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Psychobiological mechanisms of endogenous pain modulation by pain relief as reward

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LIST OF ABBREVIATIONS

ACC	*anterior cingulate cortex*
pgACC	*pregenual anterior cingulate cortex*
ANOVA	*analysis of variance*
BDI-II	*Beck Depression Inventory II*
BOLD	*blood oxygen level dependent*
CBP	*patients with chronic back pain*
CompCor	*component-based noise correction*
aCompCor	*anatomical component-based noise correction*
tCompCor	*temporal component-based noise correction*
CPP	*conditioned place preferences*
CSF	*cerebrospinal fluid*
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders IV*
ELPD	*expected log pointwise predictive density*
EPI	*echo-planar imaging*
FD	*framewise displacement*
FM	*patients with fibromyalgia*
GM	*gray-matter*
HC	*healthy controls*
HDI	*highest density interval*
MPI	*Multidimensional Pain Inventory*
MRI	*magnetic resonance imaging*
fMRI	*functional magnetic resonance imaging*
NAcc	*Nucleus Accumbens*
NISS	*Need Inventory of Sensation Seeking*
AR	*subscale Avoidance of Rest*
NS	*subscale Need for Stimulation*
OFC	*orbitofrontal cortex*
PAG	*periaqueductal grey*
PANAS	*Positive And Negative Affect Scale*
RL	*reinforcement learning*

RT	*response times*
SAM	*Self-Assessment Manikin*
SCID	*Structured Clinical Interview for DSM-IV*
SCL-90-R	*Symptom Check-List-90-R*
SD	*standard deviation*
STAI	*State-Trait Anxiety Inventory*
TE	*echo time*
TR	*repetition time*
VAS	*visual analogue scales*
vmPFC	*ventromedial prefrontal cortex*
VTA	*ventral tegmental area*
WM	*white-matter*

1 INTRODUCTION

Pain relief is much more than the reduction of pain. Pain is a fundamental and almost ubiquitous experience that is a prime example of an aversive event. Just as pain is aversive, pain relief is a rewarding and pleasurable experience. Despite its unpleasant nature, we need pain – at least acute pain – for survival and well-being, because pain creates the urge to escape and avoid harm. Often neglected, this motivation to escape pain is crucially promoted by the pleasure of pain relief. There is only a small body of research on the psychobiological mechanisms of pain relief that does not account adequately for this important function. In particular, the function of pain relief as reward and its role in learning by negative reinforcement have only been studied rarely and mechanisms are poorly understood yet.

This dissertation comprises two experimental studies to similar but still clearly distinct research questions. For this reason and for the ease of reading, this dissertation starts with an overview of the general topic of pain and mechanisms associated with endogenous modulation of pain. Comprehensive current theoretical perspectives of endogenous pain modulation are described that reflect the present state of the art. Based on this overarching theoretical background, the research questions addressed in the two studies are described more specifically and the two studies are presented. The aim of these two studies was to deepen the understanding of the mechanisms underlying pain relief as reward with a focus on neurochemical mechanisms (study 1), and neural correlates in terms of brain activations and potential alterations in patients suffering from chronic pain compared to healthy individuals (study 2). In addition to the specific discussion of the results of each study, finally, a general discussion integrates these results into the existing literature and outlines implications and perspectives of the findings in an overarching manner.

1.1 Acute and chronic pain

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain, IASP; Loeser & Treede, 2008). This definition not only highlights pain as a sensory and hedonic experience, but it also emphasizes the essential functions of acute pain in protecting an organism and encouraging rest in injured or damaged states. Thus, pain is highly relevant for survival by constituting an alarm system that activates nocifensive reflexes like withdrawal, prepares for responding to pain by activating autonomous functions, and guides our behavior based on learned predictions (Navratilova, Atcherley, et al., 2015; Seymour, 2019).

In contrast to acute pain, chronic pain, i.e. pain lasting longer than three months (Treede et al., 2019), loses this function as an alarm system. Moreover, chronic pain is characterized by disproportionally augmented emotional-motivational perception relative to sensory-discriminative aspects (Lethem et al., 1983). As a result, protective behaviors become dysfunctional. For example, patients with pain tend to show strongly increased and disproportional avoidance behavior. Such exaggerated avoidance behavior, although in the acute state it may help to support rest for recovery, can worsen pain and may result in anhedonia, aggravating long-term emotional distress (Borsook et al., 2016). Moreover, chronic pain patients often show dysfunctional attempts to gain relief from pain, resulting in maladaptive coping strategies, for example excessive resting or abuse of analgesics. Such maladaptive strategies create a vicious circle with facilitation of pain and loss of functioning (such as impaired coping with everyday life or muscle deconditioning) in the long term (Flor, Birbaumer, et al., 1990; Fordyce, 1982).

Individuals suffering from chronic pain often show comorbid mental disorders (Ohayon & Stingl, 2012) and largely reduced quality of life (Joustra et al., 2015). Especially, affective and anxiety disorders are common in patients with chronic pain (Castro et al., 2009). Chronic pain is also associated with increased anhedonia, which is at least partially independent of depression (Garland et al., 2020). Such comorbidities highlight the close relation between chronic pain and altered emotional as well as motivational

states (Bushnell et al., 2013). Not surprising, chronic pain also constitutes a significant burden for society by challenging healthcare systems and causing high socioeconomic costs (Rask et al., 2017). For example, in Germany chronic pain generates approx. 38 billion Euro health related costs every year, with only a quarter of these costs being caused by direct costs for medical services (German Pain Society [Deutsche Schmerzgesellschaft], https://www.dgss.org/patienteninformationen/herausforderung-schmerz/). Estimates for the prevalence of chronic pain in the German population range from 3.5-25 % (Häuser et al., 2013) depending on the exact definition of chronic pain. Despite an enormous increase in our knowledge on mechanisms of nociception and pain processing in the last years, the pathogenetic mechanisms of chronic pain, in particular non-specific or primary chronic pain (World Health Organization, 2019), remain poorly understood. Due to this lack of understanding, pain treatment is typically only symptom-oriented and lacks efficacy. In fact, effect sizes for therapy of chronic pain conditions are small and patients often do not report persistent pain relief (Gatchel et al., 2014).

1.2 Pain and reward

Pain perception is not static. Instead the perception of pain adapts very dynamically to a multitude of factors such as biological, environmental, homeostatic, emotional, and motivational influences. This specific feature of the pain system fulfils the purpose of pain to function optimally as a warning and alarm system. With that pain not only signals potential harm, but adapts the urgency of such alarms to external and internal conditions to optimize behavioral outcomes including decision making. One specific factor that has a major effect on pain perception is the prospect and the reception of reward. As pleasurable stimuli that induce approach behavior, rewards are emotionally and motivationally opposite to pain. Maybe because of this, reward can strongly modulate how pain is perceived.

1.2.1 Endogenous modulation of pain perception by rewarding stimuli

A reward is defined as a stimulus that an individual will work for to achieve it. In contrast, a punishment is a stimulus that an individual will try to avoid. Accordingly,

receiving the respective stimulus elicits pleasure in the case of a reward, but is aversive when a punishment is received. Pain is a prototypic punishing stimulus: it induces a strong motivation to avoid it and a negative hedonic feeling when it cannot be avoided. Thus, from a motivational perspective pain and reward can be conceptualized as the opposite ends of a continuum. Reward and pain both guide behavior in order to optimize well-being by balancing homeostatic needs of an organism (Leknes & Tracey, 2008).

Specifically, pain has been described as a deviance from homeostatic balance that elicits the motivation to restore the bodily equilibrium in a comparable manner to other homeostatic drives such as temperature, hunger, or thirst (Craig, 2003). Similarly, rewards typically serve the purpose of maintaining or reinstating homeostasis. Whether a specific stimulus is experienced as rewarding depends on the current state of an individual. For example, being thirsty increases the motivational drive to drink and the otherwise neutral taste of water is highly appreciated. Hence, the motivational drive and the hedonic value associated with a specific stimulus depend on the current needs of the organism. Accordingly, studies have shown, for example, that the pleasantness of foods decreases with increasing saturation (Kringelbach et al., 2003; Small et al., 2001) and warm temperatures are perceived as more pleasant in cold ambient temperatures compared to warm ambient temperatures (Cabanac et al., 1972; Mower, 1976). Similarly, even painful stimuli can be perceived as pleasant in case they indicate avoidance of relatively greater harm (Leknes et al., 2013).

The interesting observation that is common to these findings is that perception of a specific stimulus is not solely defined by the stimulus characteristics, but depends on the needs and the resulting motivation of an individual. Therefore, endogenous mechanisms modulate the hedonic experience of a stimulus depending on the current state of the organism to convey the subjective utility (Buckland et al., 2015; Kurnianingsih & Mullette-Gillman, 2016). This becomes especially evident when envisaging situations in which attracting and repelling motivators are present at the same time. For example, depending on the current state it might be favorable to endure a certain pain to obtain a relatively more important appetitive stimulus (e.g. food) or to endure hunger when it appears more important to escape from a painful situation. In

such situations, the subjective utility of avoiding or achieving opposing attractors might interact and mutually affect each other. Indeed, endogenous modulation of pain perception when pleasant stimuli are present at the same time has been shown for a number of appetitive stimuli such as palatable food (Foo & Mason, 2009; Zmarzty et al., 1997), pleasant odors (Villemure et al., 2003; Villemure & Bushnell, 2009), music (Roy et al., 2008; Zhao & Chen, 2009), erotic images (men) (Meagher et al., 2001), and sexual behavior (animals) (Forsberg et al., 1987). Rhudy et al. (2005, 2006) showed that pleasant emotions induced by pictures decreased perception of pain while unpleasant emotions resulted in enhanced pain perception. Endogenous pain modulation can also be induced by monetary rewards and losses (Becker, Gandhi, et al., 2013; Becker, Gandhi, Pomares, et al., 2017), pointing to a specific role of the reward valuation system, as money has no direct effect on the homeostatic state. In a choice task with concurrent appetitive and aversive outcomes, Talmi et al. (2009) showed that when a monetary reward can only be achieved at the cost of pain, the probability to accept the pain is a function of the amount of money that can be obtained, implying an interactive (compared to additive) valuation process of the combined benefit. While the effect of this valuation process on pain was not assessed in this study, Becker, Gandhi, Chen, et al. (2017) showed that endogenous pain inhibition induced by monetary wins is stronger, the larger the motivational conflict. That is, participants that assigned a higher subjective utility to obtaining money relative to avoiding pain, and therefore had a stronger motivational conflict when receiving pain and money, showed stronger pain inhibition. These results show that indeed the perception of pain can be modulated by the interaction with rewarding stimuli. Moreover, the association of subjective utility and pain inhibition suggests that endogenous modulation is involved in balancing motivational drives in conflicting situations by modulating the pain perception and the associated motivational drive.

1.2.2 Motivation-decision model of pain

Endogenous pain modulatory effects in motivational conflicts are more formally described in the influential motivation-decision model of pain (Fields, 2006, 2018). According to this model, an unconscious process that integrates information about the

homeostatic state of the individual, nociceptive and other sensory input, and the evaluation of potential rewards and threats, precedes conscious perception of pain. In case of conflicting motivations (e.g. avoiding pain or gaining a reward), pain is inhibited according to the model if the decision is to respond to the reward, or facilitated, if the decision is to respond to the pain. Based on the result of the evaluation process, top-down modulatory processes control nociceptive upstream from the spinal cord via opioidergic ON- and OFF-cells in the periaqueductal grey (PAG), dorsolateral pons, and rostral ventromedial medulla (RVM; Fields, 2004, 2007). Such bidirectional control of incoming nociceptive signals allows shaping pain perception to support behavior that best serves survival and well-being. In other words, anything that in a given situation is perceived as more important for survival and well-being than responding to pain can induce pain inhibiting effects. In contrast, in situations in which escape or avoidance is prioritized, endogenous pain facilitation will occur. For example, response to pain is inhibited when a threatening event requires immediate actions that interfere with the response to the noxious stimulus (Fanselow, 1986). Pain inhibiting effects of rewards have been shown in animals (Dum & Herz, 1984), but also in humans, as described above (Becker, Gandhi, et al., 2013; Becker, Gandhi, Pomares, et al., 2017).

However, for beneficial decisions not only the actual presence of conflicting motivations is important. In an extension of the motivation-decision model, Fields (2018) emphasized that any cue that predicts a potential reward or threat can have similar effects on the modulation of nociceptive transmission. Hence, the expectation of a reward is assumed to inhibit pain perception and other pain related responses. The most prominent example for the effect of expectations is the pain inhibitory effect of placebo treatment. Here, pain inhibition can be conceptualized as a reward that is predicted by the placebo (Seymour & Dolan, 2013). Placebo effects have been shown to be opioid sensitive and to activate brain areas involved in descending control of nociceptive transmission as described by motivation-decision model (Eippert, Bingel, et al., 2009; Wager et al., 2007).

Given that nociceptive input signals actual or potential tissue damage, pain itself and any changes of pain intensity can also serve as predictive cues (Fields, 2018). The pain of an acute injury often predicts prolonged and sometimes even more intense pain

before recovery. In contrast, a decrease in nociceptive input predicts reduced threat of tissue damage (Fields, 2018). Indeed, it has been shown that relatively small reductions in noxious stimulation can lead to a disproportionally strong reduction in pain perception (a phenomenon that has been termed “offset analgesia”; Grill & Coghill, 2002; Yelle et al., 2008, 2009). Interestingly, the opposite effect, that is, a disproportional increase in perceived pain intensity following a small increase in noxious stimulation has also been shown (Alter et al., 2020).

1.2.3 Pain relief as reward

The above-described findings suggest that endogenous pain modulation may amplify changes in pain perception even in absence of a motivational conflict but with the anticipation of reward. Nonetheless, it is conceivable that such pain modulation by anticipated reward supports the selection of beneficial behavior in line with the predictions of the motivation-decision model of pain (i.e. avoidance or escape in the case of an increase and relief seeking in case of a reduction of nociceptive input). One such anticipated reward in the absence of a motivational conflict might be pain relief when being in pain. Although it seems to be trivial that pain relief is an important goal when in pain, the way relief acts as a signal for altering subsequent behavior has not been investigated often. It has been shown that higher pain intensity induces stronger perceived relief (Fust et al., 2020). Further, pain relief is not only characterized by the physical reduction in stimulus intensity but is also perceived as pleasant, indicating its rewarding properties (Leknes et al., 2008). However, considering the predictive value of a decrease in noxious input, the prospect of pain relief when being in pain should specifically mediate endogenous pain modulation in case that the reception of pain relief is bound to an active decision process. Findings of Becker et al. (2015) corroborate this assumption by showing that pain relief that was received after active decision making in a motivated state increased the perception of pain relief compared to a mere reduction in pain intensity (passive). Similar to placebo effects, the chance to achieve relief enhanced the perceptual pain modulation. While one advantage of such inhibitory effects may be to increase the salience of the relief to favor related actions over alternative motives, increased relief might also promote learning of actions

that can lead to pain relief in the future. In this perspective, the informational value of pain relief as a learning signal is emphasized (Seymour, 2019) and with that the importance of negative reinforcement by pain relief. In humans, it has been shown that negative reinforcement by pain relief can induce perceptual sensitization (Becker et al., 2008, 2011). Direct evidence for operant conditioning of motivated behavior by pain relief comes from studies in animals (Navratilova et al., 2012; Navratilova, Xie, et al., 2015).

1.2.4 Neurobiological correlates of pain and reward

The assumption that common brain circuits integrate motivational aspects of both pain and reward is supported by findings showing overlapping neurobiological substrates in terms of involved anatomical structures and neurotransmitter systems (Leknes & Tracey, 2008). Specifically, the neurotransmitters dopamine and endogenous opioids have essential roles for the processing of pain as well as rewards. In addition, several brain areas that are involved in the processing of pain have also been implicated in the context of rewards. These areas include the amygdala, prefrontal cortex, insula, and anterior cingulate cortex (ACC). Although this suggests that these brain systems are involved in the interaction of pain and reward, the mechanisms of how this results in pain-modulatory effects are still not fully understood (Becker et al., 2012).

According to the motivation-decision model of pain, the brain circuit, that is thought to mediate pain modulatory effects based on the combined evaluation of current needs and available rewards and threats, consists of various structures including the prefrontal cortex, the hypothalamus, and the amygdala which provide input for the brainstem nuclei that exert control on relay neurons in the dorsal horn of the spinal cord (Fields, 2007). The decision process that integrates various sources of information is thought to be mediated by the dopaminergic mesolimbic pathway, with an important role of midbrain dopamine neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAcc) in the ventral striatum (Fields, 2006).

1.2.4.1 Dopamine and endogenous opioids in pain and reward processing

Both the neurotransmitters dopamine and endogenous opioids are known to be implicated in the processing of pain and reward, but their functions differ. Pain inhibitory effects of the activation of opioid receptors are well known (Bagley & Ingram, 2020). Release of endogenous opioids has been related to a reduction of pain sensitivity (Pasternak, 2005; Przewłocki et al., 1999). Further, various studies have shown pain modulating effects of endogenous opioids in several types of endogenous pain modulation in humans. For example, using positron emission tomography (PET) activation of μ-opioid receptors was shown during placebo analgesia and this activation was associated with perceived pain reductions due to the placebo manipulation (Scott et al., 2008; Wager et al., 2007). Scott et al. (2008) also showed that nocebo effects, that is, an increase of perceived pain following a corresponding expectation, were associated with a decrease of opioid release. In line with this, blocking opioid receptors was found to reduce effects of a placebo treatment (Eippert, Bingel, et al., 2009). In addition, endogenous inhibition of the nociceptive flexion reflex by concurrent noxious heat stimulation was shown to be reversible using an opioid receptor antagonist (Willer et al., 1990). Interestingly, endogenous opioids also seem to be involved in the perception of pain relief, which could be shown to be reduced by an opioid receptor antagonist (Sirucek et al., 2021). Here, blockade of opioidergic transmission using naltrexone not only reduced the perceived relief after the offset of a noxious heat stimulation, but also the perceived pleasantness associated with that relief.

This points to a striking similarity to the processing of rewards, where endogenous opioids have been associated with the hedonic experience of rewards (“liking”) (Berridge et al., 2009; Smith et al., 2011; Tindell et al., 2005). Microinjections of opioid agonists in specific “hedonic hotspots” in the NAcc enhanced liking responses to sweet taste rewards in rats, an effect that was not observed outside these areas (Peciña & Berridge, 2005; Smith & Berridge, 2005, 2007). Furthermore, in both, humans and animals, food pleasantness is reduced by opioid antagonists (Fantino et al., 1986;

Kelley et al., 1996; Smith & Berridge, 2007; Yeomans & Gray, 1996; Yeomans & Wright, 1991).

In the context of reward processing, dopamine is known for its role in signaling reward expectations and related prediction errors (Glimcher, 2011; Schultz, 2016). Midbrain dopamine neurons increase their firing rates in response to unexpected rewards (positive prediction error). However, once an animal has learned that a specific cue predicts a reward to come, dopaminergic neurons increase firing in response to the cue, but decrease their firing rate when an expected reward does not occur (negative prediction error; Glimcher, 2011). Dopaminergic activity in response to unexpected rewards, that shifts to a response to the cue when this reliably predicts a reward, can be described by so called temporal difference (TD) models (Sutton & Barto, 1998), a class of computational models that describe how reward expectations are acquired through reinforcement learning. The fact that activity of dopaminergic neurons closely reflects prediction error signals as predicted by these models supports the assumption that dopamine plays a crucial role in shaping reward related behavior.

However, some dopaminergic neurons also increase their activity in response to cues predicting both rewarding and aversive stimuli, suggesting that they reflect the motivational value of the cues instead of their valence (Matsumoto & Hikosaka, 2009). In line with this finding, Hamid et al. (2015) showed that relatively slow (“tonic”) changes in dopamine levels in the NAcc were associated with motivational vigor while phasic dopamine responses reflected the expected value of rewards. Some authors have argued that dopaminergic signaling indicates incentive salience (“wanting”) that is the motivational drive to approach or work for a reward (Berridge et al., 2009; Smith et al., 2011; Tindell et al., 2005). In line with this view, it has been shown that a lack of dopamine impairs motivation to seek reward (Cagniard, Balsam, et al., 2006) while increased dopamine enhances efforts to seek reward (Cagniard, Beeler, et al., 2006). However, dopaminergic activity related to the predictive value of a cue can be dissociated from dopaminergic activity related to motivational value (Mohebi et al., 2019; Saddoris et al., 2015). Accordingly, dopamine appears to play a crucial role in learning as well as in the motivational value of rewards.

In pain, dopamine has typically been assumed to have general antinociceptive effects (Hagelberg et al., 2003; Jarcho et al., 2012; Potvin et al., 2009). However, the picture of dopaminergic effects in pain processing appears to be more complicated (A. M. W. Taylor et al., 2016). Using a bidirectional pharmacological manipulation, Becker, Ceko, et al. (2013) found that neither increased nor decreased dopamine availability had an influence on thermal pain thresholds when compared to a placebo condition. Instead of assuming simple antinociceptive effects of dopamine, it is conceivable that dopamine instead modulates the motivation to avoid or to endure pain depending on the situational context. Supporting this assumption, Becker, Gandhi, et al. (2013) found that increasing dopamine availability can also enhance pain faciliatory effects of monetary losses on perceived pain with no effects on baseline pain sensitivity without monetary losses. Effects of dopamine on pain were only present when pain modulation occurred in a motivational conflict, and in that case enhanced perception of the more salient stimulus. Dopaminergic effects of motivation and incentive salience in pain fit the above described role of dopamine in processing of rewards.

In summary, dopamine and endogenous opioids appear to be involved in mediating motivational and hedonic aspects, respectively, in the interaction of pain and reward. Based on the assumption that similar mechanisms mediate pain modulation in presence of a motivational conflict but also enhance motivation for pain related behavior in absence of a conflict, dopamine and endogenous opioids are also candidates for mediating the endogenous modulation of pain that underlies rewarding pain relief.

1.2.4.2 Neural correlates of pain and reward interactions

Despite a large body of research that shows overlapping brain regions implicated in the processing of pain and reward (Leknes & Tracey, 2008), only a few studies have investigated neural correlates of an interaction between pain and reward directly. In healthy volunteers, Talmi et al. (2009) investigated neural correlates of the integration of monetary rewards that were associated with concurrent painful stimulation in a choice task. Using functional magnetic resonance imaging (fMRI), they found that activation in the ACC and the NAcc, that was positively related to the expected

probability of winning money, was attenuated by the expectation of pain. This paralleled findings on the behavioral level that indicated attenuated sensitivity to rewards (that is, with a high compared to a low probability of a concurrent painful stimulation higher monetary rewards were needed for a respective choice). Becker, Gandhi, Pomares, et al. (2017) found that the pain modulatory effect of monetary wins on pain perception was associated with activation in the orbitofrontal cortex (OFC). Interestingly, this activation in the OFC was correlated with activation in other brain regions, such as somatosensory cortex, insula, and ACC that are associated with pain processing (Apkarian et al., 2005).

Furthermore, several fMRI studies that investigated the effects of expectations on pain perception point to a mediator role of the pregenual anterior cingulate cortex (pgACC) in the modulation of perceived pain (Atlas et al., 2010; Leknes et al., 2013). This area has also been implicated in mediating placebo induced modulation of pain (Bingel et al., 2006; Eippert, Bingel, et al., 2009; Wager et al., 2007; Zubieta et al., 2005). Moreover, these studies also showed that placebo related activity is mediated by opioidergic neurotransmission and involves activation of descending control pathways including PAG and VTA (Eippert, Bingel, et al., 2009; Wager et al., 2007), but also activation in the NAcc, a key structure of the mesolimbic reward circuit (Wager et al., 2007; Zubieta et al., 2005). Activations in brainstem structures involved in descending pain control such as the PAG and the VTA have also been found during offset analgesia (Derbyshire & Osborn, 2009; Yelle et al., 2009). This finding might suggest that pain inhibitory effects during offset analgesia are mediated by the same descending pain inhibitory system as other kinds of pain modulation. However, one study that directly tested the hypothesis that offset analgesia is mediated by endogenous opioids found no effect of an opioid receptor antagonist on the magnitude of offset analgesia (Martucci et al., 2012). Evidence for an involvement of the reward circuitry comes from a study that used fMRI to compare brain activity during offset analgesia between pain patients and healthy controls: Zhang et al. (2018) found relatively higher activity in controls not only in areas associated with endogenous pain modulation, such as ACC and brainstem, but also in the medial prefrontal cortex and the NAcc.

While these results support the assumption that integrating competing motivations and relief related information is mediated by activations in midbrain reward and decision circuits and subsequent descending control of nociceptive input, it is less clear how the resultant endogenous pain modulation is involved in shaping behavior to optimally respond in a given situation.

1.3 Neural correlates of pain relief as reward

In a series of animal studies, it has been demonstrated that relief from ongoing pain induces conditioned behavior (T. King et al., 2009; Navratilova et al., 2012; Navratilova, Xie, et al., 2015). This was shown using a conditioned place preferences (CPP) paradigm in which rodents showed a preference for a chamber associated relief from ongoing pain induced by a drug (T. King et al., 2009). Importantly, animals that were not in pain did not show the same preference, indicating that this behavior was not induced by inherently rewarding effects of the drug, but elicited by rewarding effects of the pain relief. Interestingly, CPP induced by pain relief was associated with activation of the mesolimbic reward system: CPP in animal models of post-surgical pain and migraine was accompanied by activation dopaminergic cells in the ventral tegmental area and dopamine release in the NAcc (De Felice et al., 2013; Navratilova et al., 2012). Moreover, Navratilova, Xie et al. (2015) showed that negative reinforcement by pain relief and associated activation of dopaminergic cells in the NAcc depend on opioid signaling in the rostral ACC (Navratilova, Xie, et al., 2015), suggesting that both dopaminergic and opioidergic neurotransmission are involved in negative reinforcement by pain relief. Independent of a role as a reward, studies in humans have shown that pain relief is associated with activation in regions commonly found to be involved in processing of rewards (Gerber et al., 2014; Leknes et al., 2011). For example, increased activation in the NAcc, which is known for its central role in reinforcement learning (Schultz, 2016), has been found in response to (passive) pain offset (Baliki et al., 2010; Becerra et al., 2013; Becerra & Borsook, 2008). Further, an association of reinforcement by pain relief with activation in the ACC (Navratilova, Xie, et al., 2015) suggests that the affective component of the pain perception is closely

related to the motivational component. The ACC has been related to the perception of pain aversiveness (Rainville et al., 1997).

Specifically, Becker et al. (2015) showed that pain relief obtained in a motivated state increased perceives pain relief as compared to a mere (passive) reduction in pain intensity, confirming that rewarding pain relief engages endogenous pain inhibition. Interestingly, the magnitude of pain inhibition in this study was associated with participants' personality trait of novelty seeking, which has been associated with enhanced midbrain dopamine availability (Leyton et al., 2002; Savage et al., 2014; Zald et al., 2008). However, the specific neural mechanisms underlying the pain inhibitory effect of rewarding pain relief have not been investigated so far.

1.4 Neural correlates of impaired reward processing in chronic pain

Changes in how endogenous mechanisms control the translation of nociceptive input to perceived pain, and specifically the midbrain dopamine network have been related to affective symptoms in patients with chronic pain (Baliki & Apkarian, 2015; Mitsi & Zachariou, 2016). Specifically, impaired emotional decision making and altered fear related learning have been shown in patients with chronic pain (Apkarian et al., 2004; Meulders et al., 2015, 2018), but overall findings on reward processing in chronic pain are heterogenous (Kim et al., 2020; Martucci et al., 2018). Activation of the reward circuitry in response to passive pain onset and offset have been shown to be altered in patients with chronic pain (Baliki et al., 2010; Loggia et al., 2014). Further, functional connectivity between the NAcc and the medial prefrontal cortex has been shown to predict the transition of subacute to chronic back pain (Baliki et al., 2012). Such observations may suggest that pain related activations in the reward circuitry are affected in chronic pain, but the relation to changes in pain perception and pain related behavior is not clear. In addition, these studies did not investigate reward processing directly.

In general, impaired endogenous pain inhibition has been hypothesized to contribute to exaggerated pain perception in chronic pain (B. K. Taylor & Corder, 2014). As described above, expectations of pain and pain relief provide a link between the reward

and decision system and descending control of pain perception. A reduced magnitude of pain inhibition during offset analgesia has been shown in patients with chronic pain (Kobinata et al., 2017; S. Zhang, Li, et al., 2018). Specifically, Zhang et al. (2018) showed that healthy controls showed higher activation in the NAcc, medial prefrontal cortex, ACC, and brainstem during offset analgesia compared to patients with chronic pain. This is interesting because this suggests that indeed impaired responses in the reward circuitry are related to impaired endogenous pain inhibition. Specifically, in chronic pain, obtaining pain relief is much sought after and an attenuation of perceived pain relief when obtained might have consequences on relief related motivation and behavior. Yet, if impaired endogenous modulation in chronic pain has direct effects on relief seeking in chronic pain has not been investigated.

1.5 Summary and aim of the dissertation

Based on previous results that showed pain inhibitory effects of pain relief gained in a motivated state the aim of the studies presented in this thesis was to investigate reinforcement learning induced by pain relief as reward and its effects on perceptual modulation. Exploiting that fact that engaging in a gambling task induces a motivated state Becker et al. (2015) showed that winning pain relief induces pain inhibition resulting in lower perceived pain compared to a control condition in which pain relief was not bound to an active decision. Active decisions were operationalized in a wheel of fortune game in which participants could choose between two colors and would win pain relief if the wheel landed on the color they had chosen. In contrast, in a control condition the outcome of the game (pain relief or pain increase) was not bound to an active decision. This paradigm allows to assess endogenous modulation caused by the perceived controllability that is given by the influence on subsequent outcomes. However, in that previous study outcomes of the game choices were equally associated with chances to win pain relief. For the studies described in this dissertation, the experimental paradigm was extended by implementing a probabilistic reward schedule that provided the chance to learn reward contingencies based on pain relief and pain increases as outcomes of the wheel of fortune game. This modification of the experimental task allowed to test whether pain relief as reward is capable of

inducing reinforcement learning. In addition, using computational modelling of choice behavior in the relief seeking task allowed to specifically investigate how endogenous modulation supports reinforcement learning.

Two studies were implemented that focused on neurochemical underpinnings of the interaction of pain and reward (study 1) and brain activation associated with increased pain inhibition (study 2). Study 2 further had the aim to investigate a potential impairment of reward related pain inhibition in patients with chronic pain.

2 STUDY 1 - ENDOGENOUS MODULATION OF PAIN RELIEF: EVIDENCE FOR DOPAMINERGIC BUT NOT OPIOIDERGIC INVOLVEMENT[1]

2.1 Introduction Study 1

When we are in pain, our desire for pain relief and the pleasure of pain relief are universally appreciated. However, research into the state of pain has gained considerably more attention than that of relief. Theoretical perspectives on pain typically focus on its aversiveness, reflecting the powerful incentive to avoid harm wherever possible. Perceived pain is highly sensitive to the motivational context, with modulatory processes appearing to endogenously tune pain perception to help optimize the way in which it controls responses and action (Fields, 2018; Seymour, 2019). However if pain is ongoing, there is an equally potent new incentive to reduce or escape from it, in which pain relief arises as a strong positive motivational force and a reinforcement signal in its own right (Leknes, Brooks, Wiech, & Tracey, 2008; Becker, Gandhi, Kwan, Ahmed, & Schweinhardt, 2015). However, how relief acts as a signal for shaping behavior is less studied: in particular, it is not clear the extent to which the perception of relief is also sensitive to endogenous modulation; and if so, how such modulation is neurally mediated.

In general, endogenous modulation of pain involves a number of different processes mediated by distinct descending signaling pathways (Bannister, 2019). Opioid-based mechanisms are important for many of these. Work in rodents has shown that endogenous opioid activity in the anterior cingulate cortex is necessary and sufficient to induce the rewarding effects of relief from pain (Navratilova, Xie, et al., 2015). In humans, the perceived pleasantness and magnitude of pain relief has been shown to decrease with administration of the opioid antagonist naltrexone, confirming a role of opioids in pain relief perception (Sirucek et al., 2021). Other forms of endogenous

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modulation, such as the placebo effect, are also opioid-sensitive (Benedetti, 1996; Eippert, Bingel, et al., 2009; C. D. King et al., 2013). Alongside this, however, dopaminergic-based mechanisms also have a clear role. For instance conditioned place preference induced by pain relief is associated with activity in midbrain dopaminergic neurons (Navratilova et al., 2012; Navratilova, Xie, et al., 2015; Xie et al., 2014). In the case of primary rewards, dopamine is implicated in the active motivation to obtain reward ("wanting"), while endogenous opioids mediate the hedonic experience of reward ("liking"). (Barbano & Cador, 2006, 2007; Berridge et al., 2009; Sherdell et al., 2012; Smith et al., 2011; Tindell et al., 2005). However, the extent to which this distinction might hold for pain relief is not clear.

In theoretical models of pain motivation, endogenous modulation of pain is considered an action in its own right, with the pain system making active 'decisions' to tune incoming pain signals so as to optimize responding in a given situation (the '*Motivation Decision Model of Pain':* Fields, 2006, 2007, 2018). One example of this is in inhibition of pain of external rewards, which allows suppression of immediate nocifensive responses that could interfere with more important goals. Studies in humans indicate that this is dopamine sensitive (Becker, Gandhi, et al., 2013). But whether purely endogenous modulation of pain relief is dopamine sensitive is not known, not least because relief modulation is not well characterized to begin with. Evidence does exist that active pain relief-seeking, when compared to passive relief receipt, is associated with enhanced pain relief perception, and this phenomenon is associated with novelty-seeking traits (Becker et al., 2015). This would fit with information-processing accounts of endogenous modulation (Seymour, 2019), which propose that pain is modulated to optimize prospective control of behavior. Whether this is sensitive to opioidergic or dopaminergic (or both) signaling is not known.

The aim of the present study was therefore first to better characterize information processing aspects of relief motivation, and second to investigate the roles of dopaminergic and opioidergic signaling. We expected that pain relief would be modulated by the value of information it carries, as hence enhanced by i) active vs passive reception and thus controllability, since this reflects potential to exploit relief information; ii) unpredictability, since this reflects the extra information carried by surprising events, and iii) trait novelty-seeking, since this reflects individual information

sensitivity. At the same time, we aimed to identify the potential role of dopamine and opioids for each of these factors, in particular to explore whether increased dopamine availability would enhance endogenous pain relief under these conditions, and whether modulation could be reduced by blocking opioid receptors. Finally, we aimed to identify whether modulation of relief was also apparent in the explicit decisions that arise in probabilistic learning, to determine whether perception of relief can be dissociated from instrumental choice.

To test these hypotheses, we employed a previously developed wheel of fortune task utilizing relief of a tonic capsaicin-sensitive thermal pain stimulus as 'wins', and allowing to quantify endogenous pain inhibition induced by gaining pain relief in active versus passive conditions (Becker et al., 2015). To test the roles of dopamine and opioids, healthy volunteers ingested either a single dose of the dopamine precursor levodopa (150mg), the opioid antagonist naltrexone (50mg), or placebo in separate testing sessions (double-blinded, placebo controlled cross-over design). To allow also the assessment of reinforcement learning, a probabilistic reward schedule associated with the participants' choices in the wheel of fortune was implemented.

2.2 Results Study 1

2.2.1 Endogenous modulation of active pain relief seeking under placebo

To test whether playing the wheel of fortune induced endogenous pain inhibition by gaining pain relief during active (controllable) decision making, a test condition in which participants 'won' relief of a tonic thermal pain stimulus in the game was compared to a control condition with passive receipt of the same outcomes (Figure 1). As a further comparator the game included an opposite condition in which participants received *increases* of the thermal stimulation as punishment. This loss condition was also complemented by a passive condition involving receipt of the same nociceptive input.

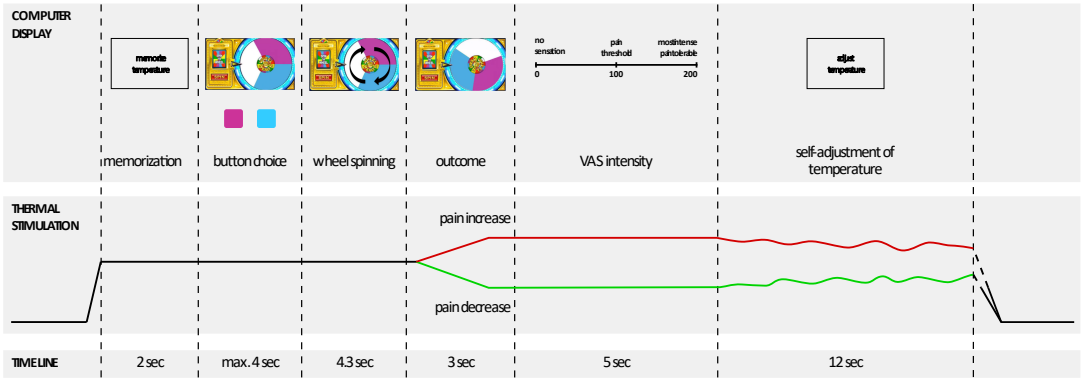

Figure 1: Time line of one trial with active decision making (test trials) of the wheel of fortune game. In each test session, one of the two colors (pink and blue) of the wheel was associated with a higher chance to win pain relief (counterbalanced across subjects and drug conditions). Pain relief (win) as outcome of the wheel of fortune game is depicted in green, pain increase (loss) in red. In passive control trials and neutral trials subjects did not play the game but had to press a black button after which the wheel started spinning and landed on a random position with no pointer on the wheel. Trials with active decision making were complemented by passive control trials without decision making but the same nociceptive input (control trials), resulting in the same number of pain increase and pain decrease trials as in the active condition. In neutral trials the temperature did not change during the outcome interval of the wheel. In all trial types, participants had to adjust the temperature to the memorized sensation at the beginning of the trial as an operationalization of a behavioral assessment of pain sensitization and habituation across the course of one trial. Adapted from (Becker et al., 2015).

2.2.1.1 Ratings of perceived pain

Replicating previous results, in the placebo (i.e. non-drug) condition participants rated the thermal stimulation as less intense after actively winning pain relief compared to the passive control condition, as rated on visual analogue scales (VAS) from "no sensation" (0) over "just painful" (100) to "most intense pain tolerable" (200). Furthermore, participants also rated the stimulation as more intense after actively losing compared to the passive control condition (Figure 2 A; interaction 'outcome × trial type', $F(1,1040) = 64.14$, $p < 0.001$; pairwise comparisons: win: test vs. control

p < .001; lose: test vs. control, p < 0.001). This shows that perception of both relief and pain are enhanced by active (instrumental) controllability, as hypothesized.

2.2.1.2 Behaviorally assessed pain perception

In addition to the VAS ratings, participants performed a validated perceptual task (Becker et al., 2011; Kleinböhl et al., 1999) allowing to assess perception of the underlying tonic pain stimulus, which is specifically sensitive to perceptual sensitization and habituation. In this procedure, participants re-adjust the stimulation temperature themselves after the outcome of the wheel of fortune to match their perception at the beginning of trial. Negative values (i.e. higher re-adjusted temperatures compared to the stimulation intensity at the beginning of the trial) indicate habituation across the course of one trial of the game, positive values indicate sensitization. In contrast to the VAS ratings, behaviorally assessed pain perception did not differ between test and control trials after winning as well as after losing in the placebo condition (Figure 2 D; interaction 'outcome × trial type', $F(1, 1040) = 2.53$, $p = 0.112$).

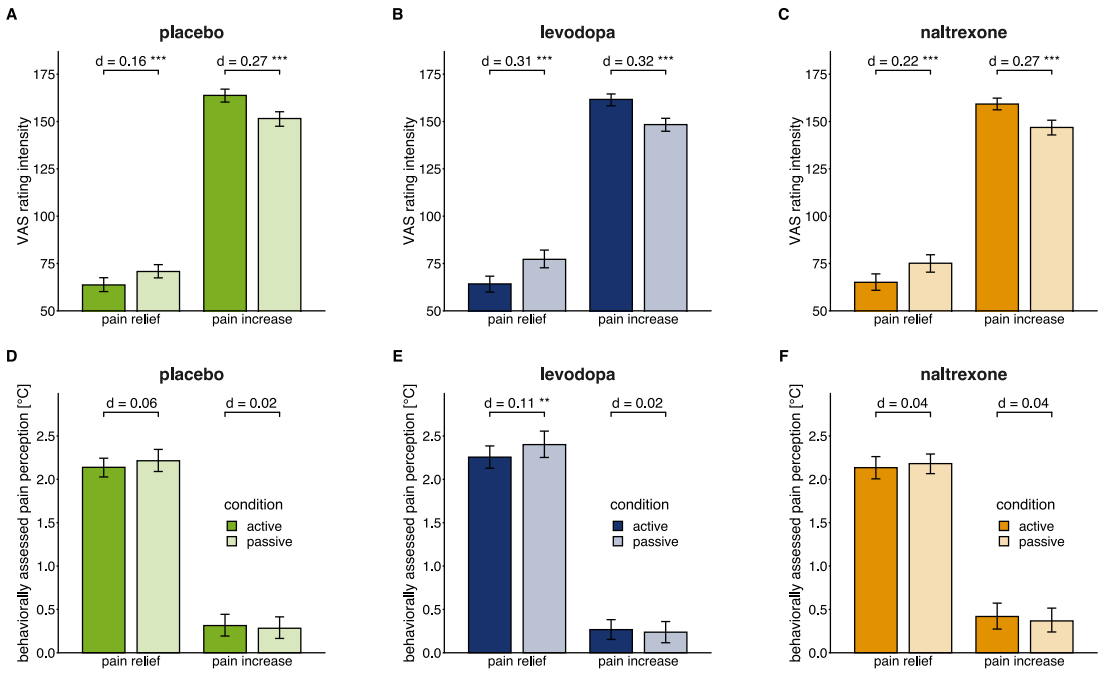

Figure 2: Means and 95% confidence intervals of means for VAS pain intensity ratings (A, B, C) and behaviorally assessed pain perception (D, E, F; within-trial sensitization in pain perception in °C) for each drug session (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28). d indicates Cohen's d as standardized effect-size of estimated effects. ** p < 0.01, *** p < 0.001, for post-hoc comparisons of test versus control trials.

2.2.2 Levodopa increases endogenous pain modulation by active relief, naltrexone has no influence on the modulation

We next examined whether endogenous modulation of pain perception within the wheel of fortune game was affected by a levodopa and naltrexone.

2.2.2.1 Manipulation check: successful blinding of drug conditions

After the intake of *levodopa,* one participant reported a weak feeling of nausea and headaches at the end of the experimental session. In 32 out of 83 experimental sessions subjects reported tiredness at the end of the session. However, the frequency did not significantly differ between drugs ($\chi^2(2) = 2.17$, $p = 0.337$). No other side effects were reported. To ensure that participants were kept blinded throughout the testing, they were asked to report at the end of each testing session whether they thought they received levodopa, naltrexone, placebo, or did not know. In 43 out of 83 sessions that were included in the analysis (52%), participants reported that they did not know which drug they received. In 12 out of 28 sessions (43%), participants were correct in assuming that they had ingested the placebo, in 6 out of 27 sessions (22%) levodopa, and in 2 out of 28 sessions (7%) naltrexone. The amount of correct assumptions differed between drug ($\chi^2(2) = 7.70$, $p = 0.021$). However, post-hoc tests revealed that neither in the levodopa nor in the naltrexone condition participants guessed the correct pharmacological manipulation above chance level ($p's > 0.997$), indicating that blinding was successful.

2.2.2.2 Ratings of perceived pain

As in the placebo condition, participants rated the thermal stimulation as less intense after active relief winning in the wheel of fortune task, and as more intense after receiving phasic pain increases ('losing') compared to the respective passive control condition under levodopa as well as naltrexone (Figure 2 B & Figure 2 C).

Moreover, the effect of active relief or increases on pain modulation was differentially modulated by the drugs (interaction 'drug × outcome', $F(2, 1587.30) = 4.52$, $p = 0.011$).

Specifically, the effect of active relief on perception was larger in the levodopa condition compared to the placebo condition (post-hoc comparison p = 0.007; Figure 3 A). No such difference was found for the naltrexone condition (p = 0.252). Endogenous modulation did not significantly differ between the levodopa and the naltrexone condition (p = 0.368). Endogenous pain facilitation induced by actively receiving pain increases assessed with VAS ratings did not significantly differ between any drug conditions (all post-hoc comparisons p's > 0.591).

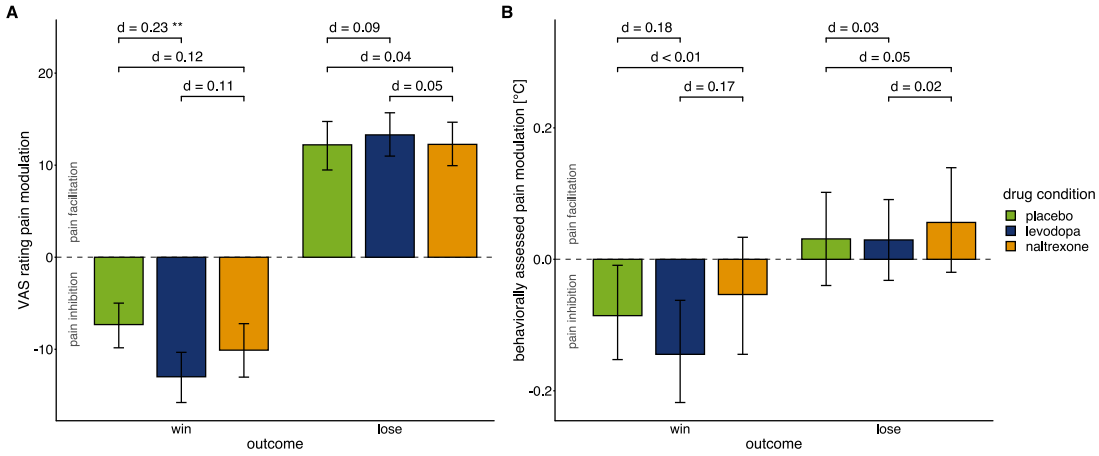

Figure 3: Effects of drug manipulation on endogenous pain modulation assessed by VAS ratings of pain intensity (A) and behaviorally assessed pain perception (B) after winning and losing in the wheel of fortune game, respectively (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28). Error bars show 95% confidence interval of the mean. d indicates Cohen's d as standardized effect-size of estimated effects. While the temporal order of sessions did affect pain modulation (supplementary figure 1: Figure 9), measures of pain sensitivity, that were not experimentally manipulated (supplementary figure 2: Figure 10), and measures of mood (supplementary figure 3: Figure 11) did not significantly differ between drug conditions.

Table 1: Means (M) and standard deviation (SD) of means for pain modulation in VAS ratings of perceived intensity and the behaviorally assessed pain perception (negative values indicate pain inhibition; positive values indicate pain facilitation).

	pain modulation in VAS ratings of pain intensity						pain modulation in behavioral measure (°C)					
	placebo n = 28		levodopa n = 27		naltrexone n = 28		placebo n = 28		levodopa n = 27		naltrexone n = 28	
outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
win	-7.31	21.51	-12.98	23.54	-10.09	23.79	-0.09	0.64	-0.14	0.66	-0.05	0.74
lose	12.21	21.12	13.29	20.48	12.26	22.27	0.03	0.59	0.03	0.54	0.06	0.68

Endogenous pain inhibition under placebo and levodopa showed a high positive correlation (r = 0.591, p = 0.001). This correlation suggests that levodopa linearly

increased endogenous pain-inhibitory effects of actively winning relief in the game dependent on endogenous pain inhibition mechanism in the placebo condition. In summary, the levodopa results show that the enhanced of relief perception during active controllability is dopamine-sensitive.

2.2.2.3 Behaviorally assessed pain perception

In contrast to the placebo condition, participants showed less behaviorally assessed sensitization in active compared to passive trials when obtaining pain relief under levodopa (Figure 2 E) consistent with an extension of pain-inhibitory effects of winning pain relief through to the underlying tonic pain stimulus. Under naltrexone, test and control trials did not significantly differ in the behaviorally assessed pain perception (Figure 2 F) as for the placebo condition. Across drugs, behaviorally assessed pain modulation did not significantly differ between placebo, levodopa, and naltrexone (interaction 'drug × outcome': $F(2, 1592.73) = 1.87$, $p = 0.154$; Figure 3 B).

2.2.3 Levodopa and naltrexone influence relief reinforcement learning in the wheel of fortune task

To investigate whether pain relief gained in active relief seeking was associated with an impact on choice related to reinforcement learning, one of the 2 choices in the wheel of fortune was associated with a fixed 75% chance of winning pain relief ($choice_{high\ prob}$) while the other choice only had a 25% chance to win pain relief ($choice_{low\ prob}$). Participants were not informed of these probabilities in advance. We tested if the proportion of choices of the more rewarding option was higher in the last two out of five blocks of four test trials each of the game, when the subjects already had the chance to explore and learn the different outcome probabilities.

Participants selected the color of the wheel of fortune associated with a higher likelihood for winning relief in 64% (SD = 28%) of in the placebo condition, consistent with a reinforcement learning effect. Thus, participants chose the color associated with the higher likelihood for winning above chance ($\chi^2(1) = 6.64$, $p = 0.010$) on a group level, indicating successful learning.

However, participants' performance significantly differed between the placebo and the drug conditions (main effect of 'drug': $\chi^2(2)$ = 11.89, p = 0.003). In contrast to the placebo condition (post-hoc comparison p < 0.001), under levodopa and under naltrexone participants' choices did not significantly differ from chance (post-hoc comparisons p's > 0.759). Correspondingly, post-hoc comparisons show that choice behavior significantly differed in the placebo compared to the levodopa condition (p = 0.015) and compared to the naltrexone condition (post-hoc comparison p = 0.004), while choices did not significantly differ between levodopa and naltrexone (post-hoc comparison p = 0.915; Figure 4). This shows that both, dopamine and opioids, may have an influence on relief-related learning and choice.

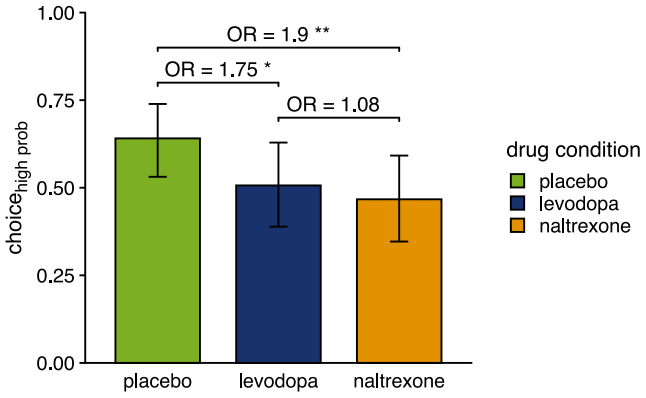

Figure 4: Proportion of choices of the color associated with a higher chance of winning pain relief (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28). OR indicates odds ratios as effect size of estimated effects between drugs. *p<0.05, ** p<0.01.

In an additional exit interview at the end of each session, participants were asked whether they believed that one color of the wheel was associated with a higher chance of winning pain relief. The proportion of participants who reported this color correctly was not above chance (binomial test: p's > 0.5; placebo: 50%, levodopa: 37%, naltrexone: 39.3%). Nevertheless, participants' belief whether one color of the wheel of fortune task was associated with a higher chance of winning or not significantly influenced their choices (p < 0.001) and this influence on choices, and thus on learning, depended on the drug condition (interaction 'drug × belief': $F(2)$ = 6.91, p = 0.032). Group effects of successful learning, i.e. selecting the color with a higher chance of winning, were driven by participants who were able to report this association ($p(choice_{high\ prob}|correct\ belief)$ = 0.737, $p(choice_{high\ prob}|false\ or\ no\ belief)$ = 0.545; post-hoc comparison: p = 0.007)

under placebo and naltrexone (p's < 0.001) but not under levodopa (p = 0.922). This suggests that successful decision making was at least partly dependent on explicit contingency awareness.

2.2.4 Unpredictability and endogenous pain modulation

We next tested whether outcome unpredictability was associated with endogenous pain modulation, and whether this prediction differed between drugs. Prediction errors describe the difference between an expected and a received outcome for positive (here pain relief) as well as negative outcomes (here phasic pain increases) (Glimcher, 2011; Schultz, 2016), and thus capture a measure of unpredictability or surprise, that determines how much learned values need to be updated. To obtain estimates for such prediction errors, we fit different reward learning models, with a drift diffusion process as the choice rule to participants' choice and reaction time data. The best predictive accuracy was found for model 4 that used an individually scaled outcome sensitivity, and a sigmoid function to map expected values for the two choices to the drift rate of the diffusion process (Table 2; see *Methods and Materials*, section *Estimation of prediction errors and their role in endogenous pain modulation* for details on parametrization of reward learning models).

Table 2: Model comparison. Models are ordered by their expected log pointwise predictive density (*ELPD*). $ELPD_{diff}$: difference to the *ELPD* of winning model 4. $se(ELPD_{diff})$: standard error of the difference in *ELPD*.

Model	*ELPD*	$ELPD_{diff}$	$se(ELPD_{diff})$
Model 4	-837.71	0	0
Model 3	-845.44	-7.73	1.51
Model 2	-997.33	-159.62	15.77
Model 1	-998.33	-160.62	15.95

Posterior predictive simulations from the best-fitting model appropriately describe the observed choices (Figure 5). However, none of the model parameters could exclusively explain the differences between levodopa and naltrexone compared to placebo: the 95% highest density intervals (HDI) for the difference between all group level parameters of the drug effect enclosed zero (see Figure 12 on page 60). Among the parameters affecting value updating (positive (η_+) and negative (η_-) learning rate and outcome sensitivity (ρ)) only η_- showed marginally higher central tendency for

naltrexone compared to placebo, indicating a higher learning rate for punishments, but the 95% HDI still enclosed zero. The parameters affecting the mapping of expected values to the drift rate (v, $v_{\max}$) as well the other parameters affecting the drift diffusion decision process (non-decision time τ, boundary separation α, and a-priori bias β) were comparable in the placebo, levodopa, and naltrexone conditions.

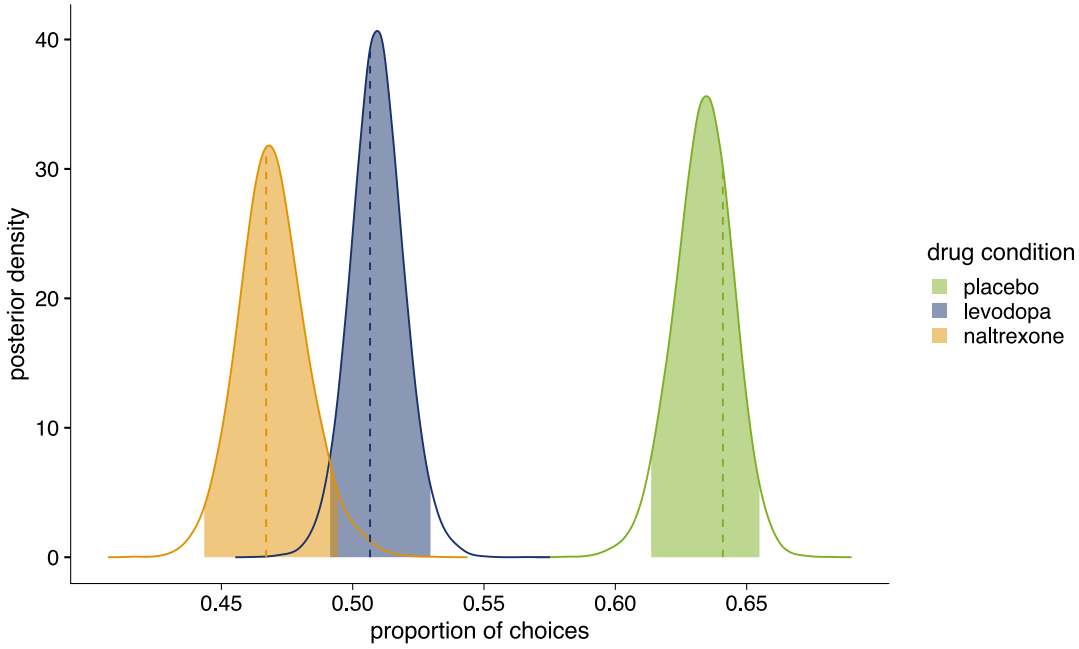

Figure 5: Posterior distribution of the proportion of choices in favor of $choice_{high\ prob}$ (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28). Colored areas show 95% highest density interval (HDI_{95}). Dashed lines indicate observed proportion of choices in favor of $choice_{high\ prob}$. Placebo: $p(choice_{high\ prob})$ = 0.641, HDI_{95} = [0.614,0.655], posterior p-value (*pp*) = 0.320); levodopa: $p(choice_{high\ prob})$ = 0.507, HDI_{95} = [0.491,0.530], *pp* = 0.679; naltrexone: $p(choice_{high\ prob})$ = 0.467, HDI_{95} = [0.443,0.494], *pp* = 0.611. Figure 12 on page 60 shows comparison of drug conditions for each parameter of winning model 4.

Prediction errors estimated by using subject level parameters of the model showed a significant main effect for the prediction of endogenous pain modulation indicated by VAS ratings ($F(1, 1600.3) = 452.9$, $p < 0.001$). A negative estimate of the prediction error (β_{PE} = -0.36) indicates that outcomes that are better than expected (positive prediction errors, which occur when receiving relief) were related to increased relief perception (pain inhibition). Conversely outcomes that are worse than expected (negative prediction errors, occurring with pain increases) were associated with increased pain facilitation (Figure 6). In other words, the more unexpected the relief,

the greater the perception of that relief; and the more unexpected the pain increase, the greater the perception of that pain.

The effect of prediction errors on pain modulation showed a significant interaction with the drug condition ($F(2, 1599.5) = 7.529$, $p < 0.001$). Post-hoc analysis confirmed that the negative linear relationship significantly differed from zero for all conditions ($p's < 0.001$), but this relationship was significantly stronger for levodopa compared to placebo ($p < 0.001$) with no significant differences for naltrexone compared to placebo ($p = 0.083$). Overall, this shows that relief is enhanced to unpredictability, and this effect is sensitive to dopamine.

Estimated prediction errors also showed a significant main effect for the prediction of behaviorally assessed pain modulation ($F(1, 1602.1) = 9.00$, $p = 0.003$), with a negative estimate (β_{PE} = -0.06) suggesting that sensitization decreased with smaller prediction errors. No significant interaction with of prediction error with drug conditions was found for behaviorally assessed pain perception (interaction 'PE × drug': $F(2, 1600.1) = 0.96$, $p = 0.384$).

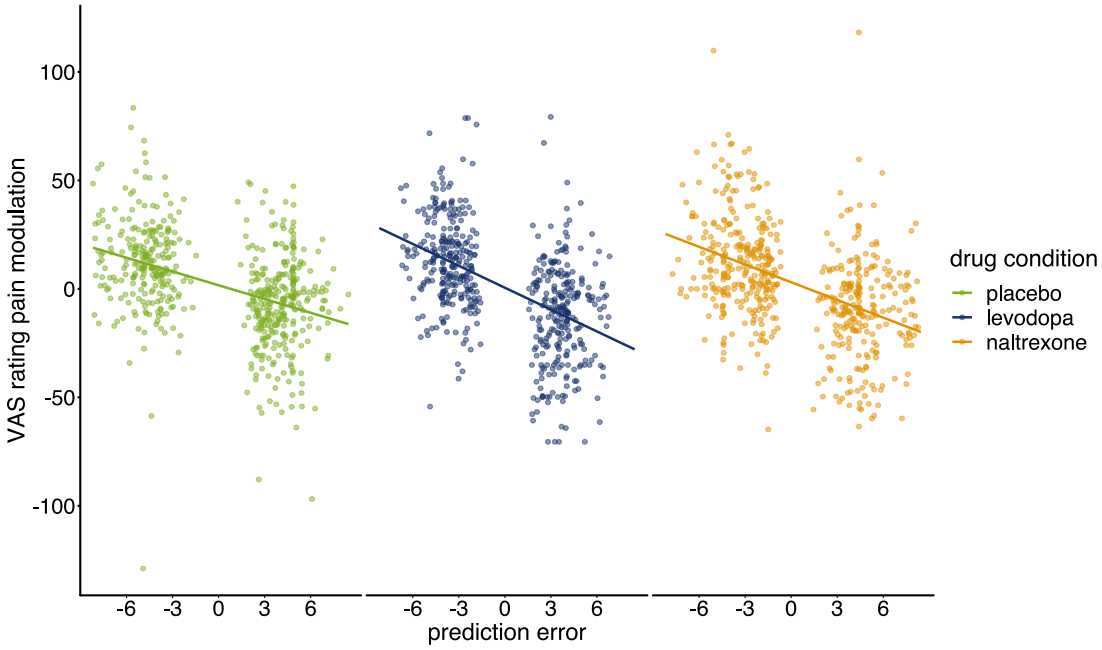

Figure 6: Pain modulation in VAS ratings predicted by prediction error for each condition (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28). Regression lines indicate prediction from the mixed effects model with predictors 'PE', 'drug', and their interaction.

2.2.5 Novelty seeking is linearly associated with increased endogenous pain modulation by pain relief under levodopa

Previous data suggest that endogenous pain inhibition induced by actively winning pain relief is associated with a novelty seeking personality trait: greater individual novelty seeking is associated with greater relief perception (pain inhibition) induced by winning pain relief (Becker et al., 2015). Replicating these results, we found here that endogenous pain modulation, assessed using self-reported pain intensity, induced by winning was correlated with participants' scores on novelty seeking in the NISS questionnaire (Need Inventory of Sensation Seeking; Roth & Hammelstein, 2012; subscale 'need for stimulation' (NS); r = -0.412, p = 0.036). A similar association between novelty seeking and endogenous pain modulation was found in the levodopa condition (r = -0.551, p = 0.004). More importantly, the higher a participants' novelty seeking score in the NISS questionnaire, the greater the levodopa-related endogenous pain modulation when winning compared to placebo (NISS NS: r = -0.483, p = 0.017, Figure 7). Pain modulation after losing was not associated with novelty seeking in placebo (r = 0.083, p = 0.687) and levodopa (r = -0.164, p = 0.433).

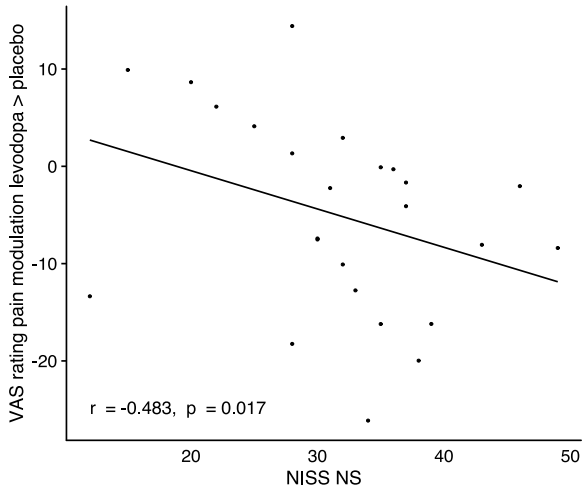

Figure 7: Correlation of changes in endogenous pain modulation induced by winning pain relief under levodopa compared to placebo with individuals' scores on the 'need for stimulation' subscale of the NISS questionnaire, n = 24.

No significant correlations with NISS novelty seeking score were found for behaviorally assessed pain modulation in the placebo and levodopa conditions during pain relief or

pain increase (|*r*|*'s* < 0.24, *p's* > 0.266). Similarly, the difference in pain modulation during pain relief or pain increase between the levodopa and the placebo condition did also not correlate with novelty seeking (|*r*|'s < 0.22, *p's* > 0.295).

2.3 Discussion Study 1

The results show that i) the perception of relief is sensitive to endogenous modulation during motivated behavior, ii) this modulation scales with the informational content of the relief, being enhanced when relief is actively controllable, more unexpected, and especially in high trait novelty seeking individuals, iii) this information-specific modulation is sensitive to manipulation of dopamine signaling, with no evidence of a role of opioidergic signaling; iv) however both dopaminergic and opioidergic signaling have an influence on relief-seeking, which may be at least in part dissociable from relief perception. Overall, this shows that dopaminergic signaling is involved in a fundamental component of the endogenous modulation of pain relief.

Theories of the endogenous modulation of pain propose that one of the reasons that pain is modulated is to optimize motivational behavior, in terms of responding, learning, and decision making (Fields, 2018; Seymour, 2019). That is, pain is increased in situations in which it has a more important role in shaping behavior – for instance when it directs a change in behavior (instrumentally controllable), when it is partly unpredictable (i.e. contains new information), and

in otherwise dangerous contexts. This theory centralizes the functional role of pain as a signal for behavioral control i.e. concerned with the *prospective* control of behavior. In principle, this can be extended as a potential account for the modulation of relief, because the offset of pain is also important as a control signal for guiding behavior, one which occurs in the context of an ongoing noxious event, such as an injury of some sort. We have previously found preliminary evidence of this, by showing that relief perception is enhanced by active controllability (Becker et al., 2015). Here we intended to test this more precisely, by looking at the role of controllability as well as unpredictability, and also compare to the modulation of phasic increases in tonic pain.

We also set an additional prediction, in that we expected to find that modulation by information content would be greater in novelty-seeking individuals (Becker et al., 2015). This is because novelty seeking describes an explicit information-seeking tendency, in which new information is explored with the potential to lead to knowledge of better outcomes that can be exploited in the future (Wittmann et al., 2008). This

illustrates the common basis for intrinsic motivation for novelty and information-seeking for exploitable benefit, and hence we can predict that high trait novelty seekers might be more sensitive to information that occurs through relief outcomes.

Overall, all three predictions were borne out by the data: relief perception as measured by VAS ratings was enhanced by controllability, unpredictability and novelty-seeking tendency, consistent with the hypothesis that relief is sensitive to the exploitable information it carries. This provides the first clear formal framework for understanding a key component of relief perception. The principles for controllability and unpredictability also extended to increases in pain, consistent with the notion that increases in tonic pain act in a similar way to phasic pain operating from a pain-free baseline.

Both dopamine and opioids are implicated in relief processing, although their precise roles remain unclear. We found endogenous relief modulation here was modulated by enhanced dopamine availability induced by the intake of levodopa. Importantly, all three core aspects of informational-sensitivity were modulated by levodopa: active controllability, unpredictability, and association with novelty seeking. In contrast to our hypothesis, pharmacologically blocking opioid receptors using naltrexone did not modulate endogenous pain inhibition in the context of the task. The doses and methods used here are comparable to those used in other contexts which have identified opioidergic effects (Chelnokova et al., 2014; Eikemo et al., 2017; C. D. King et al., 2013; Sirucek et al., 2021), suggesting that opioidergic effects on relief information are at least not substantial.

These findings also illustrate potential parallels with the previous observation of endogenous pain inhibition by extrinsic monetary reward co-occurring with experimental pain (Becker, Gandhi, et al., 2013). In this context, monetary reward represents an independent and potentially competing incentive, and when this co-occurs with pain, it means that optimal responding may require suppression of pain responses, especially innate responses that could interfere with reward acquisition. In both cases, the common principle may be the active ‘decision’ by the pain system to tune incoming pain signals to optimize behavior. Note that the personality trait of novelty seeking has also been associated with enhanced dopaminergic activity due to

lower midbrain (auto)receptor availability (Leyton et al., 2002; Savage et al., 2014; Zald et al., 2008), which further supports a general role for dopamine in information-sensitive behavior (Kakade & Dayan, 2002; Vellani et al., 2020).

The role of dopamine in pain relief in the context of reinforcement is supported by findings of increased dopamine release induced by pain relief in the Nucleus accumbens of rats (Navratilova et al., 2012; Xie et al., 2014). Dopamine release was related to the development of conditioned place preference that could be blocked by dopamine antagonists (Navratilova et al., 2012). Further, Navratilova, Xie, et al. (2015) showed that dopamine release in the Nucleus accumbens and conditioned place preference in response to pain relief depend on opioidergic signaling: both were blocked by opioid antagonism in the anterior cingulate cortex, an area encoding pain aversiveness. In humans, Sirucek et al. (2021) showed that perception of passively received pain relief is at least partly mediated by opioidergic neurotransmission. However, in that task, received pain relief did not carry behaviorally relevant information. Increased opioid activity in the anterior cingulate cortex has been shown to be associated with selectively decreased pain aversiveness with unaltered sensory pain components (Gomtsian et al., 2019; Maruyama et al., 2018; Navratilova, Xie, et al., 2015). In contrast, the present study aimed at quantifying the effect of controllability on the relief perception, with these methods possibly not capturing the effects of opioid blockade on positive affective quality components of the relief experience. Overall, the finding that the modulation of pain relief was not modulated by naltrexone may suggest the possibility that a genuinely opioid-independent mechanism causes this type of pain inhibition.

One key difference in the current version of the wheel of fortune task, compared to the previous version described in (Becker et al., 2015), is that participants' choices had a non-random association with outcomes i.e. this was a true instrumental (operant) contingency between actions and outcomes. This allowed us to assess a basic measure of learning – whether subjects are able to learn to select more frequently the option with the better (75% chance of relief) over worse (25% chance of relief) outcome. That both levodopa and naltrexone conditions were associated with a reduction of the frequency of choosing the better option, indicates that signals mediated by both neurotransmitters may be involved in choice. However, the data

argue against a simple transposition of experienced relief (measured by VAS) into decision value, which for a stationary task such as this, should lead to more deterministic actions in the levodopa condition but no effect under naltrexone compared to placebo. The association of explicit contingency awareness and choice in our task illustrates the fact that multiple decision systems ('model-based' and 'model-free') might be involved in even simple instrumental tasks, and hence that more sophisticated task manipulations are needed to decompose these different components (Langdon et al., 2018). However, our key finding is that there is at least a simple dissociation between the drug effects on experienced relief and decision making.

Such dissociation may be due to differential involvement of dopamine and endogenous opioids in different yet interacting aspects of reward and punishment processing. Dopamine has been related to instrumental learning due to its prominent role in mediating reward and aversive prediction errors (Glimcher, 2011; Matsumoto & Hikosaka, 2009; Schultz, 2007, 2016). Correspondingly, effects of dopaminergic modulation on value-based decision making and brain activity related to reward prediction errors in the Nucleus accumbens have been reported (Pessiglione et al., 2006). On the other hand, impaired learning functions under dopaminergic medication are known from research in Parkinson's disease (Breitenstein et al., 2006; Pizzagalli et al., 2008; Santesso et al., 2009; Vo et al., 2016) and have been attributed to dopamine overstimulation (Cools et al., 2001; Vaillancourt et al., 2013). Others argued that dopamine overstimulation does not impair learning of associations or reward expectations, but only the transfer to overt actions (choice behavior) (Beeler, 2012; Beeler et al., 2010). Accordingly, Kroemer et al. (2019) found reduced model-free control of choice behavior under levodopa (i.e. a decrease in direct reinforcement of actions by rewards) while both, neural reward prediction error signals and also model-based learning remained unaffected. Given the involvement of multiple decision systems in our task a potential overstimulation with dopamine could have led here to choices not being guided by values learned from reinforcement. At the same time, dopamine has also been implicated in motivational aspects (incentive salience) of reward processing (Berridge et al., 2009; Smith et al., 2011; Tindell et al., 2005). Hence, dopamine may have increased motivational drive and related facilitation of pain

modulation in the present task, while at the same time increased dopamine availability may have interfered with reinforcement learning. Opioids have been related to both, incentive salience and the hedonic value of rewards (Berridge et al., 2009; Meier et al., 2021). In humans, bidirectional manipulations have shown that opioid agonism increases while opioid antagonism decreases “wanting” (i.e. incentive salience) as well as “liking” of attractive faces (Chelnokova et al., 2014). The same mechanism was also shown for the effort to work for and the response bias for higher monetary rewards indicating that opioid manipulations affect motivation but also choice behavior (Eikemo et al., 2017). Such effects could explain here why the participants in this study did not develop a preference for choosing more frequently the option associated with a higher chance to win pain relief under naltrexone.

The data may have clinical implications. Reward learning has recently been shown to play a role in the transition of acute to chronic pain with a specific pattern of Nucleus accumbens activity in response to a cue predicting pain relief being predictive for chronification (Löffler et al., 2022). This makes pain relief processing a potential leverage point for prevention strategies. Although levodopa or dopamine agonists are not generally used as analgesics in the clinical management of chronic pain, it may be that they could have a potential adjuvant role in management programs, for example when used in the context of rehabilitation strategies that aim to harness endogenous control mechanisms. It is also worth noting that Parkinson’s disease has a well-recognized association with chronic pain, beyond that which can be explained by motor effects, and in keeping with a potential core role for dopamine in the pathogenesis of chronic pain in some contexts (Beiske et al., 2009).

In summary, our study shows that dopamine has a core role in pain relief information processing, by which it modulates the way in which information tunes the modulation of pain to meet motivational demands.

2.4 Materials and Methods Study 1

2.4.1 Participants

Thirty healthy volunteers (16 female, 14 male; age: mean = 27.1 years; SD = 7.9 years) participated in this study. Exclusion criteria were present pain or pain conditions in the last 12 months, mental disorders, excessive gambling, substance abuse behaviors, alcohol consumption of 100 ml or more of alcohol per week, regular night shifts, or sleep disorders. Based on previous studies a medium effect size was expected (Becker et al., 2015). The a priori sample size calculation for an 80% chance to detect such an effect at a significance level of $\alpha=0.05$ yielded a sample size of 28 participants (estimation performed using GPower version 3.1; (Faul et al., 2007) for a repeated-measures analysis of variance (ANOVA) with within-subject factors). The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, and written informed consent was obtained from all participants prior to participation according to the revised Declaration of Helsinki (World Medical Association, 2013).

2.4.2 Testing sessions

Each participant performed three testing sessions on separate days. Each session comprised a pharmacological intervention and a wheel of fortune game to assess modulation of reward-induced endogenous pain modulation by the interventions. Participants received in one session levodopa to transiently increase the availability of dopamine, in one session the opioid receptor antagonist naltrexone to block opioid receptors, and in one session a placebo for control. To ensure complete washout of the drugs, the testing sessions were separated by at least 2 days (plasma half-life for levodopa: 1.4 hrs (Nyholm et al., 2012); plasma half-life for naltrexone: 8 hrs (Wall et al., 1981)). After obtaining written consent in the first testing session, participants were familiarized with the thermal stimuli, the rating scale, and the wheel of fortune game to decrease unspecific effects of novelty and saliency. In each testing session the thermal pain threshold and pain tolerance were assessed prior to playing the wheel of fortune game to determine the stimulation intensities in the wheel of fortune game.

2.4.3 Thermal stimulation

All heat stimuli were applied using a 25 x 50 mm contact thermode (SENSELab—MSA Thermotest, SOMEDIC Sales AB, Sweden). The baseline temperature was set to 30°C. Rise and fall rates of the temperature were set to 5°C/s. All thermal stimuli were applied to the inner forearm of participants' non-dominant hand after sensitization of the skin using 0.075% topical capsaicin cream to allow for potent pain relief as reward and pain increase as punishment without the risk of skin damage (Becker et al., 2015; Gandhi et al., 2013). By activating temperature-dependent TRPV1 (vanilloid transient receptor potential 1) ion channels capsaicin as the active ingredient of chili pepper induces heat sensitization (Holzer, 1991). To ensure that the entire area of thermal stimulation during the wheel of fortune game was sensitized the cream was applied to an area on the forearm exceeding the area of stimulation by about 1 cm on each side. After 20 min, the capsaicin cream was removed (Dirks et al., 2003; Gandhi et al., 2013) and the thermode was applied. If participants reported the baseline temperature of the thermode (30°C) as painful because of the preceding sensitization this temperature was lowered until it was perceived as non-painful, which was needed in 8 out of 83 sessions (3 placebo sessions, 1 levodopa session, and 4 naltrexone sessions) that were finally entered into the analysis (see below). The temperature was decreased to 28°C (1 placebo session, 4 naltrexone sessions) or 26°C (1 placebo session, 1 levodopa session). The need to lower the baseline temperature was not significantly different between drug conditions (Fisher's exact test, $p = 0.52$).

2.4.4 Determination of stimulation intensities

Participants' heat pain threshold and heat pain tolerance were assessed using the method of limits three times prior to the wheel of fortune game. The temperature of the thermode increased from baseline with 1°C/s. Participants were instructed to press the left button of a three-button computer mouse when the pain threshold was reached. The respective temperature was recorded while the temperature further increased. Participants were instructed to press the button again when the pain tolerance threshold was reached. The respective temperature was recorded and the temperature immediately returned to baseline. The arithmetic mean of the temperatures corresponding to the recorded pain threshold and tolerance in the three trials was used

as an estimate of the individual heat pain threshold and heat pain tolerance, respectively.

After this threshold and tolerance assessment, an adjustment procedure resembling a staircase method was implemented to determine the stimulation intensities in the wheel of fortune game. Participants received heat stimuli of 20s duration and continuously rated the perceived intensity of these stimuli on a computerized visual analogue scale (VAS) ranging from “no sensation” (0) over “just painful” (100) to “most intense pain tolerable” (200) (Becker et al., 2013; Villemure et al., 2003) while the stimuli where presented. The temperature of the first trial was set to the mean of the previously determined pain threshold and tolerance. If the rating at the end of the stimulation was outside a range of 150±10 on the VAS, the temperature for the next trial was adjusted according to the difference to a target rating of 150. This adjustment was determined by multiplying the difference (150 – current rating) by 0.02 and adding the result in °C to the previous temperature. Further, temperature increases between trials were limited to a maximum of 0.5°C to avoid overshooting of ratings. The procedure was repeated until a rating between 140 and 160 on the VAS was achieved, aiming at a temperature perceived as moderately painful. The corresponding temperature was used as the stimulation intensity in the wheel of fortune game.

2.4.5 Wheel of fortune game

A wheel of fortune game, adapted from a previously established version (Becker et al., 2015), was used to provide participants with the possibility of winning pain relief. The game comprised three types of trials: *test* trials, in which participants played the wheel of fortune game and received pain relief or pain increases according to the outcome of the game; *control* trials, in which participants did not play the game, but received pain relief or pain increases as in the test trials; and *neutral* trials, in which participant did not play the game and no pain relief or pain increases were implemented. A trial always started with an increase of the temperature to the previously determined tonic pain stimulation intensity. When the stimulation intensity was reached, participants were instructed to memorize the temperature perceived at this moment (Figure 1). After this memorization interval, participants were presented with a wheel of fortune display that was divided into three sections of equal size but different color.

In the *test* trials, participants were asked to select one of two colors (pink or blue) of the wheel by pressing a corresponding button (left or right) on the mouse. This started the wheel spinning (4.3 s) until it stopped on either the blue or pink section. When the wheel came to a stop and the pointer of the wheel indicated the color the participant had chosen, the stimulation temperature decreased with the aim to induce pain relief (win condition). If the pointer indicated the color the participant had not chosen, the temperature was increased (lose condition). In the *control* trials, participants had to press a black button unrelated to the sections of the wheel of fortune using the middle mouse button, after which the wheel started spinning as in the test trials. In contrast to the test trials, no pointer was displayed in the control trials and the wheel stopped at a random position. After the wheel came to a stop, the stimulation temperature decreased or increased, resembling the course of stimulation in the test trials, but without winning or losing. By this procedure, nociceptive input in test and control trials was kept the same, allowing to test specifically for endogenous pain modulation induced by winning and losing in the wheel of fortune game.

In *neutral* trials, participants had to press a black button, as in the control trials, after which the wheel also started spinning. In these neutral trials, the pointer of the wheel always landed the third color of the wheel (white), which could not be selected in test trials, and the stimulation temperature did not change. Neutral trials were used to estimate changes in pain perception occurring over the course of the experiment due to habituation or sensitization independent of the outcomes of the wheel of fortune game.

After the interval of the temperature change (in the test trials: outcome of the wheel), participants rated the perceived intensity of the current temperature using the same VAS as described above (Figure 1). After this rating, participants had to adjust the stimulation temperature themselves to match the temperature they had memorized at the beginning of the trial. This self-adjustment operationalizes a behavioral assessment of perceptual sensitization and habituation within one trial (Becker et al., 2011, 2015; Kleinböhl et al., 1999). Participants adjusted the temperature using the left and right button of the mouse to increase and decrease the stimulation temperature. Self-adjusted temperatures lower than the stimulation intensity at the beginning of the trial indicate sensitization across the trial, while higher temperatures

indicate habituation. After this behavioral assessment, the stimulation temperature went back to baseline and after a short break (5 s) the next trial started.

In total, the wheel of fortune game comprised of 45 trials, split into five blocks. Each block consisted of 4 *test* and 4 *control* trials followed by one *neutral* trial. *Test* and *control* trials were presented in a predefined, pseudorandomized sequence. In contrast to the previous version of the wheel of fortune (Becker et al., 2015), the outcome of the wheel occurred with certain likelihood to allow for learning to optimize the outcomes of the wheel of fortune. One of the colors (pink or blue) was associated with a 75% chance of winning, while the other was associated with a 25% chance of winning (counterbalanced across participants and testing sessions). If participants did not select a color in the test trials, the neutral outcome (white) of the wheel was displayed and the temperature did not change. The temperature changes in the *control* trials (pain relief or increase) were matched to the outcomes of the *test* trials to ensure that the same number of pain relief and pain increase trials were presented in test and control trials.

Pain relief was implemented by a reduction of the stimulation intensity of 3°C and pain increase was implemented by a rise of 1°C. The magnitude of these temperature steps was determined and optimized in pilot experiments with the aim of inducing potent pain relief and pain increase without inducing ceiling and floor effects.

Although the main focus of the study was to test different effects on pain relief as implemented in win trials and their corresponding control trials with a decrease in nociceptive input, lose trials and their complementing control trials were crucial to the experimental design. First, for playing the game lose trials were an integral part because of the implemented likelihood for winning which necessarily needs to be accompanied by the chance of losing. Additionally, the risk of losing was thought to increase the participants' engagement in the game, which in turn was expected to enhance the motivated state induced by playing the wheel of fortune game. Second, they allowed for testing whether pain modulation was driven by controllability or unspecific effects such as arousal and distraction in test compared to control trials of the wheel of fortune game (c.f. Becker et al., 2015).

All experimental procedures involving thermal stimulation were controlled by custom-programmed Presentation scripts (Presentation® software, Version 17.0, http://www.neurobs.com) providing instructions and other visual cues on a computer screen in front of the participants.

2.4.6 Pharmacological manipulations

Participants ingested in one testing session *levodopa*, in another *naltrexone*, and in another a placebo (microcrystalline cellulose), following a double-blind, cross-over design with counterbalanced order. Levodopa is an amino acid precursor of dopamine leading to a transient systemic increase of dopamine availability. To inhibit peripheral synthesis of dopamine from levodopa, the single dose of 150 mg levodopa (p.o.) was combined with 62.5 mg of a benserazide to prevent peripheral side effects such as nausea (Rinne et al., 1975). Naltrexone is an opioid receptor antagonist with predominant receptor binding affinity at μ-opioid receptors together with a lower binding affinity at κ-opioid receptors and a much lower affinity at δ-opioid receptors (Raynor et al., 1994). Participants received a single dose of 50 mg naltrexone (p.o.) that has been shown to induce more than 90% receptor blockade (Weerts et al., 2013).

After drug intake, a waiting period of one hour started. This waiting time was chosen based on peak plasma concentrations of levodopa and naltrexone at approximately 1 h to 1.5 h after ingestion (Nyholm et al., 2012; Wall et al., 1981). At the end of each testing session, participants indicated whether they thought that they had received the placebo or one of the drugs (response alternatives: ‘placebo’, ‘levodopa’, ‘naltrexone’, or ‘don’t know’) to test for potential unblinding.

2.4.7 Questionnaire and exit interview

Novelty seeking as personality trait was assessed using the Need Inventory of Sensation Seeking (NISS; Roth and Hammelstein, 2012). The NISS consists of the subscales *Need for Stimulation* (NS) and *Avoidance of Rest* (AR). We used the NS subscale as a measure for novelty seeking as it reflects the “need for novelty and intensity” (Roth & Hammelstein, 2012). Before playing the wheel of fortune game the affective state of subjects was assessed using computerized versions of the Self-Assessment Manikin (SAM Bradley & Lang, 1994; Lang, 1980) and a German version

(Krohne et al., 1996) of the Positive And Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). At the of each session, an exit interview was performed, asking for the following information: (1) which drug participants believed to have ingested; (2) if participants believed that choosing one of the two colors was associated with a higher chance to win pain relief; (3) whether participants perceived a difference between test and control trials; (4) whether participants had the impression that the stimulation temperature at the beginning of each trial varied across trials; (5) whether participants had problems indicating their perception on the VAS scale; and (6) whether participants had problems readjusting the initial temperature. Participants gave first yes/no answers and then were asked to specify their answers using open-ended questions.

2.4.8 Statistical analysis

For the statistical analysis, 2 participants were excluded, one participant due to the failure to comply with experimental procedures and one due to technical failure of the equipment. For one additional participant, data of one session (levodopa) are missing due to drop-out. Thirty-two out of 3735 single trials of all the remaining sessions were not recorded due to technical failures. In 42 trials, participants did not press a button within the respective interval in the wheel of fortune game. These trials were excluded from the analyses. Note that the NISS questionnaire was missing for two additional subjects due to initial issues at the beginning of the data collection.

To test if blinding was successful we fit a mixed-effects logistic regression with the subjects' assumption on the ingested drug (as reported in the exit interview, see above) being correct as dependent variable. We used 'drug' as a fixed factor and to account for repeated measures we modelled a random intercept for each subject. Post-hoc general linear hypothesis tests were used to compare estimated proportions of correct assumptions against chance.

To confirm that the manipulation of the motivated state (test vs. control trials) of the participants by playing the wheel of fortune game did induce pain modulation as intended in each session, we analyzed the VAS ratings and the behavioral pain measure as outcome measures separately for each session with 'trial type' and 'outcome' as well as their interaction as fixed effects. To account for the repeated

measures design we modelled a random intercept for each participant and a random slope for outcome of the wheel within each participant.

To obtain an estimate for endogenous pain modulation in each test trial, we subtracted the mean value of all control trials of either the pain relief or the pain increase trials from the value of the winning or losing test trials separately for each session for both the VAS ratings and the behavioral pain measure. Using these differences, negative values indicate pain inhibition and positive values indicate pain facilitation. Estimates for pain modulation were analyzed using linear mixed model procedures with the fixed factors 'drug' (levodopa, naltrexone, placebo), 'outcome' (win, lose), 'order' of sessions (1, 2, 3), and their interaction separately for ratings and behaviorally assessed pain perception as dependent variables. The factor 'session number' was added to control for effects of temporal order independent of the drug manipulation that was found to influence pain modulation (see Figure 9 on page 57). Other factors such as baseline pain perception or mood did not affect pain modulation and were not included in further analysis (see Figure 10 and Figure 11 on pages 58 ff). To account for the repeated measures design we modelled a random intercept for each participant and a random slope for outcome within each participant.

Unbeknown to the subjects, one of the colors in the wheel of fortune was associated with a higher chance to win pain relief. To test whether participants learned to select this color from the implemented reward contingencies we looked at choice behavior in the last 2 blocks of trials only. In this latter phase of the task subjects already had the chance to explore differences in outcomes associated with their choices and were thought show exploitation if they had learned about the contingency. We fit a mixed-effects logistic regression with the subjects' choices as dependent variable. For a single session we fit an intercept only model where the intercept represents the group level estimate for the probability to choose the color associated with a higher chance of winning pain relief ($choice_{high\ prob}$). Drug was used as an additional within-subject factor when testing for differences among levodopa, naltrexone, and placebo. To account for repeated measures, we modelled a random intercept for each subject. To assess the effect of the subjects' belief about which color was associated with a higher chance to win pain relief (as reported in the exit interview, see above) we added the factor 'belief' (either "correct belief" or "false or no belief") to this model.

To test whether endogenous pain modulation due to winning pain relief was related to participants' personality trait of novelty seeking, pain modulation represented by the differences between test and control trials in the wheel of fortune in VAS ratings and the behaviorally assessed pain perception of the placebo and the levodopa condition were correlated with the NISS NS scores. To test further whether increases in pain modulation induced by levodopa were associated with novelty seeking, differences in pain modulation between the levodopa and placebo session were also correlated with the NISS NS scores. Before calculating these correlations, multivariate outliers were tested using a chi-square test on the squared Mahalanobis distance using an α of 0.025 (Filzmoser, 2016), leading to the exclusion of one value for the correlation with the difference of pain modulation between the levodopa and placebo session.

The significance level was set to 5% for all analyses. All statistical analyses were performed using statistical computing software R version 3.5.3 (R Core Team, 2019). Mixed model analyses were performed using the *lme4* package (Bates et al., 2015). All linear mixed models were estimated using restricted maximum likelihood. Kenward-Roger correction as implemented in the *lmerTest* package (Kuznetsova et al., 2017) was used to calculate test statistics and degrees of freedom to account for the sample size. For general linear mixed-effects models Wald χ^2 was calculated using *car* package (Fox, John & Weisberg, 2011). Post-hoc tests and effect sizes were calculated on estimated marginal means using the *emmeans* package (Lenth, 2020) where appropriate. Tukey adjustment was used to account for multiple comparisons in post-hoc tests.

2.4.9 Estimation of prediction errors and their role in endogenous pain modulation

To analyze how mechanisms of instrumental learning contribute to the observed choice behavior and how this related to reward-induced pain modulation we fitted reinforcement learning (RL) models to participants' choices in test trials of the wheel of fortune game. Such models were initially formulated for associative learning (Bush & Mosteller, 1951; Rescorla & Wagner, 1972) and adapted for instrumental learning (Sutton & Barto, 1998). RL models assume that actions are chosen based on the expected outcome. Learning is described as the adaptation of expectations based on experiences. Thus, learning is driven by the discrepancy between a present

expectation and the obtained outcome, namely the *prediction error*. The speed of adaption of the expectation is described by the *learning rate*, which defines the exponential decay of the influence of previous outcomes on the currently present expectation. For trial-by-trial instrumental learning paradigms, the update of the expectation of an outcome related to a given action (in the present study: choice in the wheel of fortune) is operationalized by calculating the expected value Q of a choice as follows:

$$Q_{choice,t+1}=Q_{choice,t}+\eta\times\delta_t \quad (1)$$

where $Q_{choice}$is the reward expectation for a given choice, t denotes the trial, η is the learning rate, and δ_t is the prediction error in trial t. The learning rate η determines the speed of adaption; the higher η the more is the expectation influenced by recent compared to former experiences. Since updating of expectations has been shown to differ dependent on the sign of the prediction error (Fontanesi et al., 2019; Gershman, 2015; Pedersen et al., 2017), we modelled independent learning rates for positive (η_+) and negative (η_-) prediction errors:

$$Q_{choice,t+1} = Q_{choice,t} + \eta_+ \times \delta_t, if\ \delta_t > 0 \quad (2)$$

$$Q_{choice,t+1} = Q_{choice,t} + \eta_- \times \delta_t, if\ \delta_t \leq 0 \quad (3)$$

The prediction error as the difference between the actual and the expected outcome in trial t is formulated as follows:

$$\delta_t = R_t - Q_{choice,t} \quad (4)$$

with R_t as the outcome of the choice in trial t.

In the wheel of fortune game, outcomes were implemented as changes in stimulation intensities. Accordingly, R_t was positive (+1) for temperature decreases in win trials or negative (-1) for temperature increases in lose trials. The formula shown above assumes a constant outcome sensitivity. To capture potential modulation of the outcome sensitivity, we implemented a scaled outcome sensitivity so that the reward in trial t was multiplied by an individual scaling factor ρ yielding a scaled prediction error:

$$\delta_t = (\rho \times R_t) - Q_{choice,t} \quad (5)$$

Q values were initiated to zero and calculated separately for choices of the color associated with a higher chance to win pain relief ($Q_{high\ prob}$) and choices of the color associated with a lower chance to win pain relief ($Q_{low\ prob}$).

While RL models traditionally used a softmax choice rule (Daw & Doya, 2006; Luce, 1959), recent studies on value-based decision making have implemented variants of the drift diffusion model (Ratcliff, 1978; Ratcliff & Rouder, 1998) to map expected values to choices (Fontanesi et al., 2019; Pedersen et al., 2017; Peters & D'Esposito, 2020). The drift diffusion model describes decisions as accumulation of noisy evidence for two choice options until a predefined threshold, representing either of the two options, is reached. Such drift diffusion models take response times (*RT*) of decisions into account and model mathematically cognitive processes underlying the decision process. Figure 8 depicts such a decision process. The range between the decision boundaries is represented by the boundary separation parameter α. Higher values of α lead to slower but more accurate decisions, that is, α represents the speed vs. accuracy tradeoff. The position of the starting point *z* between the boundaries is determined by *a priori* biases β toward one of the two options. This parameter β represents the relative distance of z between the boundaries. It can range from 0 to 1 where a value of 0.5 indicates no bias, values below indicate a bias for the lower choice and values above 0.5 a bias for the upper choice. The non-decision time τ describes time needed for processes that are unrelated to the decision process (e.g. stimulus processing). Correspondingly, the reaction time is defined as $RT = \tau + decision\ time$. Acquisition of evidence starts from the starting point *z* at time τ as a random walk. The slope of this random walk is determined by the drift rate ν and a decision is made when either the upper or lower boundary is reached. Higher drift rates result in faster and more accurate decisions. The probability of the *RT* when choosing option x can then be calculated using the Wiener first-passage time distribution (Ratcliff, 1978):

$$RT(x) = Wiener(\alpha, \tau, \beta, \nu) \quad (6)$$

where $Wiener()$ returns the probability that x is chosen with the observed RT.

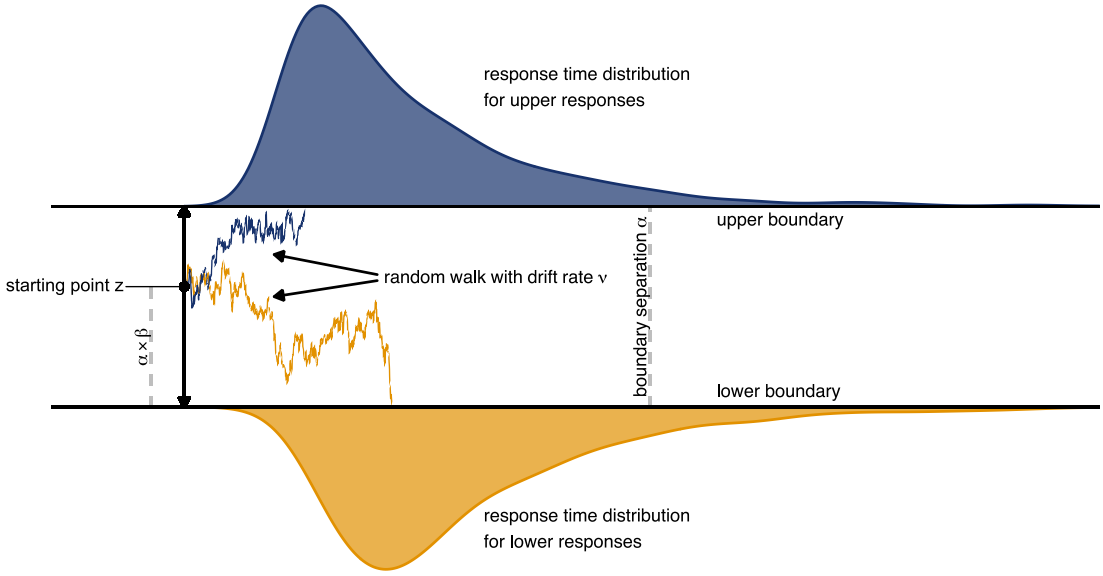

Figure 8: Schematic depiction of the drift diffusion model. Accumulation of evidence starts at point z which is defined by the a-priori bias β and the boundary separation α. Noisy evidence is integrated over time (represented by sample paths in blue and orange, for upper and lower boundary choices, respectively).

Most variants of reward learning models that use the drift diffusion process as a choice rule replace the constant drift rate by an individually scaled difference of expected values for the both options (Fontanesi et al., 2019; Pedersen et al., 2017; Peters & D'Esposito, 2020). Thus, the drift rate ν_t, varies across trials as a function of the difference between expected values of the two choice options that in the wheel of fortune corresponded to $Q_{high\ prob}$ and $Q_{low\ prob}$, respectively. We implemented a linear mapping of the difference in expected values like Pedersen al. (2017) where this difference is multiplied by the scaling factor ν:

$$\nu_t = (Q_{high\ prob} - Q_{low\ prob}) \times \nu \quad (7)$$

As an alternative scaling method we implemented a non-linear function as suggested by Fontanesi et al. (2019) in which the scaled difference in expected values is mapped to the drift rate using a sigmoid function, which more closely resembles the non-linear mapping of the softmax function:

$$\nu_t = S((Q_{high\ prob,t} - Q_{low\ prob,t}) \times \nu) \quad (8)$$

where $S(x)$ is defined as:

$$S(x) = \frac{2 \times \nu_{max}}{1 + e^{-x}} - \nu_{max} \quad (9)$$

With that, $\pm\nu_{\max}$ defines the upper and lower limit of the drift rate, respectively, while the shape or slope of the sigmoid function depends on the scaled difference of expected values.

In summary, we combined different parameterizations of the outcome sensitivity (static or scaled) and the mapping of expected values to the drift rate (linear or sigmoidal) into different models (Table 3).

Table 3*:* Model specification. Models 1-4 were defined using different combinations of parameters for reward sensitivity and the mapping of expected values to the drift rate. A 'static' reward sensitivity means that pain increase and pain decrease were defined as -1 and 1, respectively (see Equation 4). A 'scaled' outcome sensitivity means that pain decrease was defined as $-\rho$ and pain decrease as ρ (see Equation 5). A 'linear' drift rate mapping means that the drift rate ν_t for each trial was defined as the difference of expected values multiplied by ν (see Equation 7). A sigmoid mapping of the drift rate means that ν_t was defined by a sigmoid function bounded at $\pm\nu_{\max}$. (see Equation 8 und Equation 9). All models included two learning rates (η_+, η_-), the non-decision time τ, the boundary separation α, and the a priori bias β.

Model	outcome sensitivity	drift rate mapping
Model 1	static	linear
Model 2	scaled	linear
Model 3	static	sigmoid
Model 4	scaled	sigmoid

We used hierarchical Bayesian modeling to fit the reward learning models to the choices of the participants in the test trials. Hierarchical models estimate group and individual parameters simultaneously to mutually inform and constrain each other, which yields reliable estimates for both, individual and group level parameters (Gelman et al., 2013; Kruschke, 2014). Posterior distributions of the parameters were estimated using Hamiltonian Monte Carlo sampling with a No-U-Turn sampler as implemented in the probabilistic language Stan (Carpenter et al., 2017) via its *R* interface *rstan* (Stan Development Team, 2020). For each model parameter, we included a global intercept and the main effect of drug (levodopa, naltrexone, placebo). Both, intercept and main effect were allowed to vary for each participant and we modelled a correlation of individual terms for the drug effect across participants to account for repeated measures. We used a non-centered parameterization to reduce dependency between

group and individual level parameters (Betancourt & Girolami, 2015). Therefore, both intercept and drug effect were defined by their location (group level effect), scale, and error (individual effects) distributions. A logistic transformation was applied to the learning rate (η_+, η_-) and a-priori bias (β) parameters to restrict values to the range of $[0, 1]$. The location parameters for the intercept of the learning rate were given standard normal priors ($\mathcal{N}(0,1)$) and the scale of these parameters were given half-normal priors ($\mathcal{HN}(0,1)$). The location of the drug effect on learning rate parameters were also given standard normal priors while the scale was given a half-normal prior of $\mathcal{HN}(0,0.1)$ to prevent allocation of high prior density at the edges of the range after logistic transformation, resulting in an almost flat prior. The location parameter for the intercept of the a-priori bias was given a normal prior of $\mathcal{N}(0, 0.5)$ and the scale was given a half-normal prior $\mathcal{HN}(0,0.1)$. The location parameter for the drug effect was given a normal prior of $\mathcal{N}(0,0.5)$ and the scale was given a half-normal prior of $\mathcal{HN}(0,0.1)$. To ensure that the non-decision time (τ) was bounded to be lower than the reaction time the parameter was equivalently transformed to the range [0,1] and multiplied with each subject's individual minimum reaction time in a given session. Priors were the same as for the learning rate, i.e. yielding a flat prior after transformation. We used an exponential transformation to constrain the reward sensitivity parameter (ρ), the boundary separation (α), drift rate scaling factor (ν), and the boundary of the drift rate ($\nu_{\max}$) to be greater than 0. The location of the global intercept was given a normal prior of $\mathcal{N}(0.1,0.1)$ for the reward sensitivity, a normal prior of $\mathcal{N}(0,0.1)$ for the boundary separation, a normal prior of $\mathcal{N}(0.2,0.2)$ for the drift rate, and a normal prior of $\mathcal{N}(0.5,0.2)$ for the drift rate boundary. For the exponentially transformed parameters the scale of the global intercept was given a half-normal prior of $\mathcal{HN}(0,0.1)$, the location of the drug effect was given a normal prior of $\mathcal{N}(0,0.5)$, and the scale of the drug effect was given a half-normal prior of $\mathcal{N}(0,0.1)$. Individual effects for the intercept as well as for the drug effect were all given standard normal priors. The correlation matrix of individual drug-level effects for each parameter was given a LKJ prior (Lewandowski et al., 2009) of $\mathcal{LKJ}corr(1)$. All models were run on four chains with 4000 samples each. The first 1000 iterations were discarded as warm-up samples for each chain. The convergence of chains was confirmed by the potential scale reduction factor $\hat{R}$.

The fitted models were compared for their best predictive accuracy using *K*-fold cross-validation (Vehtari et al., 2017). For the cross-validation, we split data into $k = 10$ subsets with each subset containing data of 2-3 participants and calculated the expected log pointwise predictive density (ELPD) based on simulations for each hold-out set y_k using parameters estimated from re-fitting the model to the training data set $y_{(-k)}$. We calculated $ELPD$s, their differences, and the standard error of the differences using the *R* package *loo* (Vehtari et al., 2020). A higher $ELPD$ indicates a better predictive accuracy. Such a better predictive accuracy was assumed if the difference in $ELPD$ ($ELPD_{diff}$) for two models was at least 2 times the standard error of that difference ($se(ELPD_{diff})$).

For the best fitting model, we performed posterior predictive checks by simulating replicated data sets from posterior draws. As the test statistic for the posterior predictive check we examined the proportion of choices in favor of the option associated with a higher chance to win pain relief ($choice_{high\ prob}$) in the last 2 blocks of the wheel of fortune game and compared the proportions observed in this data to the distribution of proportions found in the simulated data sets.

From the best fitting model, we used group level estimates for the main effect of 'drug' to compare model parameters between drug conditions using the 95% highest density interval (HDI) of the difference of their posterior distributions.

The means of individual parameter posterior distributions were used to estimate prediction errors for single trials. To test whether these prediction errors predict endogenous pain modulation induced by the wheel of fortune task, we used linear mixed models with the fixed factors 'prediction error' and 'drug', and their interaction. A random intercept for each subject was included to account for repeated measures. Separate models for VAS ratings and behaviorally assessed pain perception as dependent variables were calculated.

2.5 Supplementary figures Study 1

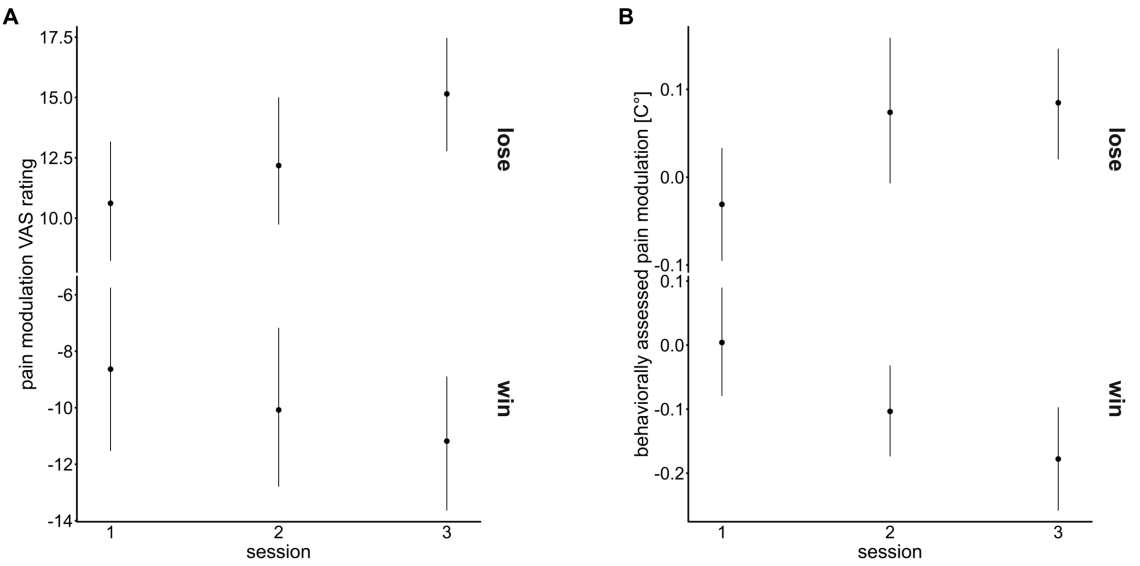

Figure 9 (supplementary figure 1 of Figure 3): Means and 95% confidence intervals of the mean for pain modulation in (A) VAS ratings and (B) behaviorally assessed pain modulation for each testing session. Mixed-effects models testing whether the temporal order of the testing sessions, independent of the order of the application of the drugs, had an effect on pain modulation in win and lose trials of the wheel of fortune did not show a main effect of 'session number' (pain modulation VAS ratings: $F(2, 1593.70) = 1.28$, $p = 0.279$; behaviorally assessed pain modulation: $F(2, 1599.84) = 0.86$, $p = 0.425$) but point to a differential effect of temporal order for win and lose outcomes (interaction 'outcome × session number': pain modulation VAS ratings: $F(2, 1593.77) = 3.00$, $p = 0.050$; behaviorally assessed pain perception: $F(2, 1597.27) = 7.94$, $p < 0.001$). Hence, temporal order was included as an additional main effect when testing the effect of 'drug' on pain modulation.

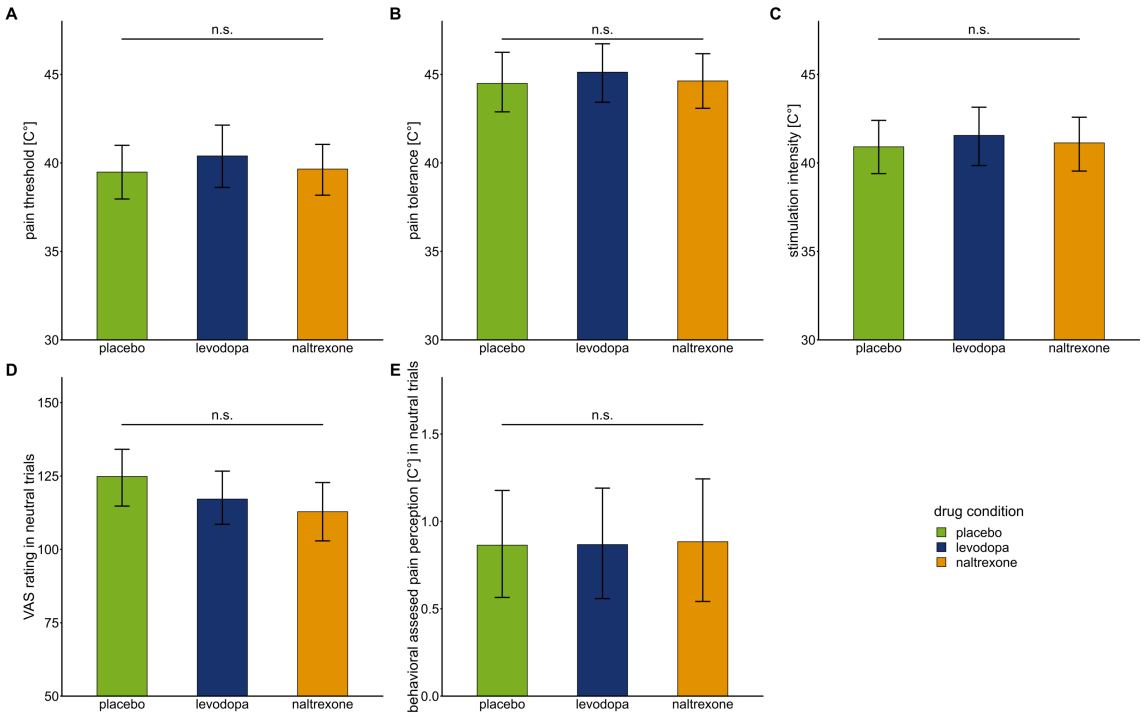

Figure 10 (supplementary figure 2 of Figure 3): Bars show means and error bars 95% confidence intervals of the mean for (A) pain threshold, (B) pain tolerance, (C) stimulation intensity, (D) VAS ratings in neutral trials (in which participants did not play the game and the temperature stayed constant), and (E) behaviorally assessed pain perception in neutral trials for each drug condition. Mixed-effects models using drug condition (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28) to predict measures of baseline pain sensitivity showed no significant main effect for 'drug': pain threshold: $F(2,53.21) = 0.64$, $p=0.529$; pain tolerance: $F(2,53.18) = 0.31$, $p = 0.736$; stimulation intensity: $F(2,53.2) = 0.30$, $p = 0.745$. Mixed-effects models using drug condition to predict VAS ratings and behaviorally assessed pain perception in the neutral condition of the wheel of fortune task showed no significant main effect for 'drug': VAS ratings: $F(2,53.31) = 2.12$, $p = 0.131$; behaviorally assessed pain perception: $F(2,53.13) = 0.01$, $p = 0.990$

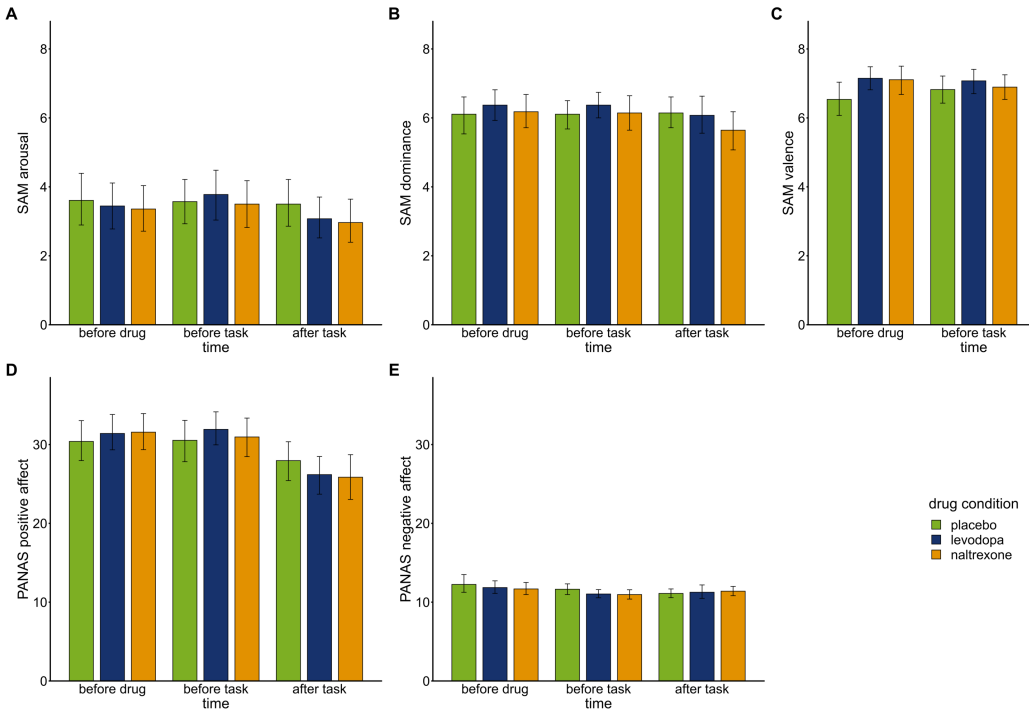

Figure 11 (supplementary figure 3 of Figure 3): Mood was assessed over the course of each experimental session before drug intake, before playing the wheel of fortune game, and after playing the game using computerized versions of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994; Lang, 1980) and a German version (Krohne et al., 1996) of the Positive And Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). Bars show means and error bars 95% confidence intervals of the mean for SAM subscale (A) arousal, (B) dominance, (C) valence, and PANAS subscales (D) positive affect, and (E) negative affect at each time point. To test whether drug conditions (placebo: n = 28, levodopa: n = 27, naltrexone: n = 28) differentially affected mood we fit separate mixed-effects models predicting subscales of SAM and PANAS by 'drug', 'time', and their interaction. SAM ratings for arousal, dominance, and valence did not show any significant main effects of 'drug' (arousal: $F(2,213.2) = 1.56$, $p=0.214$); dominance: $F(2,213.29) = 1.03$, $p = 0.359$; valence: $F(2,213.41) = 0.74$, $p = 0.479$) nor significant interactions for 'drug × time' (arousal: $F(4,213.0) = 0.69$, $p = 0.599$; dominance: $F(4,213.00) = 0.88$, $p = 0.4771$; valence: $F(4,213.00) = 2.28$, $p = 0.062$). Participants' positive affect assed with the PANAS did not show a significant main effect of 'drug' ($F(2,213.25 = 0.05$, $p = 0.954$) nor a significant interaction of 'drug x time' ($F(2, 213.00) = 1.60$, $p = 0.176$). Similarly, negative affect assessed with the PANAS did not show a significant main effect of 'drug' ($F(2, 213.51) = 0.93$, $p = 0.376$) nor a significant interaction of 'drug × time' ($F(2, 213.00) = 0.79$, $p = 0.533$).

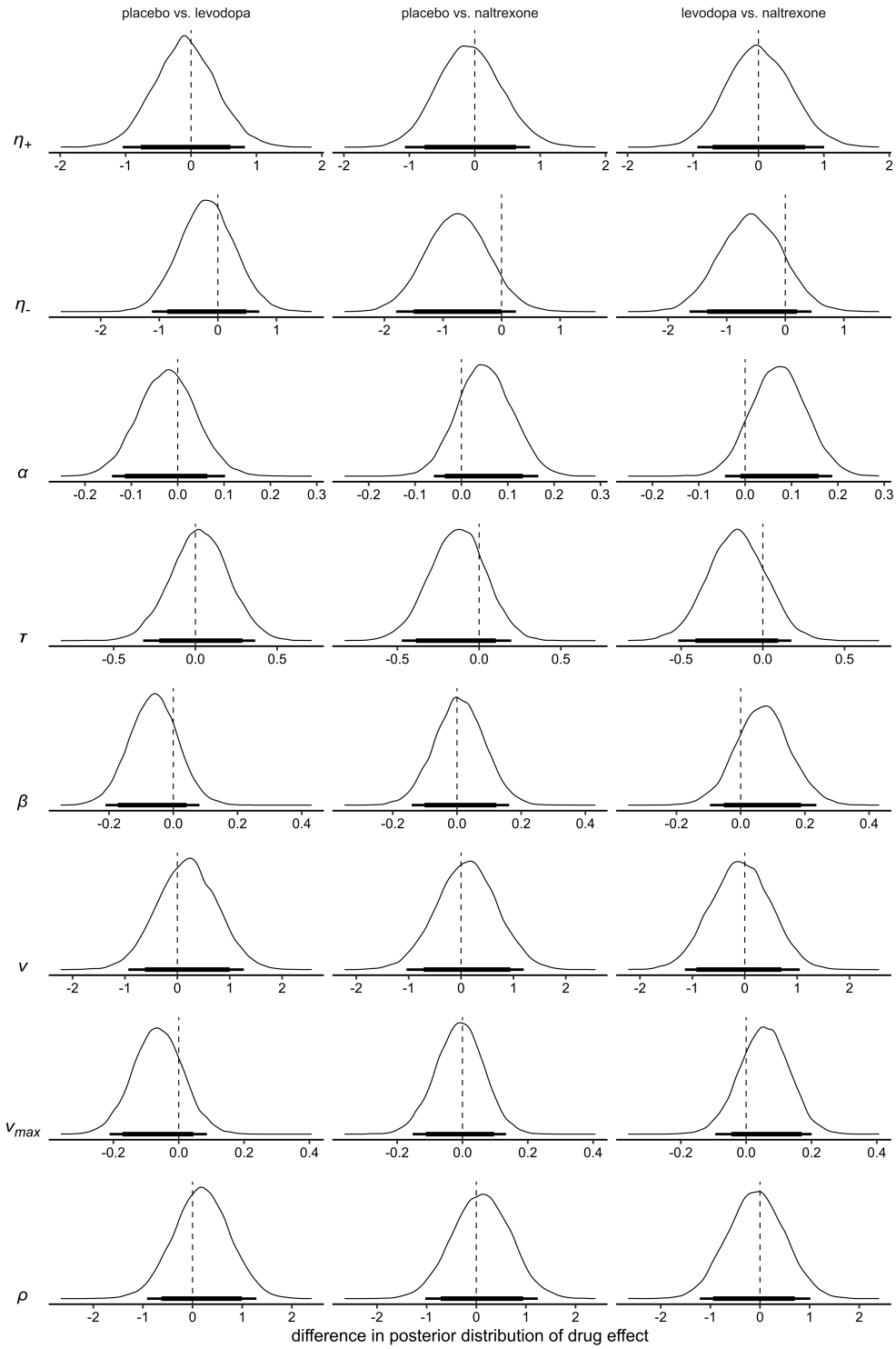

Figure 12 (supplementary figure 1 of Figure 5): Differences of the posterior distributions of group level parameters for the main effect of drug in model 4. Thick black bars indicate the 85% HDI, thin bars indicate the 95% HDI. η_+: learning rate for positive prediction errors; η_-: learning rate for negative prediction errors; α: boundary separation; τ: non-decision time; β: a-priori bias; v: drift-rate scale factor; v_{max}: drift-rate boundary; ρ: outcome sensitivity.

3 STUDY 2 - PAIN RELIEF AS REWARD: ALTERED LEARNING PATTERNS AND NEURAL CORRELATES IN CHRONIC PAIN PATIENTS[2]

3.1 Introduction Study 2

Almost everybody knows pain and with that the pleasure of pain relief. When we are in pain, we desire pain relief. In particular in chronic pain, seeking pain relief can become an all dominating goal. The aversiveness of pain fulfills essential functions for survival and well-being, because it guides behavior to escape from pain, to rest for recovery, and to avoid harm in the future (Seymour, 2019). Adaptively responding to nociceptive signals involves numerous processes ranging from nociceptive reflexes to active behavior based on learned predictions. When in pain, the rewarding nature of pain relief further motivates such adaptive behavior and facilitates learning (Navratilova, Atcherley, et al., 2015; Seymour, 2019). This highlights that pain relief is more than a mere reduction in nociceptive input. Accordingly, research in humans and animals has demonstrated its rewarding properties and its capability to induce learning as negative reinforcement (Becker et al., 2008; Leknes et al., 2008; Navratilova et al., 2012; Navratilova, Xie, et al., 2015). With such rewarding properties, pain relief should have the capacity to modulate pain perception endogenously, fostering optimal decision making (cf. Fields, 2006, 2018). Correspondingly, Becker et al (2015) showed that pain relief gained in a motivated, active decision making state compared to reductions of pain intensity in a passive state amplifies relief perception. Replicating and extending these results, we recently showed that such endogenous pain modulation scaled with prediction errors (Desch et al., 2022), suggesting that the better than expected the outcome the stronger endogenous pain inhibition. Prediction errors induce learning and thus, this relationship suggests that reward-induced endogenous pain modulation promotes learning of harm avoidance (Seymour, 2019). Pain inhibition

[2] **Desch, S.**, Schweinhardt, P., Flor, H., & Becker, S. (in preparation). Pain relief as reward: Altered learning patterns and neural correlates in chronic pain patients. Manuscript prepared for submission at *Scientific Reports*.

induced by pain relief achieved in a motivated, active state as well as its association with prediction errors were both increased by dopamine (induced by levodopa intake). These findings highlight the role of dopamine in the effects of pain relief in line with dopamine's known fundamental role in reward processing (Glimcher, 2011; Matsumoto & Hikosaka, 2009; Schultz, 2016). Nevertheless, the neural correlates of the modulatory effects of pain relief as reward on pain perception have not been investigated so far.

Independent of a rewarding context or motivated state, passive pain and pain relief reception have been shown to activate brain structures of the reward valuation system, namely the Nucleus Accumbens (NAcc) and anterior cingulate cortex (ACC) (Becerra et al., 2013; Becerra & Borsook, 2008). Further, altered activation in the mesolimbic reward system in anticipation of pain onset and offset (Loggia et al., 2014) and changes in functional connectivity between core regions of the reward circuitry (Yu et al., 2020) have been found in chronic pain. Specifically, the transition from subacute to chronic could be predicted by increased functional connectivity between the ventromedial prefrontal cortex (vmPFC) and the NAcc (Baliki et al., 2012). Importantly, Löffler et al. (2022) recently extended this result by showing a relation to reward prediction errors in this prediction of the transition to chronic pain. This result supports the assumption that reward processing changes with chronic pain (Mitsi & Zachariou, 2016). Accordingly, maladaptive reward processing has been suggested as a core characteristic underlying chronic pain and comorbid motivational and emotional disturbances (Borsook et al., 2016). Focusing specifically on established chronic pain, Löffler et al. (2022) further showed that in chronic pain not the same pattern of increased functional connectivity in response to reward prediction errors is present, but decreased responses in the vmPFC. However, findings on neural correlates of reward processing in chronic pain are mixed. While Martucci et al. (2018) described decreased activation during reward anticipation and increased activation in response to loss avoidance in the vmPFC in patients with fibromyalgia compared to healthy controls, they did not find any difference in brain responses to monetary wins. Using a very similar task, Kim et al. (2020) could not replicate these findings in a mixed sample with fibromyalgia and back pain patients. Instead they found reduced activation of striatal areas during anticipation of rewards and losses in these patients compared to healthy

controls, which were associated with response times as indicators of incentive related behavior. In addition to these inconsistent results, it remains unclear how the observed alterations in reward processing relate to pain perception and pain-related behavior in chronic pain. Increased motivation to seek relief might render pain relief a more relevant reward in chronic pain. Accordingly, reduced endogenous pain modulation during offset analgesia as a form of passive relief reception has been related to dampened activation in the reward circuitry, with ACC activation being associated with clinical pain in patients with neuropathic pain (S. Zhang, Li, et al., 2018). Specifically the pregenual anterior cingulate cortex (pgACC) has been related to pain modulation in an instrumental relief seeking task in healthy participants (Zhang et al., 2018).

Based on these considerations, we aimed to investigate reward related endogenous modulation of pain perception and its underlying neural mechanisms in patients with chronic pain. We implemented a probabilistic relief seeking task combined with functional magnetic resonance imaging to identify neural correlates of reward processing and endogenous modulation. Specifically, we expected patients with chronic pain to exhibit reduced endogenous pain inhibition by rewarding pain relief and corresponding differences in neural activation within the reward processing network.

3.2 Materials and Methods Study 2

3.2.1 Participants

We recruited 29 healthy controls (HC, 26 patients with fibromyalgia (FM), and 11 patients with chronic back pain (CBP). Participants were recruited through press releases of the Central Institute for Mental Health (CIMH), Mannheim, and announcements on the institute's website as well as through flyers put on display at general practitioners, physiotherapy practices, local supermarkets, fitness centers, and cultural institutions, and distributed via support groups. In addition, back pain patients were recruited from samples of two different previous studies conducted at the same institute, if they had agreed to be contacted again for further recruitment. In addition to the safety criteria for the magnetic resonance imaging (MRI) such as metal implants or claustrophobia, general inclusion criteria were age above 17 years and sufficient command of the German language to understand task instructions and fill in questionnaires. Exclusion criteria for all participants were opioidergic or dopaminergic medication, neurological conditions, and dermatologic conditions. Healthy controls were excluded, if they reported regular use of pain medication, any medical condition, acute or ongoing pain or any psychological. Patients with fibromyalgia were included, if they fulfilled the diagnosis criteria according to Wolfe et al. (2010). Patients with back pain were included, if they reported an ongoing episode of back pain of at least three months duration. Patients were excluded if they reported any physical condition that could explain their most severe pain symptoms or if they fulfilled the criteria of a borderline personality disorder due to known alterations in pain perception in borderline personality disorder (Fales et al., 2021) and a known comorbidity with fibromyalgia (Penfold et al., 2016).

General eligibility was assessed in a telephone screening covering MRI safety criteria, current medication, and physical conditions prior to study participation. If participants reported any current or past psychological symptoms, a screening for psychological conditions based on the German version of the Structured Clinical Interview for DSM-IV (SCID) axis I (Wittchen et al., 1997) was performed. Due to known high comorbidities, the German version SCID axis I (Wittchen et al., 1997) and axis II (Fydrich et al., 1997) was performed in all patients with fibromyalgia prior to the testing

session. In patients with back pain this interview had been performed in the previous studies from which they were recruited and the respective information was used with patients' written consent. For FM, it was confirmed that they fulfilled the criterion of either a widespread pain index (WPI) score ≥ 7 and a symptom severity (SS) score ≥ 5 or a WPI score of 3–6 and a SS score ≥ 9 (Wolfe et al., 2010). In total, two patients were excluded from study participation due to indications of comorbid borderline personality disorder. Another five participants dropped out before an appointment for the experimental session could be scheduled, resulting in 29 HC, 19 FM, and 11 CBP who completed the testing. Characteristics of the sample included in the statistical analysis are reported in Table 5.

Regular use of medication was not an exclusion criterion in patients and intake was assessed via self-reports. Regular use was reported for angiotensin-converting-enzyme (ACE) inhibitors (1 FM), anticonvulsants (1 FM), antidepressants (6 FM), tumor-necrosis-factor-α (TNF-α) blocker (1 FM), L-type calcium channel blockers (1 FM), NSAIDs (17 FM, 1 CBP), other non-opioid analgesics (1 FM), quinines (1 FM), thyroid hormones (4 HC, 4 FM, 2 CBP), insulin (1 HC, 1 CBP), beta blockers (1 CBP), and proton-pump inhibitors (1 CBP). In the FM group, 14 participants fulfilled the criteria of a major depressive disorder (9 currently remitted), 3 participants fulfilled criteria of an anxiety disorder, 1 participant fulfilled the criteria of an eating disorder, and 1 participant fulfilled the criteria of a substance dependence in the past.

Based on a previous study with a similar design, a medium effect size was expected (Becker et al., 2015). Originally, it was planned to recruit patients with fibromyalgia and healthy controls. A corresponding *a priori* sample size calculation for an 80% chance to detect such an effect size at a significance level of $\alpha=0.05$ yielded a sample size of 28 participants per group (estimation performed using GPower version 3.1; (Faul et al., 2007) for a ANOVA with repeated measures and between-within interaction). Due to problems recruiting a sufficient number of fibromyalgia patients, we decided to also include participants with chronic back pain based on studies suggesting comparable alterations in reward processing and dopaminergic signaling in patients with chronic back pain and fibromyalgia (Albrecht et al., 2016; Kim et al., 2020; Martikainen et al., 2015; Wood et al., 2007).

The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, and written informed consent was obtained from all participants prior to participation according to the revised Declaration of Helsinki (World Medical Association, 2013).

3.2.2 Testing session

Each participant performed one testing session comprising familiarization and preparation in the laboratory and an MRI scanning session. In the laboratory part, after obtaining written consent, capsaicin cream was applied at the stimulation site as a pre-treatment to prepare the participants' skin for the thermal stimulation used in the main experimental paradigm (see details below). Participants were familiarized with the rating scale and the wheel of fortune game to decrease unspecific effects of novelty and saliency and they filled in several computerized and paper-pencil questionnaires. The MRI part started with an introduction to the thermal stimulation device, the response unit, and the visual display once participants were positioned on the MRI scanner bed. Threshold procedures and determination of stimulation intensities were followed by three training trials to familiarize participants with the experimental task (see details below). Image acquisition then started with the wheel of fortune task with functional magnetic resonance imaging (fMRI), followed by the acquisition of a structural image. At the end of the MRI session, participants completed an exit interview (see below) outside the scanner.

3.2.3 Wheel of fortune game

A probabilistic relief-seeking task was carried out during fMRI. This task was adapted from (Becker et al., 2015) and is described in detail in Desch et al. (2022). In each trial of the task, participants played a 'wheel of fortune' gambling task in which, unbeknown to the participants, the choice of one out of two colors (blue and pink) was associated with a higher chance (75%) to win pain relief and a lower chance (25%) of a pain increase as outcome of the game while the other color was associated with reversed outcome probabilities (counter-balanced across participants within each experimental group) while receiving a tonic heat-pain stimulus. The condition of active choice was accompanied by a passive control condition in which participants could not decide

between the two colors, but received the same nociceptive input. An additional neutral condition with no change in stimulation intensity served as control condition to estimate changes in pain perception over the course of the experiment.

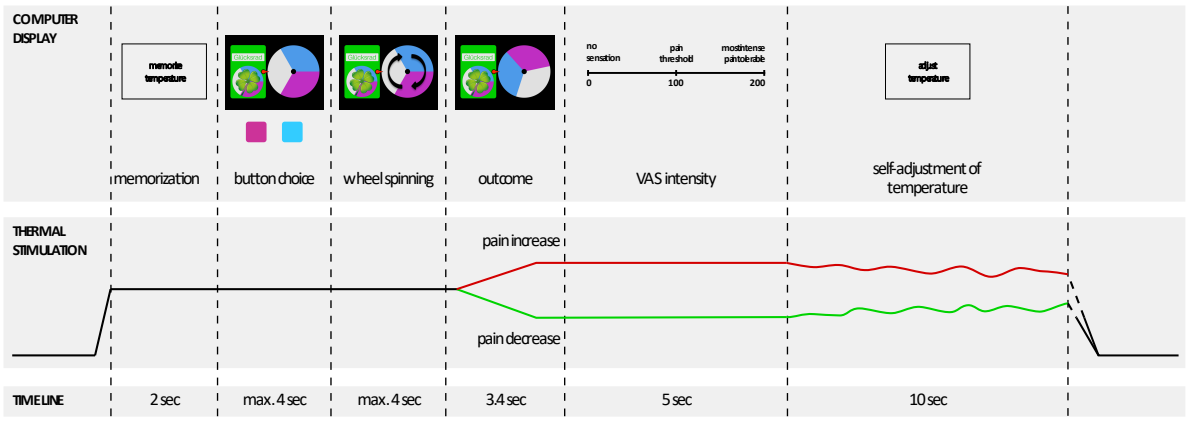

Figure 13: Time line of one trial with active decision making (test trials) of the wheel of fortune game. For each participant, one of the two colors (pink and blue) of the wheel was associated with a higher chance (75%) to win pain relief (counterbalanced across participants within each group). Pain relief (win) as outcome of the wheel of fortune game is depicted in green, pain increase (loss) in red. Trials with active decision making were complemented by passive control trials without decision making. Outcomes of active trials were repeated in subsequent control trials, resulting in the same number of pain increase and pain decrease trials as in the active condition. In passive and additional neutral trials participants did not play the game, but had to press a black button after which the wheel started spinning and landed on a random position with no pointer on the wheel. In the neutral trials, the temperature did not change during the outcome interval of the wheel. In all trial types, participants had to adjust the temperature to the sensation memorized at the beginning of the trial which provided a behavioral assessment of pain sensitization and habituation across the course of one trial. Adapted from (Becker et al., 2015).

Figure 13 depicts the course of one active decision making trial in the wheel of fortune game. After thermal stimulation increased from baseline temperature to a predetermined, moderately painful intensity at the beginning of each trial, participants were asked to memorize their current sensation (2s). In the active decision making condition (test trials), a wheel of fortune that was divided into three sections of equal size but different color (blue, pink, and white) and two buttons (blue and pink) were displayed on the screen. Participants were asked choose between blue and pink to bet on the outcome of the wheel of fortune (max. 4s) by selecting a respective button using a 4-button response unit. After pressing the button their choice was indicated by a red frame around the chosen button displayed for 0.5s before the wheel started spinning (3.6-4s). When the wheel came to a stop the pointer of the wheel indicated the outcome. If the outcome color matched the color the participants had chosen, the temperature was decreased by 3°C (pain relief, win trials), otherwise the temperature was increased by 1°C (pain increase, lose trials). In the passive condition (control trials) as well as in neutral trials, only a single black button was displayed which

participants had to press. As in the active condition, the wheel started spinning after this button press, but the wheel had no pointer and landed randomly on a color. In the passive condition (control trials), temperature changes after the wheel stopped spinning mirrored outcomes of previous trials of the active condition (test trial) to ensure the same nociceptive input across the active and the passive condition. In neutral trials the temperature did not change after the wheel came to a stop. In a 5s rating period following the outcome display of the wheel of fortune game and the respective temperature change, participants were asked to report their current perception on a visual analogue scale (VAS) scale ranging from “no sensation” (0) over “just painful” (100) to “most intense pain tolerable” (200) (Becker, Gandhi, et al., 2013; Villemure et al., 2003). After this rating, participants were instructed to re-adjust the temperature to match the sensation they had memorized at the beginning of the trial, thereby allowing for a behavioral assessment of perceptual sensitization or habituation within one trial (Becker et al., 2011, 2015; Kleinböhl et al., 1999). At the end of this 10s self-adjustment interval the temperature returned to baseline. Trials were intermitted by 5s inter-trial intervals with thermal stimulation at baseline temperature and a fixation cross on the screen. In total the experiment consisted of 45 trial split into five blocks. Each block comprised of four trials of the active condition, four control trials, and one neutral trial.

3.2.4 Thermal stimulation

All heat stimuli were applied using a 27 mm diameter contact thermode (Contact Heat Evoked Potentials, CHEPS; PATHWAY Pain & Sensory Evaluation System, Medoc Ltd. Advanced Medical System, Israel). The baseline temperature was set to 30°C. Rise and fall rates of the temperature were set to 20°C/s. To allow for potent pain relief as reward and pain increase as punishment without the risk of skin damage, all thermal stimuli were applied to the inner forearm of participants’ non-dominant hand after sensitization of the skin using 0.075% topical capsaicin cream (Becker et al., 2015; Gandhi et al., 2013). Capsaicin as the active ingredient of chili pepper induces heat sensitization of the skin by activating temperature-dependent TRPV1 (vanilloid transient receptor potential 1) ion channels (Holzer, 1991). The cream was applied to a circular area with a diameter of approximately 5cm to ensure that the entire area of

thermal stimulation was sensitized. After 20 min, the capsaicin cream was removed (Dirks et al., 2003; Gandhi et al., 2013).

3.2.5 Determination of stimulation intensities

The thermode was applied after participants were positioned on the MRI scanner bed. Before any MRI measurements started, the participants' heat pain threshold and heat pain tolerance were assessed three times each using the method of limits. The temperature of the thermode increased from baseline with 1°C/s. Participants were instructed to press the upper middle button of a 4-button response unit when they perceived the temperature as painful (pain threshold) in the first three trials and when could not tolerate stronger stimulation (pain tolerance) in the second three trials. The respective temperatures were recorded and the temperature immediately returned to baseline. The arithmetic mean of the temperatures corresponding to the recorded pain threshold and tolerance in the three trials was used as an estimate of the individual heat pain threshold and heat pain tolerance, respectively.

To obtain a stimulation intensity in the wheel of fortune task that was perceived as moderately painful, we used an additional adjustment procedure, resembling a staircase method. In each trial participants received heat stimulation of 20s duration and continuously rated the perceived intensity of the ongoing stimuli on the VAS scale described above. In the first trial, stimulation intensity was set to the mean temperature of the obtained pain threshold and pain tolerance. In each subsequent trial the temperature was adjusted until a trial a rating of 150±10 on the VAS was obtained, indicated a moderately painful stimulation intensity (for details see Desch et al., 2022).

3.2.6 Questionnaire and exit interview

To assess psychological symptoms and personality traits, all participants filled in several questionnaires. To assess depressive symptoms and depression severity, we used the German version (Hautzinger et al., 2006) of the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996), to assess general psychological strain the German version (Franke, 2000) of the Symptom Check-List-90-R (SCL-90-R; Derogatis & Cleary, 1977) and the German version (Laux, Glanzmann, Schaffner, & Spielberger, 1981) of the State-Trait Anxiety Inventory (STAI; Spielberger, Goruch,

Lushene, Vagg, & Jacobs, 1983). Subjects with chronic pain also completed the German version of the West Haven-Yale Multidimensional Pain Inventory (MPI; Flor, Rudy, Birbaumer, Streit, & Schugens, 1990) to assess components of the chronic pain experience. The affective state of participants was assessed using computerized versions of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994; Lang, 1980) and a German version (Krohne et al., 1996) of the Positive And Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). At the end of each session, after MRI scanning was completed, an exit interview was performed, asking for the following information: (1) whether participants believed that choosing one of the two colors was associated with a higher chance to win pain relief; (2) whether participants perceived a difference between test and control trials; (3) whether participants had the impression that the stimulation temperature at the beginning of each trial varied across trials; (4) whether participants had problems indicating their perception on the VAS scale; and (5) whether participants had problems readjusting the initial temperature. For all questions, participants gave first yes/no answers and then were asked to specify their answers using open-ended questions.

3.2.7 Magnetic resonance imaging acquisition

Magnetic resonance imaging was performed on a 3 Tesla Tim TRIO whole body scanner (SIEMENS Healthineers, Erlangen, Germany), equipped with a 32-channel head coil. All experimental procedures were controlled via custom-programmed Presentation scripts (Presentation® software, Version 18.3, http://www.neurobs.com/). For visual presentation we used an 18.5'' screen (G922 HDL, BenQ Corporation, Taipeh, Taiwan) located at the rear of the tube that participants could look at via a mirror construction mounted on the head coil. For all experimental procedures (pain thresholds, VAS scales, choices) participants used a 4-Button Diamond Fiber Optic Response Pad (HHSC-1X4-D, Current Designs, Inc., Philadelphia, USA). Shimming of the scanner was done to account for maximum magnetic field homogeneity and a standard gradient field map was recorded at the beginning of each measurement.

For the task-based functional MRI protocol, 51 contiguous axial slices (slice thickness: 2.5 mm, no gap, in-plain voxel size: 2 × 2 mm) were acquired using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence with generalized autocalibrating

partial parallel acquisition (GRAPPA) technique (acceleration factor 2, repetition time (TR) = 3200 ms, echo time (TE) = 30 ms, matrix size = 96 × 96, field of view (FoV) = 192 × 192 mm^2, flip angle (α) = 90°, bandwidth (BW) = 2368 Hz/px). Slices were tilted 30° clockwise from the AC-PC plane to reduce signal drop-out in orbitofrontal areas.

For structural reference, we used a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2530 ms, TE = 3.26 ms, TI = 1100 ms, matrix size = 256 × 256, FoV = 256 × 256 mm^2, flip angle (α) = 7°, bandwidth (BW) = 200 Hz/px) with 176 sagittal slices.

Field maps were obtained using a gradient echo sequence (TR = 530 ms, TE 1 = 4.92 ms, TE 2 = 7.38 ms, FoV and matrix identical to EPI).

3.2.8 Statistical analysis

3.2.8.1 Behavioral data

For the statistical analysis, 5 participants were excluded because more than 10% of the test trials (active decision making condition) were missing (due to technical failure and/or participants not responding in time). Of the remaining participants, 19 out of 2430 single trials were not recorded due to technical failure. Further, in 26 trials, participants did not press a button in time to make a choice in the wheel of fortune game. These trials were excluded from the analyses. One participant did not fill in the STAI state subscale (STAI-S).

Pain threshold and stimulation temperature as well as state measures of mood (SAM, PANAS, STAI-S) were compared between groups using standard linear models. Sample characteristics (age, BDI-II, SCL-90, STAI trait subscale) were also compared using standard linear models. The distribution of gender was compared between groups using a χ^2 test based on Monte Carlo simulation. MPI scores were compared between FM and CBP using Welch's t-test to account for unequal variances.

To confirm that the controllability manipulation by the active decision making vs. the passive condition (test vs. control trials) in the wheel of fortune game did induce endogenous pain modulation as intended, we analyzed the VAS ratings and the behavioral pain assessment as outcome measures separately within each group with

'trial type' and 'outcome' as well as their interaction as fixed effects. To account for the repeated measures design we modelled a random intercept for each participant and a random slope for outcome of the wheel within each participant.

To obtain an estimate for endogenous pain modulation in each test trial, we subtracted the mean value of all control trials of either the pain relief or the pain increase trials from the value of the winning or losing test trials for each participant for both the VAS ratings and the behavioral pain measure. For these differences, negative values indicate endogenous pain inhibition and positive values indicate endogenous pain facilitation. To compare this endogenous pain modulation, as the primary outcome measure, between the t wo groups of patients we fit linear mixed models with the fixed factors 'group' (HC, FM, CBP), 'outcome' (win, lose), and their interaction in separate models for ratings and behaviorally assessed pain perception as dependent variables. To account for the repeated measures design we modelled a random intercept for each participant. Since we did find any differences in pain modulation between the two chronic pain conditions (see Results section) all subsequent analyses were performed with three levels for the group factor (HC, FM, CBP).

To test whether participants learned to select this color preferentially based on the implemented reward contingencies, we analyzed choice behavior in the last 2 blocks of trials only. In this later phase of the task, participants already had the chance to explore differences in outcomes associated with their choices and to learn the contingencies. For this purpose, we fit a mixed-effects logistic regression with the participants' choices as dependent variable. We fit an intercept only models for the group of healthy controls, where the intercept represents the group level estimate for the probability to choose the color associated with a higher chance of winning pain relief ($choice_{high\ prob}$). We fit an additional mixed-effects logistic regression to test for differences between groups in choosing $choice_{high\ prob}$ between groups. To account for repeated measures, we modelled a random intercept for each subject.

The significance level was set to 5% for all analyses. All statistical analyses were performed using statistical computing software R version 3.5.3 (R Core Team, 2019). Mixed model analyses were performed using the *lme4* package (Bates et al., 2015). All linear mixed models were estimated using restricted maximum likelihood. Kenward-

Roger correction as implemented in the *lmerTest* package (Kuznetsova et al., 2017) was used to calculate test statistics and degrees of freedom to account for the sample size. For general linear mixed-effects models Wald χ^2 was calculated using *car* package (Fox, John & Weisberg, 2011). Post-hoc tests and effect sizes were calculated on estimated marginal means using the *emmeans* package (Lenth, 2020) where appropriate. Tukey adjustment was used to account for multiple comparisons in post-hoc tests.

3.2.8.2 Estimation of prediction errors and their role in endogenous pain modulation

The active condition of the wheel of fortune is a two alternative forced choice task. Because of the implemented a probabilistic reward schedule, participants had the chance to learn from reinforcement by the outcomes of the wheel of fortune to choose the color associated with a higher chance to win pain relief ($choice_{high\ prob}$). We used reinforcement learning (RL) models (Rescorla & Wagner, 1972; Sutton & Barto, 1998) to model such instrumental learning processes and to obtain trial-wise estimates of the expected value (Q-value) associated with a given choice and prediction errors associated with the actual outcome. Trial-wise updates of Q-values were modelled by multiplying the prediction error δ_t (defined as the difference between the current expectation Q_t and the actual outcome R_t) with separate learning rates (η_+, η_-) for positive and negative prediction errors, respectively. As the choice rule we implemented a drift diffusion process (Ratcliff, 1978; Ratcliff & Rouder, 1998), which has been shown to supersede the traditionally used soft-max choice rule (Fontanesi et al., 2019; Pedersen et al., 2017). Such drift diffusion models take response times into account and describe decisions as the accumulation of noisy evidence for two choice options until a predefined threshold (boundary), representing either of the two options, is reached. The preference for one of the two options depends on the *a priori* bias β for one of the options, the boundary separation α, that describes the speed versus accuracy tradeoff, and the drift rate ν towards one of the options. RL models that use the drift diffusion process as the choice rule map the difference between expected values for the two choice alternatives to the drift rate ν_t of the diffusion process in each single trial (Fontanesi et al., 2019; Pedersen et al., 2017). We fitted and compared the same models as in a previous study with the same experimental task (Desch et al.,

2022). Accordingly, we varied two parts of the parametrization of the RL models to test which combination of parameters would best fit the data. First, the prediction error could either be static, meaning that it was calculated as the mere difference between the outcome (coded as 1 for pain relief and -1 for pain increase) and the expected value, or scaled, meaning that the outcome was multiplied with an individual reward sensitivity parameter ρ. Second, we varied the way that the difference of expected values was mapped to the drift rate. This could either be a linear mapping, for which this difference was scaled with a single parameter ν to obtain the drift rate ν_t for a single trial (Pedersen et al., 2017), or non-linear, using a sigmoid function as suggested by Fontanesi et al. (2019). The upper and lower limit of this function are defined by $\pm\nu_{max}$, respectively, while its shape depends on the scaled difference of expected values. This variation resulted in four different models as depicted in Table 4.

Table 4*:* Model specification. Models 1-4 were defined using different combinations of parameters for reward sensitivity and the mapping of expected values to the drift rate. A 'static' reward sensitivity means that pain increase and pain decrease were defined as -1 and 1, respectively. A 'scaled' outcome sensitivity means that the outcome was multiplied by a reward sensitivity parameter ρ. A 'linear' drift rate mapping means that the drift rate ν_t for each trial was defined as the difference of expected values multiplied by the model parameter ν. A sigmoid mapping of the drift rate means that ν_t was defined by a sigmoid function bounded at $\pm\nu_{\max}$. All models included two learning rates (η_+, η_-), the non-decision time τ, the boundary separation α, and the a priori bias β.

Model	outcome sensitivity	drift rate mapping
Model 1	static	linear
Model 2	scaled	linear
Model 3	static	sigmoid
Model 4	scaled	sigmoid

The models were fitted to the participants' choices and response times in active decision making trials using hierarchical Bayesian modeling which provides reliable estimates for individual and group level parameters (Gelman et al., 2013; Kruschke, 2014). We used Hamiltonian Monte Carlo sampling with a No-U-Turn sampler as implemented in the probabilistic language Stan (Carpenter et al., 2017) via its *R* interface *rstan* (Stan Development Team, 2020) to estimate posterior distributions of the parameters. For each model parameter, we included a global intercept and the main effect of group (HC, FM, CBP). Both, intercept and main effect were allowed to vary for each participant. We used a non-centered parameterization to reduce dependency between group and individual level parameters (Betancourt & Girolami,

2015). We used the same transformations and priors as described in (Desch et al., 2022). Priors used for the main effect of group were the same as those used for the main effect of drug in the previous study and no correlation between parameters was modelled (because there were no repeated measures in this study). All models were run on four chains with 4000 samples each. The first 1000 iterations were discarded as warm-up samples for each chain. The convergence of chains was confirmed by the potential scale reduction factor $\hat{R}$.

The fitted models were compared for their best predictive accuracy using tenfold cross-validation (Vehtari et al., 2017). From the cross validation we calculated the expected log pointwise predictive density ($ELPD$) based on simulations for each hold-out set y_k using parameters estimated from re-fitting the model to the training data set $y_{(-k)}$. We calculated $ELPD$s, their differences, and the standard error of the differences using the *R* package *loo* (Vehtari et al., 2020). A higher $ELPD$ indicates a better predictive accuracy. Such a better predictive accuracy was assumed if the difference in $ELPD$ ($ELPD_{diff}$) for two models was at least 2 times the standard error of that difference ($se(ELPD_{diff})$).

For the best fitting model, we performed posterior predictive checks by simulating replicated data sets from posterior draws. As the test statistic for the posterior predictive check we examined the proportion of choices in favor of the option associated with a higher chance to win pain relief ($choice_{high\ prob}$) in the last two blocks of the wheel of fortune game and compared the proportions observed in this data to the distribution of proportions found in the simulated data sets.

From the best fitting model, we used group level estimates for the main effect of 'group' to compare model parameters between groups using the 95% highest density interval (HDI) of the difference of their posterior distributions.

The means of individual parameter posterior distributions were used to estimate prediction errors for single trials. To test whether these prediction errors predict endogenous pain modulation induced by the wheel of fortune task, we used linear mixed models with the fixed factors 'prediction error' and 'group', and their interaction. A random intercept for each subject was included to account for repeated measures.

Separate models for VAS ratings and behaviorally assessed pain perception as dependent variables were calculated.

3.2.8.3 Magnetic resonance imaging data

3.2.8.3.1 Preprocessing of magnetic resonance imaging data

Preprocessing of magnetic resonance imaging data was performed using the *fMRIPrep* pipeline, version 20.0.7 (Esteban et al., 2019; Esteban, Ciric, et al., 2020), which is based on *Nipype* 1.4.2 (Esteban, Markiewicz, et al., 2020; Gorgolewski et al., 2011). Before applying this pipeline, we performed the following preparatory steps: For two participants the anatomical T1-weighted images were corrupted. For these participants, we replaced the T1-weighted images with a study template. To create this template, we registered the T1-weighted images of all remaining participants to the structural image of one randomly chosen subject using `flirt` (FSL 5.0.9; Jenkinson & Smith, 2001) and calculated the mean of these images. The resulting mean anatomical image was used as replacements of the original corrupted anatomical scans during registration of the fMRI data. We confirmed by visual inspection that parcellation and registration to the standard space worked well for these participants. In twelve participants, the fMRI scanning had to be interrupted due to technical failures of the thermode. The scanning was resumed starting with the next the trial after the last trial completed in the wheel of fortune game. In such cases, all functional images were concatenated into a single four-dimensional image for each subject.

3.2.8.3.2 Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` (Tustison et al., 2010), distributed with ANTs 2.2.0 (Avants et al., 2008). The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9; Zhang, Brady, & Smith, 2001). A T1w-reference map was computed after registration of 2 T1w images (after INU-correction) using `mri_robust_template` (FreeSurfer 6.0.1; Reuter, Schmansky, Rosas, & Fischl, 2012). Volume-based spatial

normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* (Fonov, Evans, McKinstry, Almli, & Collins, 2009; TemplateFlow ID: MNI152NLin2009cAsym).

3.2.8.3.3 Functional data preprocessing

For the blood oxygen level dependent (BOLD) run the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A B0-nonuniformity map (or *fieldmap*) was estimated based on a phase-difference map calculated with a dual-echo GRE (gradient-recall echo) sequence, processed with a custom workflow of *SDCFlows* inspired by the `epidewarp.fsl` script (http://www.nmr.mgh.harvard.edu/~greve/fbirn/b0/epidewarp.fsl) and further improvements in HCP Pipelines (Glasser et al., 2013). The *fieldmap* was then co-registered to the target EPI (echo-planar imaging) reference run and converted to a displacements field map (amenable to registration tools such as ANTs) with FSL's `fugue` and other *SDCflows* tools. Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using `flirt` (FSL 5.0.9; Jenkinson & Smith, 2001) with the boundary-based registration (Greve & Fischl, 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL 5.0.9; Jenkinson, Bannister, Brady, & Smith, 2002). BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 (Cox & Hyde, 1997). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in*

original space, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor* Behzadi, Restom, Liau, & Liu, 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces).

Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (Abraham et al., 2014), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation (https://fmriprep.readthedocs.io/en/latest/workflows.html).

The above boilerplate text was automatically generated by *fMRIPrep* with the express intention that users should copy and paste this text into their manuscripts *unchanged*. It is released under the creative common license (https://creativecommons.org/publicdomain/zero/1.0/).

3.2.8.4 General Linear Model

Further fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: spatial smoothing using a 5-mm full width at half maximum Gaussian, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001) with regressors of interest for the anticipation (time interval when the wheel was spinning) in active (ant_{active}) and passive ($ant_{passive}$) trials, the outcome interval (starting with the temperature change until beginning of the VAS rating) separately for pain relief in active ($relief_{active}$) and passive ($relief_{passive}$) trials, and pain increase in active ($increase_{active}$) and passive ($increase_{passive}$) trials. In a second model, we included regressors for parametric modulation obtained from RL models. Specifically, we added a regressor weighted by Q values for the taken choice for the anticipation interval in active trials ($ant_{active,Q}$), and regressors weighted by the prediction error for the outcome interval in active trials separately for win ($relief_{active,PE}$) and lose ($increase_{active,PE}$) trials. We included regressors of no interest for time intervals when participants memorized the temperature at the beginning of the trials, when they made

their choice in active, passive, and neutrals trials, as well as for the intervals of ratings and temperature self-adjustment (separately for relief and increase outcomes, and for neutral trials), for choice, anticipation, and outcome intervals of discarded trials, and for the initial increase of temperature at the beginning and the return to baseline temperature at the end of each trial for both models. The model regressors were convolved with a double-gamma hemodynamic response function and the first temporal derivatives were included. Additionally, we included nuisance regressors for framewise displacement (FD), global signal, the first five CompCor components each derived from the eroded white matter and CSF masks, respectively, and for time points that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS, as extracted by *fMRIPrep*.

Group level analysis was performed using a mixed-effects model, implemented in FLAME (Beckmann et al., 2003; Woolrich et al., 2004) with separate variances for each group (HC, FM, CBP). We were interested in changes of brain activation induced by the controllability manipulation (active versus passive condition) and the parametric modulation by parameters of RL models (Q-values during anticipation and prediction errors during pain relief and pain increase). Since we did not expect large changes in brain activation related to these aspects, we specifically looked at several regions of interest that have been related to pain perception (Apkarian et al., 2005; Treede et al., 1999) and reward processing (Liu et al., 2011). Specifically, we created anatomically defined masks using the Harvard-Oxford Cortical Structural Atlas and the Harvard-Oxford Subcortical Structural Atlas (signal intensity minimum at 30%) for the primary and secondary somatosensory cortex (SI&SII), insula, nucleus accumbens (NAcc), and amygdala. Additionally, we used several masks of sub-regions of the medial frontal cortex that were found to be significantly associated to pain and/or reward in a large-scale meta-analysis (De La Vega et al., 2016). Based on this study, these sub-regions were labelled ventromedial prefrontal cortex (vmPFC), pregenual anterior cingulate cortex (pgACC), posterior dorsal (pdMCC), anterior dorsal (adMCC), posterior ventral (pvMCC), and anterior ventral (avMCC) midcingulate cortex, and supplementary motor area (SMA. Statistical inference was based on a voxel-based threshold of $z = 2.3$, cluster corrected at $p < 0.05$.

3.3 Results Study 2

3.3.1 Sample characteristics

Table 5: Participant characteristics for all participants included in the statistical analysis. Means and standard deviations for each group are displayed. BDI-II, Becks Depression Inventory; STAI-T, State-Trait Anxiety Inventory – trait subscale; SCL, Symptom Checklist; MPI, West Haven-Yale Multidimensional Pain Inventory.

	HC	FM	CBP
N	26	18	10
Age	50.5 (9.41)	51.56 (7.11)	45.7 (16.43)
Gender (m/f)	8 / 18	1 / 17	3 / 7
Global Severity Index (SCL-90-R)	0.13 (0.15)	0.76 (0.49)	0.28 (0.28)
BDI-II	2.54 (2.87)	17.33 (12.29)	7.10 (10.70)
STAI-T	30.04 (6.12)	44.67 (11.10)	34.00 (12.29)
Pain severity (MPI)		3.72 (1.00)	2.60 (0.83)
Interference (MPI)		4.09 (0.96)	1.97 (0.64)
Negative mood (MPI)		2.99 (1.18)	2.03 (1.44)
Support (MPI)		4.14 (1.77)	2.30 (1.09)
Life control (MPI)		3.47 (1.16)	4.40 (1.12)

Age and gender did not differ significantly between healthy controls (HC), patients with fibromyalgia syndrome (FM), and patients with chronic back pain (CBP) (Table 5; age: $F(2,51) = 1.09$, $p = 0.344$; gender: $\chi^2 = 4.34$, $p = 0.139$). In contrast, general psychological strain (SCL-90-R, global severity index), severity of depressive symptoms (BDI-II), and trait anxiety differed significantly between the groups (*p's* < 0.001). For all these scales, the scores were higher in FM compared to HC (*p's* < 0.001) and in FM compared to CBP (*p's* < 0.015), with no difference between CBP and HC (*p's* > 0.338). In addition, the chronic pain experience as assessed with the MPI differed between FM and CBP. Specifically, FM scored significantly higher on pain severity ($t(22) = 3.188$, $p = 0.004$), interference ($t(25) = 7.00$, $p < 0.001$), and support ($t(26) = 3.40$, $p = 0.002$), while FM and CBP did not differ significantly in

negative mood ($t(16) = 1.79$, $p = 0.093$) and life control ($t(19) = -2.08$, $p = 0.052$) as assessed with the MPI.

3.3.2 Endogenous modulation of active pain relief seeking in healthy controls

3.3.2.1 Ratings of perceived pain in the wheel of fortune task

Replicating previous results, in the group of healthy controls participants rated the thermal stimulation as less intense after actively winning pain relief compared to the passive control condition on the visual analogue scale. Furthermore, participants rated the stimulation as more intense after actively losing compared to the passive control condition (Figure 14 A; interaction 'outcome × trial type', $F(1,960) = 46.39$, $p < 0.001$; pairwise comparisons: win: test vs. control $p < 0.001$; lose: test vs. control, $p < 0.001$). This shows that active (instrumental) controllability modulates both, pain and its relief.

3.3.2.2 Behaviorally assessed pain perception in the wheel of fortune task

In contrast to the VAS ratings, behaviorally assessed pain perception did not differ significantly between test and control trials after winning as well as after losing in healthy participants (Figure 14 D; interaction 'outcome × trial type', $F(1, 960) = 2.23$, $p = 0.136$).

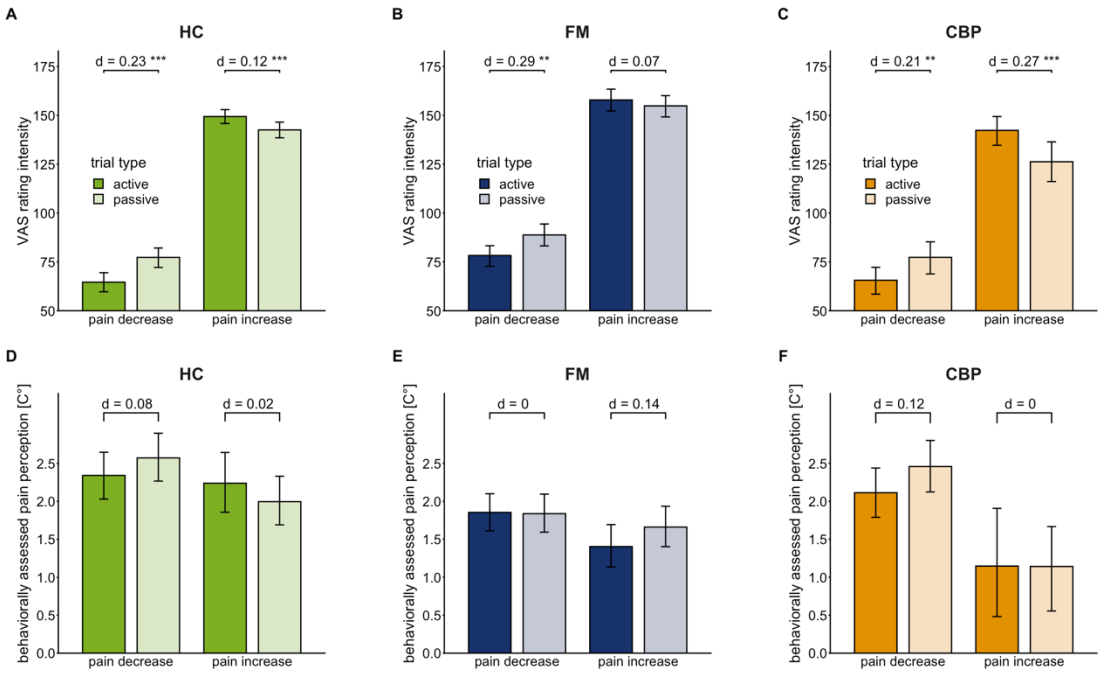

Figure 14: Means and 95% confidence intervals of means for VAS pain intensity ratings (A, B, C) and behaviorally assessed pain perception (D, E, F; within-trial sensitization in pain perception in °C) for each healthy controls (HC), patients with fibromyalgia (FM), and patients with chronic back pain (CBP). d indicates Cohen's d as standardized effect-size of estimated effects. ** $p < 0.01$, *** $p < 0.001$, for post-hoc comparisons of test versus control trials.

3.3.3 Endogenous pain modulation by active relief seeking in participants with chronic pain

We next examined whether pain sensitivity and endogenous modulation of pain perception within the wheel of fortune game was different between the two groups of chronic pain patients and healthy controls.

3.3.3.1 Pain sensitivity

HC, FM, and CPB did not show differences in their pain threshold ($F(2, 51) = 0.66$, $p = 0.523$), pain tolerance ($F(2, 51) = 0.24$, $p = 0.789$), and the individually adjusted stimulation intensity used in the wheel of fortune task ($F(2, 51) = 0.17$, $p = 0.841$). Similarly, groups showed no differences in VAS ratings in the neutral trials of the wheel of fortune game ($F(2,51) = 1.80$, $p = 0.175$) or the behavioral measure in neutral trials ($F(2,51) = 0.71$, $p = 0.496$) assessing pain perception independent of the game over the course of the experiment.

3.3.3.2 Ratings of perceived pain in the wheel of fortune task

As the HC, both FM and CPB rated the thermal stimulation as less intense after active compared to passive pain relief in the wheel of fortune task (Figure 14 B, C). In contrast, higher intensity ratings after receiving pain increases in the losing condition compared to the respective passive control condition were found in patients with chronic back pain, but not in participants with fibromyalgia syndrome (Figure 14 B, C). Overall, the effect of active relief (win) or increases (lose) of pain on pain modulation differed significantly between the three groups (interaction 'group × outcome', $F(2, 1041) = 5.39$, $p = 0.005$). However, post-hoc tests revealed that the effect of active relief (win) did not differ significantly between the groups (*p's* > 0.95). Similarly, effects of active pain increases on VAS ratings did not differ between HC and both groups of patients (post-hoc comparisons HC vs. FM: $p = 0.699$; HC vs. CBP: $p = 0.162$). But the post-hoc comparison revealed a significant larger effect of active pain increases in CBP compared to FM ($p = 0.031$), suggesting that endogenous pain facilitation in the losing condition is differentially affected in the two chronic pain conditions. Endogenous pain modulation did not show any associations with any of the clinical scores in neither the win nor the lose condition (*p's* > 0.604, Bonferroni corrected for multiple comparisons).

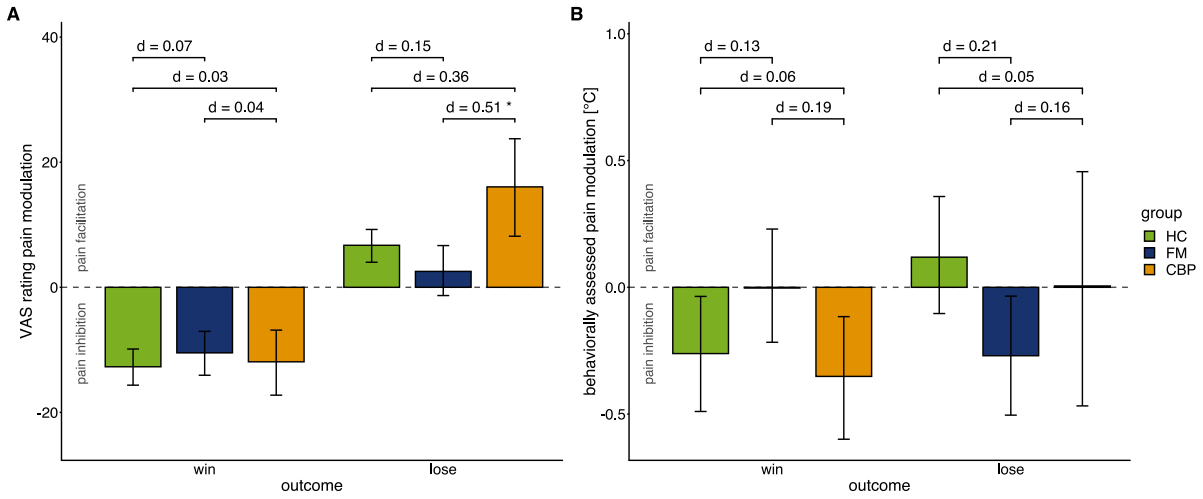

Figure 15: Endogenous pain modulation assessed by VAS ratings of pain intensity (A) and behaviorally assessed pain perception (B) after winning and losing in the wheel of fortune game. HC, healthy controls; FM, patients with fibromyalgia; CBP, patients with chronic back pain. Error bars show 95% confidence interval of the mean. d indicates Cohen's d as standardized effect-size of estimated effects.

Table 6: Means and standard deviation for pain modulation in VAS ratings of perceived intensity and the behaviorally assessed pain perception (negative values indicate pain inhibition; positive values indicate pain facilitation). HC, healthy controls; FM, patients with fibromyalgia syndrome; CBP, patients with chronic back pain.

	pain modulation in VAS ratings of pain intensity						pain modulation in behavioral measure (°C)					
	HC n = 26		FM n = 18		CBP n = 10		HC n = 26		FM n = 18		CBP n = 10	
outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
win	-7.31	21.51	-12.98	23.54	-10.09	23.79	-0.09	0.64	-0.14	0.66	-0.05	0.74
lose	12.21	21.12	13.29	20.48	12.26	22.27	0.03	0.59	0.03	0.54	0.06	0.68

3.3.3.3 Behaviorally assessed pain perception in the wheel of fortune task

Similar to the results in healthy controls, no significant differences of the effects of active pain relief or increase compared to the passive control conditions were found in FM and CBP in the behaviorally assessed pain perception (Figure 14 E & F). Across HC, FM, and CBP, behaviorally assessed pain modulation differed significantly (interaction 'group × outcome': $F(2, 1057) = 3.57$, $p = 0.029$; Figure 15 B). However, post-hoc comparisons did not reveal any significant differences between these groups after either pain decrease (*p's* > 0.37) or pain increase (*p's* > 0.16) when corrected for multiple comparison.

3.3.4 Reinforcement learning in the wheel of fortune

Based on the probabilistic reward schedule in the active condition of the wheel of fortune task, we were able to investigate whether active relief seeking had an impact on choice related to reinforcement learning. Specifically, we tested whether the proportion of choices of the more rewarding option ($choice_{high\ prob}$) was higher in the last two out of five blocks of four test trials each of the game, when the participants already had the chance to explore and learn the different outcome probabilities. On average, neither HC, nor FM or CBP chose the color associated with higher chance to win relief above chance (all *p's* > 0.36). Correspondingly, the proportion of choices in favor of $choice_{high\ prob}$ did not differ between the groups ($\chi^2(2) = 0.76$, $p = 0.685$).

3.3.5 Unpredictability and endogenous pain modulation

We next tested whether endogenous pain modulation was associated with the unpredictability of outcomes in the wheel of fortune game. To this end, we fitted different reward learning models, with a drift diffusion process as the choice rule to participants' choice and reaction time data. The best predictive accuracy was found for model 3 that modelled pain relief as positive (+1) and pain increases as negative (-1), and a sigmoid function to map expected values for the two choices to the drift rate of the diffusion process (Table 7; see *Methods*, section *Estimation of prediction errors and their role in endogenous pain modulation* for details on parametrization of reward learning models).

Table 7: Model comparison. Models are ordered by their expected log pointwise predictive density (*ELPD*). $ELPD_{diff}$: difference to the *ELPD* of winning model 3. $se(ELPD_{diff})$: standard error of the difference in *ELPD*.

Model	*ELPD*	$ELPD_{diff}$	$se(ELPD_{diff})$
Model 3	-475.39	0	0
Model 4	-481.97	-6.58	9.61
Model 2	-571.97	-96.58	14.38
Model 1	-572.26	-96.86	14.77

Highest density intervals (HDI) of posterior predictive simulations from the best-fitting model cover all the observed proportion of choices in favor of the more rewarding option, suggesting that the model adequately describes the data (Figure 16).

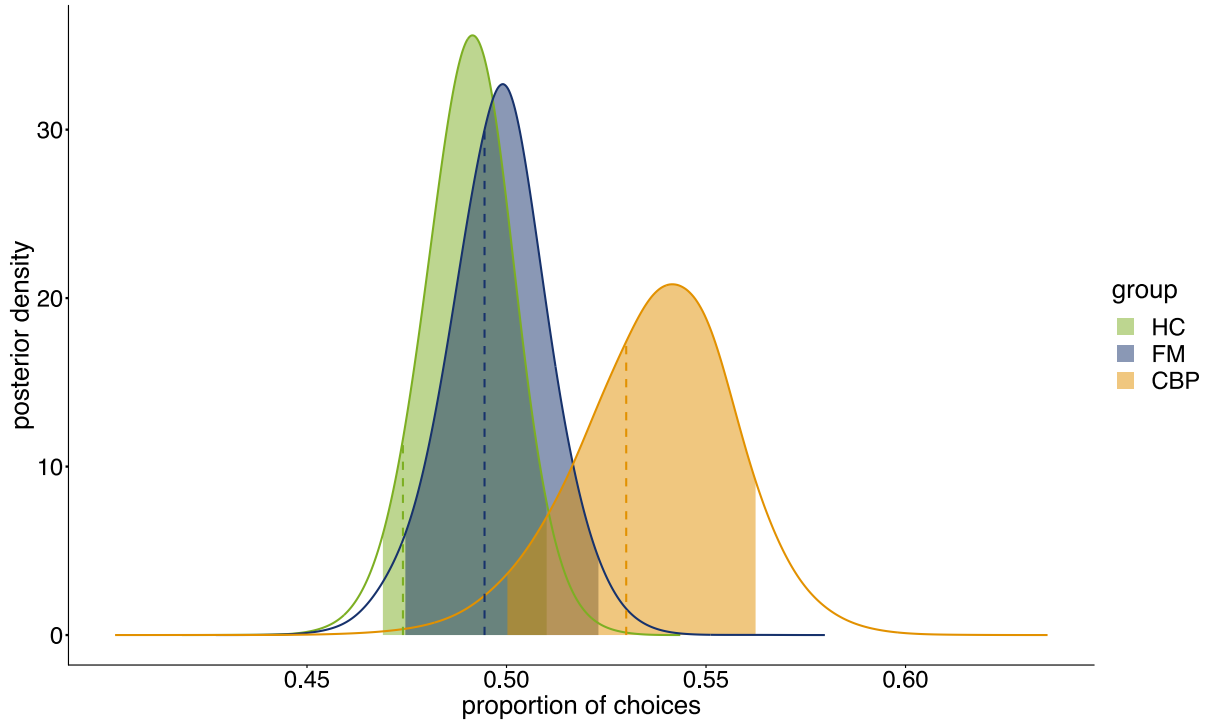

Figure 16: Posterior distribution of the proportion of choices in favor of $choice_{high\ prob}$. HC, healthy controls, FM, patients with fibromyalgia syndrome, CBP patients with chronic back pain. Colored areas show 95% highest density interval (HDI_{95}). Dashed lines indicate observed proportion of choices in favor of $choice_{high\ prob}$ HC: $p(choice_{high\ prob})$ = 0.474, HDI_{95} = [0.469,0.510], posterior p-value (*pp*) = 0.936); FM: $p(choice_{high\ prob})$ = 0.494, HDI_{95} = [0.475,0.523], *pp* = 0.605; CBP: $p(choice_{high\ prob})$ = 0.530, HDI_{95} = [0.500,0.563], *pp* = 0.663.

Based on the 95% HDI (HDI_{95}), the posterior distribution of group level differences indicated a stronger bias β for the more favorable option in FM compared to HC, indicating that FM needed less information to favor $choice_{high\ prob}$ (Figure 17). All other HDI_{95} for the difference between group level parameters enclosed zero, indicating no strong evidence for group differences. Nevertheless, weak evidence, i.e. 85% HDI of differences between group level parameters not covering zero, was found for a higher learning rate for positive prediction errors (η_+), a shorter non-decision time τ (relative to the participants' minimum reaction times), and the shape parameter of the sigmoid function ν in CBP compared to HC. The shape parameter ν in the model has a similar effect as the inverse-temperature parameter implemented in models that use a softmax function as the choice rule. Higher values of ν indicate more deterministic choices of the option associated with a higher expected value, while lower values indicate more random choices or explorative behavior. Thus, choices in CBP were less deterministically based on expected values than in HC.

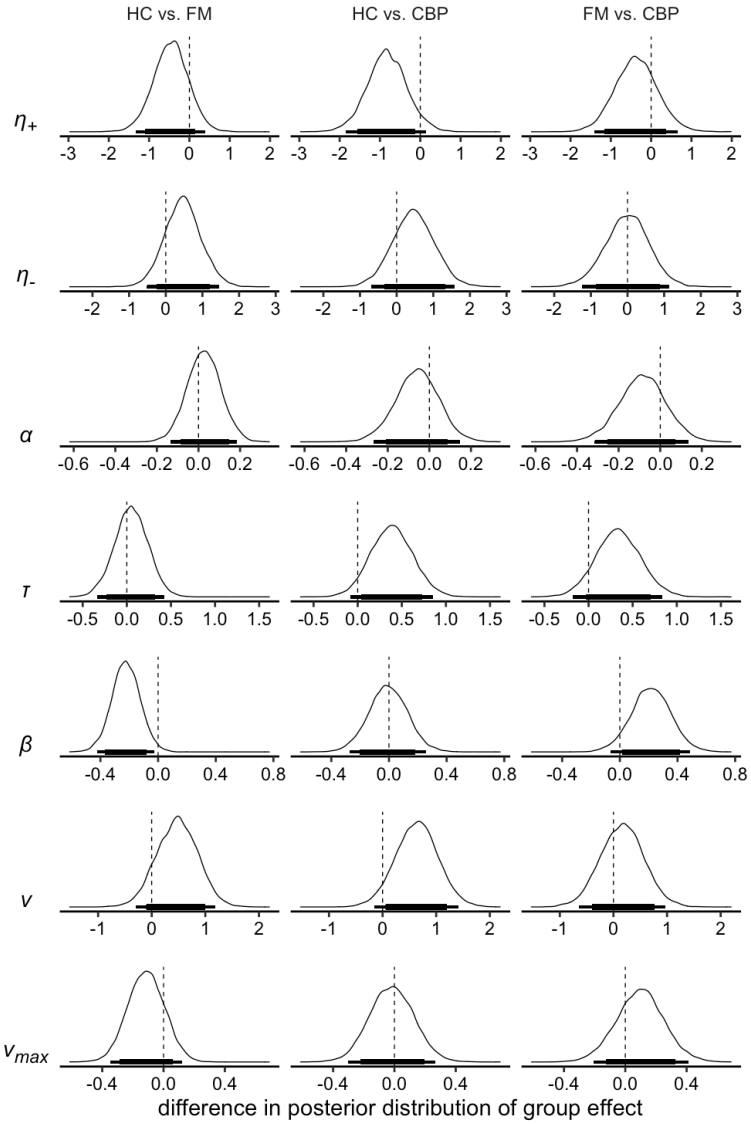

Figure 17: Differences of the posterior distributions of group level parameters for the main effect in model 3. Thick black bars indicate the 85% HDI, thin bars indicate the 95% HDI. η_+: learning rate for positive prediction errors; η_-: learning rate for negative prediction errors; α: boundary separation; τ: non-decision time; β: a-priori bias; ν: shape parameter of sigmoid function; ν_{max}: drift-rate boundary.

When comparing the distributions of estimated learning rates for positive and negative prediction errors between groups (Figure 18), weak evidence suggests a higher learning rate for negative compared to positive prediction errors in HC (Figure 18; η_+: mean = 0.203, HDI_{95} = [0.119, 0.294]; η_-: mean = 0.327, HDI_{95} = [0.189, 0.477]). HDI_{95} of the differences in estimates for the two learning rates in patients all covered zero. Nevertheless, they did not show the same asymmetry in the relationship of learning rates: in FM estimates showed almost identical learning rates for positive and negative prediction errors (η_+: mean = 0.287, HDI_{95} = [0.156, 0.419]; η_-: mean = 0.236, HDI_{95} =

[0.111, 0.365]), while in CBP the mean of the learning rate for positive prediction errors was higher compared to that for negative prediction errors (η_+: mean = 0.366, HDI_{95} = [0.197, 0.549]; η_-: mean = 0.242, HDI_{95} = [0.094, 0.419]), suggesting an inverse pattern compared to HC.

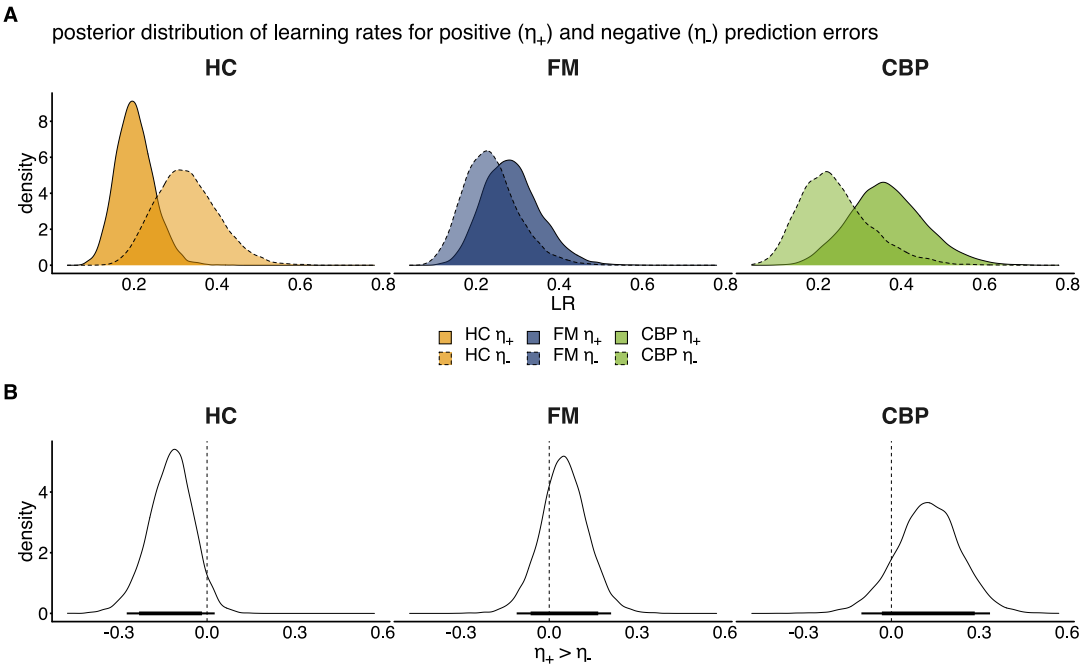

Figure 18*:* (A) Posterior distribution of learning rates (unconstrained group level parameters transformed to the range of [0,1] using inverse logit transformation) for positive (η_+) and negative (η_-) prediction errors for healthy controls (HC), patients with fibromyalgia (FM), and patients with chronic back pain (CBP). (B) Posterior distribution of the difference between learning rates for HC, FM, and CBP. Thick black bars indicate the 85% HDI, thin bars indicate the 95% HDI.

Replicating previous results (Desch et al., 2022), we found that prediction errors estimated by using subject level parameters of the model showed a significant main effect for the prediction of endogenous pain modulation indicated by VAS ratings across all groups ($F(1, 1024) = 114.59$, $p < 0.001$). As indicated by the negative estimate of the prediction error (β_{PE} = -0.30), better than expected outcomes (positive prediction errors) were related to increased relief perception while worse than expected outcomes (negative prediction errors) were associated with increased pain facilitation (Figure 19). That is, the more unexpected the outcome, the stronger is the endogenous modulation towards relief or pain, respectively.

The effect of prediction errors on pain modulation differed significantly between groups ($F(2, 1025) = 4.851$, $p = 0.008$). Post-hoc comparisons confirmed that the negative linear relationship significantly differed from zero for all groups (p's < 0.001) and this relationship was significantly stronger in CBP compared to FM ($p = 0.005$). No differences of this relationship were found between HC vs. FM ($p = 0.295$) and HC vs. CBP ($p = 0.095$).

Across all groups, the estimated prediction errors did not show a significant main effect for the prediction of behaviorally assessed pain modulation ($F(1, 1032) = 0.46$, $p = 0.496$).

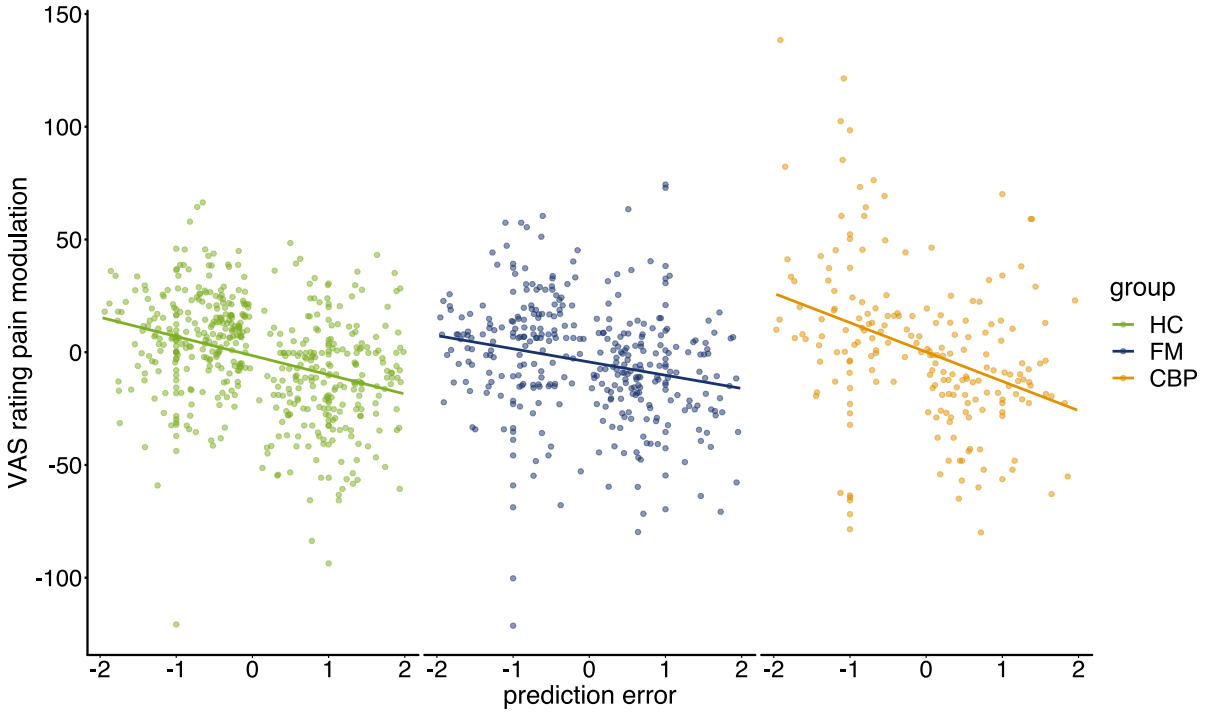

Figure 19: Pain modulation in VAS ratings predicted by prediction error for each group: HC, healthy controls; FM, patients with fibromyalgia syndrome; CBP, patients with chronic back pain. Regression lines indicate prediction from the mixed effects model with predictors 'PE', 'group', and their interaction.

3.3.6 Functional magnetic resonance imaging results

As a manipulation check, we first assessed brain responses to pain increase versus pain relief independent of the active and passive condition in the wheel of fortune game across the outcome and the rating interval. Pain increase compared to pain relief resulted in significant activation in the insular cortex contralateral to the site of

stimulation in each of the groups, with no differences in activation between these groups (Figure 20, Table 8).

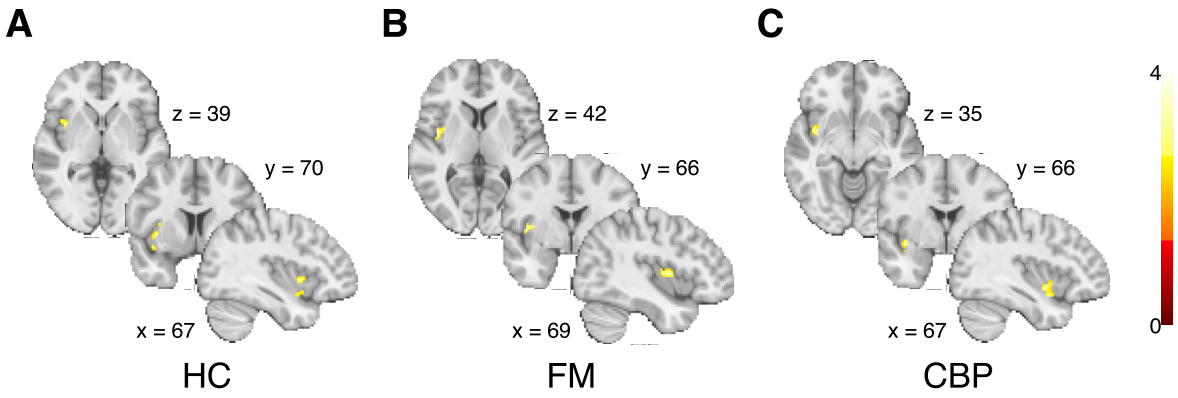

Figure 20: Increased activation in response to pain increase compared to pain relief in the insular cortex in healthy controls (HC), patients with fibromyalgia (FM), and chronic back pain patients (CBP). Color scale shows z scores (corrected within given mask at z > 2.3, cluster-based threshold p < 0.05). Slices are positioned at peak z-values for each group, voxel coordinates given w.r.t. to MNI152NLin2009c template (Fonov et al., 2009).

Table 8: Brain activation greater in response to pain increase compared to pain relief (corrected within given mask at z > 2.3, cluster-based threshold p < 0.05). Voxel coordinates are given w.r.t. to MNI152Nlin2009c template (Fonov et al., 2009). pvMCC, posterior ventral midcingulate cortex. HC, healthy controls; FM, patients with fibromyalgia; CBP, patients with chronic back pain.

Mask	Group	Cluster size (voxels)	z score peak	Peak coordinates (voxels)		
				x	y	z
Insular cortex	HC	100	3.02	67	70	39
	FM	65	3.28	69	66	42
	CBP	78	3.17	67	66	35
pvMCC	HC	57	3.23	50	70	59

As one main focus, we assessed brain activation induced by the controllability manipulation, i.e. the active versus passive condition, looking at the contrasts ([$relief_{active}$ vs. $relief_{passive}$] and [$increase_{active}$ vs. $\mathrm{increase}_{\mathrm{passive}}$]). No significant

brain activations could be found in these contrasts in neither of the a priori defined regions of interest.

Nevertheless, when including the parameters derived from the RL models in the fMRI analyses (model 2), we found that the expected values (Q values) of the participants' choices were negatively associated with activation in the pgACC in HC (Figure 21, Table 9), suggesting that activation in this area decreases the more positive and increases the more negative the outcome expectation for the selected choice is. No similar association with the expected value (Q value) was found in FM or CBP, but the negative association was found to be significantly stronger in HC compared to FM. In addition, prediction errors after winning were also negatively associated with activation in the pgACC in HC. In other words, expected compared to surprising positive outcomes are associated with more activation in this the pgACC. As before, a similar but weaker association was found in FM compared to HC.

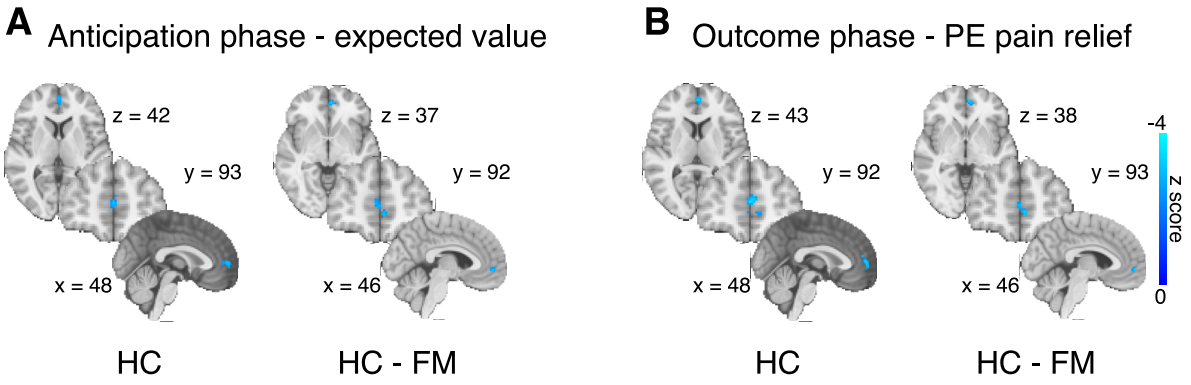

Figure 21: Parametric modulation of pregenual anterior cingulate cortex (pgACC) activation by expected value (A) and prediction errors in pain relief trials (B) in healthy controls (HC) and HC compared to patients with fibromyalgia (FM). Color scale shows z scores (corrected within given mask at $z > 2.3$, cluster-based threshold $p < 0.05$).

Table 9: Cluster sizes and peak z scores (corrected within given mask at z > 2.3, cluster-based threshold p < 0.05) for parametric modulation of activation in regions of interest by expected value and prediction errors in pain relief. Voxel coordinates are given w.r.t. to MNI152NLin2009c template (Fonov et al., 2009). pgACC, pregenual anterior cingulate cortex; NAcc, nucleus accumbens; HC, healthy controls; FM, patients with fibromyalgia.

Parametric modulation	Mask	Group	Cluster size (voxels)	z score peak	Peak coordinates (voxels)		
					x	y	z
expected value	pgACC	HC	66	-3.19	48	93	42
		HC > FM	100	-3.19	46	92	37
prediction error pain relief	pgACC	HC	110	-3.56	48	92	43
		HC > FM	42	-3.35	46	93	38
	NAcc	HC > FM	16	-3.05	54	69	34

3.3.7 Mood and affect

The groups did not differ in terms of *positive affect* ($F(2, 51) = 0.175$, $p = 0.184$) but in *negative affect* ($F(2, 51) = 7.42$, $p = 0.002$) assessed using the PANAS scales. Post-hoc tests showed that the *negative affect* was stronger in FM compared to HC ($p = 0.002$) and compared to CBP ($p = 0.013$) but did not differ between HC and CBP ($p = 0.982$). The groups also differed significantly in *arousal* ($F(2, 51) = 4.89$, $p = 0.011$), *dominance* ($F(2, 51) = 6.11$, $p = 0.004$), and *valence* ($F(2, 51) = 4.55$, $p = 0.015$) assessed using the SAM. Post-hoc comparisons showed that *arousal* was higher in FM compared to HC ($p = 0.033$) and compared to CBP ($p = 0.023$) with no difference between HC and CBP ($p = 0.725$). *Dominance* was lower in FM compared to HC ($p = 0.003$), with no difference compared to CBP ($p = 0.424$) and between FM and CBP ($p = 0.287$). Similarly, *valence* was lower in FM compared to HC ($p = 0.011$), with no difference between HC and CBP ($p = 0.700$) or between FM and CBP ($p = 0.265$). State anxiety assessed via STAI-S differed significantly between groups ($F(2, 50) = 6.06$, $p = 0.004$), with higher scores in FM compared to HC ($p = 0.004$), but no difference compared to CBP ($p = 0.068$) and no difference between HC and CBP ($p = 0.914$). Importantly, none of these assessments of mood and anxiety was associated with endogenous pain modulation after winning or losing in the wheel of fortune (all *p's* > 0.200, Bonferroni corrected for multiple testing).

3.4 Discussion Study 2

The present results replicate previous findings of endogenously enhanced pain relief perception by active decision making, but these effects were unexpectedly not different in chronic pain patients. Both, patients with FM and CBP, showed endogenous pain inhibition after active vs. passive relief reception comparable to HC. Similarly, an association of prediction errors with endogenous pain modulation, as found before, was not different between patients with chronic pain and HC. These findings suggest that motivationally driven enhancement of relief perception is a robust phenomenon that seems to survive maladaptive changes of pain chronification. Nonetheless, neural correlates point to dampened activation associated with learning from active pain control in chronic pain compared to HC.

Endogenous modulation of nociceptive signaling likely serves the purpose of optimizing its role as a learning signal, thereby facilitating prospective behavior to minimize future harm (Seymour, 2019). Accordingly, perception of pain and pain relief should be enhanced when this promotes escape from or avoidance of pain depending on the situational and motivational context. Hence, the modulatory effect should be stronger when pain or relief result from a controllable action (reinforcing the respective behavior) and when the result of the action is relatively unexpected (increasing the update of expectations) (cf. Seymour, 2019). Correspondingly and confirming our hypothesis, we found the modulatory effect of active relief to be enhanced in HC as indicated by ratings of perceived intensity.

However, contrary to our hypothesis, this effect was not impaired in patients with chronic pain. This hypothesis was based on the assumption that reward processing is impaired in chronic pain (Borsook et al., 2016; Mitsi & Zachariou, 2016). Further, conditioned pain modulation (CPM), considered as an indicator of the capacity for endogenous pain inhibition (Yarnitsky, 2010), has been found to be impaired in chronic pain patients (Lewis et al., 2012), although results are heterogenous, suggesting that underlying mechanisms might be differentially affected depending on the specific pain condition (Gerhardt et al., 2017). Differential impairments among different pain conditions point to a complex picture regarding altered mechanisms of endogenous

pain modulation in chronic pain (Fernandes et al., 2019). Accordingly, it could be assumed that reward-induced pain inhibition relies on different underlying processes.

Another example of endogenous pain inhibition resulting from learned expectations of pain relief is placebo analgesia. In line with our results, several studies suggest that placebo analgesia is not altered in chronic pain patients (Frangos et al., 2021; A. Power et al., 2020). Interestingly, placebo-analgesia has been linked to dopaminergic and opioidergic neurotransmission in brain areas associated with reward processing such as NAcc (Scott et al., 2008). Specifically, opioid receptor antagonists have been shown to reduce the pain-inhibitory effects of placebos (Benedetti, 1996; Eippert, Bingel, et al., 2009). In contrast, we found in a previous study evidence for the involvement of dopamine in endogenous pain modulation by rewarding pain relief, but no evidence for the involvement of opioids (Desch et al., 2022), hinting at mechanistic differences between these two phenomena.

Unlike pain inhibition, endogenous pain facilitation induced by receiving pain increases in active vs. passive states was found in HC and CBP, but not in FM in the present study. A role of endogenous pain facilitation in chronic pain has been discussed, implying increased facilitation in FM (O'Brien et al., 2018; Staud et al., 2001, 2003) while findings in back pain patients are inconsistent (Aspinall et al., 2020; Den Bandt et al., 2019). Endogenous pain facilitation is typically assessed by testing temporal summation, in which pain facilitation is reflected by increased perceived pain with repeated or tonic stimuli of the same intensity. However, the resulting pain facilitation might reflect state-based predictions that increase motivation to escape the painful situation rather than providing information relevant to guide prospective behavior. Thus, while the comparatively long stimulation in the current paradigm might have induced some temporal summation, likely a different mechanism was involved here as well.

Replicating previous results (Desch et al., 2022), endogenous pain modulation in the wheel of fortune game scaled with the extent to which changes in pain as the outcomes of the game were unexpected (indicated by prediction errors). This supports the view that perception of pain is intrinsically modulated according to its informational value (Seymour, 2019). We found no evidence that this association differed in pain patients

compared to HC, although an increase in the strength of this association was found in CBP compared to FM. Albeit the finding has to be interpreted with caution given the present sample sizes, this result might give some hints on less impairment of learning in CBP compared to FM. Similarly, Kim et al (2020) found stronger impairments of reward related behavior in FM compared to CBP that was paralleled by stronger depressive symptoms and anhedonia. Even though not related to endogenous pain modulation in our study, we also found stronger depressive symptom intensity, higher general psychological strain, and higher trait anxiety in our sample of FM compared to CBP.

Despite the fact that none of the groups showed a bias towards selecting the more rewarding option in the wheel of fortune, computational modelling results hint at a difference in underlying cognitive processes. Such discrepancies between model parameters and observed choice behavior have been described before in studies on drug effects on reinforcement learning (Chakroun et al., 2020; Jepma et al., 2022) and suggest that different underlying processes can results in comparable behavioral outcomes. Although not more successful, FM needed less evidence to choose the more rewarding option and it seems that CBP updated their expectations stronger following pain relief, but at the same time based their decision less strongly on expected values. With regard to underlying mechanisms, a recent study suggests that positive and negative prediction errors contribute differentially to updating expectations based on different underlying neural circuits (Jepma et al., 2022). Specifically, Jepma et al. (2022) found stronger learning rates for received compared to avoided pain in a pain avoidance task. In line with this finding, we found that in HC negative prediction errors when receiving pain had a stronger effect on updating expectations compared to positive prediction errors when receiving pain relief. Moreover, this pattern appears altered in chronic pain: While we found no considerable difference between learning rates in FM, this pattern was reversed in CBP, i.e. these patients showed stronger learning based on positive prediction errors.

Validating the principal strategy of the experimental task used here, we found that comparatively small increases vs. decreases in stimulation intensity were reflected in increased activation in the insular cortex contralateral to the stimulation site independent of the active/passive condition in the wheel of fortune. The insula is known

to be a central hub in the processing of painful stimuli (Apkarian et al., 2005; Schweinhardt & Bushnell, 2010; Segerdahl et al., 2015; Wiech & Tracey, 2009). In contrast and contrary to our hypothesis, we did not find any differences in brain activation between the active vs. passive condition corresponding the perceived changes in pain, neither pain relief nor in the pain increase trials. However, Becker et al. (2017) found as well no brain activation that was directly related to perceived reward-induced pain inhibition, but rather a more complex network of brain areas that seem mediate this pain reward interaction.

Nevertheless, changes in brain activation corresponding to experimentally induced endogenous pain modulation have been reported in different contexts before, for example related to perceptual modulation by expectations (Atlas et al., 2010), the context of relative pain relief (Leknes et al., 2013), and viewing positively valued images (Younger et al., 2010). One methodological aspect in which our study differed was that we compared brain activation related only to a small change in temperature during ongoing stimulation while the previous studies all compared longer intervals of the complete stimulation phase. Possibly, this has impacted the power in our study to find related brain responses. However, the aim of investigating the mechanisms of pain relief necessarily comes with such restrictions because it requires the preceding induction of pain.

Modulation of perceived pain intensity by expectations has been associated with activations in the anterior cingulate cortex and anterior insula (Atlas et al., 2010; Leknes et al., 2013; Younger et al., 2010). We aimed to characterize brain responses related to expectations of pain relief and pain increases (anticipation) and violation of such expectations (prediction errors during outcome) based on computationally modelling of choice behavior. With that, we found that both expectations during anticipation and reward prediction errors were inversely related to activation in the pgACC in HC. Similarly, Atlas et al. (2010) found pgACC activation to be negatively related to perceived pain intensity, suggesting a role of the pgACC in endogenous pain modulation. This assumption is supported by several studies on placebo analgesia and uncontrollability of pain, in which a role of the pgACC in mediating pain modulation via opioidergic activity and/or connectivity to areas such as amygdala and the PAG has been reported (Bingel et al., 2006; Eippert, Bingel, et al., 2009; Salomons et al., 2007,

2015). Specifically, Atlas et al. (2010) found stronger activation in the pgACC during low painful stimulation when low pain was expected (as opposed to moderate and high pain) compared to during moderately painful stimulation when high pain was expected (i.e. positive prediction error). Similarly, the inverse relationship of pgACC activation and positive prediction errors in our study suggests relatively higher activation, when relief was expected, and lower activation when the outcome was better than expected. Focusing on instrumental relief learning and complementing the results, Zhang et al. (2018) found increased activation of the pgACC and decreased perceived pain when uncertainty of expected outcomes was high (i.e. high absolute prediction errors). This finding suggests that pain modulation mediated by pgACC activation supports learning from pain related reinforcement. However, our finding that neural correlates of model-based parameters of relief learning in the pgACC were dampened in FM compared to HC emphasizes the need to investigate the specific brain circuits that mediate reinforcement by pain relief engages. Although impaired responses to anticipation of passive pain and pain relief (Loggia et al., 2014) and reduced functional connectivity in reward related circuits (Park et al., 2022) have been shown in FM, results on neural correlates of reward processing remain heterogenous (Kim et al., 2020; Martucci et al., 2018).

3.4.1 Limitations

Difficulties in the recruitment process forced us to include patients with different chronic pain conditions, resulting in a heterogenous sample. Hence, the informative value of group differences in the current study is limited due to the small sample sizes of the patient groups. In addition, the power to detect potential group effects was low. Differences between FM and CBP may point to differential impairments in pain modulation and relief related learning for these pain conditions, but future studies need to replicate these findings. The assumption of interrupted reward processing is commonly based on affective symptoms and a high comorbidity with depression (Apkarian et al., 2013; Borsook et al., 2016). Similarly, some studies showed an association of symptom severity with alterations in reward related tasks (Apkarian et al., 2004; Kim et al., 2020). Despite significant differences in psychological burden

between FM and CBP in our sample, we found no association of pain modulation and symptom severity.

In contrast to earlier findings (Becker et al., 2015), we found a pain modulatory effect in ratings of perceived intensity, but did not find a comparable modulation in our behavioral assessment of pain perception. In contrast to this previous study, the temperature steps used as outcomes in the current experiment were considerably smaller (increases of +1°C instead of +5°C and decreases of -3°C instead of -7°C) which may have reduced the effects on the behavioral discrimination task. Similarly, while we have previously shown that participants were able to learn from reinforcement by pain relief and pain increases in the wheel of fortune game (Desch et al., 2022), we could not replicate this finding here. A major difference to that previous study was the implementation of the paradigm in the context of the fMRI measurement. The environment in the scanner may have distracted participants and thereby prevented them from acquiring awareness of differences in reward probabilities.

In summary our results show that pain modulation by rewarding pain relief is a robust phenomenon and that pain inhibition by rewarding pain relief does not appear to be affected in chronic pain conditions. Similarly, an association of endogenous pain modulation with prediction errors did also not differ in patients with chronic pain. However, further research is needed to enhance our understanding of how neural mechanisms subserve the effects of reward related endogenous modulation of pain perception and learning from pain relief.

4 GENERAL DISCUSSION

The aim of the present thesis was to investigate the specific mechanisms underlying the endogenous modulation of pain relief in a motivated state and its role in reinforcement learning. Pain is not a constant or static perception. In contrast, perceived pain intensity can change from moment to moment. However, these fluctuations in perceived pain do not necessarily mirror changes in the nociceptive input. Endogenous mechanisms appear to integrate nociceptive input with other information to form what is then consciously perceived as pain. The role of the pain system in protecting the organism by selecting and adjusting behavioral responses based on current needs emphasizes that pain perception serves as a behavioral control signal that promotes motivational drives. Hence, endogenous modulation of the pain perception enables the pain system to provide optimized signals that guide adaptive behavior (Seymour, 2019). Specifically, when in pain there is a strong motivation to escape the painful situation. With that pain relief becomes an important goal, eliciting a strong positive motivational drive. Endogenous mechanisms should therefore enhance the perception of pain relief in behaviorally relevant contexts.

Endogenous pain modulation plays an important role in solving motivational conflicts in case of concurrent and competing motivations. In addition, learning from pain and pain relief is also crucial to minimize and avoid harm in the future. To investigate psychobiological mechanisms of endogenous pain modulation in the context of relief seeking the studies described in this dissertation used a ‘wheel of fortune’ gambling task with pain relief and pain increases implemented as wins or losses. The task allows to asses endogenous pain modulation by comparing perceived pain between an active choice condition and a passive control condition in which outcomes are not related to the participants’ behavior. In this task, which represents an extension of the task used by Becker et al. (2015), we implemented probabilistic reward contingencies that provided the chance to learn over the course of playing the game, which choice was associated with a higher chance of winning pain relief. This modification of the experimental task allowed investigating whether pain relief as reward is capable of inducing reinforcement learning and how endogenous modulation is involved mediating learning from pain relief.

Based on this experimental task, two studies were implemented to investigate neurobiological mechanisms in pain relief as reward and whether endogenous modulation of pain relief or relief related learning were altered in chronic pain. The aim of the first study was to investigate how the informational content of pain relief affects endogenous modulation of relief perception and to scrutinize the contribution of dopaminergic and opioidergic signaling in this modulation and related instrumental learning. This study showed that pain relief was enhanced when obtained in a motivated state and that pain modulation was stronger the more unexpected outcomes were, that is when changes in pain intensity carried new information that could aid learning of adaptive behavior. Moreover, the effects of active decision making and unpredictability were enhanced by dopamine, suggesting that dopamine plays an important role in processing informational aspects that are relevant for control of prospective behavior. In contrast and contrary to the initial hypothesis, blockade of endogenous opioid receptors did not affect endogenous modulation of pain relief. In the placebo condition, i.e. with no pharmacological manipulation, participants learned to select the choice that was associated with a more favorable outcome more frequently, indicating successful reinforcement learning. This effect was not found under enhanced dopamine availability or blockade of opioid receptors.

The second study focused on reward related endogenous modulation of pain and pain relief perception and its neural correlates in healthy controls and in patients with chronic pain. In this study we replicated the finding of enhanced pain modulation as a result of active decision making and the association of stronger pain modulation with higher uncertainty of the outcome. Surprisingly, these effects did not differ in patients with chronic pain compared to healthy controls. In this study, in which participants performed the task during fMRI scanning, we found no impact of relief seeking on choice behavior in the sense of reinforcement learning. However, computational modelling of instrumental learning and associated neural correlates point to alterations of the underlying mechanisms.

4.1 Psychobiological mechanisms of pain modulation by rewarding pain relief

Both studies consistently showed that obtaining pain relief as a result of active decision making induces enhanced perception of pain relief when compared to a passive control condition. While it was previously shown that pain relief obtained in a motivated state results in increased relief perception (Becker et al., 2015), the studies presented here demonstrated this effect in a probabilistic relief seeking task, in which there was an operant contingency between actions and outcomes. Pain increases obtained during active decision making resulted in higher pain ratings compared to the control condition with passive increases. This demonstrates that the pain modulation induced by active controllability is not comparable to unspecific effects of distraction or arousal caused by playing the game, which should have inhibited pain perception in both outcome conditions.

The perceptual modulation of both, pain relief and pain increases, is in line with current models of endogenous pain modulation (Fields, 2018; Seymour, 2019). According to Fields (2018), a reduction in nociceptive input can be interpreted as predicting decreasing threat of tissue damage, while increases in nociceptive input predict stronger or prolonged pain. Endogenous modulation that amplifies both pain relief and pain increases serves to convey the saliency that changes of nociceptive input have for subsequent behavioral decisions. Seymour (2019) conceptualizes pain as a behavioral control signal with the main purpose not only to select beneficial responses in a current situation, but to also learn from experiences to mitigate and avoid future harm (S. Zhang, Mano, et al., 2018). In this perspective modulation of pain perception should enhance perception of phasic changes in nociceptive input specifically when there is an opportunity to exploit information learned about related actions (Wilson et al., 2014; Wittmann et al., 2008) and if actions provide control over pain (Braescher et al., 2016; Salomons et al., 2007, 2015; V. A. Taylor et al., 2017).

To accomplish refined control of behavior the nervous system needs to shape perception by modifying peripheral input based on contextual factors. A key pathway for endogenous modulation of nociceptive input involves descending control via important brainstem nuclei, including the PAG and rostral ventromedial medulla (RVM), which project to relay neurons in the dorsal horn of the spinal cord (Bannister,

2019; Heinricher et al., 2009). This descending control pathway depends at least in part on opioidergic neurotransmission (Fields, 2004). Placebo induced endogenous pain inhibition is assumed to activate this descending pathway (Eippert, Bingel, et al., 2009; Eippert, Finsterbusch, et al., 2009) and has also been shown to increase opioidergic activity in supraspinal brain regions including rostral and pgACC, medial orbitofrontal cortex, dorsolateral prefrontal cortex, amygdala, and anterior insula (Wager et al., 2007). Similarly, Navratilova, Xie, et al. (2015) showed that the effects of pain relief as negative reinforcement indicated by conditioned place preference depend on endogenous opioids in the ACC in rats. In humans, Sirucek et al. (2021) showed that pain relief perception can at least be partly inhibited by the opioid receptor antagonist naltrexone. Based on these finding, the hypothesis of Study 1 here was that pain inhibiting effects of rewarding pain relief could similarly be blocked by naltrexone. However, we found no evidence that pain inhibition in the wheel of fortune task was affected by this pharmacological manipulation. One explanation for this finding might be that our outcome measures were not optimized to capture the specific aspects of pain perception that are influenced by opioidergic activity. Opioid mediated neurotransmission in the ACC has been shown to selectively alter affective components of pain perception while leaving sensory-discriminative pain components unaffected (Gomtsian et al., 2019; Maruyama et al., 2018; Navratilova, Xie, et al., 2015). In our task we used pain intensity ratings and a sensory discrimination task to assess pain and pain relief perception. These methods do not predominantly measure affective aspects of the pain experience. Whether endogenous opioids potentially mediate a reduced aversiveness induced by gaining rewarding pain relief in active decision making needs to be investigated using methods tailored to disentangle sensory-discriminative and affective components of pain (Rainville et al., 1992).

Another explanation for the finding of no effects of the opioid receptor antagonist naltrexone on endogenous pain modulation may be that opioid independent, putatively supraspinal mechanisms are responsible for increased pain relief perception in active decision making compared to passive states. Offset analgesia has been suggested to be an example of pain modulation caused by the expectation of pain relief (Fields, 2018). However, Martucci and colleagues (2012) found that neither the opioid antagonist naloxone nor the opioid agonist remifentanil had an influence on the

magnitude of offset analgesia. In study 2, we found no decrease of brain activation associated with reduced perceived pain intensity due to receiving pain relief in active vs. passive states, comparable to Becker, Gandhi, Pomares, et al. (2017). Instead, pain modulatory mechanisms that do not involve descending control mechanisms that inhibit nociceptive transmission at the level of the spinal cord, but rather depend on interactions between cortical areas have been discussed for this type of endogenous pain modulation (Becker, Gandhi, Pomares, et al., 2017; Braescher et al., 2016; Wiech & Tracey, 2009). In line with this reasoning, several studies found distributed brain networks related to endogenous pain modulation with no suggestion of a direct engagement of descending control pathways (Atlas et al., 2010; Becker, Gandhi, Pomares, et al., 2017; Braescher et al., 2016).

Further and in line with studies that investigated effects of expectations, uncertainty, and pain controllability on the perception of pain (Atlas et al., 2010; Braescher et al., 2016; S. Zhang, Mano, et al., 2018), our finding that activation in the pgACC was associated with anticipation and unexpected reception of pain relief suggests that this region is involved in mediating effects of predictability on pain perception. Interestingly, Rhudy et al. (2006) found that emotional pictures modulated pain intensity ratings of both, predictable and unpredictable pain. However, the magnitude of the nociceptive flexion reflex as an indicator of spinal neurotransmission was only affected when pain was unpredictable, suggesting that pain modulation of predictable pain does not depend on inhibition at the spinal level.

The enhancement of pain modulation by rewarding pain relief by the dopamine precursor levodopa implies that cortico-limbic reward and decision networks play an important role in mediating such modulatory effects. In rats, rewarding pain relief has been shown to depend on dopaminergic signaling in the VTA and the NAcc (Navratilova et al., 2012). In humans, dopamine has previously been shown to mediate pain modulatory effects with conflicting motivations: Becker, Gandhi, et al. (2013) showed that an dopamine agonist increased pain inhibitory and faciliatory effects of monetary wins and losses respectively on pain perception. However, the role of dopamine in pain modulating effects of pain relief obtained in a motivated state have not been investigated before.

In general, dopamine has been suggested to have general antinociceptive effects. This assumption is based on several results of animal studies (Burkey et al., 1999; Jensen & Yaksh, 1984) as well as human studies that found dopamine related gene variations to be associated with clinical and experimental pain (Cevoli et al., 2006; Treister et al., 2009). While these studies show an association of dopamine related genes with pain sensitivity, the exact mechanisms of these associations remain unclear. In contrast to studies suggesting antinociceptive effects of dopamine, Becker, Ceko, et al. (2013) found no effects of either increasing or decreasing dopamine availability on thermal pain thresholds, pain tolerance, and temporal summation. This finding argues against a one directional, pain inhibiting effect of dopamine on pain. Instead, dopamine might be involved in pain processing by its role in mediating motivational salience, indicating the motivational value of both, positive and negative stimuli (A. M. W. Taylor et al., 2016). The mesolimbic dopamine system has often been associated with responses to rewards and reward predictive cues (Glimcher, 2011). However, based on findings that dopamine increases “wanting” (i.e. the motivation to work for rewards) rather than “liking” (i.e. the hedonic experience of rewards) dopamine has also been suggested to signal incentive salience of rewards that promotes approach behavior (Berridge et al., 2009). Based on the finding of dopamine neuron populations that respond to both positive and negative events (Matsumoto & Hikosaka, 2009) it has also been suggested that specific subpopulations of dopaminergic neurons code motivational salience instead of valence (Bromberg-Martin et al., 2010). If pain modulation serves to enhance motivational value as suggested by the motivation-decision model of pain (Fields, 2018), a valence independent function of dopaminergic signaling could explain opposing effects of dopamine on pain modulation in motivational conflicts (Becker, Gandhi, et al., 2013) and during relief seeking as shown here in study 1.

In addition to pain modulation induced by active decision making, both studies presented here consistently showed an association of trial by trial variation of endogenous pain modulation with prediction errors estimated by computational modeling participants’ choice behavior in the wheel of fortune task. Higher prediction errors were associated with stronger pain modulation across all choices and in both studies. This is in line with information processing accounts of endogenous modulation of pain perception (Seymour, 2019), which propose that perception of pain is

endogenously modulated according to its informational value in order to optimize prospective control of behavior. From this perspective, phasic changes in pain intensity should specifically be enhanced endogenously when uncertainty (as indicated by prediction errors) is high, because new and relevant information can be learned in such situations. In contrast, if an outcome is certainty, comparatively less informational value is conveyed and, hence, less pain modulation should occur. Whether modulation of pain perception according to its value for learning is sensitive to opioidergic and/or dopaminergic signaling has not been investigated before. Therefore, the finding of an enhanced association between prediction errors and endogenous pain modulation by dopamine in study 1 provides new insides into how the pain system achieves refined control of behavior through modulatory processes. This finding further supports the assumption that dopaminergic transmission plays an important role in mediating pain modulatory effects that support learning in the context of pain and pain relief (cf. Becker, Gandhi, et al., 2013; A. M. W. Taylor et al., 2016).

Replicating previous results (Becker et al., 2015), study 1 showed that pain modulation was higher in participants high in novelty seeking as a personality trait. More important, the present results extend this finding by showing that this relationship was enhanced by dopamine as well. Novelty seeking describes a tendency to explore new information that may only be valuable for future behavior (Wittmann et al., 2008). An enhanced motivation for such exploratory behavior might come with increased sensitivity to rewarding outcomes such as pain relief. Endogenously enhanced perception of pain relief in high novelty seeking individuals might therefore reflect their higher sensitivity to new information. The personality trait of novelty seeking has been associated with enhanced dopaminergic activity due to lower midbrain (auto)receptor availability (Leyton et al., 2002; Savage et al., 2014; Zald et al., 2008). Further, brain activation in the striatum during exploration driven decision making was found to correlate with interindividual differences in novelty seeking (Wittmann et al., 2008). These findings suggest that exploratory behavior is mediated by midbrain dopaminergic activity. The correlation of enhanced endogenous pain modulation by dopamine with novelty seeking found in study 1 suggests that dopamine promotes higher sensitivity to the informational value of relief outcomes.

In sum, the results presented in this dissertation provide novel evidence for an important role of dopaminergic transmission in mediating pain modulatory effects of rewarding pain relief. In synopsis with previous literature these results strongly suggest that mesolimbic reward and decision circuits are in involved in the endogenous modulation of pain perception by relief thereby enhancing our current knowledge on psychobiological mechanisms of pain perception in healthy states. In contrast, we found no evidence for an involvement of opioidergic transmission and descending modulatory pathways.

4.2 Reinforcement by pain relief

Nociceptive input signals actual or potential tissue damage. Such a threat of body integrity is reflected by the aversiveness of pain and the associated powerful motivation to escape and avoid harm whenever possible. This motivation to avoid pain has been widely recognized in research. However, despite the well-known pleasure of pain relief much less attention has been paid to the equally potent motivation to seek pain relief when being in pain. Pain has been conceptualized as a homeostatic drive that aims to reinstate bodily equilibrium (Craig, 2003). Accordingly, pain should elicit a strong motivation to mitigate or escape painful situations. The same principles can be applied to pain relief, and hence, behavior with the goal to achieve pain relief. Moreover, the aim of the pain system may not only be to cope with current threats, but in addition to learn about prospective behavior that protects the organism (Seymour, 2019). Accordingly, obtaining pain relief should be reinforcing, strengthening knowledge about actions that help to escape from pain. Evidence for the rewarding nature of pain relief comes from studies that showed that relief is perceived as pleasant (Leknes et al., 2008) and that even painful stimulation is perceived as pleasant, if it indicates avoidance of a relatively stronger pain (Leknes et al., 2013). Here, in study 1 we demonstrated that pain relief also induces negative reinforcement of choice behavior: participants learned to select the option associated with a higher chance to win and thus to gain pain relief more frequently. Importantly, participants were not instructed that they could optimize their outcomes based on their choices. Interestingly, data of the exit interview revealed that the learning effect was in fact driven by those participants that were able to report the contingency of choice and likelihood of winning

at the end of the task. In line with previous results, this suggests that contingency awareness mediates successful learning in the wheel of fortune task used here (Cleeremans et al., 1998; Kirsch et al., 2004).

Despite the fact that levodopa increased the effect of unpredictability on pain modulation, thereby amplifying the informational value of outcomes in the wheel of fortune task, participants did not show an increased preference for the more rewarding option in this condition. While the result is surprising, this finding argues against a simple transition of perceived relief into subjective decision value, which in case of a stationary reward schedule, as implemented in our task, should have promoted choices in favor of the more advantageous option. A possible explanation for this finding is the involvement of model-free and model-based decision systems. Model-free learning refers to direct reinforcement of actions by their consequences, as described in traditional reinforcement learning models. In contrast, model-based learning refers to the acquisition of an internal model of the task structure that allows to plan actions ahead of time based on expected future rewards (Daw et al., 2011). Since the present results suggest that relief related learning needed contingency awareness, this might suggest that such a model-based learning system build the basis of learning in our task. In line with the present results, Kroemer et al. (2019) showed that increased dopamine availability by administration of levodopa did not affect model-based learning, but rather impaired direct reinforcement of choice behavior. However, the increased dopamine availability had no effect on reward prediction error signals (measured by BOLD responses). These findings suggest that increased dopamine availability only impaired transfer of learned values to overt actions. This is in line with the “thrift” hypothesis that supposes that dopamine modulates the exploitative versus explorative behavior (Beeler, 2012; Beeler et al., 2010). This hypothesis states that higher tonic dopamine levels enable explorative behavior that deviates from decisions that are directly based on state-based predictions (i.e. predictions based on the learned value from previous experiences). However, to directly test whether such different decision systems are involved in learning by rewarding pain relief requires more sophisticated task manipulations (Langdon et al., 2018) and should be followed up in future research.

Similar to levodopa, naltrexone also reduced effects of reinforcement learning compared to the placebo condition. Naltrexone did not reduce the informational value of outcomes in the wheel of fortune game as indicated by comparable intensity ratings in the placebo and naltrexone condition. This emphasizes the notion that perceived relief does not directly translate to a decision value, because in that case reinforcement should also be comparable between the two conditions. However, endogenous opioids have been implicated in different aspects in the context of reward, with enhancing effects on “wanting”, “liking”, and choice behavior (Chelnokova et al., 2014; Eikemo et al., 2017; Meier et al., 2021). Our results suggest that at least one of these functions was disrupted by the blockade of opioid receptors but the specific contribution of endogenous opioids to reinforcement learning in the context of pain needs to be addressed in future studies.

Nonetheless, the finding that both drug manipulations impaired reinforcement in our task suggests that both, dopamine and endogenous opioids, play a role in relief seeking.

4.3 Alterations in chronic pain

Theories on the development and maintenance of chronic pain emphasize the importance of emotional and motivational aspects that characterize the pathological state. For example, the earliest version of the fear-avoidance model of pain (Lethem et al., 1983) describes chronic pain as “exaggerated pain perception” caused by disproportionally augmented emotional-motivational pain perception relative to sensory-discriminative aspects. This emphasizes already the driving and pathogenetically highly relevant role of altered emotional and motivational processing in the context of chronic pain, with comparatively small or even no effects on sensory-discriminative pain processing. Borsook et al. (2016) similarly describe that chronic pain is characterized by diminished motivation due to impaired function of reward circuits and increased negative affective states associated with an over-recruitment of limbic structures. Correspondingly, patients with chronic pain often present with comorbid affective and anxiety disorders (Castro et al., 2009) and increased anhedonia (Garland et al., 2020), which might reflect generalized impairments in emotion and reward processing. Indeed, impaired emotional decision making and altered fear

related learning have been shown in patients with chronic pain (Apkarian et al., 2004; Meulders et al., 2015, 2018). Moreover, altered activation patterns in the reward circuit have been found in response to pain onset and offset (Baliki et al., 2010; Loggia et al., 2014). Baliki et al. (2012) showed that increased functional connectivity within the reward circuit, specifically between the NAcc and vmPFC, predicts the transition from subacute to chronic pain. However, it is not clear how these changes in the function of reward circuitries relate to changes in pain perception. It is conceivable that impaired endogenous pain inhibition contributes to exaggerated pain perception in chronic pain (B. K. Taylor & Corder, 2014). In a recent fMRI study Zhang, Li, et al. (2018) found that impaired endogenous pain inhibition during offset analgesia was associated with altered activation in brain regions involved in reward processing. Yet, this as well does not show a causal relationship between altered reward processing and impaired endogenous modulation.

Based on this gap in the literature, one aim of study 2 was to test whether endogenous modulation of relief perception induced by active decision making compared to passive receipt of relief is impaired in patients with chronic pain. Contrary to our hypothesis, we did not find alterations in the endogenous modulation of relief perception in our patient sample compared to the healthy controls. This finding suggests that motivationally driven enhancement of pain relief perception is a robust phenomenon that seems to survive maladaptive changes of perception during pain chronification. Nevertheless, this finding of no differences between patients with chronic pain and healthy controls was surprising, because other types of endogenous pain modulation such as conditioned pain modulation and offset analgesia have been found to be impaired in patients with chronic pain (Gerhardt et al., 2017; Kobinata et al., 2017; Lewis et al., 2012; S. Zhang, Li, et al., 2018). Moreover, even a causal role of reduced endogenous pain inhibition in the development of chronic pain has been discussed (Yarnitsky, 2015). On the other hand and in line with the present results, placebo analgesia as a form of endogenous pain inhibition based on expectations appears not to be impaired in chronic pain patients (Frangos et al., 2021; A. Power et al., 2020). This might be interpreted as indicating the implication of similar mechanisms in placebo analgesia and endogenous pain modulation during active decision making. However, pain-inhibitory effects of placebos were found to be reduced by opioid receptor

antagonists (Benedetti, 1996; Eippert, Bingel, et al., 2009), while in study 1 we found no corresponding evidence for an involvement of endogenous opioids in endogenous pain modulation in active decision making. These heterogenous findings point to a complex picture regarding altered mechanisms of endogenous pain modulation in chronic pain. Specifically, it is needed to disentangle specific mechanisms that distinguish different types of endogenous pain modulation. Moreover, the same pain-modulatory mechanisms may be differentially affected in different pain conditions (Gerhardt et al., 2017). In line with such differential alterations, study 2 of this dissertation showed that pain facilitation induced by active decision making was stronger in CBP compared to FM and CBP showed a stronger effect of unpredictability on endogenous pain modulation compared to FM. In addition, we found a reduced association of relief prediction errors with activation in the pgACC in FM but not in CBP compared to healthy controls. These findings might suggest that the interaction of reward processing and endogenous pain modulation differs between the two conditions, but due to the small sample sizes no clear conclusions can be drawn.

The finding that endogenous modulation of pain relief enhances the informational value that it carries suggests that it plays a role in updating of decision values. Although study 2 did not replicate the finding of successful reinforcement learning by rewarding pain relief in neither healthy controls nor patients with chronic pain, results of the computational modelling of the cognitive processes underlying decision making in the context of pain and pain relief points to differences between these groups. As such, HC showed stronger updates of their expectations by negative compared to positive prediction errors. This is in line with a recent study that showed higher learning rates for received compared to avoided pain and reported separable neural representation for positive and negative prediction errors (Jepma et al., 2022). In contrast to HC, CBP showed a reversed pattern with higher learning rates for positive prediction errors compared to negative prediction errors. Similar to the previous findings on chronic pain discussed before, previous findings on the sensitivity for rewards and losses in chronic pain are heterogenous. Two studies used a monetary incentive delay task, in which response times serve as indicators for the motivation to work for monetary rewards and to avoid monetary losses. Martucci et al. (2018) found no differences in response times between pain patients and healthy controls while Kim et al. (2020) found longer

responses times in patients compared to healthy controls with no differences between rewards and losses. However, it is conceivable that increased motivation to seek relief in chronic pain might render pain and specifically pain relief as reward for patients more relevant than monetary rewards and losses. Stronger updates of expectations driven by pain relief compared to pain increases in CBP might reflect such increased motivation. Instrumental learning mechanisms and associated alterations in reward circuitries are assumed to contribute to the transition of acute to chronic pain (Apkarian et al., 2013), therefore a better understanding of impairments might help to develop treatment strategies that target and reverse maladaptive changes.

In summary, these results suggest that pain-inhibitory effects of rewarding pain relief seem to be preserved in both pain conditions while differences in learning pattern support the widely accepted assumption of impaired reward processing in chronic pain.

4.4 Implications and perspectives

The results presented in this dissertation improve the understanding of mechanisms that underlie endogenous modulation and instrumental learning induced by pain and pain relief. Moreover, the results show how these two key aspects of pain processing interact with each other. Bidirectional modulations enhance perception of both, pain and pain relief, when these signals hold relevance for behavior and learning. This provides support for the most recent theoretical frameworks of endogenous modulation of pain perception that emphasize that the main purpose of the pain system is to control and optimize current and future behavior that helps to mitigate or avoid pain (Fields, 2018; Seymour, 2019). The present results delineate psychobiological mechanisms that underlie such optimization of behavior. Specifically, the results suggest that dopamine plays a central role for the endogenous modulation as it seems to increase the informational value of perceived pain and pain relief depending on the external and internal factors such as the context and motivational drives. In contrast, opioidergic effects on relief information appear to play a minor role. Further, the neural correlate of relief expectation and prediction errors in activation of the pgACC suggests that this brain area contributes to the mediation of modulatory effects on relief perception. A better understanding of motivational effects on endogenous modulation is an important basis for novel routes for the optimization of treatment and prevention of chronic pain.

Currently available therapeutic strategies are often unspecific and do not achieve satisfactory effects in many patients (Gatchel et al., 2014). Specifically, in chronic pain, seeking pain relief is a dominating behavioral drive. However, maladaptive strategies to seek pain relief may contribute to the transition of acute to chronic pain. In a recent study, we provided evidence that reward learning based on prediction errors is implicated in the process of chronification of pain (Löffler et al., 2022). Interestingly, the activation pattern in the NAcc in response to a cue predicting pain relief differentiated patients with subacute back pain that recovered from those who did not recover from their pain six month later. This suggests that learning from pain relief might contribute to the process of pain chronification. The studies presented here provide additional insights in the psychobiological mechanisms that drive learning by pain relief. To target maladaptive learning processes prior to the transition to chronic pain and thus to prevent the development of chronic pain is a goal that requires more research to better understand mechanistic differences of the responding of the reward system during and after this transition. Such an approach is further supported by the finding that already manifested chronic pain is characterized by different alterations in the reward processing network compared to those alterations present at sub-acute states that predict the development of chronic pain (Baliki et al., 2012; Löffler et al., 2022). Our finding that dopamine increases endogenous pain inhibition may be exploited for the development of refined multidimensional therapeutic strategies. Dopaminergic drugs such as levodopa produce a transient increase of dopamine availability with a relatively short half-life of plasma concentrations (Nyholm et al., 2012). This might offer the possibility to harness pain modulatory effects of the drug in specific behavioral or physiotherapeutic treatments with limited side effects outside the therapeutic setting. Dopaminergic effects on endogenous pain modulation could be used to enhance relief perception with the goal to promote reinforcement of adaptive strategies. However, development of such treatment strategies needs further research to better understand how learning by pain relief affects clinical pain. Findings from experimental pain stimulation cannot directly be transferred to clinical pain. For example, based on their experimental findings Baliki et al. (2010) hypothesized that patients with chronic back pain experienced their clinical pain as less unpleasant during an experimental painful stimulation. They found an inverted NAcc activation in

response to the offset of the experimental stimulation in chronic pain patients compared to healthy controls and concluded that in patients the offset of the experimental stimulation predicted an aversive event, namely the increased perception of their clinical pain. Such interactions between experimental findings and clinical pain, and specifically, the altered motivational significance of experimental pain in patients with chronic pain could be exploited and needs to be considered when translating experimental findings into clinical treatment strategies.

The important role of the pain system in creating predictions that guide behavior has been acknowledged in recent theories on pain (Fields, 2018; Seymour, 2019). These theoretical accounts allow specifying hypotheses about learning mechanisms that underlie behavioral and perceptual observations that can be tested by comparing experimental data to mathematical formulations of these mechanisms. These mathematical models make assumptions about the processes that are responsible for the observed effects, and thus, allow to test whether specific psychological and neural processes reflect these theoretical assumptions. Here, we used a mathematical model of reinforcement learning that enabled us to test the effects of the theoretically predicted process of value updating by prediction errors on endogenous modulation and choice behavior. Such computational models have a high potential for novel mechanistic insights and with that a great benefit for research. In particular, the possibility to specify precise hypotheses not only on behavioral outcomes but also with regard to the underlying mechanisms, for example in terms of brain circuits, promise valuable insights. Thus, future studies should exploit the opportunities of computational modelling as a tool to mechanistically test theory driven hypotheses.

4.5 Limitations

The work described here deepens the understanding of mechanisms underlying the endogenous modulation of pain and its relief in the context of motivated behavior. Yet, the results need to be considered in the light of several limitations.

The assessments used in the studies of this thesis focused on sensory discriminative components of pain perception. This leaves out a key aspect of pain perception, which is its affective component. As discussed above affective or emotional-motivational components of pain can be separated from sensory-discriminative components and

they appear particularly relevant in the context of chronic pain. In human studies, assessing the affective component of pain and pain relief is usually operationalized by asking for ratings of pleasantness or unpleasantness of a perception, for example, on visual analogue scales (Leknes et al., 2008; Sirucek et al., 2021), which was not implement in the paradigm used here. Future studies should include such a measure to test whether the affective component of pain and relief is similarly modulated by motivational aspects. In addition, the findings of endogenous modulation of pain and pain relief were found in ratings of perceived stimulus intensity, while the sensory discrimination task implemented as a behavioral measure of pain sensitization or habituation did not show comparable results. In contrast, Becker et al. (2015) found comparable effects of pain relief as reward gained in a motivated state in intensity ratings and the same behavioral measure as used here. One methodological difference between the study by Becker et al. (2015) and the present studies, are larger absolute changes in thermal stimulation intensity for pain relief as reward and pain increases as punishment in the present studies. For the intensity ratings participants were asked to rate their perception resulting from pain relief and increases. In contrast, the sensory discrimination task focused on perceptual modulation of the initial tonic pain stimulation before outcomes were delivered. It is conceivable that this measure is more sensitive to changes caused by active decision making when phasic intensity changes, and with that the informational value of the outcomes, are larger. Whether the difference in the magnitude of change in stimulus intensities indeed causes the observed differences in the results, needs to be addressed in future studies as the sensory discrimination task may provide valuable information about the modulation of the underlying tonic painful stimulus.

In both studies participants were not explicitly instructed that they could optimize their outcomes based on their choice in the experimental task, which constitutes a key difference to many other studies on reward learning (Jepma et al., 2022; Pessiglione et al., 2006; Seymour et al., 2012; S. Zhang, Mano, et al., 2018). Study 1 showed that reinforcement by pain relief induced successful learning. Interestingly, information obtained from the post-hoc interview suggests that this learning was related to explicit contingency awareness. However, the finding of successful reinforcement learning was not replicated in study 2. It is conceivable that the implementation of the task in

the context of the fMRI scanning was distracting and prevented participants from acquiring awareness of reward contingencies. The role explicit awareness of reward contingencies in learning by pain relief should be further investigated in future studies.

Study 1 revealed effects of dopaminergic signaling on endogenous modulation in terms of an enhancement of the informational value of pain relief, while no effects of the opioid receptor antagonist naltrexone were found. The study did not implement sufficient manipulation checks to show that the drug administration truly was effective for naltrexone. The dose of 50 mg was shown to induce more than 90% blockade of μ-opioid receptors (Weerts et al., 2013) and the same dose has been used in several previous studies before that found effects of blocking endogenous opioids in the context of reward processing, pain inhibition, and relief perception (Chelnokova et al., 2014; Eikemo et al., 2017; C. D. King et al., 2013; Sirucek et al., 2021). However, we cannot rule out the possibility that there are opioidergic effects on pain modulation by rewarding pain relief although such effects were not captured by the outcome measures in our study.

Study 2 aimed to find neural correlates of the pain modulatory effects found on the behavioral level. Similar to Becker, Gandhi, Pomares, et al. (2017), we found no brain activation that was directly related to modulation of the perceived pain intensity in terms of differences in pain processing areas between the active and the passive condition. While this study also focused on neural correlates of instrumental learning, future research might benefit from applying more refined analysis strategies to also uncover neural activations associated to the endogenous modulation of pain and pain relief.

Finally, findings of study 2 on altered endogenous modulation and relief related learning in chronic pain patients should be interpreted with caution because of the small sample sizes of patient groups. Separating the patient sample into subgroups based on their clinical diagnosis further reduced the power of the statistical analyses. Nevertheless, the present results hint at altered learning patterns and differences in affected mechanisms between FM and CBP. Future studies should with sufficient power to detect possible effects should investigate both, general impairments of pain relief as a rewarding stimulus, and differences in impaired mechanisms in distinct chronic pain conditions.

4.6 Conclusion

The studies presented in this dissertation provide new insights into psychobiological mechanisms of pain relief as a reward. They demonstrate the complex interaction of cognitive, perceptual, and behavioral processes that forms the basis for the pain system to optimally serve homeostatic needs and guide prospective behavior. The finding that endogenous modulation of perception enhanced the informational value of pain and pain relief during active decision making was shown across both studies with no alterations of this effect in patients with chronic pain compared to healthy controls. This suggests that motivationally driven enhancement of pain relief perception is a robust phenomenon that appears to be spared by maladaptive changes during pain chronification. The mediating effect of enhanced dopamine availability on informational aspects of endogenous modulation gives new insights into the role of dopaminergic signaling in pain perception and might serve as a leverage point to optimize or develop new treatment strategies that combine pharmaceutical and behavioral interventions. In contrast to the a priori hypothesis of an involvement of the opioidergic system in pain inhibitory effects of rewarding pain relief we found no effect of the opioid receptor naltrexone on endogenous modulation. In addition, fMRI results did not show neural correlates of the behavioral effect of endogenous modulation, while they hint at mechanisms relevant in the association of endogenous pain modulation and prediction errors, i.e. uncertainty of expected outcomes. In sum, the present results provide a comprehensive picture into the psychobiological mechanisms of pain relief perception and associated learning in healthy states and in chronic pain, thereby closing some imminent gaps in the current literature. Nevertheless, several open questions remain and further research is necessary, particularly to elucidate the neural mechanisms of endogenous perceptual modulation. The findings presented here provide a basis for such future research on the motivational aspects of pain relief and its role in chronic pain.

5 SUMMARY

Pain is much more than a sensory experience. Pain has strong emotional and motivational components that fulfill crucial functions for survival and well-being, because they drive behavior to avoid and escape from pain. This motivation is also reflected in the opposite and rewarding nature of the pleasure of pain relief. Both endogenous modulation of the perception of pain and pain relief are thought to promote the motivational drive and with that behavior that serves homeostatic needs. In contrast to pain and despite this crucial role of pain relief as reward, the psychobiological mechanisms underlying pain relief perception as well as related learning remain poorly understood. The aim of this dissertation was to deepen our understanding of psychological and neurobiological mechanisms of pain relief in healthy humans and possible alterations of these mechanisms in patients suffering from chronic pain.

In a first experimental study, the role of the neurotransmitters dopamine and endogenous opioids in pain modulation and reinforcement learning were investigated using a probabilistic relief seeking task in healthy volunteers. The results showed that the informational value of pain and pain relief was endogenously enhanced in states of active decision making compared to passive states. This endogenous pain modulation scaled with perceived uncertainty of expected outcomes. Dopamine increased endogenous pain and pain relief modulation, while no evidence for the involvement of endogenous opioids was found. Successful reinforcement learning as found in the placebo condition was impaired by dopamine and endogenous opioids.

The same probabilistic relief seeking task was used in a second study to investigate neural correlates of learning driven by pain and pain relief using functional magnetic resonance imaging in patients with chronic pain and healthy controls. This study replicated the effects of endogenous pain modulation by its informational value, while no alterations in patients with chronic pain were found compared to healthy controls. This result suggests that motivationally driven enhancement of pain relief perception is a robust phenomenon that appears to be spared by maladaptive changes during pain chronification. However, compared to healthy controls patients with fibromyalgia showed a stronger bias towards relief related cues during learning, but a weaker

association of activation in the pregenual anterior cingulate cortex with relief prediction errors. These findings suggest that although the informational content of pain relief seems to be preserved in patients with chronic pain, subtle differences in the underlying mechanisms may reflect altered reward processing in chronic pain, which have been discussed before.

In sum, the results highlight the important role of motivation and prospective control of behavior for endogenous modulation of pain and pain relief and provide insights in underlying psychobiological mechanisms in healthy states and in chronic pain.

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