from which the increase or decrease in the dependent variable is estimated given the different levels of the predictor. If interaction effects are modeled in the design matrix (by hand or by the internal building of a model matrix in a package), the main effect of a predictor in the model output can only be interpreted at the lowest factor level of the predictors, which are also included in the interaction term. For example, if an interaction effect of experimental group and intensity is modeled, then the estimated effect of intensity will only refer to the effect of intensity in the experimental group that is included as the reference category, but won't be informative regarding the effect of intensity at group average. By more complex coding, also a zero intercept or baseline can be included in the model, from which all effects can be estimated. However, if interaction effects are present, the interpretation of

main effects can be misleading, because the average estimate might let the effects appear more consistent than they actually are. The predictor or regression weights are typically described as β values and I will use the terms interchangeably throughout the results sections of this thesis.

A typical way to implement those models is the use of packages like lme4 (Bates et al., 2015). In lme4, model parameters are estimated by optimizing a restricted maximum likelihood (REML) criterion. Because the exact null distribution for the parameters is unknown in linear mixed models, an approximation of the degrees of freedom is necessary. The package "lmerTest" (Kuznetsova et al., 2017) uses the Satterthwaite's method as default to make it possible to derive *p*-values from those models. Due to time constraints, this approach was implemented for the statistical analyses in study 2. However, rating data in study 1 were analyzed with Bayesian methods, that are described in the next section.

2.5.2 Bayesian data analysis

Bayesian methods represent an alternative way to estimate model parameters. In contrast to REML optimization, the full Bayesian approach allows for uncertainty in the estimated parameters (Bates et al., 2015) and outputs the entire probability distribution of the estimated parameter space. Furthermore, it does not rely on null hypothesis testing, but allows to derive the actual probability of parameter values. The Bayesian approach makes all prior assumptions regarding distributions of parameters explicit by design (Kruschke, 2021), because the assumptions regarding data distribution are included in the form of priors, which are combined with observed data points (likelihood) to derive the probability of model parameters (posterior). Bayesian parameter estimation for the linear mixed models was performed in study 1, using the Hamilton Monte Carlo (HMC) sampler implemented in Stan (Betancourt, 2017; Stan Development Team, 2024). The random effects and error structure was modeled in parallel to the approach outlined in Sorensen et al., 2016. Design matrices were self-written in R (R Core Team, 2020). Also, more complex mechanistic models were applied to explain effects in study 1. Those models were also implemented

in Stan and are described in detail in section 3.1.

Sampling Instead of optimizing a maximum likelihood criterion, estimates are derived by sampling from a simulation of the combined probability space of the parameters. Stan implements a No-U-Turn sampler, an adaptive type of a HMC sampler (Betancourt, 2017). The sampler determines the most likely values of model parameters by running physical simulations of the posterior distribution of the model parameter space and samples values in respect to their estimated probability given the model, prior and likelihood (McElreath, 2020). For the sampling process, the number of iterations, separate chains performing the sampling and the number of warm up trials need to be defined. The following settings were applied: number of iterations = 4000, number of chains = 4, number of warm up iterations = 1000. For parameter recovery of the cognitive models, the number of iterations was changed to 1000 (plus 500 warm-up iterations) for time efficiency reasons.

Model convergence and sampling diagnostics To check that the sampling process did not encounter any problems, possibly due to errors in the model, trace plots and the shape of the posterior distributions for the parameters were visually inspected. Trace plots plot the samples of the chains in sequential order. An additional measure of chain convergence is the $\hat{R}$ measure, which compares the within-chain to the between-chain estimates of parameters (Vehtari et al., 2021). A $\hat{R}$ values > 1.00 indicates that a chain did not converge (McElreath, 2020), i.e., that it got stuck in another area of the probability space. Additional model diagnostics are pairs plots of the parameter samples and the number of effective samples. With pairs plots, the shape of the posterior densities of each parameter as well as their inter-correlations can be examined; the number of effective samples corrects the number of samples with respect to auto-correlation in the sampling process (Gelman, 2014; Stan Development Team, 2024). $\hat{R}$, trace and pairs plots were checked for each model fitted with Stan. These measures were evaluated for all models used throughout this work.

Highest posterior density intervals The shape of the resulting distribution of model parameter estimates can be evaluated by computing highest posterior density intervals (HPDI). HPDIs cover the range of parameter values (e.g. predictor weights) that has a specified probability mass. For example, if the probability of a parameter to be zero would be very high, the HPDI would cover mainly zero and very small values. In context of predictor weights within the linear mixed models, this would indicate that low or absent influence of the predictor on the dependent variable, i.e., that changes in the predictor did not result in changes in the dependent variable. In contrast to *p*-values and confidence intervals derived in frequentist analysis approaches, HPDIs directly indicate the probability of regression coefficients (Kruschke, 2015). In sum, they communicate how compatible different parameter values are with the model and the data, depending on the prior choice (McElreath, 2020).

Priors A crucial step in Bayesian data analysis is the definition of priors. Priors represent sensible assumptions about the distribution of the model parameters. They encode the prior state of information before the model has ”seen” the data. While the approach outlined in Sorensen et al., 2016 uses flat uniform priors for the predictor weights in a linear mixed model, it has been advocated to use ”weakly informative” or regularizing priors in regressions instead (Gabry et al., 2019). This is because uniform priors place to much probability on very high and low values. In context of the regression models applied in this study, the weakly informative priors for the predictor weights rendered the analysis more conservative, because they placed more weight on zero. Thereby, the priors protect the analysis from overfitting. The priors in the more complex models depend on the assumptions in the different models. All priors are described in methods section of study 1 (3.1).

Expected log-pointwise predictive density One strategy to estimate the predictive accuracy of models with Bayesian estimation procedures is leave one out cross-validation (McElreath, 2020). In this type of cross validation, one observation is left out from the sample, the model is trained on remaining observations and the left-out data point is predicted. The (log-)probability of the left-out data point under the model assumption is evaluated.

This is repeated of all observations and the summed log-probabilities then constitutes a measure for the accuracy of the model: the expected expected log-pointwise predictive density (ELPD). To avoid fitting the model over and over again (which would take very long due to the sampling procedure), the impact of observations can be evaluated using importance weighted samples from the posterior distribution (Vehtari et al., 2015). By using these weighted observations, the models out of sample accuracy can be estimated and the impact of the single observations is approximated. Study 1 used Pareto smoothed importance sampling for the approximation of these importance weights (Vehtari et al., 2015, 2017) . One diagnostic of this method are the Pareto-$\hat{k}$ values, which shape the distribution that smooths the importance weight. If $\hat{k}$ values are too high, the importance weights cannot be reliably estimated and thus also the results of the cross-validation cannot be interpreted. Because this was the case for some of the models, a more robust method that employs a novel mixture estimator for ELPD was applied (Silva & Zanella, 2022). A higher positive value of ELPD indicates a higher probability of the data given the posterior over parameters. ELPD is relevant for model comparison, i.e., to decide if one model explains the data better than an alternative model. A difference of ELPD < 4 between models is considered small. If ELPD differences between models are larger than 4 and data includes more than 100 observations model comparison results can use the standard error of the difference for interpretation (Sivula et al., 2022). Leave one out cross validation and model comparison was done using the loo package in R (Vehtari et al., 2024).

Parameter recovery When testing new models, it is important to verify that they behave as intended under the best possible conditions (Wilson & Collins, 2019). This can be done with parameter recovery. Parameter recovery describes the process of simulating datasets with known parameter values. After the simulation, the models of interest are tested and parameter values are derived. The resulting parameters estimated by the model are compared with the input values of the simulation. This recovery procedure ensures that a model can at least theoretically perform as intended. In a perfect scenario, the input and output

parameters are highly correlated. For the mechanistic models tested in study 1, data sets of 60 hypothetical participants were simulated, using the structure of the different models. The sample size was chosen to be close to the empirical one. The resulting parameter values were correlated with the parameter input of the simulation. Additionally, the input- and output parameters were plotted against each other in a scatter plot, see Figures A1 to A3. Successful recovery was determined based on correlation coefficients and visual inspection of the scatter plots.

2.6 Software

Behavioral data of both studies were preprocessed, analyzed and visualized using MATLAB R2020a (The MathWorks Inc., 2020), R (R Core Team, 2020), especially using the lme4 package (Bates et al., 2015), rstan (Stan Development Team, 2024) and Python. P-values from linear mixed models were estimated using the lmerTest package (Kuznetsova et al., 2017). Figures of behavioral data were created with the ggplot2 package in R (Wickham, 2016). Questionnaires in study 2 were implemented in LimeSurvey (LimeSurvey GmbH, n.d.). Preprocessing and analysis of fMRI data were conducted with SPM12 build 7771 (Friston, 2011) in MATLAB R2020a (The MathWorks Inc., 2020). Figures of fMRI results were created with nilearn (Nilearn contributors et al., 2025). The experimental tasks were programmed using the Psychtoolbox extension (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007).

3. Empirical Study 1

> *The problem of disentangling the effects of [actual] controllability from predictability may be next to logically impossible.*
>
> Seligman, 1975

In his quote, Seligman (1975), raises the issue, that when an event is controllable, it naturally is also predictable. For example, if the intensity of a painful stimulation can be self-controlled, it can also be precisely predicted. This interrelatedness of controllability and predictability of stimuli can pose a challenge when trying to estimate the influence of control on pain. Many studies established that expectations, and the precision of these expectations can influence pain perception (Büchel et al., 2014; Geuter, Koban, & Wager, 2017; Grahl et al., 2018). Therefore, when studying effects of control, it might not be clear which of the two environmental features, controllability or predictability, actually caused changes in pain perception. The disentanglement requires an experimental condition, where the level of predictability of pain is matched to the level of predictability that results as a by-product of control.

Effects of predictability were shown to interact with stimulus intensity regarding modulatory effects on pain (Pavy et al., 2024): high pain is rated as more intense when its intensity is predictable, whereas low pain is rated as less intense under predictable conditions (Zaman et al., 2021). This stems from the effect that predictability anchors expectations at the intensity level of the stimulation, while unpredictability leads to widely distributed expectations. This is because, in the unpredictable case, the best guess about the stimulus intensity, is the expected value, i.e., the average of all possible intensities. Following the expectation-integration framework of the Bayesian pain model, expectations that are centered at an average intensity produce an interaction effect, because perception of both,

stimuli of low intensity and high intensity, will be biased towards the mean of all possible outcomes.

Keeping these results in mind, hypotheses about the pain modulatory influence of control can be formulated, which integrate the known effect of predictability. For example, it might be that controllability decreases pain perception across all intensity levels. This is hypothesized by accounts that put forward control as a general safety signal, which produces hypoalgesia (Salomons, 2004); or controllability might increase pain across all intensity levels, as theorized by the informational value theory of pain (Seymour, 2019). Both effects would not result in an interaction effect with predictable, but solely with the unpredictable pain. It could also be the case, that controllability even strengthens the interaction effect of predictability by internally increasing expectation precision through self-involvement. Finally, effects of control over pain intensity could potentially be fully explainable by predictability, resulting in an equivalent strength of interaction effects of both, when compared to unpredictable pain.

To test for specific effects of control, this empirical study accordingly implemented a predictable condition that provided the same level of information about pain intensity as the control condition, without actually granting control. In addition, to measure net effects of predictability, another experimental condition was included, where pain was neither controllable nor predictable. Thus in the three conditions pain was either (i) controllable and predictable, (ii) predictable, but uncontrollable or (iii) unpredictable and uncontrollable. As outcome variable, pain intensity ratings were collected. The experimental paradigm was tested as a within-subject design in a behavioral sample and then in a independent sample, which completed the task during functional magnetic resonance imaging (fMRI).

The fMRI study aimed to explore the neural bases of the effects of controllability and predictability on pain processing. Results of early imaging studies report control-induced changes in brain regions that are associated with the descending pain modulatory system (e.g. the insula and ACC) and the exertion of cognitive control (lateral prefrontal cortex) during pain (Salomons, 2004; Wiech et al., 2006). This was interpreted in light of an emotional

reappraisal mechanism induced by control. Following the argumentation of the studies, the effects resulted from activation of prefrontal brain regions that conveyed safety signals to pain processing regions upon detection of control. These regulatory neural pathways then supposedly contributed to pain reduction. However, the reported activation differences in brain regions like ACC and anterior insula are especially prone to also result from different levels of predictability, because unpredictable stimuli are usually more salient and both regions are typically activated by unexpected and salient stimuli, as discussed in the introduction. Also multiple studies showed that different pain expectations recruit the ACC (Schenk et al., 2024), insula (Horing & Büchel, 2022) and PAG (Roy et al., 2014). Specifically the PAG seems to be responsive to different precision level of expectation (Grahl et al., 2018). Thus the effects reported by earlier studies might in fact not be related to control-induced hypoalgesia, but stem from different levels of predictability. So, the collection of fMRI data was necessary to reveal if and where an overlapping and/or specific influence of control on neural pain processing might be present.

3.1 Methods

Sample 59 participants were included originally in the behavioral study. During data preprocessing, five participants had to be excluded from the study (four made to many errors in the task (in >10% of color-matching trials), one person did not understand the task). A final dataset of 54 participants was analyzed. An independent sample of 64 participants participated in the fMRI study. Participants who were included in the behavioral study were not eligible. Five participants had to be excluded from the analysis (two had a very low pain threshold, one thought that they were deceived by the experimenter, one mad to many errors in the task and one had an incidental neurological finding). Behavioral data from 59 participants were analyzed, while four imaging data sets were excluded due to excessive or frequent head movement, as determined by visual inspection. This allowed for the analysis of functional brain activity from a total of 55 individual datasets.

Thermal stimulation settings Thermal stimulation was performed as described in the general methods. The baseline temperature was set to 32°C the rise/fall rate was set to 15°C/s in the behavioral and 13°C/s in the fMRI sample, due to different software limitations of the thermode models. The maximally allowed temperature was set to 49°C for safety reasons. If calibration suggested higher temperatures, they were adjusted to that upper limit. Stimuli had a plateau duration of 4s and were calibrated to correspond to rating targets of 30, 50, and 70 on a 0-100 VAS.

Study design The study investigated within-subject effects to reduce between-subject error. All participants completed runs of the controllable, predictable and unpredictable pain condition. After establishing the paradigm in the behavioral sample, it was used to investigate concurrent neural activity during the improved task with functional brain imaging. Pain ratings and answers to questionnaires were collected in both samples.

Experimental procedure After arriving, participants received information regarding the thermal stimulation, experimental task and measuring procedures and signed informed consent. Additionally, they filled out the questionnaires and provided demographic information. Then participants were familiarized with the thermode and underwent a calibration procedure to determine individual stimulus intensities. After the calibration procedure, participants performed each experimental condition twice, resulting in six runs. Each run included 15 trials, so in total participants completed 90 experimental trials. The condition ordering was pseudo-randomized to ensure that each condition would be presented once in the first half and once in the second half of the experiment. For instructive reasons, participants did three test trials of each conditions before the tasks started in the first half of the experiment. The thermode was placed on the participants left forearm at three different locations throughout the experiment. The location of the thermode was changed after each run. Each skin patch was stimulated twice after the same time interval, to guarantee the same duration of recovery. The positioning order was pseudo-randomized to counterbalance conditions. After completion of the task, participants filled out the payment form and

participants in the fMRI sample additionally completed a short exit questionnaire. Each run took approximately 7 min; including the instruction, preparation and calibration period, the experimental sessions had an overall duration of approximately 2 - 2.5 hours each.

Task All participants completed two runs of the three experimental conditions, in which pain intensity was either (i) controllable and predictable, (ii) predictable but uncontrollable, or (iii) unpredictable and uncontrollable. In all three experimental conditions, low, medium and high intensity heat pain stimuli (corresponding to VAS ratings of 30, 50, and 70) were applied to the left forearm of the participants.

Controllable condition In the controllable condition, participants determined the stimulus intensity that would be applied later in the same trial (choice task). The pain intensity levels were represented by three differently sized (small, medium and large) and colored (purple, yellow, turquoise) circles, which were shown at the beginning of one trial (see Figure 3.1). To make a choice, participants had to select the button displayed on the lower part of the screen that matched the color of the circle sized correspondingly to the desired intensity level (i.e., they had to press the button with the same color as the largest circle, if they wanted to select the highest stimulus intensity). To guarantee that participants received the same number of stimuli at all three intensity levels in the controllable condition as in the other two conditions, a limitation was imposed on the free choice: each intensity had to be selected five times in one run (15 trials in total). When participants tried to select an intensity level for a sixth time, one of the other available intensity levels would randomly be chosen by the computer program. Participants were instructed to avoid that behavior, but to choose deliberately. Inside the circles, numbers were shown that indicated how often the corresponding intensity level was still available. A zero was displayed after the intensity level had been selected five times. A time limit of 4s was imposed for the choice period. Choice was executed by pressing a key on a keyboard (behavioral sample) or a button on a button box device (fMRI sample). The chosen circle was then highlighted for 3s and the respective stimulus intensity was applied after a jittered expectation phase of 2-5s during

which a white fixation cross appeared on the screen. After the cued stimulation period, the white fixation cross was shown again for 2-5s. Participants then rated the pain intensity of the stimulus on a VAS scale (8s max.). The starting position of the rating bar was randomized to be shown at some new position between 30 and 70 in each trial to avoid systematic anchoring effects. During the inter-trial interval (ITI) of 2-4s the fixation cross was shown. The position and colors of the circles and the color-button mapping for the motor response was randomized across trials to control for perceptual similarity and spatial remapping. For an schematic overview of the time-course of the task see Figure3.1.

Predictable condition In the predictable condition, the trials also started with the display of the three circles, but all circles were shown in the same color. Participants had to do a ”color-matching task”, i.e., select the button that matched the color of the circles. This task was introduced to control for motor responses and to keep participants focused. In contrast to the controllable condition, the button press in the predictable condition did not have an impact on the intensity of the subsequent pain stimulus in the trial. Importantly, participants were informed about the upcoming stimulus intensity in each trial, by the highlighting of the circle that represented the upcoming stimulus intensity. Also, participants were informed about the number of times the different intensity levels would be applied again during the current run, by the numbers shown inside the circles. The anticipation, stimulation, and rating phases, as well as the ITI, were designed to be equivalent to the controllable condition.

Unpredictable condition In the unpredictable condition, participants did the same color-matching task as in the predictable condition. However, they were not informed about the upcoming stimulus intensity or about the remaining trials of each intensity application in the run. Instead, a zero was shown inside of all circles from the start and all circles were highlighted after the response in the color-matching task. The expectation, stimulation, and rating phases, as well as the ITI were equivalent to the other conditions. Intensity sequences in the predictable and unpredictable conditions were defined by the experimental

script.

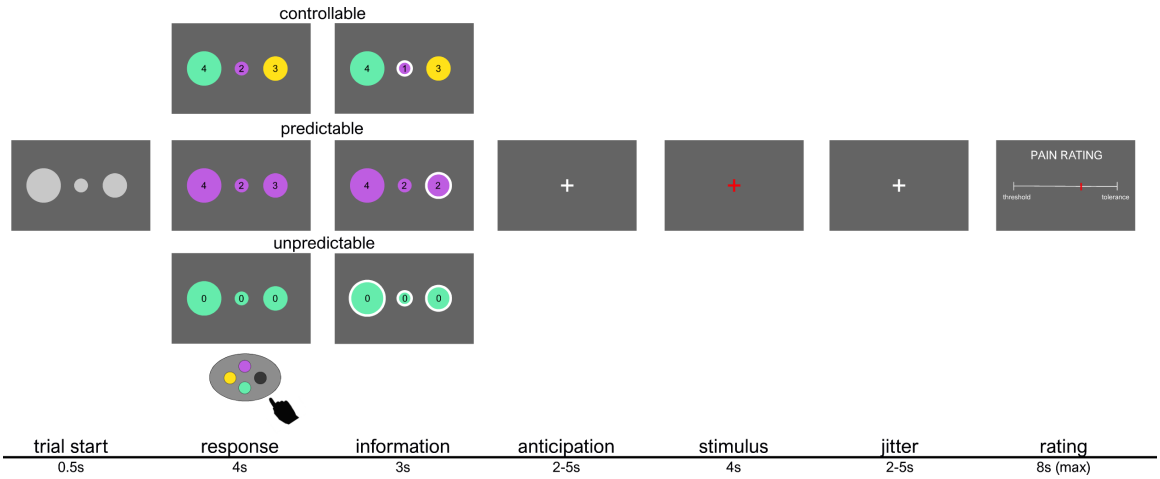

Figure 3.1. Time-course of one experimental trial. Participants either chose the upcoming stimulus intensity (controllable runs) or confirmed the color of the circles (predictable, unpredictable runs) by selecting the correct button displayed on the lower part of the screen. The number of remaining stimuli of each intensity level were shown inside the circles in the controllable and predictable condition. In the unpredictable condition a zero was shown inside the circles for the duration of the entire run. To guarantee ratings for all intensity levels in controllable runs, the limitation was imposed that participants had to select each intensity level five times in one run. After the button press, the circle was highlighted, which corresponded to the intensity in size that was either self-chosen (controllable) or script-determined (predictable). In the unpredictable condition, all circles were highlighted for 3 seconds. After a jittered anticipation phase (2-5s), a white fixation cross turned red and a 4s long painful heat stimulus of either low (VAS 30) medium (VAS 50) or high (VAS 70) intensity was applied. After stimulus offset the cross turned white (2-5s jitter) before the rating scale was shown.

Intensity sequence generation While the intensity sequences were determined by participants' choices in the controllable condition, they had to be predefined for the predictable and unpredictable condition. Here, the aim was to match the sequences of intensities as closely as possible to the controllable condition, to avoid confounding order-effects. In a within-subject design, there are different strategies to implement this matching procedure across conditions. One strategy is to use the sequence that was determined by the participant's choice in the controllable condition and apply this to the other conditions, where no choice is possible. However, this requires that the controllable condition always is completed before the other conditions, making it impossible to completely counterbalance their order. Also, this strategy provides the experimenter with only one sequence per experi-

mental half, which could make the intensity sequences in the unpredictable condition unintentionally predictable. The other option would be to yoke across participants, that is, to apply the chosen intensity sequence of one participant to the next. This would only be a valid approach if one assumes similar choice behavior across participants. Because conditions should be counterbalanced to control for habituation to the painful stimulation and because systematics in choice behavior were unclear before starting data collection, no yoked design was implemented. Thus, in the behavioral sample, the stimulus intensities in predictable and uncontrollable runs varied randomly and were consequently uniformly distributed among trials.

After analyzing the choice pattern of the behavioral sample, it became visible there was a shared structure in the sequence in which participants selected the intensities. Participants tended to select high intensity stimuli rather in the beginning, stimuli of medium intensity in the middle and of low intensity toward the end of a run (see section 3.2.1). After observing this effect, the intensity sequence generation for the predictable and unpredictable conditions was adapted to match that choice pattern instead of creating uniform distributions. The frequencies of stimulus intensities in controllable trials of the behavioral sample were used as probabilities to create intensity sequences for the predictable and unpredictable runs. Due to the limit of choosing each intensity five times and the probabilistic structure that was applied without any additional sequence criterion in this approach, the generated intensity sequences showed an unwanted increase of high intensity stimuli towards the end of the predictable and unpredictable runs. When this became visible during data collection (after collecting data from 34 participants), the procedure was adapted again. For approximately the second half of the fMRI sample (n=25), intensity sequences of controllable runs from the behavioral study were applied, in the predictable and unpredictable condition.

Questionnaires Demographic information was collected from the participants, in addition to the state form of the State-Trait-Anxiety Inventory (STAI) (Laux et al., 1981) and a

German version of locus of control (LC) questionnaire (Krampen, 1991). The fMRI sample completed a qualitative exit questionnaire. To ensure that participants did not incorrectly assume that they were deceived by the experimenter, they were asked if they felt that they got the temperature they selected (controllable condition) or were informed about (predictable condition). Finally, they were asked how many different stimulus intensities they perceived and if they had any further comments about the study.

Behavioral data analysis

Linear Models Linear model implementation followed the statistical approach outlined in sections 2.5.1 and 2.5.2. Design matrices that specified fixed main and interaction effects as well as the subject identifier for the random intercept were created. Regression parameters, namely intercept, β-weights and random effects and the error term were estimated using HMC sampling. Resulting posterior distribution shapes, 95% HPDI and ELPD were analyzed to evaluate the effects. Reaction times were analyzed using linear mixed effects models in lme4 (Bates et al., 2015), due to time constraints.

Reaction Times To detect differences in cognitive demand between the conditions and to verify that participants made deliberate choices in the controllable condition, the reaction times (RT) in the different tasks (choice; color-matching) were compared. The RT in the choice task was defined as the time period between the appearance of the options on the screen and the button press indicating the choice. In the color-matching task, the RT refers to the time until the button showing the same color as the circles was pressed. Predictors included session number, trial number and condition as fixed; and the subject identifier as a random intercept effect.

Choice behavior To detect general choice patterns in the controllable condition, intensity frequencies over trials were analyzed with simple linear models. The models included the trial number ($t \in [1, 15] \cap \mathbb{Z}$) as predictor for the dependent variable y, the

occurrence frequency of the intensity levels in percent. This analysis was conducted particularly for the controllable condition, as it aimed to reveal a shared strategy of participants to order the intensity levels in a run. Distinct models were fitted for each intensity level (low, medium, high). The models for low and high intensity had the following form, including an intercept α, a slope β for the predictor, and an error term ϵ.

$$y = \alpha + \beta t + \epsilon \tag{3.1}$$

To predict the frequencies of the medium intensities across trials, a quadratic term was included in a second model, to account for the inverted U-shape observed during visual examination of the raw data.

$$y = \alpha + \beta_1 t + \beta_2 t^2 + \epsilon \tag{3.2}$$

Pain intensity ratings Differences in pain ratings were analyzed with linear mixed effects model (LMM) to account for repeated measurements of each subject. In addition to the subject identifier as a random intercept effect, the dummy coded condition identifier (controllable, predictable, unpredictable), the linear term for the stimulus intensity and the interaction terms of condition and intensity were included as fixed effects in the design matrix (X). Run and trial numbers were included to control for habituation/sensitization effects. To derive all pairwise interaction parameters, the model was fitted twice: once with the controllable condition as reference category and then with the predictable condition as reference category (see section 2.5.1). The mean ratings (μ) were modeled, with the following parameters: group intercept (α), vector of predictor weights of fixed effects (β), estimate for subject-specific error (ϵ_s); see equation 3.3. Ratings y were approximated assuming a normal distribution around predicted mean and the unexplained error variance (σ_ϵ); see equation 3.4.

$$\mu = \alpha + (X\beta) + \epsilon_s \tag{3.3}$$

$$y \sim N(\mu, \sigma_\epsilon) \tag{3.4}$$

Priors for the regression weights were defined as $\beta \sim cauchy(0, 2.5)$ and the intercept as $\alpha \sim N(0, 50)$. Uniform priors over $[-\infty, +\infty]$ were implemented for the error terms, to avoid shrinking of the variance terms.

Standard deviations of pain intensity ratings As a proxy for expectation uncertainty, within-subject standard deviations of all condition-intensity combinations were analyzed with an additional set of LMMs. The design matrices differed slightly from the rating models, because intensity was coded as a factor with three distinct levels and not as a linear term. This approach was necessary because of the quadratic relationship between intensity level and rating variability that was visible upon inspecting the raw data. Therefore, additional pairwise differences between intensity levels were investigated: high vs. medium, low vs. high, low vs. medium. Again, the models were fitted twice: once with the unpredictable condition and the low intensity as baseline and once with the controllable and the medium intensity as baseline. The model structure to predict average standard deviation was followed the equations 3.3 and 3.4. Priors for the regression weights were defined as $\beta \sim cauchy(0, 2.5)$ and the intercept as $\alpha \sim N(0, 25)$. Uniform priors over $[-\infty, +\infty]$ were implemented for the error terms, to avoid shrinking of the variance terms.

Expectation Integration Models To investigate what mechanism might have contributed to the effects found in the linear model analysis, a set of mechanistic expectation-sensation integration models was applied to the rating data. The models follow Bayesian notions of pain perception and provide predictions of trial-wise pain intensity ratings, while taking different expectation values into account. Through model comparison it can be determined how likely pain ratings, the measure for individual pain perception, were produced

by different mechanisms. The models have different sets of group-level and subject-level parameters and by sampling, the most likely parameter configuration to predict the data pattern is determined. All models share the aspect that the ratings are approximated by a normal distribution with a specific mean μ_1 and variance τ_1^2, i.e., the posterior distribution, which can be written as $\theta \sim N(\mu_1, \tau_1^2)$. The posterior distribution is based on the approximations of two normal distributions that, respectively, represent the probability of expectation intensity and intensity of sensory input. The posterior resulting from a normal prior and a normal likelihood can be analytically derived by normal-normal integration(Gelman, 2014). The mean of the posterior distribution μ_1 is the precision-weighted and normalized sum of the prior mean μ_0 and the likelihood mean y (see equation 3.5). The precision (inverse variance) of the posterior distribution $\frac{1}{\tau_1^2}$ is the sum of the prior and likelihood precision (equation 3.6).

$$\mu_1 = \frac{\frac{1}{\tau_0^2}\mu_0 + \frac{1}{\sigma^2}y}{\frac{1}{\tau_0^2} + \frac{1}{\sigma^2}} \tag{3.5}$$

$$\frac{1}{\tau_1^2} = \frac{1}{\tau_0^2} + \frac{1}{\sigma^2} \tag{3.6}$$

An equivalent way to express the posterior mean is the prior mean that is adjusted to the likelihood mean y (equation 3.7). The magnitude of this adjustment depends on the ratio of prior variance to total variance, i.e., if the prior is very precise it gets adjusted less, it is imprecise the adjustment to the likelihood is larger. Hence, the influence of the prior on the posterior mean results from the precisions of both distributions.

$$\mu_1 = \mu_0 + (y - \mu_0)\frac{\tau_0^2}{\sigma^2 + \tau_0^2} \tag{3.7}$$

In this study, only pain ratings were collected to inform the posterior, but no expectation ratings that could additionally inform the modeling of the prior distribution. Therefore, the data did not enable the identification of distinct prior and likelihood precision, because either the precision of the prior or the likelihood could be the cause of a change in the posterior

precision, as they are dependent in the formula. Therefore, the precision ratio was replaced by a parameter α (equation 3.8) that indicated how strongly the prior would influence the posterior (equation 3.9). Because α represents a ratio, it was constraint to range between 0 and 1. An α value close to zero would reflect a greater influence of the prior on the posterior mean, because it reflects low variance in the prior distribution and thus a higher degree of expectation precision. A value close to one reflects more variance in the prior relative to the likelihood distribution and therefore the posterior mean is drawn more to the likelihood mean.

$$\alpha = \frac{\tau_0^2}{\sigma^2 + \tau_0^2}; \alpha \in [0, 1] \tag{3.8}$$

$$\mu_1 = \mu_0 + (y - \mu_0)\alpha \tag{3.9}$$

Apart from the precision ratio, the prior mean and the likelihood mean need to be defined. The likelihood mean y in a trial t was defined as the VAS rating target of the specific trial and therefore could have values 30, 50 or 70, depending on the intensity i of the stimulus. Furthermore, a linear term was subtracted from the likelihood mean to account for habituation or sensitization over trials in a run. The likelihood mean reflects the peak of the probability distribution of the sensory component of pain.

$$y_t = y_i - ht; y_i \in \{30, 50, 70\} \tag{3.10}$$

The prior mean μ_0 represents the central measure of the expected intensity of pain. Its definition is crucial to implement the hypothesized rating differences between the experimental conditions. In contrast to the controllable and predictable condition, the upcoming pain intensity was unknown to the participants in the unpredictable condition. In the following paragraph, two approaches to include this aspect in the models are outlined. Informed by earlier accounts on unpredictability of pain, the models implemented a prior mean that varied closely around the expected value of the three possible stimulus intensities, corre-

sponding to an average value of 50 on the VAS.

Baseline model Two versions of a ”baseline model” were set up to test different implementations of an average expectation in the unpredictable condition. One version of the models defined a *fixed* prior mean in the unpredictable condition: as a free parameter, this fixed prior was kept constant in all unpredictable trials. It was determined individually for each subject by drawing it from the group-level normal distribution (see Table A1, prior mean for medium intensity). The second, *dynamic*, implementation of the average prior mean, accounted for the possibility that participants actually tracked how often each intensity level was applied throughout an unpredictable run. For example, the probability of receiving very intense pain would be reduced after the occurrence of multiple subsequent highly painful stimuli. The dynamic unpredictable prior mean was defined as the summed product of outcome probability and the prior mean values of the different intensity levels (drawn from normal distributions around their likelihood values 30, 50 or 70). The outcome probabilities of the intensity level, which weighted the prior means, were negatively related to the number of previous occurrences, and defined by dividing the remaining number of occurrences by the remaining trials in a run ($w = \frac{5}{15}$ for all intensity levels in trial one; $w_i = \frac{4}{14}$ in trial 2, if the intensity level had been chosen, and $w_i = \frac{5}{14}$ for the other two intensity levels, etc.). The prior means of the different intensity levels were multiplied with their probability weights and summed to form the unpredictable prior mean for the next trial (equation 3.11). The prior mean again varied around the value of 50, but a slight change would be predicted by the dynamic model over time, especially after the same intensity level had been applied repeatedly.

$$\mu_{0,unp.} = w_{30}\mu_{0,30} + w_{50}\mu_{0,50} + w_{70}\mu_{0,70} \tag{3.11}$$

Allowing the change in the unpredictable prior mean, was the first step to implement expectation effects that could possible have contributed to effects on pain ratings. The predicted ratings in the controllable and predictable condition by this model were defined

as samples directly from the hypothesized prior distributions. This is possible, because a change in the sensory component of the model, i.e. the likelihood, was unlikely in this study setup, where stimulus intensities were calibrated to meet individual pain levels and kept constant throughout conditions. Prior means in the controllable and predictable condition were derived from six distinct normal distributions representing the hypothesized prior distributions for low, medium and high intensity stimuli. The individual prior means for each subject were drawn from these normal distributions on group-level, that were centered at different means for the intensity levels. The prior means were free to vary across conditions, providing each participant with a set of nine prior means in the dynamic version and seven prior means in the fixed version of the model. Both models included the habituation term as a subject-specific free parameter.

Different alpha parameters Because the expectation-integration models should also reveal if different mechanism produced differences in rating average and dispersion between the controllable and predictable condition, an extension regarding the alpha parameters was added consecutively to the models. First, the model was extended to differentiate between the parameter in the unpredictable condition (α_u) and a (shared) parameter for the two other conditions (α_{cp}). Then, because this was the main interest of this analysis, the parameter was split up further, and a model with three different parameters ($\alpha_u, \alpha_c, \alpha_p$) was tested. Unfortunately, similar to full Bayesian model versions, that were tested at the very preliminary stages of data analysis, model parameter recovery for the three parameter model was not successful (see Figure A1).

Mean-shift and precision-change model To follow an alternative approach to compare mechanisms in the controllable and predictable condition, the baseline model was then tested with additional constraints regarding parameter distributions. Two different versions of the baseline model were tested, to detect by model comparison, if rather different mean expectations (*mean-shift model*), or differences in expectation precision (*precision-change model*) produced different pain ratings in the controllable and predictable condition. Im-

portantly, if no constraints are imposed on the distributions and assuming constant mean values, a change in prior or likelihood precision alone could not lead to a change in posterior precision. However, in the context of pain ratings as an outcome variable, hard boundaries are imposed on the lower and upper limit of the distributions (VAS 0 indicating the pain threshold and VAS 100 indicating pain tolerance level). Therefore, all distributions were truncated to produce positive values below 100. In case of truncated distributions, different precisions can actually lead to a bias in mean ratings when sampling from the posterior distribution, particularly on the scale extremes. Less precise posterior distributions will produce higher mean values at the lower intensity level, and lower values on the high intensity level, because the values are more dispersed in only one direction on the scale.

In the mean-shift version of the baseline model the implementation of μ_0 followed the description above. Importantly, the prior means between the controllable and predictable were allowed to differ, while their standard deviation was constraint to be equal. For each participant an individual set of seven (fixed model) or nine (dynamic model) prior means was fitted, while only one dispersion parameter σ was allowed. Parameters were sampled from group-level distributions (see Table A1).

The precision-change model tested a different constraint on the parameters between the controllable and predictable condition. While all conditions shared the same standard deviations for the posterior means in the mean-shift model, the precision-change model allowed different values for the standard deviations σ for the distributions of ratings in the controllable, predictable and unpredictable condition. Parameters of both models were recoverable, see Figures A2 and A3.

Nullmodels Finally, the models were compared with a nullmodels. The first nullmodel included only the habituation term for the likelihood mean and sampled ratings from the same intensity specific distribution for all conditions. A second nullmodel applied the same structure for the predictable and controllable condition as the baseline model, but did not include the expectation integration in the unpredictable condition.

FMRI data analysis

Data acquisition Structural and functional scans were acquired with a 3T magnetic resonance scanner (PRISMA; Siemens, Erlangen, Germany) with a 64-channel head coil. First, a structural T1-weighted magnetization-prepared rapid acquisition gradient echo image was acquired, with a voxel size of 1.0mm^3 and 240 slices. Then, functional data was collected in six runs with a T2* weighted gradient echo-planar imaging (EPI) sequence of 50 slices (voxel size = 2.0mm^3) and the following parameter settings: TR = 1.5s, TE = 26ms, flip angle = 60°, FOV = 224mm, multiband factor = 2, GRAPPA PAT factor = 2.

Preprocessing The functional images were slice-timing corrected, realigned and co-registered to the structural T1-weighted images using a non-linear coregistration approach. For this approach, nonlinear spatial normalization was performed on segmented mean EPI images to map them to the segments of the T1-weighted images. Then, warp fields to map the T1-weighted images to template space (MNI ICBM 152; 2009c Nonlinear Asymmetric) were computed and combined with the warp fields from native space to T1-segment space. All warp fields used in the co-registration procedure were computed with the DARTEL toolbox (Ashburner, 2007).

First-level analysis For the first-level analysis, preprocessed functional images were masked with the smoothed (3mm at full-width half maximum (FWHM)) and skull-stripped structural image. General linear models (GLM) with hemodynamic response function convolved regressors, as implemented in SPM (Friston, 2011), were computed. For all models, physiological noise (heartbeat, breathing) was modeled using the RETROICOR method as from the TAPAS toolbox (Frässle et al., 2021) and a total of 24 motion regressors (translation, rotation, pitch in all three spatial dimensions and their temporal derivatives) were included as nuisance regressors to the first level design matrices (Friston et al., 1996). Additionally, because all runs were concatenated for the first-level matrix of each participant, session intercepts were included to account for session specific error variance. After esti-

mating first level results, beta images were normalized to MNI space and smoothed with a 4mm FWHM smoothing kernel. The event onsets were defined for the different models as described below.

Condition-dependent pain processing The onsets of pain stimulation were defined at the start of the stimulus plateau (stimulus onset plus the time the thermode needed to reach the targeted temperature), separately for the three conditions. Each of the regressors was defined as a boxcar with a duration of 4s, corresponding to stimulus length. Z-standardized pain ratings were added to the onset regressors as parametric modulators. This resulted in a total of six regressors of interest (one onset and one parametric modulator regressor for each condition). In a second model, z-standardized pain intensity levels (not ratings) were included as parametric modulators as a direct equivalent to the analysis of the behavioral data.

Task-related neural activity Because the study consisted of a sequence of a condition-dependent task (choice vs. color-matching) and the stimulation, additional GLMs were defined, which included the onset times of the different tasks in all three conditions to investigate potential task-dependent differences in neural activity. Also, a finite impulse response (FIR) model was set up to allow time-resolved comparisons between the conditions, particularly at the time-point of stimulus onset, to exclude confounding baseline differences between the conditions, possibly elicited by the different tasks. Regions of interest for the comparisons of FIR time bins were the regions resulting from analysis of condition-dependent pain processing, to exclude a confound for this effect of interest.

Models for visualization A final model including each intensity-condition combination as distinct onset regressor, served for the visualization of the effects (resulting in 3 x 3 = 9 regressors in total). This was necessary to evaluate if activity pattern in the brain corresponded to the condition differences regarding pain ratings and visualize effects of pain intensity.

Second-level analysis For group-level analysis, the smoothed and normalized first-level beta images were analyzed with a flexible factorial model. Pain onsets and parametric modulators (pain ratings, intensity levels) were analyzed with one-way ANOVA on group level. Contrasts of pain onset compared to baseline, between intensity levels and conditions were computed. For the effects of condition, pain onset regressors were contrasted. For the effect of pain intensity and interactions, parametric modulators were evaluated. First the contrast between the two predictable and the unpredictable condition (C, P vs. U) was computed, and in a second step, the controllable and the predictable condition were compared. Finally, for the interaction effects, the parametric modulators of each condition were contrasted in both direction, to implement positive and negative intensity scaling for both conditions, i.e., the intensity modulator was positively scaled for one condition in one comparison and then negatively in the second comparison with the same condition. Concerning the FIR model of task, contrasts were computed across the time bins prior to stimulation onset. Correction for multiple comparison was performed with family-wise error (FWE) correction and the significance threshold was set to p <.05 on whole-brain level.

3.2 Results

3.2.1 Behavioral Results

General quality check

The samples did not differ in distribution of self-reported age, gender, state anxiety, internality or externality of locus of control. The stimulation temperatures were similar between samples. Sampling diagnostics and model convergence for all linear (mixed) and expectation-integration models were assured by visual examination of trace plots, evaluation of $\hat{R}$ values, pairs plots and posterior distribution. Additionally, model structures were optimized until no convergence warnings regarding effective sample size or $\hat{R}$ resulted during the sampling procedure. All tables summarizing demographics, calibration outcomes,

model parameters and diagnostics can be found in the appendix (Tables A1 to A9).

Choice behavior

Participants in both samples shared a common pattern of choice behavior in the controllable condition: they selected high intensity stimuli preferentially at the beginning and the low intensity stimuli towards the end of a run (see Figure 3.2). The medium intensity stimuli were mainly selected in the middle of a run. Slopes fitted to the frequency of the high intensity stimuli by the linear models were clearly negative in both samples. The corresponding 95% HPDIs did not include zero; behavioral sample: β = -3.59, HDPI = [-4.45, -2.65]; fMRI sample: β = -2.63, HPDI =[-3.42, -1.76]. The slopes of the fitted lines for frequency of low intensity stimuli were positive, indicating an increase towards the run's end; behavioral sample β = 3.08, HPDI = [2.18, 3.96]; fMRI sample: β = 2.21, HPDI = [1.19, 3.19]. The distribution of choice frequencies of the medium intensity level was better explained by the model including a second order polynomial term as assessed by leave-one out cross validation, confirming the quadratic shape of the frequency distribution (behavioral sample: $ELPD_{lin}$ = -58.9, $ELPD_{poly}$ = -55; fMRI sample: $ELPD_{lin}$ = -56.7, $ELPD_{poly}$ = -52.9). These findings imply that participants shared a common behavior in selecting high pain at the beginning and saving low pain for the end of a run. The systematics in choice patterns posed an additional challenge for the stimulus intensity sequences across the experimental conditions. As described before, the sequences in the unpredictable and predictable condition originally defined by randomly drawing from a uniform distribution, and were changed according to the empirical choice systematics for the fMRI sample. The improvement of the matching procedure is visible from the time-resolved analysis of frequency differences of intensities between the conditions (see Figure 3.2)). All model parameters and sampling diagnostics are summarized in Table A3.

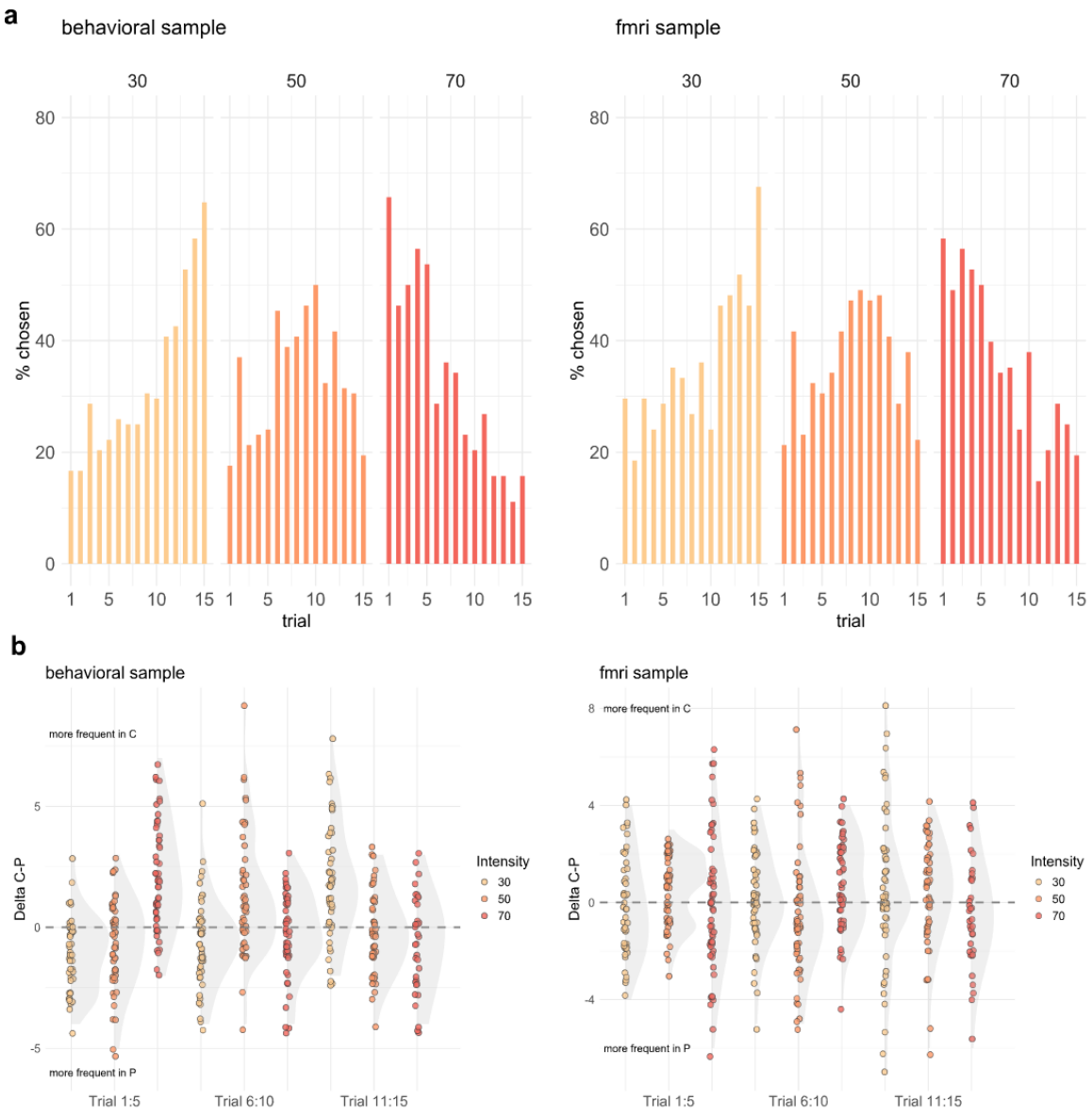

Figure 3.2. Choice behavior and matching of intensity sequences in both samples. **a)** Participants in both samples show the same tendency in choice behavior. They select preferentially stimuli of high intensity (70) at the beginning of a run and keep stimuli of low intensity (30) for the end of a run. **b)** Visualization of evaluation of matching between the controllable and predictable condition. Within-participant differences between stimulus intensity frequencies are grouped in three bins of 5 trials, separate for each intensity level. For each time bin and intensity level, the frequency of predictable stimuli was subtracted from the frequency of controllable stimuli. A positive value indicates a higher frequency in controllable trials, and a negative value indicates a higher frequency in predictable trials. The matching in the fMRI sample was improved as visible from the distribution plots.

Reaction Times

Reaction times were longer in the choice task (controllable condition) than in the color-matching task, which was performed in the other conditions (M$\pm$SD in behavioral sample: controllable: 1.76s$\pm$0.84s; predictable: 1.46s$\pm$0.87s; unpredictable: 1.36s $\pm$0.84s; fMRI sample: controllable: 1.72s$\pm$0.66s, predictable: 1.09s$\pm$0.47s, unpredictable: 1.02s$\pm$0.45s). This is an indicator for higher cognitive demand in the controllable condition, showing that participants took the task seriously.

Pain intensity ratings

On average, pain intensity ratings decreased over trials and sessions, indicating a general habituation to the thermal stimuli (behavioral sample: β_{trial} = -0.19, $\beta_{session}$ = -1.38; fMRI sample: β_{trial} = -0.40, $\beta_{session}$ = -0.36). Pain intensity ratings increased with increases higher intensity levels (behavioral sample: $\beta = 1.59$; fMRI sample: β = 1.45). 95% HPDIs did not cover zero, see Tables A4 and A5. In addition, there was an interactive effect of intensity and condition. In both samples, participants rated unpredictable pain at a low intensity level as more intense than predictable or controllable pain. This effect reversed for the medium intensity and flattened for the high intensity in the behavioral sample. In the fMRI sample, there was no difference between conditions for the medium intensity level and at the high intensity level the effect reversed: participants rated controllable and predictable high intensity stimuli as more painful than unpredictable stimuli, see Figure 3.3. The interaction was strongest between the controllable and unpredictable condition (behavioral sample: β = -0.07, HPDI =[-0.13, 0.00]; fMRI sample: β = -0.29, HPDI = [-0.35, -0.23]). In the fMRI sample there was also an interaction between the predictable and unpredictable condition predictable vs. unpredictable: β = -0.2, HPDI = [-0.27, -0.14]; and the controllable and predictable condition (controllable vs. predictable: β = -0.08, HPDI = [-0.14, -0.02]). The same trend effects were present in the behavioral sample, although the HPDIs of the interaction parameters covered zero, indicating very small effect sizes (pre-

dictable vs. unpredictable: β = -0.04, HPDI = [-0.11, 0.02]; controllable vs. predictable: β = -0.02, HPDI = [-0.07, 0.04]). Due to the interaction effect that crosses over intensity levels, analysis of condition main effects are not warranted, because this would make the data appear more consistent than they are. All estimates for both samples including standard errors of the mean, effective sampling size, HPDI and random effects are summarized in tables A4 and A5.

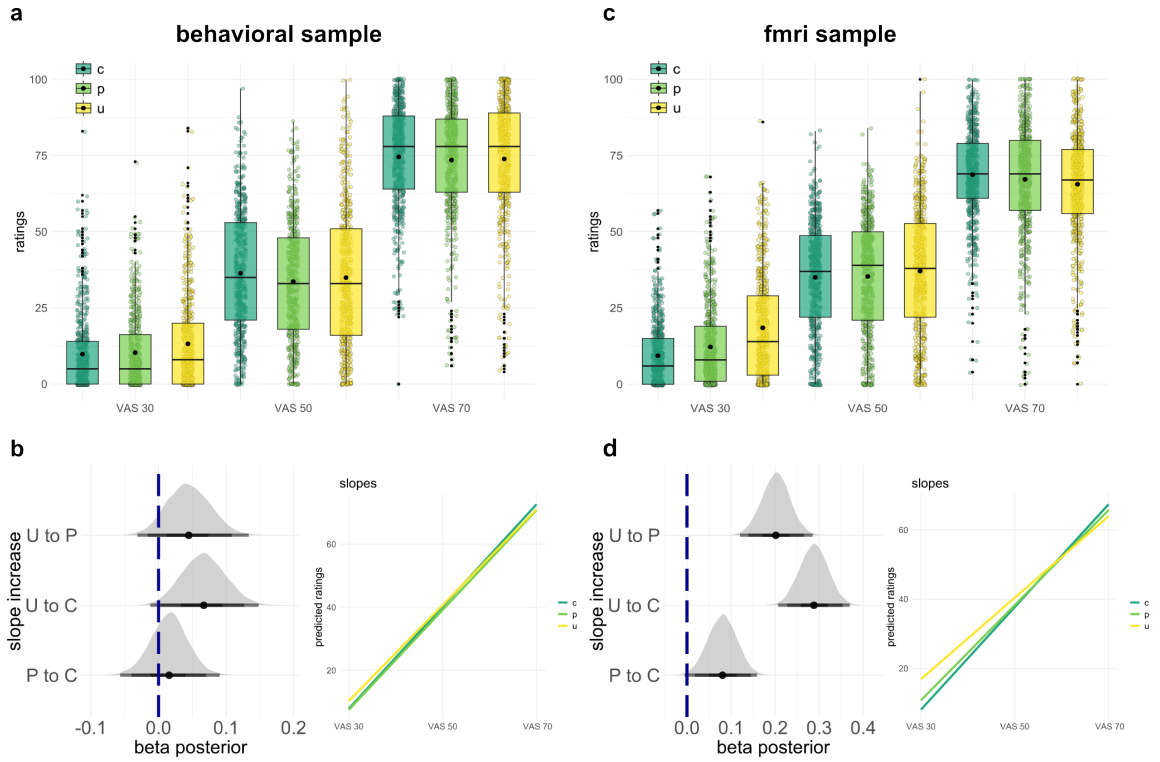

Figure 3.3. Pain ratings of the **a)** behavioral (n = 54) and **c)** fMRI sample (n = 59) in the controllable (dark green), predictable (light green) and unpredictable (yellow) condition. Large black points in the boxes show the mean of all ratings, boxes show the 25th to 75th percentile around the indicated median line; whiskers extend to $\pm$ 1.5 IQR; outliers are shown as small black points. Below, posterior distributions of the interaction parameters and as schematic figures, fitted lines from the linear models are shown for the behavioral **b)** and the fMRI sample **d)**. The grey curves show the estimated probability density of the parameter values. A positive value of the interaction parameter (beta) indicates an increase in slope over intensities for the indicated condition pair, i.e. when moving from the unpredictable to the predictable condition (U to P), from the unpredictable to the controllable condition (U to C), and from the predictable to the controllable condition (P to C). If posteriors do not include zero, this indicates an effect on the ratings. Please note that for visualization purposes the effects were recoded by multiplying the posteriors with -1. The schematic line plots illustrate the changes in slope between the conditions, which is quantified by the interaction parameter.

Standard deviations of pain intensity ratings

The standard deviations of pain ratings were compared between conditions, because the consistency of ratings indicates how precise the expectation about the painfulness were. Indeed, the standard deviations of pain intensity ratings differed for the intensity levels and conditions, see Figure 3.4. Standard deviations of ratings were lower in the controllable and predictable than in the unpredictable condition (behavioral sample: β_{UC} = -2.45, β_{UP} = -2.09; fMRI sample: β_{UC} = -4.41, β_{UP} = -3.31; no HPDI covered zero). In addition, standard deviations were higher for the medium intensity level than for the other two intensity levels, and higher for the high intensity level than for the low intensity level. Importantly, in the fMRI sample, standard deviations were higher in the predictable relative to the controllable condition: β_{CP} = 0.98, HPDI = [0.02, 2.04], indicating possible differences in expectation precision between the conditions; see all β values and HPDIs in Tables A6 and A7 in the appendix .

Expectation-integration models

Parameter recovery of simulated datasets was successful for the fixed and dynamic version of the basic mean-shift model with one scaling parameter for the unpredictable condition (α), the precision-change models with one scaling parameter and the two null models. Not all parameters of the model implementing three distinct α parameters were recoverable, therefore it was not fitted to the true rating data. Formal model comparison suggested that the models, which were based on the baseline model and implemented an expectation bias for the unpredictable condition (mean-shift and precision-change models), explained the rating patterns better than the null models. The α parameter was high overall (M$\pm$SD = 0.74$\pm$0.18), due to the overall strong influence of the likelihood, i.e., calibrated pain intensity, in the unpredictable condition. The models including a dynamic unpredictable prior mean explained the ratings better than the versions with fixed centered prior mean. This indicates that participants possibly updated their expectations in the unpredictable condi-

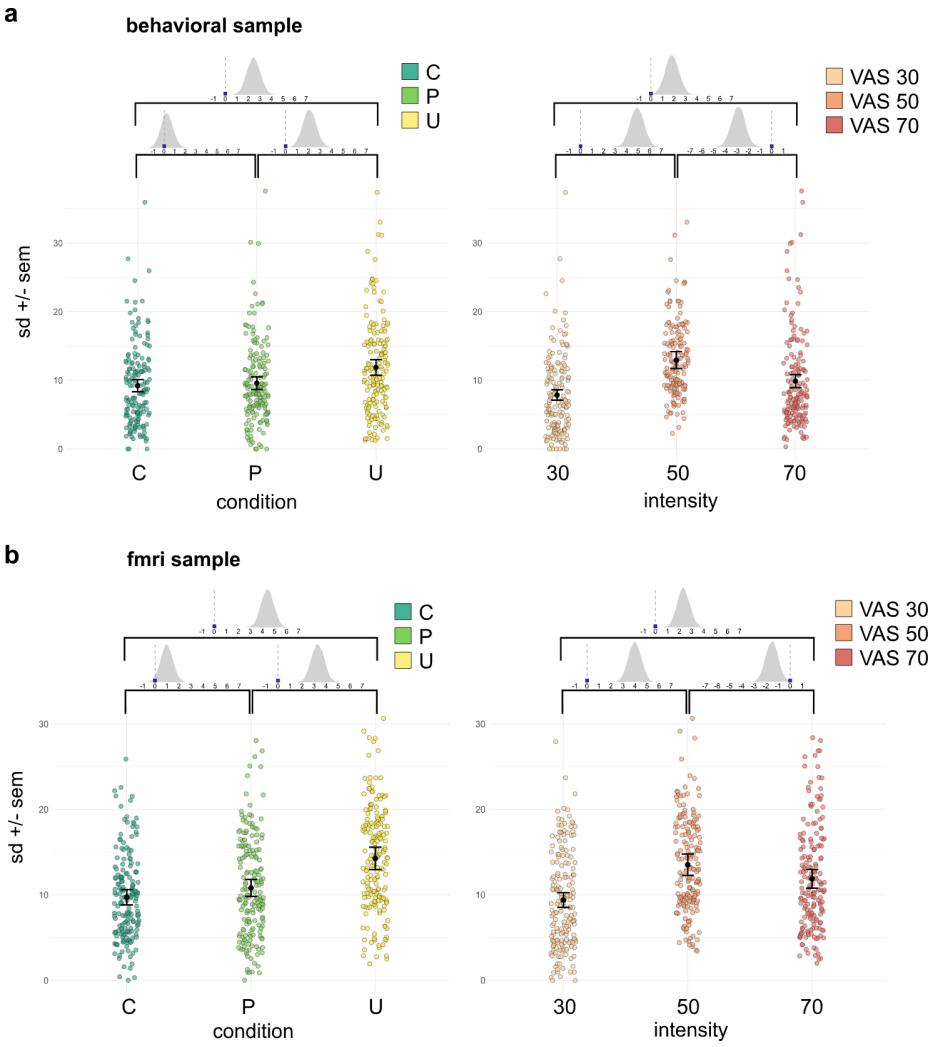

Figure 3.4. Standard deviations of pain intensity ratings, separately for both samples. **a)** Standard deviations were higher in the unpredictable than in the predictable and controllable condition and higher for the medium than the low and high intensity in the behavioral sample. **b)** In the fMRI sample, standard deviations were higher in the unpredictable than in the predictable and controllable condition, and additionally higher in the predictable than the controllable condition. Regarding intensity levels, standard deivations were higher for the medium than the low and high intensity in the fMRI sample, showing the same pattern as in the behavioral sample. Please note that for the visualization purposes the effects were recoded by multiplying the posteriors values with -1

tion over time. In addition, the precision-change models explained the data better than the mean-shift models, supporting the hypothesis that differences in expectation precision produced differences in pain ratings, which was already suggested by the analysis of standard deviations. Accordingly, the standard deviation for the prior, as estimated by the precision-change model was highest in the unpredictable condition, followed by the predictable standard deviation and lowest estimated standard deviation in the controllable condition. The precision-change model with a dynamic prior mean in the unpredictable condition showed the best fit to the data. Figure 3.5 shows the result of model comparison and the predictions of the mean-shift and precision-change models compared to the true data.

3.2.2 Neural Results

Pain processing

The analysis of the parametric modulation of neural activity at pain plateau onset showed activation in typical pain processing regions. The BOLD signal scaled with z-scored pain ratings in bilateral central operculum and posterior and anterior insula, middle cingulate gyrus, putamen, somatosensory and motor cortices and thalamus. The peak of the pain intensity effect was located in central operculum, see Figure 3.6. The analysis including z-scored intensity levels, not ratings, resulted in an equivalent pattern.

Condition-dependent pain processing

Contrasting the predictable and controllable condition with the unpredictable conditions at pain onset showed higher BOLD signal in the bilateral anterior insula, the SMA, middle cingulate cortex, ACC, cerebellum and PAG compared to the predictable and controllable conditions (contrast C,P < U). Furthermore, comparing the predictable with the controllable condition showed higher BOLD in the predictably condition in the SMA, dorsal ACC, PAG, precunues, parietal cortex and cerebellum (contrast C < P). These findings show a parametric relationship of pain elicited activity over conditions, namely that the highest BOLD

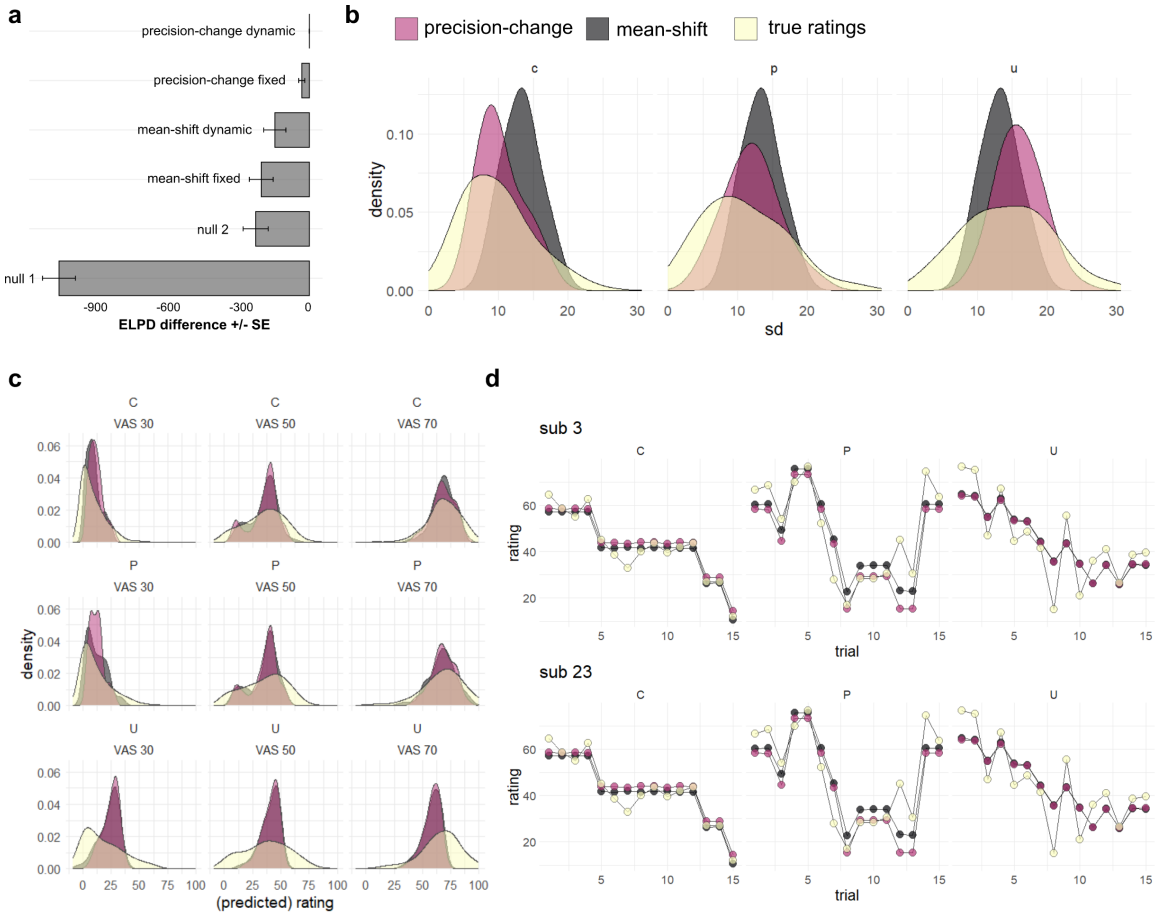

Figure 3.5. Model comparison and predictions. **a)** Model comparison results using the leave one out cross validation using robust mixture estimates. Bars depict expected log point-wise predictive density (ELPD) $\pm$ the standard error of the difference. Higher ELPD values indicate a better model fit. The winning precision-change model implemented a dynamic prior mean and allowed different standard deviations for the priors in the conditions, while keeping the means constant across conditions. The mean-shift model allowed varying prior means, but constraint the standard deviations to be equal. **b)** Density curves depict the distribution of the estimated standard deviation of the different models with dynamic unpredictable prior mean against the distribution of true standard deviations (yellow). The precision-change model (pink) is better able to capture the differences between the conditions than the mean-shift model (grey). **c)** Predicted and true rating distributions in the three conditions for the three intensity levels. Mean-shift and precision-change model make similar predictions. **d)** Model predictions for pain ratings in two exemplary subjects. Yellow points show the true rating averages, pink points show trial-wise predictions of the precision-change, grey points show predictions of the mean-shift model.

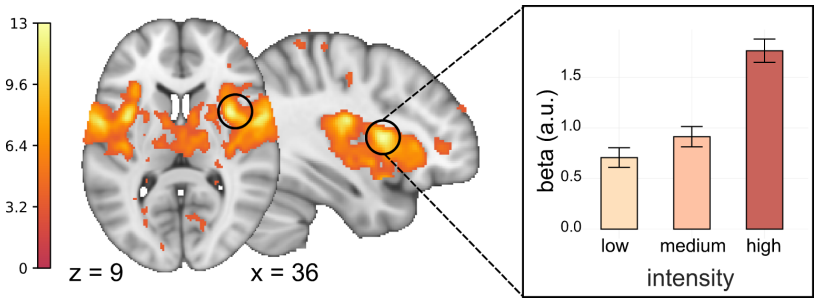

Figure 3.6. Neural activation in response to perceived pain intensity. Contrast image shows the parametric effect of perceived painfulness, as measured by pain intensity ratings. The regions with the highest BOLD signal increase in response to higher pain ratings was the central operculum at at voxel = [36, 7.5, 9], T = 12.76. On the right, the extracted parameter from this voxel estimated with a model including separate onset regressors for low, medium and high pain are shown to visualize the parametric effect.

signal resulted from unpredictable pain, followed by predictable and controllable pain. The reversed contrast (C,P > U) showed that the BOLD signal was relatively higher during both predictable conditions in rostral parts of the ACC, hippocampus and precuneus. Effects were relatively smaller in this contrast (see 3.7. The rACC and a small subpart of the central operculum showed additionally higher BOLD signal during controllable than predictable pain (C > P).

Interaction with of condition and intensity

No interaction effect was significant at the whole brain FWE significance level of p <.05. Visual inspection at a lower significance threshold (uncorrected p <.001) showed that activity in a cluster in the rACC followed the intensity rating pattern, i.e. activity scaled positively with intensity in the controllable and negatively with intensity in the unpredictable condition. Activity during predictable pain also scaled positively with intensity, but less than during controllable pain. To evaluate at what level this activation would become significant, a post-hoc small volume FWE correction using an ACC mask was performed. By that it was possible to estimate the effect size of the activation. With small volume correction, the activation would become significant: p = .003 (see Figure A4).

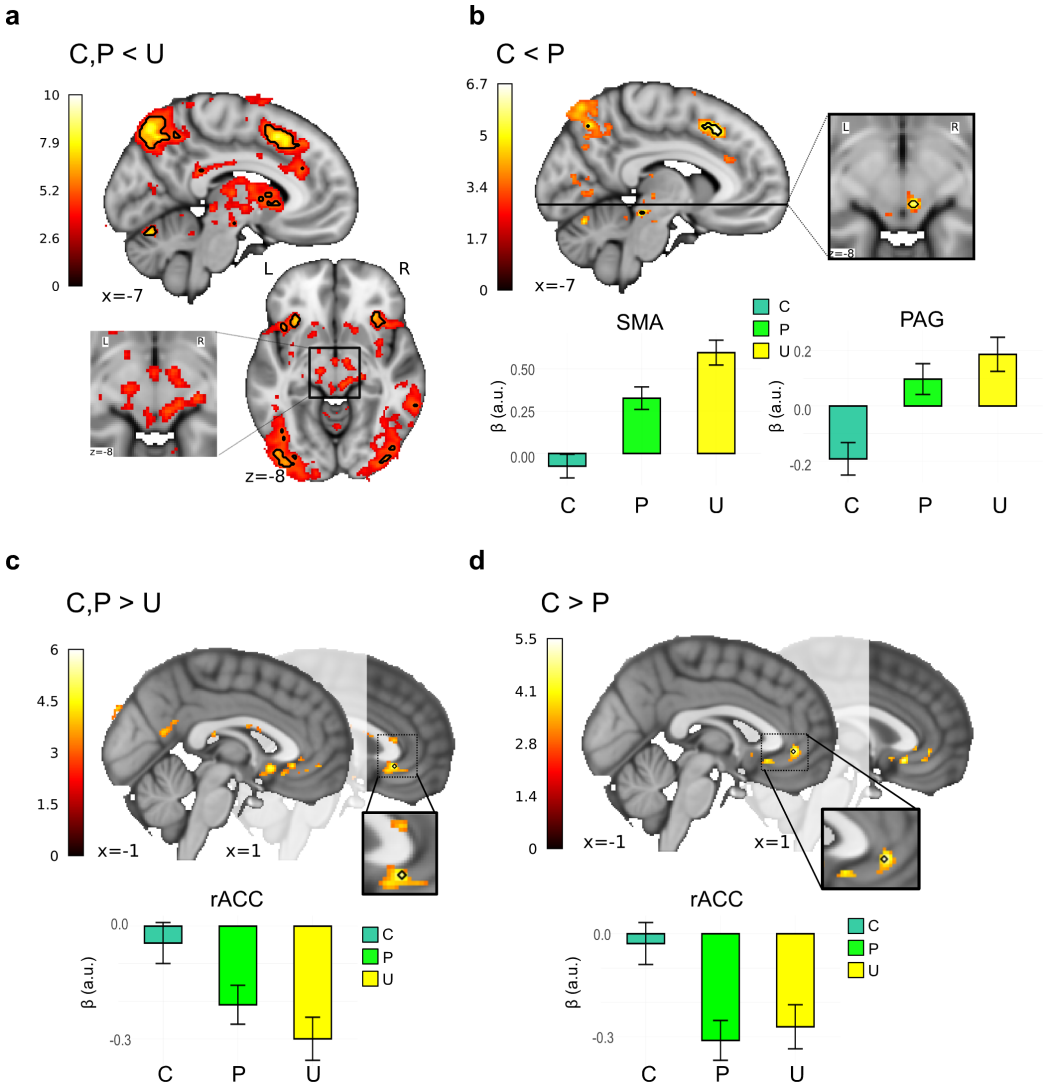

Figure 3.7. Effects of predictability and controllability on brain activity during pain. Overlay in hot colors are derived from statistical maps at p <.001 (unc.). Black contours indicate regions that were significant at p <.05 after whole-brain FWE correction. Barplots show parameter estimates for the conditions (dark green: controllable, light green: predictable, yellow: unpredictable), which were derived from voxels that showed significant activation differences. **a)** Regions that responded with relatively lower activity to predictable pain. **b)** Regions showing an additional effect of controllability and parameter estimates for the conditions, for the SMA [-7.5, 21, 45] and the PAG [6, -27, -7.5]. Both regions exhibited reduced activity in response to predictability and controllability. **c)** Regions that responded with increased activity to predictable pain. A cluster in the rACC [1.5, 28.5, -6] was significant after whole-brain FWE correction. **d)** Controllability had an additional effect on prefrontal brain activity, with a significant cluster in the rACC [-1.5, 40, -3].

Task-related activity

The controllable task elicited different activation patterns than the predictable and unpredictable task (see Figure A5). During the choice task, the supplementary motor cortex,

anterior and middle cingulate cortex, bilateral anterior insula, precuneus, thalamus, brain stem and cerebellum showed higher BOLD signal than during the color-matching task (C > P). Although the task was the same for the predictable and unpredictable condition, BOLD signal was significantly different between the predictable and unpredictable condition at task-onset. The BOLD signal in the bilateral anterior insula, parietal cortex, thalamus and brain stem was higher in the predictable than in the unpredictable condition (P > U). The FIR model covering time bins from task onset up to stimulus onset showed significant differences between the conditions up to the time point 10.5-13.5s after time onset (i.e. average of time bins 8 & 9) in the SMA and the PAG. Including the rise time of the thermode to reach the desired temperature, the stimulus reached its peak intensity at 10-13s after the task onset, thereby suggesting that it is unlikely that task induced pre-stimulus effects influenced the condition effect during stimulation.

3.3 Discussion

This study focused on the confounding effect of predictability when studying control-induced effects on pain processing. It also investigated to what extent controllability possibly modulates pain above predictability. Behavioral intensity ratings and neural activity were compared between painful heat stimuli of either controllable, predictable, or unpredictable intensity in a within-subject design. Pain ratings showed a bias towards the extremes of the rating scale in the controllable and predictable condition, whereas they were drawn towards the middle of the ratings scale in the unpredictable condition. Thus, ratings were biased towards the predicted intensity level, when a precise prediction of intensity was possible. This effect was even stronger for the controllable condition in the fMRI sample, which experienced better matched intensity sequences. In addition, the ratings were less variable in the predictable condition than in the unpredictable condition in both samples, reflecting an increased precision of expectations. Again, there was an additional effect between the controllable and the predictable condition in the fMRI sample, with higher rating con-

sistency in the controllable condition. This result also indicated an increased expectation precision with control. Furthermore, the comparison of two mechanistic models suggested that rather an increase in precision and not a bidirectional shift in expected pain intensity led to the observed effects. These results confirm the hypothesis of changes in expectation through control, but would not suggest a general increase or decrease of perceived pain intensity by controllability. In addition, the different levels of expectation precision in the three conditions were accompanied by changes in BOLD-signal in rostral ACC, PAG and the SMA.

The interactive effect introduced by predictability confirms the results of multiple studies (C. A. Brown et al., 2008; Zaman et al., 2021; Pavy et al., 2024). It fits well in the Bayesian framework, that postulates that pain perception can be explained by the integration of expectation and sensory input (Büchel et al., 2014). The possibility to precisely predict the intensity of a painful stimulus anchors expectations and results in a percept that will be centered on the expected value. In the unpredictable case, the best guess about pain intensity will be the average of all possible outcome options, so it will be centered on the mean of the rating scale. Integrating the mean-centered and less precise expectation with the actually received stimulus intensity is followed by a bias to the mean in the percept. In fact, this effect was present in the rating data. Interestingly, while the rating data from the behavioral sample suggested that effects of controllability could be explained by predictability alone, because there was no difference between the controllable and predictable condition, there was an additionally enhanced interaction effect between the controllable and predictable condition in the fMRI sample. This is particularly relevant, because in this sample, the conditions were better matched regarding intensity sequences. Changes in ratings were very likely to be produced by changes in expectations, because sensory input was principally equivalent under all conditions. This was achieved by calibrating all stimulus temperatures to subjective pain perception and keeping them constant throughout all conditions.

The study investigated control over the intensity of the painful stimulus. However, control can also be exerted over different aspects of stimuli, for example, the onset, offset,

occurrence or location (Habermann et al., 2024). Most possibly, the increase in expectation precision is relevant for all types of control, with respect to the dimension that is under control. Crucially, only those features of the stimuli become more predictable, which are controllable. For instance temporal predictability of a stimulus does not convey information about its intensity. So, general uncertainty regarding the painful stimulus depends on more than one aspect and context-dependent importance weighting of the different aspects might also play a role. Furthermore, other types of control might involve additional perceptual mechanisms, especially when self-touch or motion are part of the control processes. Here, mechanisms of sensory attenuation, often discussed in the context of motor agency, might be generated (Blakemore et al., 2000; H. Brown et al., 2013; Strube et al., 2023). The interaction effect resulting from different expectation precision with control, might also explain, why control was found to have beneficial effects on placebo interventions (Tang et al., 2019), but that it also can entail unfavorable effects as found in a study on nocebo hyperalgesia (Tang et al., 2024).

With respect to neural processing of pain, unpredictability of pain intensity was accompanied by increased activity in the anterior insula, dorsal ACC, parietal and middle frontal gyrus and the cerebellum, regions typically responding to unexpected and behaviorally relevant (salient) stimuli (Mouraux & Iannetti, 2018; Uddin et al., 2019). Activity in the SMA and the PAG was additionally attenuated during pain of self-chosen intensity. Activity in the hippocampus, precuneus and rostral ACC was increased in response to predictability and controllability of pain.

The anterior insula, PAG and anterior cingulate cortex responded with activation changes to both environmental features, predictability and controllability. Because these regions are also associated with processing of pain (Tracey & Mantyh, 2007), this highlights the need for predictability-matched control condition in studies on control over pain and shows that careful assessment of studies is warranted that did not include such a control condition. While this overlap is important to keep in mind, there was an additional significant BOLD-signal change in PAG, when contrasting the controllable and the predictable

condition, with attenuated activity if stimuli intensity was self-determined. The PAG plays a key role in pain modulation and is associated with placebo hypoalgesia and nocebo hyperalgesia (Fields, 2004; Eippert et al., 2009; Tinnermann et al., 2017; Crawford et al., 2021). The PAG responds to differences in expectation precision, with lower responding to stimuli with known intensity and higher activation levels when pain intensity is unpredictable (Lin et al., 2014). Consequently, the PAG has also be shown to respond to pain-related prediction errors (Roy et al., 2014), underlining its integrative role for expectation and ascending nociceptive information. Animal studies have also shown, that the PAG responds to unexpected shocks during fear learning, but does not respond to the same stimulation after conditioning, i.e. when the outcome is certain (Strickland & McDannald, 2022; Vázquez-León et al., 2023).

A recent study found, that rACC-PAG coupling was increased in response to placebo effects, that were enhanced by side effects (Schenk et al., 2024). Interestingly, BOLD signal in the rACC was relatively decreased during the active placebo condition in this study, although it has also been related to enhanced placebo effects (Eippert et al., 2009), distraction induced hypoalgesia (Oliva et al., 2022) and opioid analgesia (Tinnermann et al., 2022). These results have also been supported by animal studies showing that rACC neurons are crucially involved in pain modulation by expectation of pain relief (Chen et al., 2024).

Controllability also attenuated activity in the SMA. The (pre-)SMA is typically activated by motor planning or imagery (Nachev et al., 2008; Mizuguchi et al., 2013). Critically, it also enables correction of motor activity if the inhibition of an erroneous response is required (Bonini et al., 2014). The SMA and the neighboring cingulate motor areas also initiate pain triggered motor responses, i.e. removing the body from the pain source (Perini et al., 2013; Lynn et al., 2016). Relevant for putting the results of the present study into perspective is the finding, that SMA activity also increases when a painful stimulus of unexpected intensity is applied (C. Brown, 2017). This is in line with the result of this study,namely that SMA activity is attenuated with pain of self-chosen intensity, which had the highest subjective

expectation precision, as concluded from the analysis of behavioral data. Possibly this is related to higher precision of expectations reducing the demand to monitor changes in pain intensity and prepare pain-related motor responses. Unpredictability of stimulus intensity on the other hand could increase the need to accumulate evidence about how painful the stimulus is leading to higher levels of SMA activity. In addition, the anterior part of the SMA, close to the cingulum has been linked to higher order cognitive processes (De La Vega et al., 2016). For example, there is a suggested functional gradient from handling allocation of motor control in the SMA to cognitive control when moving from SMA through pre-SMA to the dorsal ACC (Shenhav et al., 2013). The activation distribution in this study, extending from SMA to pre-SMA indicates that control over pain and increased expectation precision regarding pain, not only affects motor preparation, but also general attention allocation, possibly necessary for pain evaluation.

In sum, linking the fMRI results to the differences in rating and their consistency, the relevant role of differences in subjective precision of expectations emerges. Activity increase in salience and attention processing brain areas (SMA; PAG) reflect the higher uncertainty regarding the pain intensity in the unpredictable and predictable condition relative to the controllable trials. Still, the analysis shows that there is a considerable overlap in effects on behavior and neural activity between the effects of predictability and controllability.

3.4 Limitations

The experiment consisted of a sequence of task and stimulation. The neural activation difference between the conditions at task onset in SMA, anterior insula, dorsal ACC and PAG suggests different recruitment of those attention processing regions due to increased cognitive demand in the controllable condition, which was also intended by the experimental setup. During pain, the activation pattern flipped in the opposite direction, i.e. the SMA, PAG, dorsal ACC and anterior insula were least active in the controllable condition. This ”seesaw” effect needs careful assessment, because of possible adaptation effects in the

BOLD signal. Adaptation in fMRI refers to the effect that a brain region that is sensitive to a feature, responds less to a second task, if it has previously been activated by a task that shares the relevant feature (Barron et al., 2016). This effect can be employed to investigate specificity of responding of different brain regions. It is usually related to repetition suppression, an effect visible in single-unit recording of electro-physical neuron activity. There it has been established, that showing exactly the same visual input twice with a very short inter-stimulus interval, leads to reduced responding for the second presentation (Fritsche et al., 2020). The exact relationship of repetition suppression in neural activity and BOLD are debated, as it is unclear how the neural activation effect results in the net effect on hemodynamic activity (Barron et al., 2016). However, adaptation effects need to be taken into account in this study, because they might limit the finding of differential condition effects during pain. The FIR models show that it is unlikely that the condition effects on pain processing are explainable only by adaptation. Activity in the SMA and PAG return to the same levels, before pain onset, although the effect of attenuated activity lasts quite long. This is surprising because usually adaptation processes only lead to small reduction in responding after short time period ($\sim$10% after 1s), although also changes up to $\sim$6s have been reported (Klein-Flügge et al., 2013). While the seesaw in the activity could be framed as a confound, it is also not unlikely that this might actually represent exactly the mechanism how increased precision of expectations is represented in the brain. Possibly, the salience and attention network activation is reduced in response to the choice, thereby responding less to pain stimulation. Furthermore, it could also be the case that the same ensemble of brain regions responds to the task and is then activated differentially during pain. The investigation of the exact mechanisms might be an inspiration for future studies, and calls for a in depth assessment of potential sequential effects in fMRI activity. A final limitation concerning the fMRI results is the absence of significant interaction effects during pain, which would parallel the behavioral data. While there is a trend for such an effect in the rACC, a region that would be a candidate region to find such an effect, the main effects between conditions are stronger. This might be related to the fact, that the level of

uncertainty drives the neural activity pattern and that relative to this, the interaction in pain intensity processing affects neural activity to a lower extent.

In this study control was provided over the sequence of stimulus intensities, with the limitation that all intensity levels had to be selected five times in a run. This resulted in free choice among all three intensities in most of the trials in the controllable condition and was necessary, because the overall stimulation should be the equal in all conditions. Still this poses a minor limitation, as the absence of complete control, i.e. being able to always select medium or low pain, might have reduced the subjective feeling of control. Furthermore, participants had control over different levels of pain but could not use control to achieve a positive outcome, only a less negative outcome. In addition it could be argued with regard to the unpredictable condition, that because participants were aware of the stimulation scheme in the other two conditions, intensity sequences were not maximally unpredictable. Still, compared to the other two conditions, the information level regarding stimulus intensity in each trial were considerably lower. Therefore it constitutes a good control condition. Finally, one could question how ecologically valid the choice over pain intensities is. Being also a methodological study, as a major study focus was the isolation of controllability and predictability effects, the ecological validity might be less of an issue, but still this needs to be kept in mind when discussing its findings. Lastly, a limitation regarding the application of the mechanistic model is that the parameters for the more complex models were not recoverable and that there were, in context of the study design, too few data points to estimate parameters of models with a full Bayesian structure. To better disentangle prior and likelihood, either another design, for example one that induces precise expectations and then later violates them, as in placebo experiments, or additional measures like ratings regarding the expected intensity of pain, i.e., expectation ratings, would have been necessary. On the other hand including expectation ratings might also change the behavior of participants, because they might lead to changes in attentional focus regarding pain.

3.5 Conclusions

Although some questions remain open, this study showed that subjective expectation precision is a relevant factor considering control over pain intensity. The interaction effect produced by this change of expectation precision would indicate that there is not general hypoalgetic effect of control, especially not in setups similar to this study's design. While it is true, that positive treatment outcomes could be boosted if their outcome can be controlled and is reliable, control over pain might also result in unfavorable outcomes. These findings also suggest that a lack of control, as experienced in chronic pain, could lead to a reduced expectation precision regarding positive treamtent outcomes and thereby reduce treatment effects.

4. Empirical Study 2

> *People who believe they can alleviate suffering will likely mobilize whatever ameliorative skills they have learned and will persevere in their efforts. Those who doubt their controlling efficacy are likely to give up readily in the absence of quick results.*
>
> Bandura et al., 1987

The motivation for the second study came from reports of increased perceived helplessness associated with pain severity in chronic pain patients (Samwel et al., 2006; Craner et al., 2016). The theory of learned helplessness in the context of chronic pain assumes that uncontrollable pain, which only allows passive coping strategies, leads to a generalization of perceived lack of control and passive responding to other life stressors (Yessick & Salomons, 2022). This might inhibit the exploration of active coping strategies, although they might have become possible in a new context. A similar reasoning is inherent in the fear-avoidance model of pain persistence, which outlines that adaptive strategies in response to acute pain, namely increased arousal or avoidance of pain-triggering movements, can become unfavorable over time and contribute to pain persistence, due to maintenance of pain-related fear and hypervigilance (Vlaeyen & Linton, 2012). This fear of action could contribute to lower perceived self-efficacy, increase helplessness and shift the attentional focus away from other goals (Büchel, 2023). If generalized to other contexts, lower perceived self-efficacy also lets other goals appear less achievable. According to the motivation-decision model of pain, this leads to increased pain, because no other goals are pursued, which would bias perception away from pain (Fields, 2018). An inversion of this cycle by increasing perceived control would be a promising goal of pain management therapy. But before pursuing such strategies in a therapeutic setting, multiple basic assumptions need to be

tested. For example, whether a lack of control over acute pain leads to passivity and how it influences perception remains an open question.

To explore the connection between pain perception, a lack of control and generalization, this study investigated short-term changes in learning strategies induced by uncontrollable acute pain. The study used a yoked between-subject design, which is typical for studies on learned helplessness (Maier & Seligman, 1976). One group could learn how to avoid a painful heat stimulus on capsaicin pretreated skin and instead receive a cooling relief stimulus by correctly responding to a cue (control group). This was not possible in a second group (yoked group). The sequence of painful and relieving stimuli in the second group was yoked to the control group, to ensure the same level and sequence of stimulation. An open test phase was included after the uncontrollability induction, to investigate whether different levels of perceived control in the first task would change learning behavior in a second task. In this test environment, both groups could learn how to initiate a pain-relieving cooling stimulus by detecting the correct field on a computerized grid. Learning outcomes and behavioral strategies (e.g. number of movements and successful trial outcomes) were measured in this second phase. Simultaneously, ratings of perceived pain intensity and relief pleasantness were collected during both phases. Especially, the parallel investigation of changes in perceived pain and learning represents a novel aspect, because most studies investigated either how perceived control influences pain in a single task (Salomons et al., 2015; Bräscher et al., 2016; Mosch et al., 2023), or focused on changes in learning, without investigating pain perception (Meine et al., 2020, 2021).

Learned helplessness theory would predict less active exploration and increased passivity in the yoked group during the test phase (Meine et al., 2020). The control group, on the other hand, is expected to learn faster and perform more successfully. Regarding pain perception, the literature on control-induced hypoalgesia, would predict that a higher level of perceived control reduces pain (Wiech et al., 2006; Strube et al., 2023). However, the results from other studies suggest that the control group perceives relief as more pleasant and pain as more intense, because of increased informational value (Desch et al., 2023).

Also increased outcome certainty by control could contribute to the effect. In study 1 this effect led to increased reported pain intensity, when it was executed over a highly painful stimulus and decreased reported pain intensity, when it was executed over a mildly painful stimulus.

Finally, the possible impact of trait variables such as locus of control and depression deserves attention in the context of control, learning and pain. For example, participants with a more depressive symptoms are less likely to show an illusion of control (Alloy & Abramson, 1979) and an internal locus of control has been related to attenuated prefrontal cortex activity in response to uncontrollable pain (Wiech et al., 2006). Different allocation of the locus of control could lead to changes in the behavioral strategy in response to uncontrollability, which then also influences pain perception. Therefore, different state and trait questionnaires were included in the study, to investigate how the locus of control and depressiveness influence changes in learning and pain in response to uncontrollability.

4.1 Methods

Sample 89 participants were invited for study participation after a screening for exclusion criteria via phone. Four participants had to be excluded during the calibration procedure, because they reacted very sensitive to the capsaicin treatment and rated even very low temperatures as unbearably painful. Data of eight participants had to be excluded from the analysis, because they did not comply to the experimental procedure (three subjects secretly checked their phone or talked throughout the experiment), three subjects misunderstood the task and/or failed to learn the correct action in the control condition and two subjects showed extreme habituation and rated more than 25% of pain ratings with zero. Finally, due to a technical failure, data from one participant could not be recorded during the second study phase. The resulting sample sizes were N = 77 for the first experimental phase and N = 76 for the second experimental phase.

Capsaicin application and thermal stimulation Four skin patches of the size of the thermal stimulator were marked on participants' lower leg using a paper template. Prior to the calibration procedure, 1ml capsaicin cream (hot Thermo dura® C Creme, Mylan Germany GmbH, Germany, 53mg capsaicin/100g) was applied to two of the four skin patches (0.5 ml per patch) and covered with a plastic patch for a duration of 15 minutes. The thermode was placed on the first of the treated skin patches for the calibration procedure and on the second patch for the first experimental phase. Before the second phase started, capsaicin cream was applied on the two remaining skin patches following the same procedure. Throughout the experiment, the thermode was placed on four different locations. The positioning was pseudo-randomized, with the constraint that always two adjacent positions were treated at the same time.

Thermal stimulation was performed as described in the general methods. The baseline temperature was set to 29°C for the calibration and the second experimental task. In the first experimental task, baseline temperature was set to 32°C to induce a lightly uncomfortable sensation on the capsaicin pretreated skin. For stimulation, temperature was increased (or decreased) to the destination temperature at a rate 10°C/s. The minimal and maximal allowed temperature in the first phase were 36°C and 47°C respectively. Stimuli had a plateau duration of 6s and were targeted to correspond to an intensity of 80 on a 0-100 VAS scale. Stimuli in the second phase had a variable length, depending on participants' behavior and ranged from 7s to 20s and targeted a VAS rating of 60. Temperatures between 35-46°C were allowed. If temperatures were outside the required range, they were adjusted to either the lower or the upper limit of the allowed temperature ranges. Temperatures for the first study task needed adjustment for 14 participants in the experimental group (adjusted temperature: M = 42.29°C; rating: M = 59.48) and 12 participants in the control group (adjusted temperature: M = 41.5°C; rating: M = 53.11).

Study design The study used a "yoked" between-subjects design with two experimental phases. The yoking allowed the matching of pain and relief sequences of the uncontrollable

with the controllable group to keep pain constant between conditions. In the first phase, the uncontrollability induction task (UCIT), participants in the control group learned how to receive a pain-relieving cool stimulus by pressing the correct key in response to one of four cues shown on the screen. The pain relief for participants in the yoked group occurred in the same trials as for the matched person in the control group, but was not related to their actions. In a subsequent test environment, both groups could learn how to shorten the duration of a painful stimulus and induce a pain relief, by moving and placing an agent across a computerized grid. Throughout both phases, pain intensity, pain relief pleasantness, subjective control, and helplessness were assessed by ratings on a VAS. Among others, the depressive symptoms and locus of control were measured by the Beck's Depression Inventory (BDI; Beck et al., 1996) and German version of a locus of control questionnaire (Krampen, 1991), respectively. Additional readouts of learning behavior in the test phase were the number of successful trials, the trial duration, number of visited fields and amount of switching.

Experimental procedure First, participants were instructed about the study procedure and provided informed consent. For all instructions, standardized videos were shown, and participants were given the opportunity to ask the experimenter for clarifications afterward. Then capsaicin was applied to the first two of four placements on participants' lower leg for 15 minutes. During the capsaicin treatment, participants completed a first set of questionnaires and then underwent the calibration procedure, before completing the uncontrollability induction task (UCIT) and the test phase. Before the UCIT, the thermode position was changed. Participants performed two blocks of the UCIT, which took approximately 20 minutes in total. After the UCIT, capsaicin was applied to the remaining two skin patches and participants completed a second set of questionnaires. Then participants performed two blocks of the second task (test environment). Thermode location was changed in between blocks of the second task, due to the longer task duration of approximately 20 minutes per block. Finally, participants completed an exit questionnaire with qualitative questions

about the tasks and were debriefed about the aims of the experiment and the function of the group allocation.

Uncontrollability induction task (UCIT) The first phase of the experiment was designed to induce a feeling of control in one group by successful performance in a learning task, whereas the yoked group experienced positive and negative outcomes unrelated to their behavior. This was intended to induce a low level of subjective control in the yoked group. All participants were instructed that their task was to correctly assign four fractal cues to four of six possible keys on a standard keyboard. Throughout the task, the thermode was attached to participants leg and the baseline temperature was set to 32°C to provoke a constant uncomfortable sensation on the capsaicin pre-treated skin. In the control group, a correct key press in response to the fractal cue was deterministically followed by a six second long 23°C (cooling) stimulus. The cool stimulus was followed by a relief-pleasantness rating on a VAS ranging from 0 (neutral) to 100 (very pleasant). If the response was not correct, the temperature was increased from the baseline to reach the individual VAS target of 80. The painful stimuli were followed by a pain intensity rating on a VAS ranging from 0 (minimal pain) to 100 (unbearable pain). Participants had a maximum of 10 seconds to rate the stimuli.

Before the UCIT started, two pre-exposure stimuli were applied. Then, each trial started with the presentation of one of the cues and participants had eight seconds to choose a key. The order of cue presentation was randomized. To guarantee exploration and prevent failure of learning in the control group, the relationship between cue and action was designed as follows: every third new action that was pressed in response to the same cue would be assigned to that cue. This action would then become unavailable for assignment to any of the other cues. After the initial assignment, the action would always lead to a relief, when the cue was presented again, see 4.1. After three successful relief trials for each cue, the task would end automatically, or if this condition was not met, the task would end after a maximum of 35 trials. Due to this learning criterion, the task could have a different number

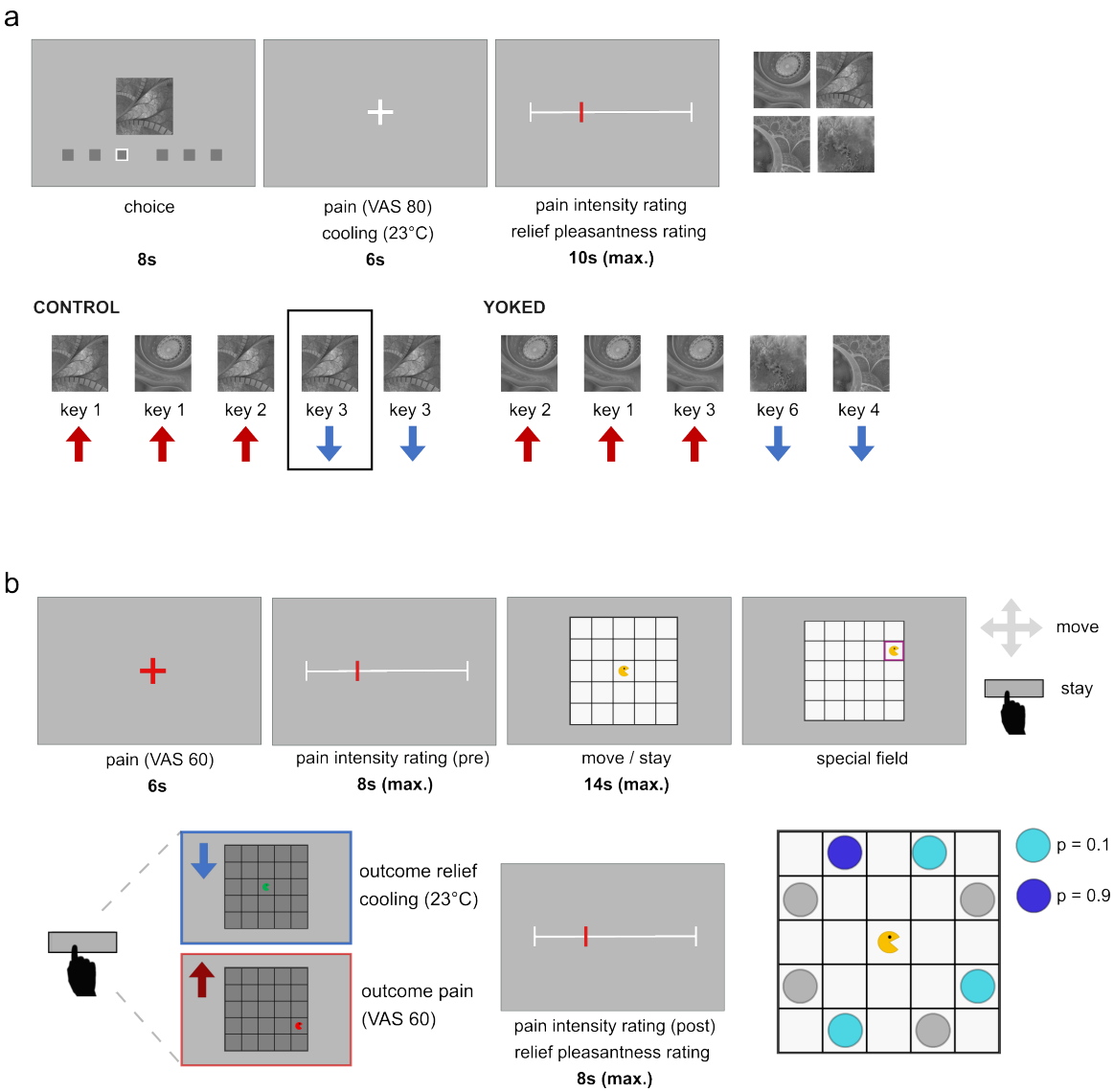

Figure 4.1. **a)** Uncontrollability induction task (UCIT). The control group learned to associate cues to key presses. Each third new action, tested in response to a cue would deterministically lead to a cooling stimulus (blue arrow) and then stay assigned to that cue until the end of a block. If the incorrect action was chosen, a painful stimulus was applied (red arrow). The sequence of pain and relief in the yoked group was matched to the control group. The cue images were presented randomly thereby producing inconsistent relationship of cues, actions and outcomes. **b)** Test environment. In each trial a tonic painful stimulus was applied. After 6s, participants rated the pain intensity. Then the grid was shown on the screen. Participants could move the character with the arrow keys and select a field to stay. Special fields were highlighted with a colored frame if moved upon. If participants selected a special field, they could receive a relief stimulus, dependent on the relief probability of that field. The relief probability was 10% for decoy fields (light blue) and 90% for the goal field (dark blue). If selected a standard field, relief probability was 0%. After the trial, participants rated the outcome (pain or relief). The gray circles show possible locations of the special fields, four out of these were selected for each instance of the task.

of trials for participants. In the second block of the task, a new set of fractals was presented and the task had to be repeated. After both blocks, participants performed a memory task in which they were asked to indicate the correct action for each of the four cues and rate their confidence in their response on a VAS scale. In addition, feelings of subjective control and helplessness were measured on three different VAS ranging from 0 to 100: (1) ”How much control did you have over the outcomes?”, (2) ”How often did you feel that you couldn’t stand the pain anymore?”, (3) ”How often did you have the feeling that you could do something to reduce the pain?”.

The yoked group received the same instructions as the control group, namely that they had to find the correct key to each cue. Unbeknownst to the participants in the yoked group, it was actually not possible for them to change the outcomes by their actions. Instead, each participant in the yoked group was matched to one participant in the control group and received exactly the same sequence of pain and relief trials as their partner. The rating procedure, memory task and control/helplessness assessments were equivalent to the procedure in the control group.

Test environment (Generalization) In the second phase of the experiment, both groups performed the same task in the test environment. The test environment was included to evaluate potential behavioral generalization effects induced by different levels of control during the UCIT. Participants performed two blocks of 20 trials. Each trial started with a painful stimulus aiming at a rating of VAS 60. After six seconds, a first pain intensity rating was collected. Then a 5x5 grid was displayed on screen and participants could use the arrow keys to move a Pacman-like character across the fields. At the beginning of each trial, the character was placed in the middle of the grid. Possible movements were: up, down, left and right. No diagonal moves were possible. By pressing the return key, participants could decide to stay on a field for the remaining duration of the trial, thereby disabling moving. Following the stay action, two outcomes were possible: either participants received a cool stimulus (23°C), or the temperature remained at the same painful intensity level until the

trial ended. According to the outcome, the character and screen frame changed their color to either green (relief) or red (pain).

Located at four of eight possible locations on the grid were special fields. These fields were highlighted with a colored frame, if the character was moved upon them. The frames very only visible while the character was placed on the field and disappeared when it was removed. The only way to receive a relief in the task was stopping on one of the special fields. While three of the fields served as decoy options with a very low relief probability (0.1), one of the fields (goal) resulted in a relief with a high probability (0.9). Participants were not informed about the relief probabilities, the number or possible locations of the decoy and goal fields or about the function of the special fields in general. They were only informed that some of the fields would look different, when moved upon and that it was possible to perform the stay action on these special fields as well as on the standard fields. They were also informed about the different possible outcomes of the stay action, but not related to the different field types. Each trial ended after 20s (6s pain and 14s in the grid) and a second pain or relief rating was collected after each trial. The special field configuration in the second block was changed, but the only possible locations for the special fields were the eight fields around the grid corners (see Figure 4.1).

Questionnaires Participants completed questionnaires at three different time points throughout the experimental session. A first set of questionnaires was answered during the first capsaicin treatment, before the UCIT (T1). This included the state forms of the Positive and Negative Affect Schedule (PANAS; Breyer and Bluemke, 2016), State-Trait-Anxiety Inventory (STAI; Laux et al., 1981), State-Trait Anger Expression Inventory (STAXI; Spielberger, C. D., 1999); as well as the trait questionnaires assessing the locus of control (LC; Krampen, 1991), self-efficacy (Jerusalem & Schwarzer, 2003) and Pain Catastrophizing Scale (PCS; Meyer et al., 2008). After completion of the first task, participants filled out a second set of questionnaires (T2). This included the PANAS, STAI and STAXI for a second time, to assess changes in mood, anxiety and anger, as well as the BDI (Beck

et al., 1996), a pain-related self-instruction questionnaire (Flor, 1991), which measures active coping in contrast to catastrophizing, behavioral inhibition and activation (BIS, BAS; Strobel et al., 2001) and demographic questions. Finally, an exit questionnaire after the second task assessed the general understanding of the tasks.

Data Preprocessing After the exclusion of participants, due to compliance issues and capsaicin sensitivity, datasets were screened for extreme habituation in the UCIT. The criterion was a rating of 0 (no or minimal pain) in > 25% of trials. In this step, two subjects were excluded. In addition, the exit questionnaire was analyzed qualitatively by two independent experimenters to assess if participants understood the tasks correctly. If the participant was flagged by both experimenters, they were excluded; if the assessment differed, the exclusion decision was made following a collaborative discussion of the pro- and contra arguments. As stated above, this resulted in the sample sizes of N = 77 for the first experimental phase and N = 76 for the second experimental phase (technical failure in one participant).

Data Analysis

Questionnaires Potential baseline differences concerning the trait questionnaires were assessed between the groups using paired t-tests for all complete pairs. Additionally, unpaired t-test were conducted to check for differences on average group level. Changes in state questionnaires (anxiety, anger, positive and negative affect) from T1 (before UCIT) to T2 (after UCIT) were analyzed using linear mixed models including the interaction term of experimental group and time point as fixed effects and the subject identifier nested in the corresponding pair number as random intercept effect to control for repeated measurements. In addition, correlation tests between the trait questionnaires were computed.

Learning and contingency measures To verify that the control group learned how to obtain relief in the UCIT, it was assessed if the task finished before reaching the maximum

of 35 trials. If this was not the case (for two persons), it was checked whether they were able to receive relief at least once. This was true for one participant, while the other was excluded from the analysis. Because the outcome sequence in the yoked group depended on the control group, it was not possible to alter the sequence of relief and pain stimuli online while participants made their choices. Hence, it could principally happen, that through their behavior spurious contingencies between key presses and outcomes emerged. In order to quantify this effect, two control measures were computed, to quantify the degree of these unwanted contingencies. First, a summed entropy-like measure for each cue-action combination was computed for those combinations that resulted in a relief at least once (for the others, the entropy would be zero or undefined). For each action the conditional probabilities of both outcomes (relief and pain) were computed, separately for each cue. To do so, the number of relief and pain trials for that cue-action combination was divided by the overall number of times the cue-action was present. Not all possible cue-action combinations were necessarily present for each subject, depending on their behavior. Then, the entropy H for each cue c was computed (see equation 4.1); the two instances of x were pain or relief. The formula was applied for each cue of both runs.

$$H_c(X) = -\sum p(x) log p(x) \tag{4.1}$$

Due to the task design, the entropy was not defined for participants in the control condition, as one cue-action combination deterministically led to relief, but different levels of entropy could occur in the yoked group. In addition to the entropy measure, the number of (different) actions that would result in a relief was computed separately for each cue. This is relevant because the number of possibly rewarding options could principally influence the degree of perceived control, and this information is not inherent in the entropy measure. Entropy and the number of relief actions were correlated with the ratings of perceived control in the yoked group and were included as a control measure to evaluate the outcomes of the memory task, i.e., it was analyzed if confidence ratings were higher for cues with low outcome entropy.

Analysis of UCIT outcomes Linear models were applied to the predict ratings of pain intensity, relief pleasantness, perceived control and helplessness in the induction task. In addition, accuracy and confidence ratings from the memory task, as well as mood, anger and anxiety changes from T1 to T2 were analyzed. Entropy and the number of relief actions were analyzed within the yoked group.

Models of control and helplessness ratings included the experimental group as predictor as well as the pair and subject identifier to respectively account for matching and repeated measurements over blocks. An equivalent model was applied to the confidence ratings resulting from the memory task. Accuracy in memory task was only assessed for the control group, as there were no correct answers for the yoked group. These analysis were conducted as a manipulation check.

The group identifier, trial number and stimulus temperature were included as predictors in the model for pain intensity ratings. To include the trial number was important, because changes induced by the experimental condition are expected to develop over time as the control group learns to obtain relief and the yoked group experiences a higher degree of uncontrollability. Random intercept effects were included to account for repeated measurements over the two blocks. Additionally, nested random effects of subjects in pairs were included to account for the matching across groups. Due to the learning criterion implemented for the control group, participants completed different numbers of trials. To guarantee that each trial number still had enough observations and that outliers would not drive the results, only trials with data points from a minimum of 20 subjects were included in the analysis. The first two trials were excluded from the analysis because they presented outliers in ratings, possibly due to an insufficient amount of pre-exposure before the task started; this was visible as a steep drop in pain ratings after trial two. This resulted in 17 trials from block one and 12 trials from block two that were included in the analysis.

For the analysis of relief pleasantness ratings, the group identifier, the average pain rating, the temperature of the pain stimuli and the trial number were included as fixed effects. The same random effect structure as for the pain ratings was tested, but because the effect

of block number was very small (resulting in a singular variance-covariance matrix), only the nested subject-pair effect was finally included. The same sample size criterion was applied as for the pain ratings. For the analysis of relief ratings, 21 trials were included from block one and 20 trials from block two.

The relationship between depressive symptoms and locus of control (externality, internality), control, helplessness, pain and relief ratings was analyzed by including the respective questionnaire scores as additional predictors in the models.

Analysis of test environment outcomes Pain ratings collected in the test phase while the stimulus was ongoing (after 6s, online rating) and after the trial was over (post-rating) were analyzed with linear models including stimulus temperature, trial number and group identifier as fixed effects. The subject identifier and block number were included as random intercept effects. Models applied to relief pleasantness ratings, included the stimulus temperature (of pain stimuli), the trial number and group identifier as fixed effects and subject identifier as random intercept. Including the pair number for the pain pre-rating model and the block number for the relief ratings did not change the variance explained by the random effects and were thereby not excluded after testing the models. The first two trials were excluded from the analysis of pain and relief ratings, because here a steep habituation effect was present, which was detected upon visual inspection. Importantly, the sequence of pain and relief stimuli in the test environment could differ drastically between participants depending on their behavior. Therefore, the comparison of ratings is confounded by the different amount of pain and relief stimuli that the participants experienced and thus the results only limited validity.

The primary readouts of the test environment were differences in the behavioral strategies of the two groups. Concerning those readouts the following measures were analyzed: the number of successful trials (resulting in reliefs), the number of times the goal or decoy location was chosen as end location, the trial duration before the stay-decision, the total and distinct number of visited fields and the number of switches. The number of fields in-

dicated how many fields the participants visited throughout one block in total, whereas the number of distinct fields did not count double visits. A ”switch” was defined as a change the last location in the trial compared to the previous trial. The models to predict these different outcomes all included the subject identifier as random effect and the group identifier and the run number as fixed effects. The trial number was included if applicable. Also the relationship of the amount of switching and the type of the last field (goal, decoy) was assessed.

Finally, the BDI score of the participants and locus of control (externality and internality scores) were included in the models to investigate the interaction between trait variables and the behavioral measures of the test phase.

4.2 Results

Trait questionnaires and demographics To verify that there were no systematic baseline differences, trait questionnaire scores were compared between the groups. Paired t-tests were computed for complete pairs. Four participants did not have a partner, because they were excluded during data pre-processing. The experimental groups did not differ significantly in BDI score ($t(35) = -0.29$, $p = 0.77$), LC internality ($t(35) = -1.46$, $p = 0.15$) or externality ($t(35) = -0.36$, $p = 0.72$). Neither did the groups differ in the other trait questionnaires: self-efficacy, pain catastrophizing, behavioral activation and inhibition, or pain related self-instructions (all $p > .05$). The sample size, age and gender distributions of the experimental groups were similar. This ensured that potential effects of the experimental manipulation were unlikely to be related to pre-existing differences between groups. For all summary statistics see Tables 4.1 and B1. The BDI score correlated positively with pain catastrophizing (PCS: $p = .02$; pain-related self instructions (catastrophizing): $p = .006$) and externality ($p <. 001$) and negatively with self-efficacy ($p = .003$). Self-efficacy was positively related to active coping subscale of the pain-related self instructions questionnaire ($p < .001$), and behavioral activation ($p = .002$).

State questionnaires Positive affect decreased in both groups from T1 to T2 (before and after UCIT). The decrease was stronger in the control group than in the yoked group, resulting in a significant interaction effect (β = 0.23, *se* = 0.1, *t*(75) = 2.17, *p* = .03). Negative affect (NA) and state anxiety (STAI) decreased from T1 to T2 in both groups (NA: β = -0.08, *se* = 0.03, *t*(75) = -2.5, *p* = .01; STAI: β = -2.21, *se* = 0.42, *t*(76) = -5.25, *p* <.001). There was no effect of time or group on anger ratings.

Table 4.1. Demographics, BDI and LC scores

group			age	BDI	LC (I)	LC (E)
	N	♀	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
control	37	28	25.51 (5.76)	8.38 (8.52)	65.16 (8.13)	43.14 (8.94)
yoked	40	29	25.25 (3.91)	7.70 (6.63)	62.05 (8.64)	42.35 (7.07)

Note. BDI: Becks Depression Inventory; LC (I): internality; LC (E): externality

Uncontrollability induction task

Control and helplessness ratings As intended by the experimental manipulation, the uncontrollability induction resulted in significant differences in control ratings between the experimental groups, see Figure 4.2. Ratings of perceived control were significantly higher in the control group than in the yoked group (M $\pm$ SD: yoked: 53.95 $\pm$ 27.92; control: 70.07 $\pm$ 22.02; β = 16.04, *p* = .0017). The groups did not differ significantly in the helplessness items.

Learning and contingency measures One person in the control group did not understand the task and pressed always the same key, resulting in zero relief trials. The subject was excluded from further analyses. In the yoked group, the average entropy was M$\pm$SD = 3.02$\pm$1.56 in block one and M$\pm$SD = 2.18$\pm$1.19 in block two. The average number of relief actions in block one was M$\pm$SD = 6$\pm$1.88 and M$\pm$SD = 4.95$\pm$1.41 in block

two. Both measures were significantly higher in the yoked group than in the control group (p <.001). By design, the entropy in the control group was always zero and the number of relief actions equal to 4, if all actions were learned, which was the case for all participants except for one person. Neither entropy nor number of relief actions correlated with control ratings on group-level.

Memory task The control group was significantly more confident in their responses during the memory task, for the cue-action combination they correctly remembered (β = 21.00, se = 3.29; p <.001) and significantly less confident for the cue-action combination they did not correctly remember (β = -22.49, se = 4.95; p <.001), see Figure 4.2 and Table B4. In the yoked group the confidence rating was significantly correlated to the outcome entropy (r(38) = -0.37, p = .019). Those cue-action combinations that had lower outcome entropy consequently were remembered with higher confidence although there was, in principle, no correct answer in the memory task for the yoked group.

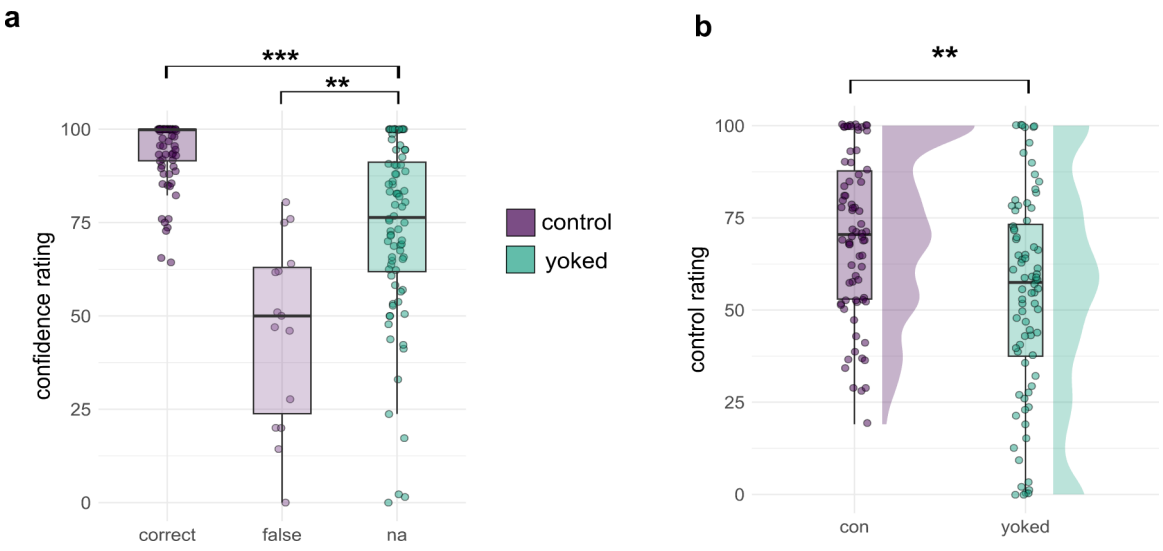

Figure 4.2. Confidence and control ratings. **a)** Confidence in the memory task was significantly higher in the control group for the correctly remembered cue-action combination (dark purple), than in the yoked group (turquoise). Most of the cue-action combinations were correctly remembered. The control group was less confident in incorrectly indicated cue-action combinations, then the yoked group average. **b)** Control ratings were higher in the control group than in the yoked group, indicating a successful experimental manipulation of subjective control.

Pain and relief ratings Pain ratings in the yoked group decreased over trials, while pain ratings from the control group were constant in block one and even increased slightly in block two, leading to a significant interaction effect of group and trial (β = 0.58, p <.001). There was a significant main effect of temperature on pain ratings, with higher temperatures resulting in higher pain ratings, despite the calibration procedure (β = 2.98, p <.001). A main effect of experimental group, tested in a separate model, was not significant. The groups also differed in the development of relief pleasantness ratings over time, resulting in a significant interaction effect (β = -0.66, p <.001). Although relief was rated as less pleasant over time in both groups (β = -0.33, p <.001), ratings in the yoked group were lower from the start and decreased less than in the control group. For visualization, see Figure 4.3. The average pain ratings significantly predicted relief ratings (β = 0.18, p <.001), indicating higher pleasantness of relief, if pain was perceived as more intense. All parameters and statistics on fixed and random effects are summarized in Table B3.

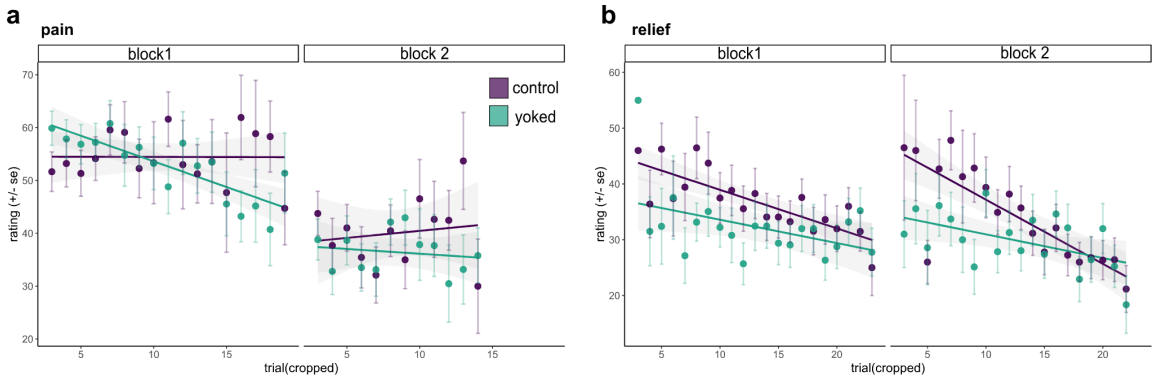

Figure 4.3. Pain and relief ratings in UCIT. Lines fitted to mean ratings of the trials with data from a minimum of 20 participants from the control group (purple) and yoked group (turquoise). Error bars depict the standard error of the mean. Separate plots are shown for block one and two. **a)** Pain ratings: the yoked group showed a stronger habituation than the control group. **b)** Relief ratings: the yoked group showed a stronger decrease in pain ratings than the control group. Relief ratings were generally lower in the yoked group, but the decrease was more pronounced in the control group.

Test environment

Pain and relief ratings The online pain ratings, which were collected in each trials before the grid was shown, differed between the groups over time. Pain was rated as increasingly higher over time by the yoked group, while ratings by the control group flattened towards the end of the first block. In the second block, pain ratings in both groups decreased, indicating strong habituation (Figure 4.4). The decrease was stronger in the control group, resulting in a significant interaction effect between group and trial number (β = -0.40, p = .003). None of the predictors alone (stimulus temperature, trial number, condition) was significantly related to ratings. The pain ratings collected post trial increased significantly over time (β = 0.38, p <.001) but were not statistically different between groups or showed an interaction effect. Relief pleasantness ratings decreased over trials (β = -0.43, p <.001). There were no other significant main or interaction effects.

Successful, goal and decoy trials The groups did not differ in the overall number of successful (relief) trials (β = -1.78, p >.05). The yoked group ended on the goal location nominally more often than the control group, but the difference only reached trend level (β = -2.09, p = .059). The groups also did not differ in the number of decoy fields (β = -0.24, p = 0.7), but participants of both group ended more often in a decoy location in the second experimental block (β = 1.47, p <.001), while there was no effect of block on the number of goal or successful trials. All measures are visualized in Figure 4.5.

Number of visited fields, switches and duration Neither the total or distinct number of visited fields, the number of switches nor trial duration differed between groups. Participants visited fewer (β = -0.08, p <.001) and explored less different fields over trials (β = -0.07, p <.001). The number of switches and trial duration decreased significantly from the first to the second experimental block and over trials (all p <.05, see B6 and B7).

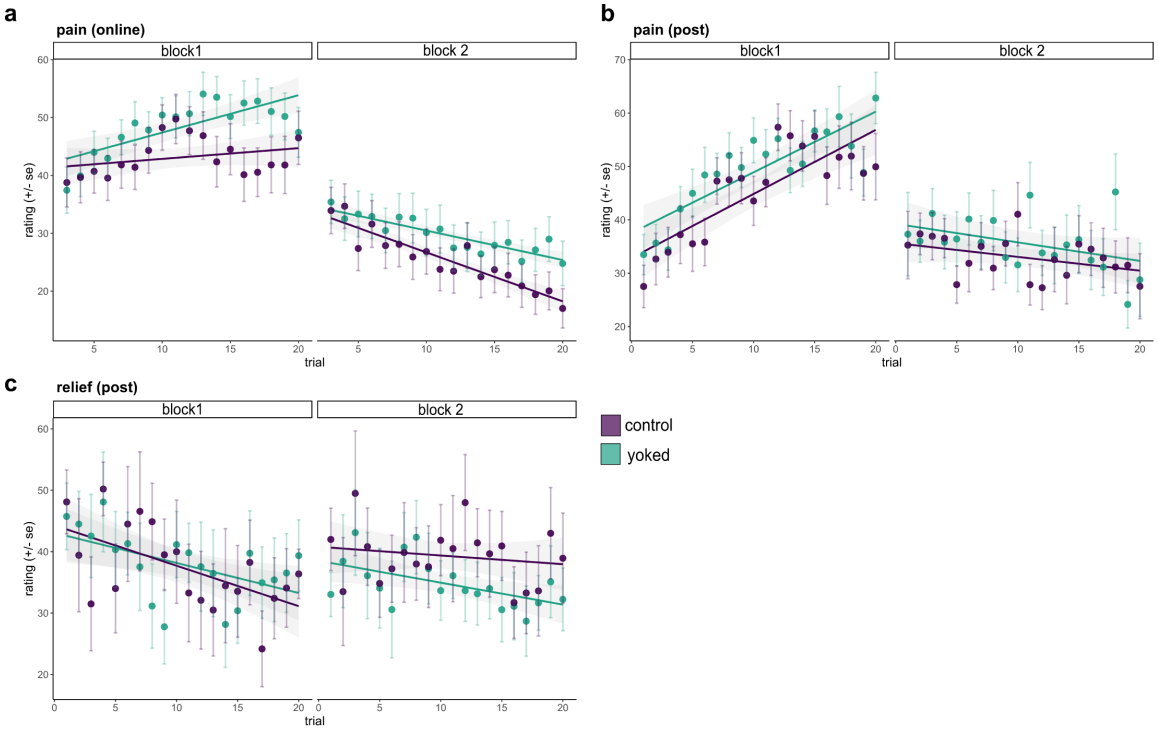

Figure 4.4. Pain and relief ratings in test environment. Lines fitted to mean ratings from the control group (purple) and yoked group (turquoise). Error bars depict the standard error of the mean. Separate plots are shown for block one and two. Note that between trials, participants received a different number of pain and relief stimuli that also had different length. **a)** Online pain ratings. The ratings were collected six seconds after trial onset, while the pain was ongoing and before the grid was shown on the screen. **b)** Post trial pain ratings of the test phase. Both pain ratings show increased pain sensitivity over time, but the online ratings in the yoked group increased more than in the control group in block one. In block two, both groups showed strong habituation to the stimulation, but pain ratings in the yoked group were higher than in the control group. **c)** Post trial relief ratings decreased over time and were similar between groups.

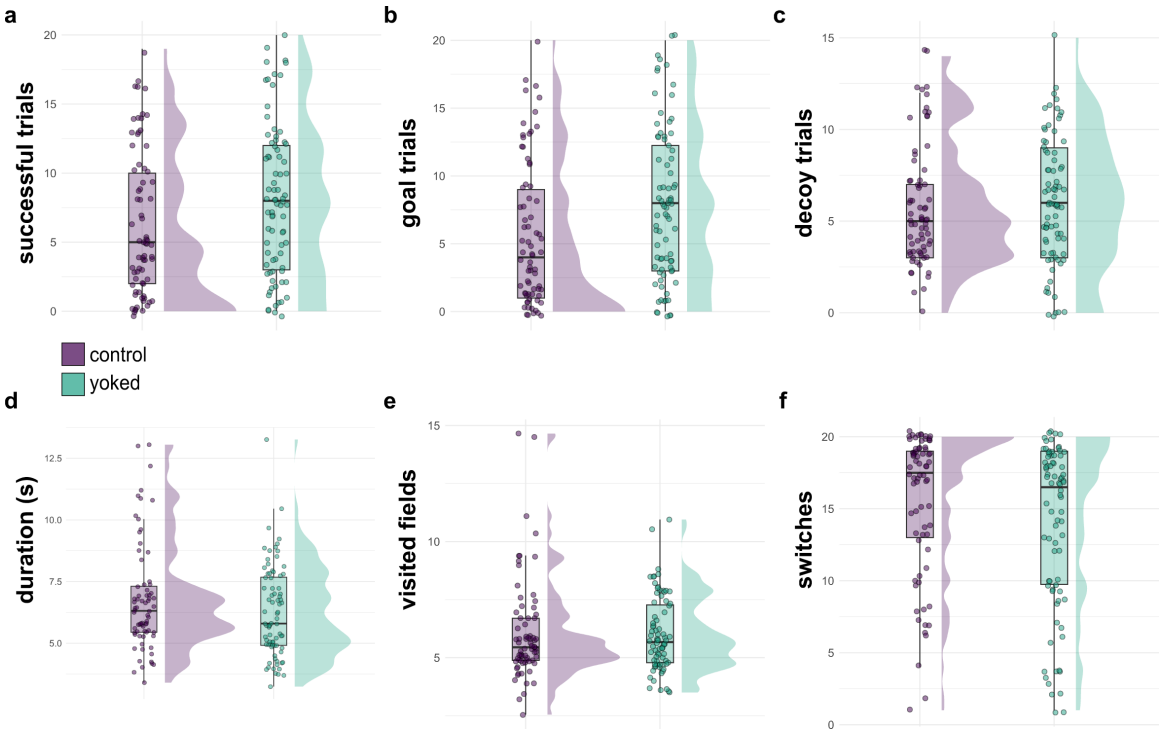

Figure 4.5. Learning measures in test phase.**a)** Number of successful trials, which resulted in a relief. Nominally the control group (purple) had a lower number of successful trials. The difference was not significant. **b)** Number of trials that ended on the goal location. Staying at the goal location resulted in a relief with 90% probability. **c)** Number of trials that ended on the decoy location. Staying at the decoy fields resulted in a relief with 10% probability. **d)** Duration of trial, before the stay action was performed. The duration decreased from block one to block two for both groups. **e)** Total number of visited fields, averaged across trials. **f)** Switches indicate a different end position than in the previous trials. The groups did not significantly differ in any of the learning measures in the test phase.

Locus of control and depressiveness

External Locus of Control Locus of control externality was not associated with pain or relief ratings during the UCIT. Neither did externality predict control, confidence, or helplessness ratings. There was a significant association of externality with pain ratings, but not relief ratings in the test environment. Higher externality was related to higher online (β = 0.69, p = .004) and post-trial pain ratings (β = 0.81, p = .002). However, there was no interaction effect of externality and experimental group on pain ratings. In addition, externality predicted a lower number of successful trials in the test environment. In fact, this effect differed for the two groups, leading to a significant interaction effect (β = 0.35, p = .008). Yoked participants received a different number of relief stimuli, dependent on their locus of control. Low externality in the yoked group, was related to more successful (relief) trials, whereas yoked participants with an external locus of control had a lower number of relief trials. No such relationship between externality and relief trials was present in the control group. This effect was driven by the parallel interaction of externality and group on number of trials that ended on the goal location (β = 0.33, p = .016). Also the relationship between externality and the number of switches differed between groups (β = -0.36, p = .01). In the yoked group, participants with high externality scores switched end location more often, while there was no such effect in the control group. There was no effect on number of decoy trials, duration or number of visited fields. For regression parameters and significance values, see Tables B8, B11, B12, B13.

Internal Locus of Control Locus of control internality was not significantly related to pain, relief, control, confidence, or helplessness ratings in the UCIT. Neither was there a significant main effect on pain ratings in the test environment. The interaction of group and internality on post-trial pain ratings was significant (β = -1.04, p = 0.048). No interaction of main effect of internality on relief ratings, number of successful, goal or decoy trials, trial duration, switching behavior or number of visited fields was present. For regression parameters and significance values, see Tables B9, B11, B12, B14.

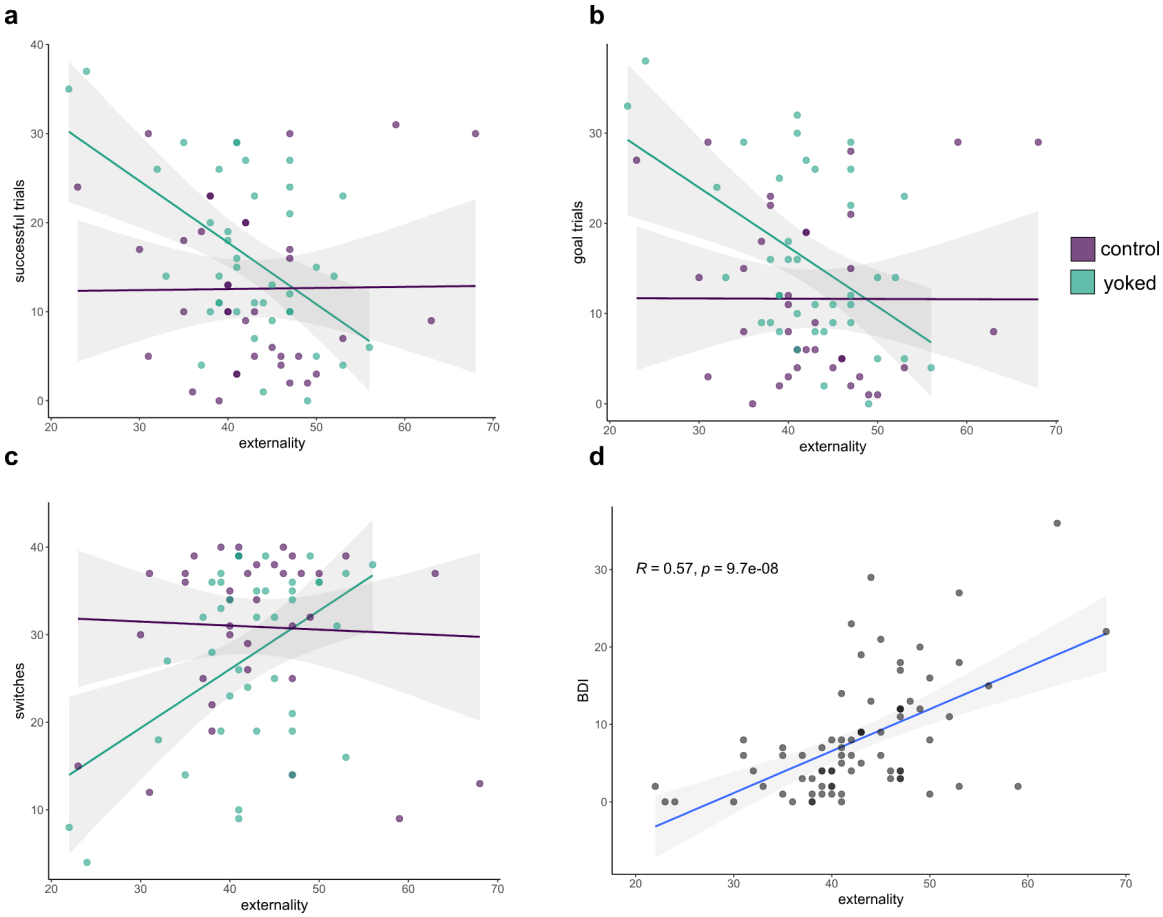

Figure 4.6. Interaction effect of group, depressiveness and externality on outcomes. **a)** Interaction of group and depressiveness (BDI score) on number of successful trials, resulting in a relief. With higher BDI score, the number of successful trials decreases in the yoked group (turquoise), but not in the control group. Yoked participants with low BDI have a higher number of successful trials than control participants. **b)** Interaction of group and external locus of control on number of successful trials. With a more external locus of control, the number of successful trials decreases in the yoked group but not in the control group. Yoked participants with low externality score, have a higher number of successful trials than control participants. **c)** The interaction effect on successful trials is driven by the same interaction present for the goal trials. Yoked participants with low externality score stayed at the goal location more often, while yoked participants with high externality score stayed at the goal location less often than the control participants. **d)** Participants in the yoked group that scored low on externality, switched less often than the control group, while yoked participants with a high externality score switched more often.

Depressive symptoms Depressive symptoms, measured by the BDI, were not related to pain intensity, relief pleasantness, control, confidence, or helplessness ratings (all $p > .05$). But the effect of the BDI score on the number of successful trials differed between experimental groups. While participants with higher BDI scores generally obtained a lower number of relief this effect was mainly driven by participants in the yoked group. Yoked participants with a low BDI score obtained relief even more often than control participants with similar BDI score. However, yoked participants with high BDI scores obtained a lower number of relief trials than control participants (β = 0.3, p = .034). This result is not surprising regarding the high correlation of externality and depressiveness ($p <$. 001).

Additionally, there was a significant main effect of BDI score on the number of goal trials (β = -0.16, p = 0.02), but the interaction term of BDI and group was not significant (p = .07). Also, a higher BDI score predicted a higher number of switches, but also this effect did not differ between groups. There was no effect of BDI on the trial duration, total number of visited fields or decoy trials. For regression parameters and significance values, see Tables B10, B11, B12, B15.

4.3 Discussion

This study investigated the effects of uncontrollability on acute pain perception and subsequent learning. It used a yoked between-groups design, to control for sequence and intensity of stimulation. In the first phase, the groups experienced different levels of control over pain. The control group learned how to avoid pain and obtain relief by learning different cue-action combinations, while the yoked group received the same stimulus sequence, but not related to their behavior. In a second phase, both groups could principally learn to shorten a tonic pain stimulus by selecting the correct field (goal) on a grid in a game-like test environment. Pain and relief perception was assessed during both tasks. Successful learning and behavior, i.e., the number of visited fields, the number of switches and the trial duration, were measured in the test environment to determine if the groups differed in the

exploration behavior and performance.

For a manipulation check, ratings of perceived control in the first phase were compared between the groups. As intended, the control group reported higher perceived control than the yoked group. Also, the confidence in the memory tasks, in which participants had to indicate the action-cue combination that would lead to relief, was higher in the control group. In contrast, the entropy of the outcomes and the number of different actions that provided relief were significantly higher in the yoked group. This shows that the experimental manipulation was successful and provides a good basis for the interpretation of the results.

During the first phase, the yoked group perceived the painful stimuli as less intense and the relief stimuli as less pleasant over time. Because the effect developed only over time, there was no significant difference in pain or relief ratings on average group level. However, this is expected, because perceived control could only have influenced pain differentially, after the control group had learned that they could change the outcome by their actions and the yoked group had experienced uncontrollability. The fact that the control group rated pain intensity and relief pleasantness higher than the yoked group can be interpreted in light of the differences in the informational value of pain and relief for each group (Seymour, 2019). For the control group, pain was actually indicative of a false response, while relief was a reliable signal for correct behavior. Especially towards the end of a block, a painful stimulus received by the control group signaled an error, which should be corrected. Thereby, pain might have gained a high level of salience (Horing & Büchel, 2022), which might have heightened its rated intensity. Relief stimuli were also more informative for the control group, especially at the beginning of the task. Over time, the associations of cue and actions were learned and relief became more frequent, reducing its relevance for learning. This possibly caused lower attention towards relief stimuli over time, resulting in a decrease in perceived pleasantness. So far, studies reporting that control increased perceived pain interpreted this result in light of lower attention towards the task in the control group, leading to less attention-induced hypoalgesia compared to the group that experienced uncontrollable pain (Salomons et al., 2015). They also put forward the explanation

of increased anger or frustration in the control group, because for the control pain actually indicated an avoidable error (González-Roldán et al., 2016). The latter could also be an alternative explanation for the results in the present study, as the increase in perceived pain intensity towards the end of the task could also be driven mainly by those control participants that had difficulties learning and perceived pain as more intense as a result of increased frustration and negative mood (Tracey & Mantyh, 2007). However, a more parsimonious explanation is the modulation of pain and relief perception by their informational content. This was also supported by a recent study, where pain increases and decreases were rated as more extreme if they were under instrumental control (Desch et al., 2023), as well as by studies reporting increased relief and placebo perception with control (Zhang et al., 2018; Tang et al., 2019; Strube et al., 2023).

In the yoked group, neither pain nor relief were informative regarding the correctness of the selected actions. Through the reduction in value as a learning signal, this might have led to an overall decrease in perceived intensity and pleasantness. This decrease in ratings might be an effect of general *blunting* of perception in response to the increased level of uncontrollability, which similarly affected positive and negative outcomes over time. Blunting refers to a general suppression of responses to positive and negative reinforcers (Huys & Dayan, 2009) through experience of uncontrollability. For example, reward-processing brain regions are less responsive if there is low action-reward contingency (Tricomi et al., 2004) or if a positive outcome resulted from a choice of a computer program in contrast to self-made choice (Romaniuk et al., 2019). This effect might be boosted by the inherent rewarding property of choice (Leotti & Delgado, 2011), for example the possibility to exert control increases positive affect in general (Stolz et al., 2020) and selected options are valued more than discarded ones after the decision has been made (Sharot et al., 2009), but see (Becker et al., 2021) where perceived pain relief was larger in a condition without control. An example for blunting towards painful outcomes is hypoalgesia triggered by inescapable shocks in animals (Grau et al., 1981). Here the body recruits its own opioidergic endogenous mechanisms to manage pain, due to a lack of alternative coping options.

While often negatively framed, this blunted response actually represents a adaptive form of passive coping with uncontrollable pain, because it would be inefficient to invest resources trying to change predetermined outcomes (Gandhi et al., 2017). It enables pain acceptance, which in fact has been related to lower reported pain intensity and longer endurance in a cold pressor task (Masedo & Rosa Esteve, 2007). However, passive coping is not always adaptive, especially if it is generalized to positive reinforcers, because then the orientation towards other goals might be inhibited (Frömer et al., 2021). Also, if passivity becomes maladaptive, when generalized to future situations, where pain might actually be shortened or avoided by active responding (Gandhi et al., 2017). The generalization effects in this study were assessed by evaluating behavior in the test phase.

Both groups completed two blocks of the test environment. Here participants moved an agent across a grid and could select different types of fields. The selection of some special fields could yield a cooling relief from a tonic painful heat stimulus. Participants were not instructed how to behave nor were they informed about the relief probabilities. They could only learn by how to receive relief by selecting different fields. The best possible field (goal) had a relief probability of 90%, three other decoy fields provided relief with a probability of 10%. In fact, none of the behavioral measures (number of successful (relief) trials, visited fields, switches or trial duration) was different between groups, but there was a trend for a higher number of successful trials in the yoked group.

The absence of effects on group level can be explained by the fact, participants in the yoked group behaved differently dependent on the allocation of their locus of control and number or severity of depressive symptoms, as measured by the BDI. An external locus of control reflects the tendency to attribute events to chance or the influence of other people, rather than to oneself (Rotter, 1966; Lefcourt, 1976). Yoked participants with high externality scores ended on the goal location less often, switched more between fields and thereby received less relief, than yoked participants with low externality scores or control participants. Yoked participants with low externality scores on the other hand received relief even more often than control participants, because they returned to the goal location more

consistently. A more external locus of control is a significant predictor of depressive symptoms (Hovenkamp-Hermelink et al., 2019) possibly via reduced reward responsiveness and higher stress sensitivity (Pizzagalli et al., 2007). Because externality and depressive symptoms were also highly correlated in present study, it is not surprising that the same interaction effects of group and BDI score were significant predictors if the number of successful trials. Importantly, there were no significant baseline differences in distribution of BDI or externality scores between groups, indicating that the effects were a result of the interactions of traits with the experimental manipulation. That people react differently to an experimental manipulation of controllability dependent on their locus of control was already reported in early studies on learned helplessness (Abramson et al., 1978; Alloy & Abramson, 1979). Especially the attribution style was put forward to explain proneness to develop the typical helplessness response, i.e., generalized passivity in situations were escape would be possible by active responding. For example, if uncontrollability and resulting helplessness is attributed to a stable, global and internal cause, it will more likely lead to a general lower self-esteem and motivational deficits (Abramson et al., 1978). Changes in generalization kernel by trait characteristics are also established in the domain of fear, where high anxiety was shown to increase perceptual generalization (Dymond et al., 2015; Norbury et al., 2018). That the locus of control influences how vulnerable people are to develop learned helplessness has also been discussed in the context of pain (Gandhi et al., 2017). Locus of control was reported to influence hyperalgesia that was triggered by uncontrollability of acute experimental pain (Bräscher et al., 2016), neural processing of pain (Wiech et al., 2006) and physiotherapy outcomes in patients with chronic pain (Álvarez-Rodríguez et al., 2022). Although, in one study a beneficial effect of control on pain-related suffering was actually greater in participants with an external locus of control (Löffler et al., 2018).

The test environment of this study was designed in a way that made exploration unnecessary, after the goal location was discovered, because the relief probabilities were constant throughout the task. Therefore, to obtain the maximal number of relief trials, the

best strategy was to always return to the goal location and a deviation of that strategy could be considered suboptimal. This makes it difficult to test predictions of classic learned helplessness theory, which would predict suboptimal behavior by higher passivity in the yoked group implying less exploration, a lower number of successful trials, visited fields and switches. The participants in the yoked group, who had a low BDI and externality score, mainly showed optimal behavior, which consisted in the exploitation of the goal field and led to a high number of relief trials and a low amount of switches. One explanation for this effect is, that they wanted to compensate the level of experienced randomness in phase one, what could have been perceived as bad task performance. The participants with high BDI and externality scores in the yoked group, visited the goal location less often and switched more. This could also be an indicator of more random and less goal-directed behavior, possibly also influenced by lower reward responsiveness if the the goal was found at least once and stronger generalization of perceived environmental uncontrollability in those participants with a high level of externality. Participants in the control group, on the other hand, neither maximally exploited the goal location, nor did they switch as often as the other yoked group participants, independent on their BDI and externality score, hinting to a more balanced exploration-exploitation behavior.

In sum, this study showed again, that the simple assumption of control-induced hypoalgesia does not hold, as pain was perceived as less intense with uncontrollable and unpredictable outcomes. It shows that a lower perceived control leads to short-term changes in learning strategies that are different dependent on participant characteristics, i.e. more exploitation in those participants who generally attribute outcomes of life events to the influence of other people or chance. Coming back to the assumptions for the potential use of therapeutic measures to increase the subjective sense of control, this study underlines that especially the attribution of pain reduction to one's own actions should be increased dependent on the context. If perceived control over life events is generally increased, this might lead to unwanted results because it might hinder pain acceptance and adaptive forms of passive coping if treatment attempts are unsuccessful (Gandhi et al., 2017).

4.4 Limitations

While the explanation for the different behavior in the yoked group (showing either random behavior due to more generalization of lack of control or increased exploitation) is intriguing, it must remain speculative. To determine if the behavior in the yoked participants with an external locus of control was actually random or just more explorative, the task should have included a change in goal locations to make exploration more beneficial than exploitation. This would require an ongoing balancing of exploration and exploitation strategies for optimal behavior. Possibly, such a task could also show if yoked participants with low BDI scores overly exploited to make up for the lack of control in the first phase. Overly exploiting one option would result in suboptimal outcomes in such an improved task, because it would lead to a longer latency before detecting a change in goal. This change of goal location was not implemented this study, because the major aim was to avoid a overly difficult task for the participants. The application of long painful stimuli limited the possible number of trials and therefore it a relocation of the goal would have been harder to learn within the trial limits. Still, an option for future studies could be to use stimuli of other pain modalities, add more trials and implement a slow change in reward probabilities across fields. Despite this limitation, the results can be very informative for future studies. They underscore once more the relevance of assessing locus of control and depressive symptoms in the context of control. Interestingly, neither externality, internality or the BDI score correlated with the VAS ratings of control in the first phase.

One additional aspect that potentially limits the findings of the study is, that control ratings in the yoked group were still quite high. This was possibly due to experienced level of unwanted contingencies and the tendency of humans to develop illusory control (Alloy & Abramson, 1982; Yarritu et al., 2014). In addition to the change in goal location over time, an improved task should either evaluate responses and outcomes in the induction task online, in order to prevent such unwanted contingencies or change the task for the yoked group to make it more random, as for example in Ligneul et al., 2022. Of course this

would make a perfect matching of tasks between groups impossible, the effects of which would need to be evaluated in pilot experiments.

Finally, the choice of thermal stimulation of capsaicin pre-treated skin posed some challenges, because participants habituated extremely to the stimulation. In the second block of the test phase, the average rating was approximately 30 on the VAS instead of the targeted rating of 60. While this is related to the employed pain modality, it might partly also be explained by changes in task performance in the second block because this changed the occurrence frequency of pain and relief stimuli, possibly resulting in temporal contrast effects on pain. In both phases pain stimuli were more frequent at the beginning and relief stimuli were more frequent towards the end of a block. Thus, an unexpectedly received relief at the beginning, or unexpected pain at the end, was additionally modulated by contrast effects. Temporal contrast effects in pain are a phenomenon that has been extensively studied (Grill & Coghill, 2002). For example, an increase in stimulus intensity is perceived as disproportionally less intense, and a reduction in stimulus intensity is perceived as disproportionally more intense, after a longer highly painful stimulation (Alter et al., 2020; Fust et al., 2021). However, at least in the first task, the stimulation frequencies were perfectly matched across groups. Thus, the different temporal development of pain and relief ratings in the yoked group indicates that the manipulation of control and not contrast effects led to the changes in perception in the first study phase.

5. Discussion

I started this PhD project with the aim understand the interplay of the subjective feeling of control and pain perception. Perceived control has often been reported in context of more beneficial trajectories in chronic pain (Cramer & Perreault, 2006) and factual control over pain medication can increase analgesic efficacy (Ballantyne et al., 1993; Macintyre, 2001). From those effects, the initial hypothesis was derived that a higher feeling of subjective control would reduce perceived pain intensity, which then could possibly be a valuable direction for the design of pain management therapies. Although this hypothesis has often been reiterated to motivate numerous studies, the relationship between perceived control and pain perception is more complex and the literature less conclusive than it could be expected. During the design of the first study, it also became apparent that expectation effects, particularly in the context of acute pain in experimental laboratory settings, would be a relevant component to consider. This broadened the scope of the first project, resulting in a rather methodological investigation of how control relates to precision of expectations and how both factors influence sensory processing of pain. The second study aimed to shed light on the outcomes of perceived control over pain on other measures than perception, drawing inspiration from learned helplessness theory. In addition to supporting an interesting new view on the informational value function of pain (Zhang et al., 2018; Seymour, 2019; Desch et al., 2023), the second study also stressed the relevance of personality traits in interplay with pain uncontrollability. After having reported and discussed the empirical results of the studies, I will now converge findings of both studies and relate them to the initial hypothesis and question how control modulates pain.

5.1 Recapitulation of research questions

Derived from the reasoning presented above, the explicit research questions for the different studies were (i) does control influence pain perception and neural processing above predictability, and (ii) does control change pain perception and behavior in a second task due to the generalization of control beliefs.

5.2 Summary of empirical studies

The first study showed, that control over pain intensity prior to the stimulation did not simply attenuate pain. Instead, control strengthened interaction effects induced by predictability through the anchoring of expectations. By that, predictable low stimulation intensities were perceived as less intense and higher intensities perceived as more intense. This effect was even stronger in the controllable than in the predictable condition. Controllability did not generally change the neural processing of pain. However, predictability of pain intensity strongly influenced brain activity in response to pain. The SMA, PAG, anterior insula, ACC, parietal cortex and thalamus were less active in the anticipation of a painful stimulus of predictable intensity. When pain intensity was additionally controllable, the activation difference to the unpredictable condition was even more extreme. Controllability effects were primarily significant in the PAG and SMA, but the activation difference showed the parametric effect in many of the aforementioned brain regions. All these regions are usually more activated in response to more unexpected sensory outcomes or when a task requires attention. So their activation does not specifically indicate changes in pain processing. This finding challenges former interpretation for control-induced attenuation of pain processing in these brain regions, especially when the controllable pain condition was confounded by predictability.

The second study implemented control over pain relief in a between-subject study and tested generalization effects. The group that perceived a lower level of control did not report

reduced, but increased perceived pain intensity, but also increased reward pleasantness. A lack of control over pain led to different behavior in a subsequent task. The type of behavioral change depended on depressive symptoms and locus of control. A higher belief in the influence of external forces on life events and more depressive symptoms in combination with the experience of uncontrollable pain led to less goal-directed behavior. A belief of a minor influence of external forces on life events and less depressive symptoms led to compensatory exploitation behavior after experiencing uncontrollable pain.

5.2.1 Synthesis of results

The combined message of both projects could be the following: control alters pain perception by increasing the expectation precision and informational value of pain. Although there are some apparent differences in the type of control manipulation and design, the study results converge regarding one aspect, that is the differential influence of control depending on outcome intensity and/or valence. Control differentially affected pain of high and low intensity, and relief perception. Control enhanced the reported intensity in contrast to the other possible outcomes in the task in both studies. In study one, the high pain stimulus was perceived as more and the low pain stimulus as less intense with control and also in study two, both outcomes were rated as more extreme with control: pain was perceived as more intense and relief was perceived as more pleasant. I would like to put forward two non-exclusive explanations for the results of the studies: higher expectation precision and informational value of pain in the control conditions. When actions matter for outcomes, the feedback about these outcomes that guides learning is naturally more relevant than if they don't. In the first study, the pain intensities received, especially in the first trials, had more informational relevance, because after receiving them, participants could estimate the range of painfulness they would experience dependent on their choice. Referring to the predictive processing perspective of pain (Büchel et al., 2014), the endogenous increase in perceived intensity by higher informational value, could reflect a strategy of the brain to reduce prediction errors and behave optimally by allocation of attentional focus.

This perceptual information guided participants' behavior when sequencing low, medium and highly painful stimuli in the control condition. But after having experienced each stimulus intensity once, there was no additional information that could be gathered to guide choice behavior. However, at that time point, the expectation precision had increased a lot, because stimulus intensities were reliably related to the choice of the participant. Thus, even though there was a little amount of new information, the predictability of outcome intensities was high. This created the interactive effects on ratings and is reflected in the parametric pattern in brain activity. Interestingly, self-involvement even subjectively increased expectation precision in comparison with the predicable-only condition, indicating a higher amount of internal uncertainty when events are determined externally. In study two, pain was perceived as more intense in the beginning, as did relief, even though it was not precisely predictable. But through the observation of outcome contingencies to actions in the control group, it was clear that painful and relieving outcomes could be connected to erroneous or correct behavior. This again increased the relevance of pain for action guiding, i.e., the informational value. The increase in prior precision would occur after some time of interacting with a (controllable) environment. At the end of the task in study two, this could have contributed to the effect that relief was still rated as more pleasant by the control group, even though behavior should have been consolidated by then (and informational value of outcomes reduced). In sum, both studies show that the informational value of pain is increased by control and possibly heightens the processing of stimulus intensities in reference to the other possible outcomes. This effect is even maintained after learning, possibly by the heightened predictability, that is inherent to controllability.

5.2.2 Limitations

While it is compelling to motivate the theory of informational value in this context, the theory itself has some short-comings regarding empirical results. For example, it expects pain to be perceived as more intense if the environment is unpredictable because there, the opportunity to learn is greatest (Seymour, 2019; Desch et al., 2023). But it does not formalize

the interactive effects of predictability over intensities that has been reliably reported (Pavy et al., 2024). This effect touches upon a second limitation that applies to both studies and that is that the outcome space was principally known in the unpredictable or uncontrollable conditions. Either it was known from the beginning by the instructions, or after the first few trials. This makes it really different from real-world experiences, because there usually the possibly perceived pain intensities are not known. For example, a migraineur might not be able to always predict how badly an attack might develop, but also not how beneficial a treatment would be. One further limitation of both studies is, that they explored only one pain modality, thermal heat pain, of rather short duration. It is generally difficult to translate findings from acute to chronic pain, also regarding the interpretation in light of informational value. Chronic pain can still be perceived as very intense, although the informational value for guidance of behavior according to endogenous needs is possibly not given. This might indicate that the an internal evaluation of the relevance of the pain signal converged on a value that is not favorable for the individual.

Another factor limiting the ecological validity of the studies is the choice of control dimension, especially in study one. While the intensity of a painful experience might be controllable by behavior in real life, i.e., when taking an analgesic that is known to be effective, control is usually not exerted over the onset of different levels of painfulness arising from a non-painful baseline. While the control modality in the second experiment, inducing a relief, by behavior, is generally more close to real world experience, the setup with the computerized task is far away from the complexity of a real pain experience. Although it is necessary to reduce processes to their controllable cores in laboratory studies, this discrepancy between the lab and the world always needs to be kept in mind.

In particular, because also other types of controllability and predictability, which might be more realistic could be investigated. For example predictability could be altered in form of different temporal development of pain over time. Coming back to the example of carrying a mug of hot coffee, the amount of painfulness can be predicted, especially if it builds up for a while before crosssing the pain threshold. Here the brain infers the painfulness based

on a auto-regressive model over time; or based on the slope of the sensory intensity. It would be interesting to investigate what happens if this predicted trajectory is violated by unpredictable change of intensity.

Finally, possible improvements of both tasks are possible. To improve the modeling analysis of study one, it would be important to collect more data points to estimate trial-wise expectations of pain and their precision. This would allow to set up a full Bayesian model instead of relying on approximations. This would also make it possible to investigate the processing of signed predictions errors in the unpredictable condition and determine if for example the PAG activity is related to aversive prediction errors, as it has been shown before (Roy et al., 2014) or to the change in predictability in general. Concerning study two, it would be relevant to include a condition that reduces the control perception even more, to avoid residual contingencies. Also a larger sample size with a wider distribution of BDI and externality scores should be tested to confirm the use of different strategies after uncontrollability confrontation depending on those traits. Especially given the fact, that locus of control did not have an influence on the effect of controllability in study one. Yet, this might be explainable by the within-subject design, because there, all participants experienced also the control condition and no one completed only the uncontrollable and unpredictable trials.

5.3 Implications for the field

The findings discussed above have multiple implications for the field. First, they stress that an equally predictable control condition is highly relevant when the specific influence of perceived contingencies of behavior and outcomes is under investigation. This is crucial in the context of pain and of utmost importance for studying changes in functional brain activity, because predictability alters the state of salience and attention processing networks to a major extent. This finding replicates once more that predictive processing also applies to pain aligns with the hypothesis that it is a universal principle of human action and

perception as the neural implementation of the free-energy principle and active inference (Poublan-Couzardot & Talmi, 2024). The present work further implies, that it is undercomplex to assume that control per se reduces perceived pain. However, it can be beneficial in the context of pain treatment by increasing outcome certainty of a positive outcome, as demonstrated by the influence of control over placebo treatments (Tang et al., 2019). In that context it is important to note, that perceived control might also be counter-productive, if lower treatment efficacy or higher pain are attributed to one's own behavior or hinders pain acceptance (Gandhi et al., 2017).

Hopefully, the literature review conducted in parallel of the empirical studies described in this thesis (Habermann et al., 2024), helps to distinguish different implementations of controllability and what their distinct influence on perception might be. When conducting future studies, experimenters should think about what control dimension they would like to investigate, for example, control over treatment onset, pain intensity or pain onset. Then, inspiration for study design and evidence evaluation can be derived from those studies that actually tested the same control manipulation, with predictability taken into account. Controllability and predictability could be principally tested separately, but not along the same dimension. For example, a study could test the effects of predictable pain intensity in combination with an uncontrollable duration, but an uncontrollable pain onset excludes the possibility to make it predictable. If studies used more similar tasks and tried to replicate findings on the behavioral and neural level, maybe settling on the control dimension that is most ecologically valid (pain offset or intensity modulation), could lead to more convincing evidence regarding control-induced effects on pain.

A final implication of the present work is, that personality traits, which are consolidated over a lifetime, naturally influence the reaction to a situational manipulation of controllability. They encode an internal prior for controllability that is carried from one environment to the next and require different levels of observational evidence to result in action changes (Huys & Dayan, 2009). This effect should be investigated in more detail by measuring prior beliefs about controllability, and how those might be affected by different conditions or events,

i.e., depression, chronic pain, traumatic experiences or chronic mild stress, when studying effects of pain uncontrollability.

5.4 Perspective

Although it would have been nice to provide a clear answer regarding effects of subjective control on pain perception, this thesis majorly identified factors that make the relationship of both more complex. However, it is important to shed light on the complexity of phenomena in order to derive a better understanding. Knowing this, future studies should use more similar tasks, investigate control dimensions more consistently or at least deliberately chose and motivate them. When revisiting earlier results on control effects of pain, we should ask ourselves, if a more simple explanation, like increased saliency by predictability can explain the effects on ratings and functional brain activity. A cool endeavor would be to come up with smart tasks that can actually separate prior, likelihood and posterior distribution by design or report from study participants. Also, how the entropy of the environment, which is objectively experienced and computed by the brain, translates to subjective reports of control and how this might be influenced by the personality prior of controllability acquired through life events should be a major focus of future studies.

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Appendix A

Table A1. Model variables and group-level priors

Model parameters	Group-level prior	Description
$\mu_{0,VAS30}$	$N(30, 100)$	prior mean low intensity
$\mu_{0,VAS50}$	$N(50, 100)$	prior mean medium intensity*
$\mu_{0,VAS70}$	$N(70, 100)$	prior mean high intensity
$log(\sigma_{\mu_0})$	$N(1.5, 0.5)$	standard deviation of prior mean
α	$N(0.5, 0.3)$	scaling parameter
h	$N(0, 1)$	habituation term
$log(\tau_0)$	$N(1.5, 0.5)$	prior standard deviation
$log(\tau_1)$	$N(1.5, 0.5)$	posterior standard deviation
μ_1		posterior mean
w		probability weights intensity
		*fixed μ_0 for all intensities

Table A2. Demographic information and questionnaire results

sample	N				age		STAI		LC (I)		LC (E)	
		♀	♂	div.	M	SD	M	SD	M	SD	M	SD
behavioral	54	31	22	1	27.15	4.54	36.59	7.06	56.76	16.86	51.39	16.54
fMRI	59	35	24	0	26.56	5.11	33.14	6.36	67.15	9.01	46.93	10.00

Table A3. Results of linear models on choice frequency

param	mean	se_mean	sd	n_eff	Rhat	HPDI_min	HPDI_max	model_name
α	8.66	0.07	4.13	3825.89	1.00	0.36	16.82	lin_low_beh
β	3.08	0.01	0.45	3785.79	1.00	2.18	3.96	lin_low_beh
σ	7.22	0.02	1.62	4513.15	1.00	4.52	10.38	lin_low_beh
α	15.64	0.07	4.54	3798.80	1.00	6.59	24.73	lin_low_fmri
β	2.21	0.01	0.50	3914.47	1.00	1.19	3.19	lin_low_fmri
σ	8.05	0.03	1.85	4155.37	1.00	4.98	11.74	lin_low_fmri
α	29.52	0.10	6.50	3906.07	1.00	17.38	43.34	lin_med_beh
β	0.48	0.01	0.71	4138.02	1.00	-0.92	1.92	lin_med_beh
σ	11.84	0.04	2.69	3839.43	1.00	7.56	17.31	lin_med_beh
α	29.52	0.10	6.50	3906.07	1.00	17.38	43.34	lin_med_beh
β	0.48	0.01	0.71	4138.02	1.00	-0.92	1.92	lin_med_beh
σ	11.84	0.04	2.69	3839.43	1.00	7.56	17.31	lin_med_beh
α	29.95	0.08	5.58	4410.20	1.00	18.81	41.05	lin_med_fmri
β	0.43	0.01	0.61	4388.21	1.00	-0.79	1.61	lin_med_fmri
σ	10.05	0.04	2.29	4172.20	1.00	6.10	14.40	lin_med_fmri
α	10.27	0.16	8.16	2711.77	1.00	-6.41	26.34	poly_med_beh
β[1]	7.26	0.05	2.35	2528.42	1.00	7.28	7.28	poly_med_beh
β[2]	-0.42	0.00	0.14	2675.59	1.00	9.38	9.38	poly_med_beh
σ	8.73	0.03	2.06	3616.42	1.00	5.44	12.93	poly_med_beh
α	13.62	0.13	6.77	2867.81	1.00	0.28	27.08	poly_med_fmri
β[1]	6.18	0.04	1.95	2662.75	1.00	9.67	9.67	poly_med_fmri
β[2]	-0.36	0.00	0.12	2838.70	1.00	5.98	5.98	poly_med_fmri
σ	7.43	0.03	1.77	3392.04	1.00	4.49	10.92	poly_med_fmri
α	62.07	0.06	4.14	4512.37	1.00	53.43	69.97	lin_high_beh
β	-3.59	0.01	0.46	4439.29	1.00	-4.45	-2.65	lin_high_beh
σ	7.53	0.02	1.65	4661.54	1.00	4.67	10.74	lin_high_beh
α	54.33	0.06	3.78	3982.86	1.00	46.87	61.94	lin_high_fmri
β	-2.63	0.01	0.41	3935.79	1.00	-3.42	-1.76	lin_high_fmri
σ	6.70	0.02	1.49	4782.92	1.00	4.21	9.66	lin_high_fmri

Note. α: intercept, β: slope, σ: error. The model name indicates the type (linear vs. polynomial) intensity (low, med: medium, high), and sample (beh: behavioral, fmri);
n_eff: number of effective samples

Table A4. Results of linear mixed models on pain ratings (behavioral sample)

predictor	mean	se_mean	n_eff	Rhat	HPDI_min	HPDI_max
intercept	-33.13	0.08	589.01	1.01	-37.00	-29.42
trial	-0.19	0.00	8802.15	1.00	-0.29	-0.09
session	-1.38	0.00	8499.79	1.00	-1.64	-1.13
intensity	1.59	0.00	2804.69	1.00	1.55	1.64
IA_CP	-0.02	0.00	2781.57	1.00	-0.07	0.04
IA_CU	-0.07	0.00	3028.21	1.00	-0.13	-0.00
IA_PU	-0.04	0.00	2746.76	1.00	-0.11	0.02
subject_error	10.39	0.01	8036.51	1.00	8.45	12.53
noise	15.46	0.00	10478.41	1.00	15.15	15.76

Note. Pairwise interaction effects of conditions. n_eff: number of effective samples;
IA: interaction effect; U: unpredictable, C: controllable; P: predictable;
The first condition indicates the reference condition for the interaction effect.
Main effects are not meaningful if interactions are defined in the model.

Table A5. Results of linear mixed models on pain ratings (fmri sample)

predictor	mean	se_mean	n_eff	Rhat	HPDI_min	HPDI_max
intercept	-30.32	0.05	1244.23	1.00	-33.72	-26.94
trial	-0.40	0.00	10503.77	1.00	-0.50	-0.30
session	-0.36	0.00	9309.97	1.00	-0.60	-0.13
intensity	1.45	0.00	3046.05	1.00	1.40	1.49
IA_CP	-0.08	0.00	3476.59	1.00	-0.14	-0.02
IA_CU	-0.29	0.00	3368.49	1.00	-0.35	-0.23
IA_PU	-0.20	0.00	3080.84	1.00	-0.27	-0.14
subject_error	7.95	0.01	9553.99	1.00	6.49	9.54
noise	15.18	0.00	12770.01	1.00	14.88	15.47

Note. Pairwise interaction effects of conditions. n_eff: number of effective samples; IA: interaction effect; U: unpredictable, C: controllable; P: predictable; The first condition indicates the reference condition for the interaction effect. Main effects are not meaningful if interactions are defined in the model.

Table A6. Results of linear mixed models on standard deviations of pain ratings (behavioral sample)

predictor	mean	se_mean	n_eff	Rhat	HPDI_min	HPDI_max
intercept	9.47	0.01	6963.74	1.00	8.19	10.83
beta_UC	-2.45	0.00	15607.34	1.00	-3.57	-1.30
beta_UP	-2.09	0.00	16189.86	1.00	-3.29	-1.00
beta_CP	0.27	0.00	17474.73	1.00	-0.87	1.35
beta_low_med	4.91	0.00	15340.13	1.00	3.76	6.09
beta_low_high	1.84	0.00	15894.08	1.00	0.68	3.01
beta_med_high	-2.87	0.00	16010.91	1.00	-4.09	-1.76
subject_error	2.94	0.00	9652.42	1.00	2.19	3.74
noise	5.32	0.00	20729.85	1.00	4.97	5.68

Note. Pairwise effects of conditions and intensity levels. Fixed effect predictors: U: unpredictable, C: controllable; P: predictable; low: low intensity; med: medium intensity; high: high intensity. Random effect: subject_error; error term: noise. The first condition in braces indicates the reference condition/intensity.

Table A7. Results of linear mixed models on standard deviations of pain ratings (fmri sample)

	mean	se_mean	n_eff	Rhat	HPDI_min	HPDI_max
intercept	12.06	0.01	9968.29	1.00	10.93	13.17
beta_UC	-4.41	0.00	18069.93	1.00	-5.44	-3.36
beta_UP	-3.31	0.00	17610.12	1.00	-4.33	-2.29
beta_low_med	3.98	0.00	17626.36	1.00	2.96	5.02
beta_low_high	2.32	0.00	17334.42	1.00	1.32	3.38
subject_error	2.34	0.00	7324.10	1.00	1.69	3.01
noise	4.94	0.00	20180.26	1.00	4.63	5.27
beta_CP	0.98	0.00	18011.92	1.00	0.02	2.04
beta_med_high	-1.50	0.00	17098.70	1.00	-2.49	-0.46

Note. Pairwise effects of conditions and intensity levels. Fixed effect predictors: U: unpredictable, C: controllable; P: predictable; low: low intensity; med: medium intensity; high: high intensity. Random effect: subject_error; error term: noise. The first condition in braces indicates the reference condition/intensity.

Table A8. Pain ratings and Temperatures for all Samples

VAS	mean_temp (°C)	sd_temp (°C)	sample
0	40.93	4.25	behavioral
30	43.56	2.63	behavioral
50	45.31	1.66	behavioral
70	47.07	1.14	behavioral
100	49.76	2.05	behavioral
0	42.09	2.86	fmri
30	44.31	2.06	fmri
50	45.79	1.67	fmri
70	47.20	1.39	fmri
100	49.50	1.81	fmri

Table A9. Parameter recovery simulation settings

model variable	values for simulation
number of subjects	60
number of trials	15
number of runs	6
likelihood mean	mean $\in \{30, 50, 70\}$, sd = 1
prior mean controllable	$\in \{30, 50, 70\}$, sd = 15
prior mean predictable	$\in \{30, 50, 70\}$, sd = 15
prior mean unpredictable	$\in \{30, 50, 70\}$, sd = 15
h	mean = 0.5, sd = 0.2
posterior sd	mean = 10, sd = 5
prior sd controllable	mean = 10, sd = 5
prior sd predictable	mean = 10, sd = 5
α_u	mean = 0.5, sd = 0.2
α_c	mean = 0.5, sd = 0.2
α_p	mean = 0.5, sd = 0.2

Note. All simulation input value parameters were sampled from truncated normal distributions around the specified mean and standard deviation. For likelihood and prior means the distributions had a lower bound at 0 and an upper bound at 100. The other parameters were constrained to lie in the interval [0,1].

Figure A1. Parameter recovery results of the model with three α scaling parameters. The parameters highlighted in violet could not be recovered sufficiently well in relation to their importance for the model. Therefore, we could not proceed with the model with three scaling parameters (α_u , α_c, α_p).

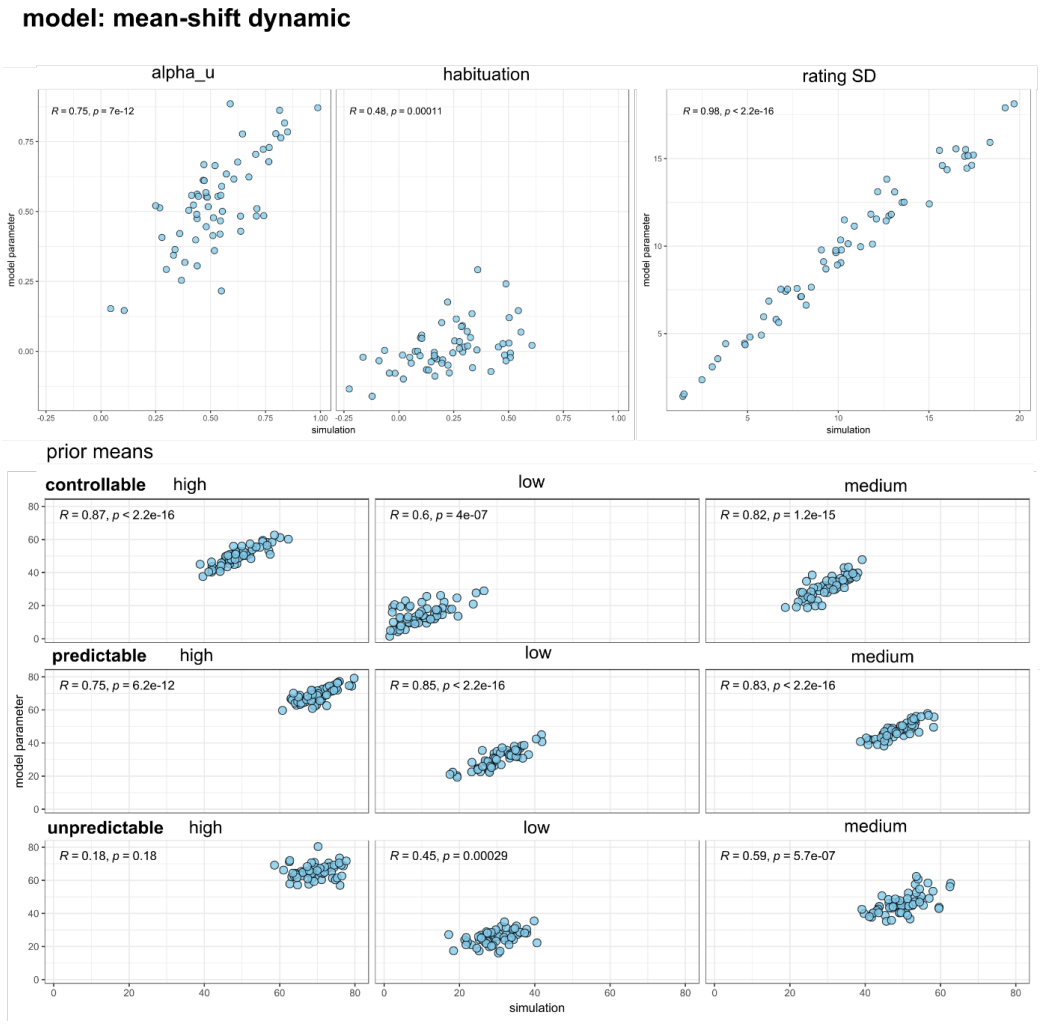

Figure A2. All parameter can be reasonably well recovered (significant correlation, visual inspection).

model: precision-change dynamic

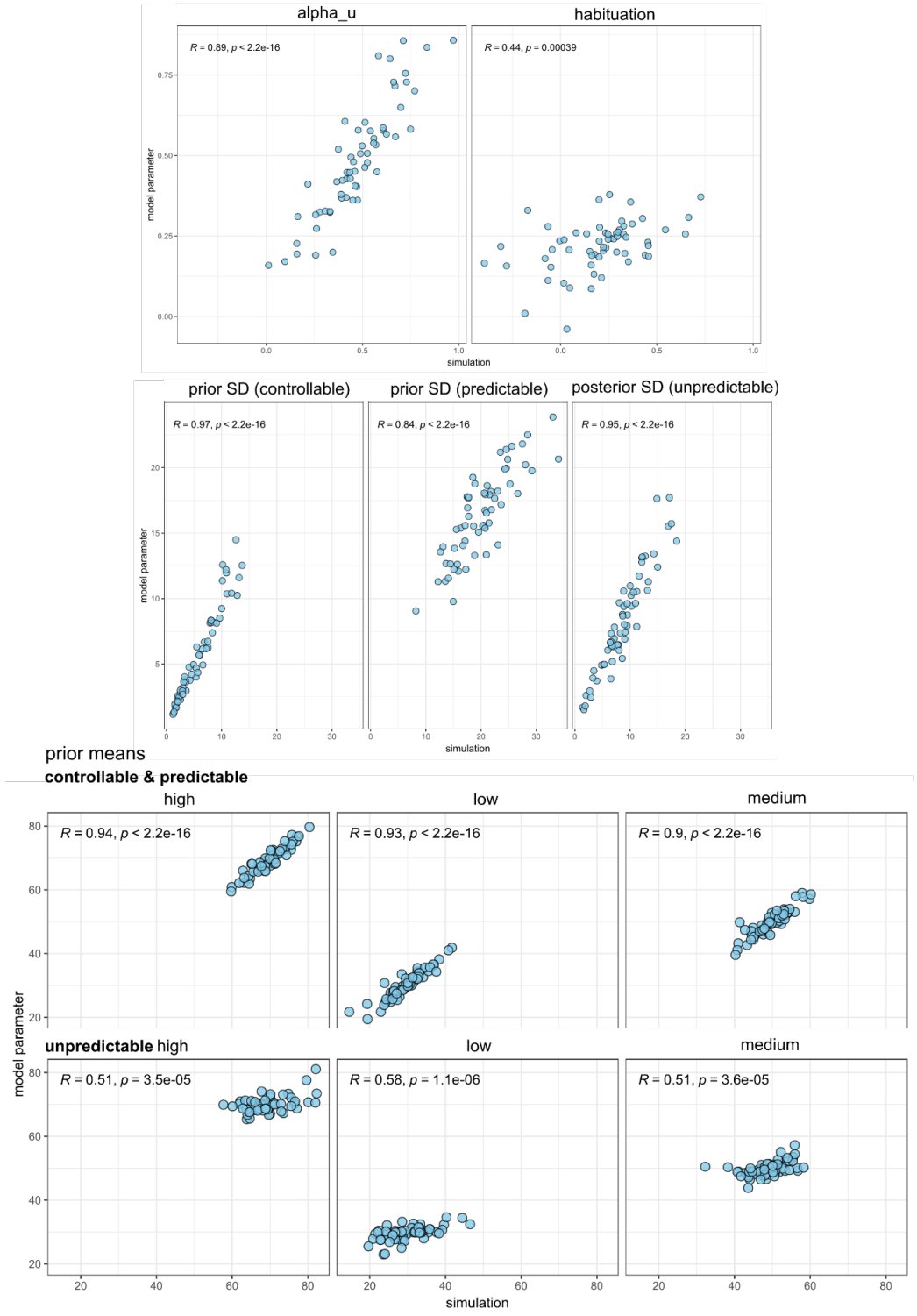

Figure A3. All parameter can be reasonably well recovered (significant correlation, visual inspection).

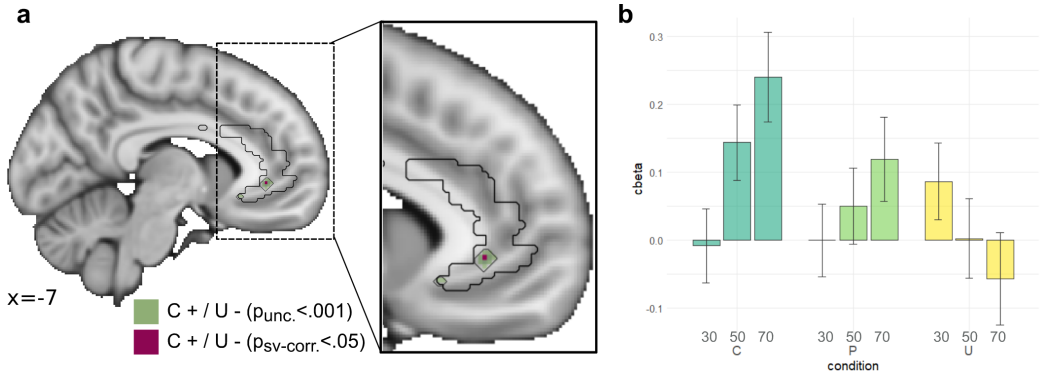

Figure A4. Interaction effect of condition and intensity **a)** Thresholded statistical maps for the interaction effect between controllable and unpredictable condition. Green areas indicate regions significant at uncorrected p <.001. Pink region shows the cluster that would be significant at p <.05 with small-volume FWE correction using the shown ACC mask. **b)** Parameter estimates of the significant interaction voxel, visualized with a 9-regressors model separately showing activity in the voxel = [-7.5, 37.5, -1.5] (T = 4.96, p (sv-corr) = .003) in the three conditions at low (30), medium (50) and high (70) stimulus intensity. While there is a positive scaling with intensity for controllable (C) and predictable (P) condition, activity decreases with intensity in the unpredictable (U) condition.

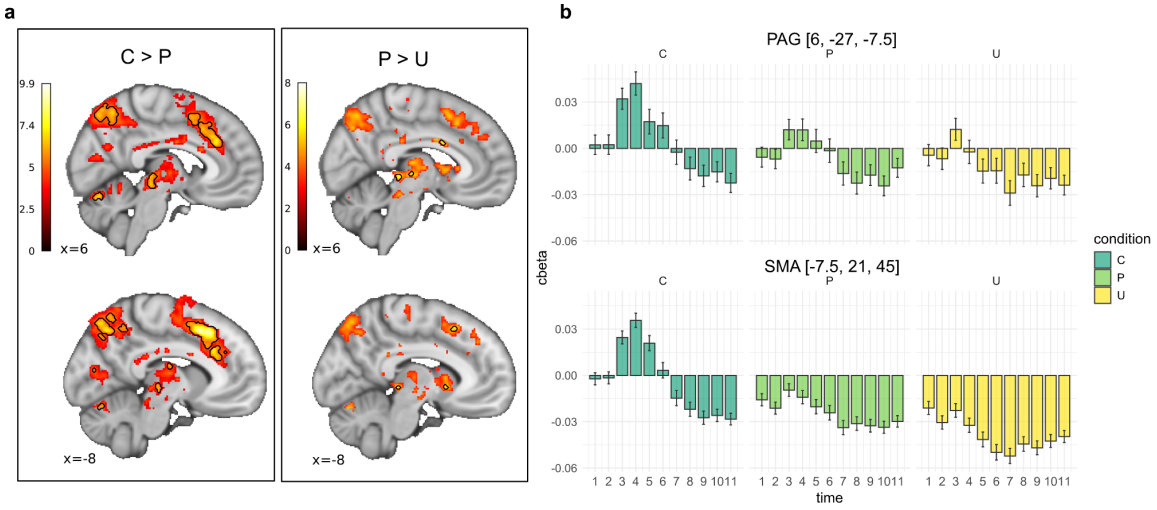

Figure A5. Effects of choice task on brain activity. **a)** Statistical maps of condition differences at task onset. Hot colors show statistical maps at uncorrected p <.001. Black contour lines indicate significant activation differences at p <.05, whole-brain FWE correction for multiple comparisons. Contrast are shown for higher activity in the controllable than predictable (C > P) and higher activity in the predictable than the unpredictable condition (P > U).**b)** Time courses derived from the FIR model starting at task onset and covering the time until stimulus onset (11 time bins of TE = 1.5s).

Appendix B

Table B1. Trait questionnaires

group	SWE	PCS	BIS	BAS	CAT	COP
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
control	30.11 (3.41)	20.19 (10.07)	2.92 (0.52)	3.14 (0.37)	1.35 (0.86)	3.43 (0.82)
yoked	29.40 (3.61)	19.23 (7.00)	2.92 (0.52)	3.03 (0.36)	1.23 (0.62)	3.39 (0.71)

Note. SWE: self-efficacy; PCS: pain catastrophizing; BIS: behavioral inhibition; BAS: behavioral activation; CAT: catastrophizing, COP: self-instruction active coping

Table B2. State questionnaires

group	PA		NA		STAI		STAXI	
	T1	T2	T1	T2	T1	T2	T1	T2
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
control	2.98 (0.52)	2.67 (0.72)	1.28 (0.41)	1.19 (0.43)	40.9 (4.08)	39.1 (4.32)	16.2 (4.02)	16.6 (4.13)
yoked	2.90 (0.58)	2.82 (0.76)	1.28 (0.31)	1.2 (0.36)	41.1 (4.22)	38.5 (5.03)	16.2 (3.44)	16.4 (3.60)

Note. PA: positive affect; NA: negative affect; STAI: state-trait anxiety inventory; STAXI: state-trait anger inventory; T1: before UCIT; T2: after UCIT.

Table B3. UCIT regression models

	Rating				
	pain	relief	control	PCS 5	PCS 12
	(1)	(2)	(3)	(4)	(5)
trial	−0.56***	−0.33***			
	(0.12)	(0.10)			
condition	−4.23	13.11***	16.04***	−0.31	6.71
	(4.03)	(3.72)	(4.76)	(5.72)	(5.50)
temp	2.98***				
	(0.48)				
pain_mean		0.18***			
		(0.04)			
pain_temp		−0.64			
		(0.43)			
trial:condition	0.58***	−0.66***			
	(0.17)	(0.14)			
Constant	−70.95***	52.79**	53.93***	22.97***	44.48***
	(21.44)	(17.59)	(3.76)	(3.97)	(3.81)
Observations	1,187	1,680	154	154	154
Log Likelihood	−4,810.75	−6,971.37	−694.37	−665.21	−687.41
Akaike Inf. Crit.	9,639.50	13,960.73	1,400.73	1,340.41	1,384.82
Bayesian Inf. Crit.	9,685.21	14,009.57	1,418.96	1,355.60	1,400.00
Note:					*p<0.05; **p<0.01; ***p<0.001

Table B4. Confidence in memory task relative to yoked group

	Dependent variable:
	value
control group false	−22.49***
	(4.95)
control group correct	21.00***
	(3.29)
Constant	73.01***
	(2.71)
Observations	169
Log Likelihood	−714.27
Akaike Inf. Crit.	1,440.53
Bayesian Inf. Crit.	1,459.31
Note:	*p<0.05; **p<0.01; ***p<0.001

Table B5. Test environment pain and relief ratings

	Rating		
	online	post	
	pain	pain	relief
	(1)	(2)	(3)
temp_pain	0.33	0.95	−0.71
	(0.52)	(0.56)	(0.55)
trial	0.07	0.38***	−0.43***
	(0.09)	(0.09)	(0.10)
condition	−0.12	−3.87	4.95
	(4.11)	(4.12)	(4.06)
trial:condition	−0.40**		
	(0.13)		
Constant	25.49	3.01	70.51**
	(22.47)	(23.36)	(21.75)
Observations	2,736	1,738	998
Log Likelihood	−11,927.68	−7,606.02	−4,266.47
Akaike Inf. Crit.	23,871.35	15,226.04	8,544.94
Bayesian Inf. Crit.	23,918.67	15,264.26	8,574.37
Note:			*p<0.05; **p<0.01; ***p<0.001

Table B6. Test environment behavioral measures (run)

	Dependent variable:				
	n_relief	n_goal	n_decoy	avg_distinct	n_switches
condition	−1.78	−2.09	−0.24	−0.02	1.65
	(1.07)	(1.09)	(0.62)	(0.32)	(1.11)
run	1.12	0.97	1.47***	0.13	−1.26*
	(0.60)	(0.63)	(0.44)	(0.13)	(0.55)
Constant	6.40***	6.45***	3.88***	5.30***	15.71***
	(1.16)	(1.21)	(0.78)	(0.29)	(1.13)
Observations	152	152	152	152	152
Log Likelihood	−454.68	−460.26	−391.11	−251.45	−451.91
Akaike Inf. Crit.	919.35	930.51	792.23	512.89	913.82
Bayesian Inf. Crit.	934.47	945.63	807.35	528.01	928.94
Note:					*p<0.05; **p<0.01; ***p<0.001

Table B7. Test environment behavioral measures (trial)

	Dependent variable:		
	n_state	n_unique_state	dur_escape
	(1)	(2)	(3)
condition	0.08	−0.02	0.52
	(0.41)	(0.32)	(0.43)
trial	−0.08***	−0.07***	−0.08***
	(0.01)	(0.01)	(0.01)
run	0.15	0.13	−0.62***
	(0.13)	(0.10)	(0.11)
Constant	6.64***	5.99***	8.06***
	(0.36)	(0.29)	(0.35)
Observations	3,040	3,040	3,040
Log Likelihood	−8,177.35	−7,604.02	−7,673.92
Akaike Inf. Crit.	16,366.69	15,220.05	15,359.85
Bayesian Inf. Crit.	16,402.81	15,256.16	15,395.97
Note:			*p<0.05; **p<0.01; ***p<0.001

Table B8. UCIT regression models with externality predictor

	Rating					
	pain	relief	control	PCS 5	PCS 12	
	(1)	(2)	(3)	(4)	(5)	(6)
trial	−0.56***	−0.33***				
	(0.12)	(0.10)				
condition	−4.29	13.10***	16.14***	−0.71	6.90	16.77***
	(4.04)	(3.74)	(4.81)	(5.70)	(5.52)	(2.79)
temp	2.97***					
	(0.49)					
pain_mean		0.18***				
		(0.04)				
pain_temp		−0.65				
		(0.44)				
EXT_CON	0.05	0.01	−0.12	0.50	−0.24	−0.04
	(0.25)	(0.21)	(0.32)	(0.36)	(0.35)	(0.21)
trial:condition	0.58***	−0.66***				
	(0.17)	(0.14)				
Constant	−72.79**	52.35**	58.81***	1.82	54.67***	74.79***
	(22.94)	(19.03)	(14.14)	(15.70)	(15.23)	(9.52)
Observations	1,187	1,680	154	154	154	154
Log Likelihood	−4,811.22	−6,972.01	−694.52	−664.35	−687.31	−650.52
Akaike Inf. Crit.	9,642.43	13,966.02	1,403.04	1,340.69	1,386.62	1,313.03
Bayesian Inf. Crit.	9,693.22	14,025.71	1,424.30	1,358.91	1,404.84	1,331.25

Note: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$

Table B9. UCIT regression models with internality predictor

	Rating					
	pain	relief	control	PCS 5	PCS 12	
trial	−0.56***	−0.33***				
	(0.12)	(0.10)				
condition	−4.17	13.80***	15.46**	1.09	6.70	16.96***
	(4.12)	(3.77)	(4.91)	(5.80)	(5.63)	(2.84)
temp	2.97***					
	(0.48)					
pain_mean		0.18***				
		(0.04)				
pain_temp		−0.69				
		(0.43)				
INT_CON	−0.02	−0.22	0.19	−0.45	0.004	−0.07
	(0.23)	(0.20)	(0.30)	(0.34)	(0.33)	(0.19)
trial:condition	0.58***	−0.66***				
	(0.17)	(0.14)				
Constant	−69.57*	68.36**	42.22*	50.90*	44.23*	77.25***
	(27.14)	(22.30)	(19.21)	(21.67)	(21.05)	(12.43)
Observations	1,187	1,680	154	154	154	154
Log Likelihood	−4,811.29	−6,971.44	−694.45	−664.50	−687.59	−650.56
Akaike Inf. Crit.	9,642.57	13,964.88	1,402.90	1,341.00	1,387.18	1,313.13
Bayesian Inf. Crit.	9,693.37	14,024.57	1,424.16	1,359.22	1,405.40	1,331.35

Note: *p<0.05; **p<0.01; ***p<0.001

Table B10. UCIT regression models with BDI predictor

	Rating					
	pain	relief	control	PCS 5	PCS 12	
trial	−0.56***	−0.33***				
	(0.12)	(0.10)				
condition	−4.18	13.20***	15.98***	−0.48	7.14	16.59***
	(4.07)	(3.76)	(4.79)	(5.75)	(5.43)	(2.72)
temp	2.98***					
	(0.48)					
pain_mean		0.18***				
		(0.04)				
pain_temp		−0.65				
		(0.43)				
BDI_sum	−0.05	−0.14	0.10	0.24	−0.62	0.21
	(0.26)	(0.22)	(0.34)	(0.38)	(0.36)	(0.21)
trial:condition	0.58***	−0.66***				
	(0.17)	(0.14)				
Constant	−70.60**	54.09**	53.15***	21.12***	49.29***	71.46***
	(21.59)	(17.74)	(4.59)	(4.96)	(4.68)	(3.38)
Observations	1,187	1,680	154	154	154	154
Log Likelihood	−4,811.18	−6,971.78	−694.50	−665.05	−686.03	−650.06
Akaike Inf. Crit.	9,642.36	13,965.56	1,402.99	1,342.10	1,384.05	1,312.11
Bayesian Inf. Crit.	9,693.15	14,025.26	1,424.25	1,360.32	1,402.28	1,330.33

Note: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$

Table B11. BDI and LC influence on pain ratings in test environment

	Dependent variable:					
	rating_pre			rating_post		
temp_pain	0.15	0.32	0.31	0.74	0.71	0.98
	(0.50)	(0.53)	(0.52)	(0.54)	(0.57)	(0.56)
trial	−0.12	−0.12	−0.12	0.38***	0.38***	0.38***
	(0.07)	(0.07)	(0.07)	(0.09)	(0.09)	(0.09)
condition	−5.07	−4.25	−4.90	−19.82	61.90	−0.53
	(3.62)	(3.87)	(3.79)	(22.76)	(32.87)	(6.06)
EXT_CON	0.69**			0.58		
	(0.23)			(0.41)		
INT_CON		−0.16			0.43	
		(0.23)			(0.34)	
BDI_sum			0.35			0.70
			(0.25)			(0.43)
condition:EXT_CON				0.37		
				(0.52)		
condition:INT_CON					−1.04*	
					(0.51)	
condition:BDI_sum						−0.44
						(0.56)
Constant	5.52	38.42	25.86	−13.38	−13.77	−3.59
	(22.78)	(27.15)	(22.38)	(27.88)	(29.71)	(23.83)
Observations	2,736	2,736	2,736	1,738	1,738	1,738
Log Likelihood	−11,927.38	−11,931.34	−11,930.57	−7,601.25	−7,604.21	−7,604.44
Akaike Inf. Crit.	23,870.75	23,878.68	23,877.13	15,220.50	15,226.42	15,226.89
Bayesian Inf. Crit.	23,918.06	23,925.99	23,924.45	15,269.64	15,275.56	15,276.03

Note: *p<0.05; **p<0.01; ***p<0.001

Table B12. BDI and LC influence on relief ratings in test environment

	Dependent variable:		
	rating_post		
	(1)	(2)	(3)
temp_pain	−0.65	−0.67	−0.67
	(0.56)	(0.55)	(0.56)
trial	−0.43***	−0.43***	−0.43***
	(0.10)	(0.10)	(0.10)
condition	33.34	−19.21	9.19
	(21.86)	(31.93)	(6.00)
EXT_CON	0.22		
	(0.39)		
condition:EXT_CON	−0.67		
	(0.51)		
INT_CON		−0.60	
		(0.31)	
condition:INT_CON		0.40	
		(0.50)	
BDI_sum			0.35
			(0.47)
condition:BDI_sum			−0.56
			(0.58)
Constant	58.78*	105.94***	66.35**
	(26.26)	(27.94)	(22.30)
Observations	998	998	998
Log Likelihood	−4,265.60	−4,264.80	−4,265.98
Akaike Inf. Crit.	8,549.19	8,547.61	8,549.96
Bayesian Inf. Crit.	8,593.34	8,591.76	8,594.11
Note:			*p<0.05; **p<0.01; ***p<0.001

Table B13. Externality influence on behavioral measures in test environment

	Dependent variable:				
	n_relief	n_goal	n_decoy	n_switches	n_state
condition	−16.69**	−16.01**	5.85	16.82**	3.37
	(5.59)	(5.77)	(3.41)	(5.88)	(2.27)
EXT_CON	−0.35***	−0.33**	0.12*	0.34**	0.04
	(0.10)	(0.10)	(0.06)	(0.10)	(0.04)
condition:EXT_CON	0.35**	0.33*	−0.14	−0.36**	−0.08
	(0.13)	(0.13)	(0.08)	(0.14)	(0.05)
Constant	22.72***	21.89***	0.95	−0.38	4.50**
	(4.27)	(4.40)	(2.69)	(4.50)	(1.73)
Observations	152	152	152	152	3,040
Log Likelihood	−453.37	−459.55	−394.78	−451.43	−8,204.70
Akaike Inf. Crit.	920.75	933.09	803.55	916.86	16,423.40
Bayesian Inf. Crit.	941.92	954.26	824.72	938.02	16,465.54
Note:					*p<0.05; **p<0.01; ***p<0.001

Table B14. Internality influence on behavioral measures in test environment

	Dependent variable:				
	n_relief	n_goal	n_decoy	n_switches	n_state
condition	5.40	2.73	−0.24	1.88	−2.19
	(8.35)	(8.58)	(0.63)	(1.13)	(3.25)
INT_CON	0.16	0.13	−0.0003	−0.08	−0.01
	(0.09)	(0.09)	(0.04)	(0.07)	(0.03)
condition:INT_CON	−0.12	−0.08			0.04
	(0.13)	(0.13)			(0.05)
Constant	−1.56	−0.24	6.11*	19.00***	6.64**
	(5.37)	(5.51)	(2.50)	(4.29)	(2.08)
Observations	152	152	152	152	3,040
Log Likelihood	−457.43	−463.29	−395.27	−454.57	−8,205.65
Akaike Inf. Crit.	928.86	940.58	802.55	921.15	16,425.31
Bayesian Inf. Crit.	950.03	961.75	820.69	939.29	16,467.45
Note:					*p<0.05; **p<0.01; ***p<0.001

Table B15. BDI influence on behavioral measures in test environment

	Dependent variable:				
	n_relief	n_goal	n_decoy	n_switches	n_state
condition	−4.03**	−2.00	−0.25	1.54	0.07
	(1.48)	(1.06)	(0.63)	(1.07)	(0.41)
BDI_sum	−0.35**	−0.16*	0.02	0.18**	0.01
	(0.11)	(0.07)	(0.04)	(0.07)	(0.03)
condition:BDI_sum	0.30*				
	(0.14)				
Constant	10.74***	9.15***	5.95***	12.39***	5.90***
	(1.17)	(0.98)	(0.88)	(1.08)	(0.35)
Observations	152	152	152	152	3,040
Log Likelihood	−453.81	−460.84	−395.10	−452.03	−8,203.64
Akaike Inf. Crit.	921.63	933.68	802.19	916.06	16,419.29
Bayesian Inf. Crit.	942.80	951.83	820.34	934.20	16,455.40
Note:					*p<0.05; **p<0.01; ***p<0.001

Abstract

Pain is an important information signal that protects bodily integrity by changing behavior in reaction to the environment. If the environment changes in accordance with an organism's intentions, it is perceived as controllable. This thesis discusses evidence regarding the influence of perceived control on pain perception. It contributes to the understanding of pain as a percept that is placed between sensory and emotional experiences, shows how environmental factors can change this percept and how consolidated beliefs about control influence outcomes of aversive experiences. Besides an extensive review of the literature about the behavioral and neuronal effects of control on pain, I conducted two empirical studies to measure the effects of control over thermal heat-pain. The first study followed a rather methodological aim of disentangling the effects of predictability and controllability on neural processing of pain. The second study investigated effects of uncontrollable pain on perception and subsequent learning. Results of the studies show that because control increases expectation precision regarding pain and its informational value, pain perception under control is biased towards the extremes of possible outcomes. That implies that pain of high intensity is perceived as more painful, and relief, or pain of lower intensity is perceived as less painful in a controllable environment. Furthermore, the neural results show overlapping patterns of controllability with predictability in salience processing regions, like the anterior insula and the anterior cingulate cortex. Importantly, controllability specifically attenuated activity in the periaqueductal gray and the supplementary motor area. Additionally, the second study showed that effects of uncontrollable pain on subsequent learning depend on general beliefs about control, resulting in less goal-directed behavior. Taken together, this thesis contributes to the improvements of future studies in the field and helps to understand the complexity of the interplay between descending pain modulation, control, and expectations.

Zusammenfassung

Schmerz ist ein wichtiges Informationssignal des Körpers, um dessen Integrität durch Verhaltensänderungen in Reaktion auf die Umgebung zu sichern. Eine Umgebung wird als kontrollierbar empfunden, wenn sie sich entsprechend den Intentionen eines Organismus verändert. Die vorliegende Arbeit diskutiert Evidenz zum Einfluss von Kontrolle auf Schmerz. Dabei platziert sie die Wahrnehmung von Schmerz zwischen purer Sensorik und Emotion. Zusätzlich zu einer umfassenden Darstellung der Literatur zu den Effekten von Kontrolle auf Schmerz und dessen neuronale Verarbeitung, habe ich im Rahmen dieser Arbeit zwei empirische Studien durchgeführt, die untersuchten, wie sich Kontrolle auf die Wahrnehmung von Hitzeschmerz auswirkt. Die erste Studie folgte dabei dem methodischen Ziel die Effekte von Vorhersagbarkeit und Kontrolle auf die neuronale Verarbeitung von Schmerz zu trennen. Die zweite Studie untersuchte die Effekte von unkontrollierbaren Schmerz auf Wahrnehmung und anschließende Veränderungen des Lernverhalten. Die Ergebnisse zeigen, dass durch Kontrolle sowohl Schmerz, als auch eine relative Schmerzlinderung als intensiver empfunden werden kann. Dies wird vermittelt über erhöhte Erwartungspräzision und Informationswert von Schmerz in einer kontrollierbaren Umgebung. Darüber hinaus zeigen sich große Gemeinsamkeiten in den neuronalen Verarbeitungsmustern von kontrollierbaren und perfekt vorhersagbaren Schmerzreizen. Dies äußert sich als Aktivitätsreduktion in Regionen des Salienznetzwerks, beispielsweise in der anterioren Insula und dem anterioren Cingulum. Kontrolle über die Schmerzintensität verringerte zusätzlich die Aktivität im periaquäduktalen Grau und dem supplementären motorischen Areal. Die zweite Studie zeigte, dass die Auswirkungen von einer unkontrollierbaren Schmerzerfahrung auf darauffolgendes Lernverhalten von allgemeinen Kontrollüberzeugungen abhängen. Eine stärkere Wahrnehmung von externen Einflussfaktoren auf Lebensereignisse führte dabei zu weniger zielgerichtetem Verhalten.

Alles in allem trägt diese Arbeit dazu bei, zukünftige Studien durch adäquate Kontrollbedingungen zu verbessern sowie das Verständnis des komplexen Zusammenspiels von Schmerzwahrnehmung, Kontrolle und Erwartungen zu erhöhen.

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Lebenslauf entfällt aus datenschutzrechtlichen Gründen

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, 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. Das gilt insbesondere auch für alle Informationen aus Internetquellen. Soweit beim Verfassen der Dissertation KI-basierte Tools („Chatbots“) verwendet wurden, versichere ich ausdrücklich, den daraus generierten Anteil deutlich kenntlich gemacht zu haben. Die „Stellungnahme des Präsidiums der Deutschen Forschungsgemeinschaft (DFG) zum Einfluss generativer Modelle für die Text- und Bilderstellung auf die Wissenschaften und das Förderhandeln der DFG“ aus September 2023 wurde dabei beachtet. Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe. Ich erkläre mich damit einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

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