Implicit Operant Learning of Pain Sensitization and Habituation in Healthy Participants and Fibromyalgia Patients

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Preface

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The studies presented in chapters 3 and 4 are intended for publication; thus, to some extent their individual introduction and discussion overlap. The introductions and discussions of these chapters, however, may also be read independently.

Many people were involved in the success of these studies, but some deserve special citation:

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Abbreviations

ACC	anterior cingulate cortex
AMH	A-fiber mechano heat
CES-D	Center for Epidemiologic Studies Depression Scale
CR	continuous reinforcement
CS	conditioned stimulus
DNIC	diffuse noxious inhibitory control
EEG	electroencephalogram
FM	fibromyalgia
fMRI	functional Magnetic Resonance Imaging
HP	healthy participants
HPA	hypothalamic-pituitary-adrenal
IASP	International Association for the Study of Pain
IBS	irritable bowel syndrome
IC	insular cortex
LTD	long-term depression
LTP	long-term potentiation
NMDA	N-methyl D-aspartate
NS	nociceptive specific
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
STAI	State Trait Anxiety Inventory
UCS	unconditioned stimulus
VAS	visual analog scale
VI	variable interval
WDR	wide dynamic range

1 General Introduction

1.1 Nociception, Pain Perception and Measurement of Pain Perception

Within body perception, pain has a special role as an alarm and protection system and it is more closely linked to affect and emotion than other types of perception e.g. visual perception. Further, noxious stimuli are processed in a specific system—the nociceptive system. However, the terms pain and nociception are not equivalent. In the basic terminology of the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such a damage" [140,162]. Nociception refers to "the neural processes of encoding and processing noxious stimuli" [140]. Pain and nociception do not necessarily have to correspond (c.f. [139]): nociceptive activity can occur without pain—e.g. under local anesthesia—and pain can be perceived without nociception—e.g. in phantom pain, or experimentally induced by the so-called thermal grill illusion [54].

Nociception

Nociceptors—receptors capable of transduction and encoding noxious stimuli—are present in the skin, the muscular system, and the viscera. However, the distribution of nociceptors differs throughout the body [42,112,261]. Nociceptors are free nerve endings of Aδ- and C-fibers that can respond to mechanical, thermal and/or chemical stimuli [98,212,213]. Aδ-fibers are myelinated, fast-conducting afferents which transmit the so-called 'first pain'; C-fibers are unmyelinated, slow-conducting afferents which transmit the so-called 'second pain' [19]. Aδ- and C-fibers project to the dorsal horn of the spinal cord, terminating in different lamina (for details see [163]). There, different kinds of lamina neurons responsive to nociceptive input exist: nociceptive specific (NS) and multireceptive or wide dynamic range (WDR) neurons. NS neurons respond only to high intensity, noxious stimuli conducted by Aδ- and C-fibers, while WDR neurons respond to a broad range of stimuli from innocuous to noxious intensities conducted by Aδ- and C-fibers as well as (mechanoreceptive) Aβ-fibers [163]. In the spinal cord, information is transmitted by several pathways, the spinothalamic tract being the most important. In addition to these ascending pain pathways, descending pain pathways from the brain stem and mid brain to the spinal cord exist. These descending pathways

contribute to the endogenous pain modulation system by modulating incoming signals and particularly inhibiting nociceptive input in the spinal cord. Central to this system is the periaqueductal gray together with endogenous opioids [164]. The processing of nociceptive stimuli is differentiated in a lateral and medial system tracing back to different nuclei of the thalamus: the lateral system projects through lateral thalamic nuclei (receiving input from the neospinothalamic tract of the spinal cord) to primary and secondary somatosensory cortex (SI and SII); the medial system projects through medial thalamic nuclei (receiving input from the palaeospinothalamic tract of the spinal cord) to the anterior cingulate cortex (ACC) and the insular cortex (IC), which projects to the limbic system [257]. SI is primarily involved in discriminating stimulus location and intensity. SII also seems to encode stimulus intensity but the representation differs from that of SI [254,256]. The ACC is involved in attentional functions and the association of pain with unpleasantness [191,196]. The IC is involved in affective and cognitive aspects of pain [85,215].

Pain Perception

The terminology of the IASP describes pain as a sensory and emotional experience. This definition characterizes pain as a subjective phenomenon with the perception of pain being directly linked to affect; pain is treated as a subjective feeling (c.f. [140]). However, pain is rather a multidimensional construct, comprising subjective experience, behavioral and physiological (somatic, visceral, neuronal) responses. Further, these dimensions do not necessarily have to correspond. For example, dissociations of subjective pain report and behavior are observable in somatoform pain disorders [60,97]. Moreover, intrinsic and extrinsic consequences —i.e. consequences inside and outside the pain system—of overt and covert pain responses affect pain. For example, due to temporal summation of nociceptive signals (sensitization as intrinsic consequence of a covert pain response), the last stimulus in a series of fast, repetitive stimuli is perceived as being more intense than the first [267] (see Section 1.2). Another example is the association of heightened pain sensitivity with high spouse solicitousness (care as extrinsic consequence of an overt pain response) in chronic pain patients [78]. Consequently, in order to distinguish the perceptive-discriminative component of pain from other components—e.g. the affective component—type and context of stimulation, responses as well as consequences, have to be considered.

Measurement of Pain Perception

Pain perception is mostly assessed with verbal reports. However, research on the phenomenon of "blindsight" [53,272] and on patients with section of the corpus callosum ("split-brain") [89] showed that some abilities of perception are not necessarily represented verbally. This research showed that perception and discrimination of somatosensory stimuli is possible without the person being aware of them—that is, they deny the perception of any stimuli in their verbal reports. Further, verbal reports depend on response criteria and are prone to response biases [53,145]. Thus, the investigation of the perceptive-discriminative component of pain with verbal reports is very difficult. Non-verbal, behavioral approaches seem to be more promising. For this purpose, visual analogue scales and instrument-based types of direct magnitude scaling are used (e.g. [20,193]). Nevertheless, these methods are still related to verbalization by instructions, understanding of the instruction and the response-set of a person. Another approach has been the measurement of brain activity in response to noxious stimuli e.g. by evoked potentials in the EEG (electroencephalogram) or fMRI (functional Magnetic Resonance Imaging). However, pain perception cannot be equated with brain responses to noxious stimuli since they are categorically different (Ryle's category-mistake, c.f. [105]).

One possibility to measure the perceptive-discriminative component of pain isolated from other components is the use of behavioral discrimination techniques. These techniques have their origin in operant methodology [228]. The same rinciple was also successfully applied by Békésy in his continuous audiometry [14]. Behavioral discrimination or discriminative behavior indicating pain perception is a behavioral response to a change in nociceptive input and/or a subjectively experienced change in sensation (c.f. [228]). Such a behavioral response is non-verbal and implicit and does not necessarily have to correlate with explicit verbal report. Prerequisite for this type of pain measurement is a test procedure in which the only information controlling behavior is obtained by changes in nociceptive afferents. Discriminative behavior as a measure for pain perception in humans was implemented for the first time in the so-called 'dual sensitization method' and in an operant conditioning procedure by Hölzl, Kleinböhl and colleagues [106,119]. In both studies, discriminative behavior was used to measure perceptual sensitization to tonic heat-pain stimulation as an indicator for dynamic changes in pain perception. Subjective pain ratings were additionally assessed. Results demonstrated a dissociation of pain measured with these two methods and the possibility of measuring

the perceptive-discriminative component of pain separated from other components.

1.2 Perceptual Sensitization and Habituation in Pain

Pain perception can be changed by activation-dependent plasticity in nociceptive pathways. This activation-dependent plasticity is triggered by repetitive or tonic noxious stimuli and is observable in reversible changes in the peripheral (auto- and heterosensitization; fatigue) and spinal (windup; long-term potentiation, LTP; long-term depression, LTD) nociceptive processing [288]. Since the same molecular processes are involved as in memory processes in the brain (LTP, LTD, NMDA-receptor mechanism), these changes are termed '(neuronal) pain memory' [117,210]. In this context, basic memory functions are sensitization and habituation [165].

Sensitization

Perceptual sensitization is a dynamical feature of pain perception that is displayed in a subjective increase in sensation [126]. Perceptual sensitization is provoked by repetitive ($\geq$ 0.3 Hz), phasic or prolonged, tonic nociceptive stimulation and persists less than a minute (short-term sensitization; [118,119,247]). Most common are thermal, mechanical and chemical stimulation methods of the skin or muscles. In accordance with the assumed underlying neuronal mechanism, perceptual sensitization is also termed 'temporal summation'. This underlying mechanism is assumed to be windup, which is an activity-dependent increase in sensitivity of the WDR-neurons in the dorsal horn of the spinal cord [69,159,192]. Although windup is used as a model and an indicator for central sensitization, it has to be distinguished from central sensitization [69,287]. According to the terminology of the IASP, central sensitization is the "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" [140]. Central sensitization is at least partially caused by LTP [210,288]. However, LTP and windup can interact: present LTP decreases the frequency of repetitive stimuli necessary to provoke windup [210]. Therefore, central sensitization can facilitate the appearance of perceptual sensitization.

While windup is assumed to appear by intense activation of nociceptive C-fibers [203], perceptual sensitization has been demonstrated to occur also with non-noxious stimuli [119,120,267]. Whether this involves spinal windup is not

known yet. However, polymodal and silent C-nociceptors are known to be active also at non-painful temperatures of 40-43°C [255,258,259]. In addition, facilitating convergent processing of warmth and nociceptive afferent input has been shown [188]. An effect of this convergent processing on perceptual sensitization cannot be excluded. In addition, as mentioned above, the appearance of windup can be facilitated by present LTP in the spinal cord [210]. Thus, perceptual sensitization caused by windup can occur at relatively low afferent input.

Habituation

Perceptual habituation is a subjective decrease in sensation to repetitive or tonic stimulation and is thus is opponent to perceptual sensitization [18,95]. However, the underlying neuronal processes of habituation differ from those of sensitization. A current view assumes a cerebral process in which repetitive stimuli are compared with previously memorized stimuli. When the perceived stimulus and the memorized stimulus are equal, a decrease in response strength is the result [179,233]. In general, these processes are well-studied. However, specifically in pain perception, only a few studies have investigated habituation processes (c.f. [95,210]). These studies found that under certain conditions—e.g. repetition rates below critical windup frequency of 0.3 Hz or non-noxious stimulus intensities that nevertheless activate nociceptors—nociceptive input to the spinal cord decreases due to peripheral fatigue of Aδ- and C-fiber nociceptors, resulting in perceptual habituation [95,118,183,255,258]. This peripheral decrease in activity is also reflected in brain activity [95]. However, in order to explain habituation in pain perception, cerebral processes are not required.

1.3 Operant Learning in Pain Perception

Operant learning or conditioning is a type of associative learning resulting in behavior becoming more or less likely to occur through the consequences following this behavior. These consequences are the operant reinforcement or punishment implemented by the contingency—i.e. the causal relationship of behavior and its consequence and its conditions. Thus, in operant conditioning, consequences of behavior can be used to modulate the occurrence and form of behavior. In the context of pain, operant conditioning can be used to modulate pain reports as well as pain perception displayed by discriminative behavior (e.g. [82,83,106,108]).

Operant Conditioning

The role of operant learning in pain and in particular in the development and maintenance of chronic pain is widely recognized. Specifically, pain expression, lowered tolerance and avoidance behavior can be enhanced by reinforcement [82,83]. Further, experimental and clinical studies have led to the integration of operant methods into pain therapy [80,110,169]. Despite the wide distribution of operant methods in pain therapy, the mechanisms mediating between nociceptive processing, environmental consequences and pain perception have rarely been investigated and remain mostly unclear [77].

Most experimental studies exploring operant conditioning of pain are limited to overt pain reports. Further, these studies used extrinsic reinforcement [8,108,137,142]. Extrinsic reinforcement is implemented by reinforcing stimuli given outside the nociceptive system, e.g. verbal or monetary stimuli. Whether pain sensitivity or rather response criteria are changed by this type of operant conditioning cannot be determined. Considering the possible dissociation between pain perception and pain report (see Section 1.1), it rather seems doubtful that pain sensitivity is changed with extrinsic reinforcement of pain reports (c.f. [53]). Several other studies demonstrated biofeedback training of increased electrocortical responses related to perceived intensity to result in increased pain ratings and vice versa [82,143,166]. Although these studies used a psychophysiological parameter, pain report as an indicator for pain sensation was used and thus, conclusions concerning changes in pain perception are not possible.

However, in operant conditioning of pain one possibility is to use intrinsic rather than extrinsic reinforcement. Intrinsic (negative) reinforcement is implemented by reinforcing stimuli given within the nociceptive system, i.e. a reduction in nociceptive input. Intrinsic reinforcement, as a perceptual experience, is supposed to directly affect pain perception, while extrinsic reinforcement is supposed to affect pain perception indirectly. The fear-avoidance theory of exaggerated pain perception [131,134,268] emphasizes such intrinsic reinforcement by reduction in nociceptive input but also by reduction in anticipatory fear though avoidance (c.f. [171]). The fear-avoidance theory implies gradual 'sensory decalibration' that starts when a person avoids nociceptive stimuli for fear of pain, causing progressively weaker nociceptive stimuli to serve as discriminative signals for covert pain responses including pain percepts. The process of gradual sensory decalibration is assumed to be implicit, i.e. without the person being aware of the changes. The de-

scribed process can provide an operant learning mechanism of enhanced pain sensitivity independent of extrinsic reinforcement and pain reports of subjective pain experience. However, this supposed implicit discrimination learning mechanism just as the link to neurophysiologic mechanisms of pain sensitization remains unclear. In contrast, the fear-avoidance theory assumes dysfunction of the muscular system as a result of its disuse due to avoidance behavior—the so-called disuse syndrome—as being causal for enhanced pain sensitivity in pain that is becoming chronic [131,268]. However, the relation of disuse to fear-avoidance is not supported by experimental studies (e.g. [31,131,231]).

Consistent with the assumption of an operant discrimination learning mechanism resulting in enhanced pain sensitivity, a study of Hölzl and colleagues for the first time successfully demonstrated operant conditioning of pain sensitivity with intrinsic reinforcement independent of subjective pain reports [106]. In order to avoid the risk of solely changing response criteria rather than pain perception, this study had some specific features: first, pain perception, in particular perceptual sensitization and habituation to tonic heat-pain stimulation, was measured by discriminative behavior (see Section 1.1). Further, this discriminative behavior and not a pain report was the target of the operant conditioning, that is, the discriminative behavior should become the operant behavior—i.e. the behavior controlled by its consequences [228]. Second, reinforcement was implemented intrinsically by contingent changes in nociceptive input, i.e. by decreases and increases in stimulus intensity. In order to assess sensory decalibration, subjective pain ratings were additionally requested. The study demonstrated that it is possible to enhance perceptual short-term sensitization as well as habituation to tonic heat-pain stimuli in healthy participants with intrinsic reinforcement, resulting in long-term changes in pain sensitivity. Furthermore, subjective pain intensity ratings gradually dissociated from physical stimulus intensities. Taken together, these results demonstrated changes in pain sensitivity and sensory decalibration as stated in the fear-avoidance theory by implicit operant discrimination learning but independent of mediating fear of pain or fear avoidance.

Awareness in Operant Learning

Learning is said to be implicit if it occurs without the awareness of the learning person—e.g. learning of skills and habits. In contrast, explicit learning is learning with awareness—e.g. learning of facts [48,222]. Implicit and explicit learning are psychologically different mechanisms where implicit learning is an instance of

nondeclarative memory, while explicit learning is an instance of declarative memory [68,237]. Thus, awareness can be used as an indicator of the underlying learning mechanism and memory system.

Awareness during operant learning mainly concerns the question whether the learning person has recognized the operant contingency i.e. the connection between behavior and its consequence within a schedule of reinforcement (c.f. [114,136,228]). Many studies have demonstrated that operant learning is possible without contingency awareness (e.g. [21,101,135,136,208,250]). However, the conditions under which operant learning can occur without awareness remain largely unclear (c.f. [114,204,222]).

Imprecise definitions and criteria are a main problem in studying awareness [48,144]. Since different types of awareness have different qualities, it is essential to clarify which type of awareness should be tested with which methods. In operant conditioning, awareness of the learning procedure, awareness of the reinforcing stimuli and contingency awareness have to be distinguished. Further, subjective and objective methods for assessing awareness are available. Subjective methods —e.g. verbal report or confidence ratings—demand a report of an internal state. Thus, these methods require introspection and therefore have been considered as indicating 'awareness of awareness' [184,260]. Due to the necessary introspection and the respective report, subjective methods indicate second-order discrimination of correct responding (c.f. [278]). In contrast, first-order discrimination is measured by objective methods examined by a test behavior, e.g. in a recognition or prediction test. However, first-order discrimination is not necessarily equivalent to awareness. First-order discrimination is possible even without awareness [167,202,278]. Thus, first- and second-order discrimination addresses different levels of procession. Only by assessing different types of awareness as well as by the use of objective and subjective methods are detailed conclusions of the underlying learning mechanisms and the prerequisite conditions possible in a learning study.

In the context of pain that is becoming chronic, it is of particular importance to determine whether operant learning of pain sensitivity can occur without awareness. Nondeclarative memory permits cumulative changes in perception and response systems [45]. Thus, in the context of pain, implicit operant learning, as an instance of nondeclarative memory, can explain the gradual development of hypersensitivity without the person's knowledge. Further, this process of gradually increasing sensitivity can be set in by largely unnoticed changes in acute pain and

can lead to gross changes in sensory scaling over time [106]. In addition, implicit learning results in automatic, inflexible reactions (c.f. [114,161])—like avoidance behavior in chronic pain—resulting in maintenance and even worsening of pain by a vicious circle of perception and reflexive pain responses. Furthermore, implicit learning also has implications for pain therapy: contingencies cannot easily be indentified and unlearned, which may explain the frequently observed resistance to therapeutic interventions in chronic pain patients [80]. A comparable resistance to change of implicitly learned behavior is supported by animal and human studies (c.f. [51,73,173]).

1.4 Pain perception in Fibromyalgia and Irritable Bowel Syndrome

Chronic pain is a prominent feature of several clinical states where pain outlasts the time of natural healing [139,162]. However, it is not clearly defined what this time of natural healing implies and therefore the temporal limit to define pain as chronic is unclear [162]. The time with which persistent constant as well as recurrent pain is stated as being chronic varies from three to six months [71,162]. Besides the duration, other criteria exist to distinguish acute from chronic pain: In contrast to acute pain, chronic pain lost its function as an alarm and protection system. In general, the cause of chronic pain is either unknown or the cause is known but incurable [139]. While in acute pain the sensory qualities dominate, affective-motivational and cognitive-evaluative dimensions of pain prevail in chronic pain (c.f. [158]). Different neurophysiologic—e.g. LTP and central sensitization [209], altered descending inhibition [164], (nonreversible) modifications of primary sensory and transmission neurons [288]—and psychological models—e.g. behavioral [83] and cognitive-behavioral models [186], the fear-avoidance model [131], diathesis-stress models [79]—of pain becoming chronic currently exist but no universally valid model is available.

Although the mechanisms of the development of chronic pain are discussed, it is unquestioned that pain perception is altered in most chronic pain patients: hypersensitivity is a clinical marker of chronic pain in which two types have been distinguished: allodynia—i.e. sensation of pain as response to non-painful stimulation and hyperalgesia—i.e. increased sensitivity to painful stimulation [119,288]. Hyperalgesia is further subclassified in primary and secondary hyperalgesia; primary hyperalgesia refers to changes in pain sensitivity within an injury, whereas secondary hyperalgesia refers to changes in pain sensitivity in undamaged tissue surrounding the injury. While secondary hyperalgesia is suggested to result from

central sensitization, primary hyperalgesia is suggested to result from a combination of peripheral and central sensitization [126,182]. Furthermore, enhanced perceptual sensitization—perceptual sensitization already at non-noxious stimulus intensities and increasing sensitization with increasing stimulus intensities—is common in chronic pain patients, in particular in chronic musculoskeletal pain syndromes (e.g. [70,119,150,174,245]). Although windup is assumed to be the process underlying perceptual sensitization, windup alone cannot explain enhanced perceptual sensitization as demonstrated in pharmacological studies [6,118] . Furthermore, windup does not contribute to the process of pain becoming chronic [102], but LTP and windup can interact so that windup is facilitated [210]. However, since it has been demonstrated that perceptual sensitization can be enhanced by operant learning [106], it can be also suggested that operant learning is the mechanism of sensitization superordinated to windup.

The focus of this thesis lies on fibromyalgia and the irritable bowel syndrome which are both so-called 'functional' or 'unspecific' chronic pain syndromes with considerable increased pain sensitivity. 'Functional' or 'unspecific' refers to the fact that etiology and pathogenesis is widely unknown in these pain syndromes. Mostly, psychological factors are assumed to facilitate pain [277]. Thus, implicit operant learning mechanism can be assumed to be of particular importance in the development and maintenance of enhanced pain sensitivity in unspecific pain syndromes.

Fibromyalgia

Fibromyalgia is a chronic, unspecific condition with widespread pain in muscles, ligaments and tendons. Fibromyalgia is diagnosed according to the criteria of the American College of Rheumatology [288]: pain is defined as widespread when it is present in the left and the right side of the body, above and below the waist with additional axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back). Widespread pain is required to be present for at least three months; for the diagnosis of fibromyalgia, additional pain in 11 of 18 tender point sites has to be present at a pressure of 4kg/cm^2. Frequent comorbid symptoms or disorders are fatigue, sleep disturbances, joint stiffness, irritable bowel syndrome, depression, cognitive dysfunction etc. (e.g. [32,125,198,281]). Reported prevalence rates of fibromyalgia range from 0.5% to 5% in the general population with women being affected more frequently than men [172,276]. Possible causes of fibromyalgia are still discussed: While some authors have stated that no cause can be found

[197], others have assumed the contribution of genetic factors, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, psychological disorders and psychosocial load factors [32]. Most contemporary models suppose the interaction of predisposing genetic and environmental factors in terms of a diathesis-stress model in the etiology and pathogenesis of fibromyalgia [16,32].

Fibromyalgia patients are characterized by a generalized pain hypersensitivity that is ascribed to a pathophysiological process in the central nervous system [185,241,243]. Pain thresholds to different stimuli—e.g. thermal and mechanical—are commonly reduced in fibromyalgia (e.g. [38,91,93,107]). These patients are also characterized by enhanced perceptual sensitization (temporal summation; e.g. [116,244,245]). In addition, deficiencies in endogenous pain modulation such as inadequate pain inhibition have been found in fibromyalgia (e.g. [127,240,246]). However, the origin of this central amplification of sensory input is still discussed [16,32]. Besides different neurophysiologic mechanisms leading to an augmentation of sensory input—e.g. inflammatory conditions and dorsal horn glia cell activity [16,32]—it can also be suggested that fibromyalgia patients learn enhanced perceptual sensitization and hypersensitivity by operant mechanisms as described above (see Section 1.3).

Irritable Bowel Syndrome

The term irritable bowel syndrome (IBS) represents a group of functional bowel disorders characterized by chronic abdominal pain, discomfort and altered bowel habits in the absence of any structural organic cause [154]. IBS is diagnosed according to the 'ROME-III criteria' [141]: recurrent abdominal pain or discomfort (i.e. an uncomfortable sensation not described as pain) at least three days per month associated with two or more of the following: (1) improvement with defecation; (2) onset associated with change in frequency of stool; (3) onset associated with change in form (appearance) of stool. These criteria have to be fulfilled for the last three months with symptom onset at least six months prior to diagnosis. Prevalence rates of irritable bowel syndrome range from 2.5% to 37% in the general population with women being more often affected than men [235]. The wide range of the prevalence rates is caused by different diagnosis criteria [235] and due to the fact that many affected persons do not visit a physician [251]. Etiology and pathogenesis of irritable bowel syndrome are unclear: for example, infections and inflammations, dysfunction of the HPA axis, genetic factors, disorders of the enteric, autonomic and central nervous system are discussed as possible pathogenetic

mechanisms [43,235,277]; only visceral hypersensitivity is generally recognized as a pathogenetic mechanism [7]. However, the mechanisms leading to this visceral hypersensitivity remain being discussed—e.g. genetic factors, inflammatory processes, peripheral and central sensitization as well as altered brain responses have been proposed [7,235]. In some but not all IBS patients also a somatic hypersensitivity has been found (e.g. [2,30,52,170,265]). Since some IBS patients demonstrate somatic hyperalgesia extending up to cervical levels, a spatially distributed secondary hyperalgesia has been suggested [170,205,264]. This secondary hyperalgesia is assumed to be the result of anatomic convergence from visceral and somatic nociceptive afferents on spinal neurons at lumbosacral levels. Due to tonic input from visceral primary afferents, these spinal neurons sensitize, resulting in a facilitation of somatic as well as visceral nociceptive input. Through long ascending propriospinal interactions, this facilitation can extend rostrally and produce a hyperexcitability of spinal neurons at thoracic and cervical levels. In addition, an abnormal function of endogenous pain modulation has been demonstrated in IBS patients contributing to the central sensitization [49,279].

IBS and fibromyalgia often occur together; reported rates of comorbidity range from 63% to 81% [125]. Due to this high comorbidity and due to the fact that both disorders are associated with abnormalities in pain sensitivity, a shared pathophysiological background has been assumed. Proposed shared mechanisms are e.g. peripheral sensitization due to inadequate healing resulting in central sensitization and thus in a vicious circle mediated by the sympathetic nervous system [266], alterations in stress systems [216], altered brain responses [40] and a trait for somatization as a common psychological cause [277]. However, just as in fibromyalgia, hypersensitivity in IBS can be suggested to be learned by operant mechanisms. Thus, patients with both somatic and visceral hypersensitivity or with both fibromyalgia and IBS can be assumed to be more vulnerable to operant learning by intrinsic reinforcement than patients with only one type of hypersensitivity.

1.5 Aims of This Thesis

By the analysis of operant learning mechanism in pain perception, the studies presented in this thesis contribute to the understanding of the gradual development and maintenance of hypersensitivity in chronic pain. For this purpose, the several characteristics of operant learning of altered pain sensitivity were tested. Further, the paradigm was implemented in chronic pain patients.

An overview of the studies and their respective aims are given in Figure 1. The following specific aims were addressed:

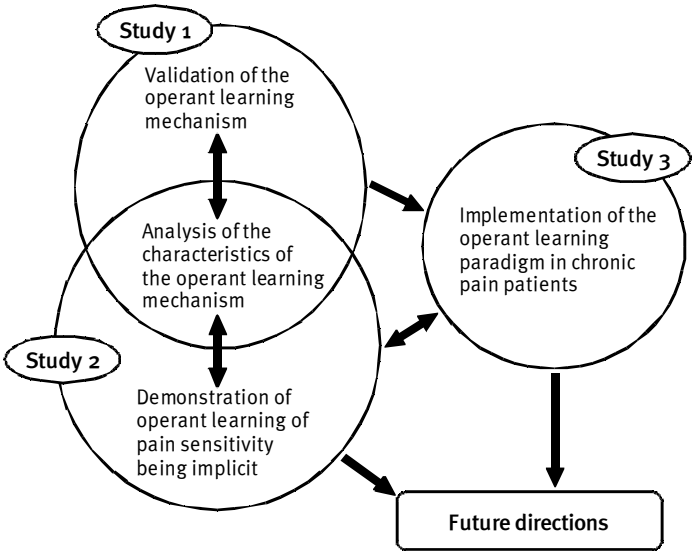

Figure 1: Overview of the studies and their respective aims. See text for details.

Validation of the Operant Learning Mechanism and Analysis of Its Characteristics

It has been demonstrated that pain sensitivity—indicated by behavioral discrimination—can be modulated by operant conditioning with intrinsic reinforcement within a discrete-trial procedure [106]. In order to validate this operant learning mechanism, a continuous operant conditioning procedure was applied in study 1, demonstrating the independency from the experimental paradigm. Further, the characteristics of this operant learning mechanism were analyzed by the implementation of different magnitudes of reinforcement and a variable interval schedule of reinforcement. By the first, a dose-dependency of this type of operant learning should be shown; by the latter, operant behavior should be uncoupled from immediate (unconditioned) effects of reinforcement in order to demonstrate that learning took place and behavior is not only controlled by immediate effects of reinforcement.

Demonstration of Operant Learning of Pain Sensitivity Being Implicit

Implicit learning mechanisms—learning without awareness—would provide a psychological explanation for the gradual development and maintenance of hypersensitivity in chronic pain without the person's knowledge. Therefore, study 2 is aimed at testing if, contingency awareness, but also awareness for the learning procedure, is necessary for operant learning of altered pain sensitivity, further, if the role of awareness of the reinforcing stimuli was assessed.

Implementation of the Operant Learning Paradigm in Chronic Pain Patients

Hypersensitivity in chronic pain patients can be assumed to be learned by operant learning with intrinsic reinforcement (see Section 1.3 and 1.4; [106]). Therefore, in order to test the vulnerability of chronic pain patients to operant learning of enhanced pain sensitization and habituation, the operant learning paradigm was implemented in fibromyalgia patients in study 3. Further, it was hypothesized that chronic pain patients who display abnormalities in pain sensitivity in more than one modality are more vulnerable to operant learning of altered pain sensitivity. Thus, in order to test this hypothesis, fibromyalgia patients assessed with the operant learning paradigm were divided into two groups: patients with and without comorbid irritable bowel syndrome.

2 Operant Conditioning of Enhanced Pain Sensitivity by Heat-Pain Titration[1]

2.1 Introduction

The role of operant learning mechanisms in the development and maintenance of chronic pain is widely recognized. Specifically, pain expression, lowered tolerance and avoidance behavior can be enhanced by reinforcement [82,83]. Experimental and clinical studies provide support for behavioral models of chronicity, and have led to the integration of operant methods into pain therapy [80,110,169]. However, the precise mechanisms that mediate between nociceptive processing, environmental consequences, and altered pain perception remain unclear [77]. Experimental studies have demonstrated that overt pain reports such as verbal or numeric ratings can be enhanced by verbal or monetary reinforcement in healthy participants [8,108,137,142,143]. Whether this reflects changes in pain sensitivity rather than response criteria is debatable (cf. [53]).

Discriminative behavior is a (differential, 'discriminating') behavioral response (non-verbal, implicit and possibly not correlated with explicit verbal report) to a change in nociceptive input and/or a subjectively experienced change in sensation ('perceptual change'). The research on implicit perception [72,272] and earlier data on implicit memory processes in pain perception [81] suggest that discriminative behavior may be dissociable from verbal pain report by specific learning. Therefore, operant learning paradigms that do not depend solely on reported pain experience should be considered.

Extrinsic reinforcement, i.e. (positive) reinforcement external to the nociceptive system, e.g. monetary reinforcement, and intrinsic reinforcement, i.e. (negative) reinforcement within the nociceptive system, may affect both pain behavior and pain perception. While extrinsic reinforcement is supposed to affect the nociceptive system indirectly, intrinsic reinforcement, as a perceptual experience, directly modulates the perception of nociceptive stimulation. Thus, intrinsic rein-

[1] Development of the experimental procedure, data collection and a first data analysis in study 1 was done as preliminary work within the framework of my diploma thesis. For the present dissertation, the data was entirely reworked and analyzed more sophisticatedly. Meanwhile, this study has been published in the journal 'Pain'. The complete reference is: [14}; doi: 10.1016/j.pain.2008.07.018.

forcement could provide a specific mechanism of operant learning, involving long-lasting changes of an organism's perceptual system and probably being one mechanism of pain becoming chronic.

A previous study by our group [106] successfully combined intrinsic reinforcement with an operant learning paradigm independent of verbal pain reports. We used short-term sensitization as a clinically valid marker of central sensitization [69,119,241] as the target of conditioning. Through operant enhancement of sensitization, gross changes in pain sensitivity could be produced without the participants' knowledge of reinforcement contingencies. This study aimed to expand some aspects of our previous study. First, in order to train enhanced perceptual sensitization to heat-pain stimulation in healthy volunteers, we employed intrinsic reinforcement by acute decreases and increases of nociceptive input contingent on discriminative behavior. In addition, different magnitudes of reinforcement were applied to demonstrate operant learning of enhanced sensitization in a dose-dependent manner [155]. Second, in order to analyze the underlying learning mechanism, we implemented a partial schedule of reinforcement, uncoupling (conditioned) operant behavior (e.g. pain avoidance) from immediate (unconditioned) effects of reinforcement (e.g. pain relief) [74]. Last, in order to show that the described operant learning mechanism is independent of the experimental paradigm, we applied a different procedure than in the previous study. We used a titration schedule originally developed in animal perception studies and behavioral pharmacology (e.g. [26,65-67,247,275]), which enabled us to track pain perception continuously and independent of verbal pain reports.

2.2 Methods

Participants

36 healthy volunteers (18 female; 17–52 years; $M = 28.7$; $SD = 6.8$) participated in this study. Seven uncompleted trials (7 of 144 trials) of four participants were excluded from statistical analysis, because the preset maximum heat intensity to avoid tissue damage was exceeded. All the participants met standard criteria (no medical or psychiatric illness, no current medication, thresholds in quantitative sensory testing within a 95% norm range [168]). An informed consent according to the revised Declaration of Helsinki was signed by all the participants and the study was approved by the Local Ethics Committee.

Apparatus for Stimulus Application

Heat stimuli were applied via a contact heat thermode system (PATH-Tester MPI 100; [88]) with a thermode size of 16 x 36 mm. The same thermode system was used in quantitative sensory testing prior to the experimental procedures. The system allows phasic and tonic stimulation within a temperature range of 12–52°C with a relative accuracy of 0.05°C. The baseline skin temperature was kept constant at 40°C for all procedures; the rate of temperature change was 0.7°C/s. All heat stimuli were given to the thenar eminence of the non-dominant hand. For the long-term stimulation during heat-pain titration, specific precautions were taken to avoid skin damage: the maximum thermode temperature was limited to 50°C and total applied energy was restricted by integrating temperature over time, terminating the procedure if a critical value was reached. This value was calculated according to human and animal data on skin burns through contact heat [33,57,126,182]. The experimental procedures were completely automatized and controlled by a separate personal computer (PC) coupled to the thermostimulator system. Thermal stimuli could be applied automatically by the PC or manually by the subject adjusting temperature with two keys on a response unit. A blue key marked with the verbal descriptor 'Cooling' was used to decrease temperature and a red key marked with the verbal descriptor 'Heating' was used to increase temperature. A computer screen placed in front of the subject was used to display instructions, control signals and rating scales.

Operant Heat-Pain Titration

An operant heat-pain titration procedure was developed to demonstrate operant learning of perceptual sensitization during ongoing heat-pain stimulation. The operant heat-pain titration was based on titration as developed originally in animal perception studies and behavioral pharmacology (e.g. [26,65-67,130,187,273,274]). The procedure was adapted to a previously established indirect method of adjustment to quantify short-term sensitization (temporal summation) to tonic thermal stimulation [119]. Its operant principle is based on a previously developed operant procedure [106]. The entire procedure was applied under the general cover instruction of examining heat and pain sensation over time. Prior to operant heat-pain titration, the individual pain threshold was measured by the method of adjustment (see [119] for a precise description): in each of three trials, participants increased temperature by pressing the heating button of the response unit until a just painful temperature was reached (self-adjusted pain threshold). A

tonic stimulation phase (30s) with this self-adjusted temperature followed. Then participants had to readjust the temperature to a just painful sensation, indicating sensitization or habituation to tonic stimuli. This readjustment was only used to check for abnormal short-term sensitization. The self-adjusted pain threshold from the last trial was used as a reference temperature in the subsequent procedure.

The operant heat-pain titration procedure consisted of four trials; each trial was composed of three intervals (Fig. 2A and B):

(a) *Reference Interval:* the stimulus temperature increased from baseline (40°C) to a painful initial temperature (self-adjusted pain threshold + 0.33°C). This initial temperature was kept constant during a reference interval of 6 s, while participants were instructed to memorize the current temperature. Concurrently, a visual analog scale (VAS) was presented on a computer screen to anchor the sensation. The VAS was vertically oriented ranging from 0 to 100 and open-ended at the top to avoid ceiling effects. Three points on the scale were labeled with a number and a corresponding verbal descriptor. The lower end of the scale was labeled 'warm sensation' (0), a point below the midpoint was labeled 'just painful' (40) and the upper end of the scale was labeled 'very strong pain' (100). For anchoring, the scale cursor automatically moved along the scale slightly above the scale point labeled 'just painful', thus indicating the appropriate scaling for the concurrent sensation. Participants were familiarized with the scale prior to the operant training procedure.

(b) *Heat-Pain Titration with Double Reinforcement:* Immediately after the reference interval, the heat-pain titration interval of 8 min duration followed. Participants received tonic heat-pain stimulation, starting at the initial temperature and increasing gradually with the programmed titration slope (0.05°C/s). Participants were instructed to keep the temperature constant according to the temperature memorized in the reference interval by continuously adjusting it with the heating and cooling buttons of the response unit. Under the task of keeping the temperature constant, no responses or additional heating responses indicated habituation, while cooling responses indicated sensitization. Thus, the self-adjusted temperature represented an indirect behavioral measurement of perceptual change (c.f. [106,119]). During heat-pain titration, discriminative behavior (i.e. pushing cooling and heating buttons) was the target of double reinforcement, that is target and opponent behavior were reinforced and punished concurrently. Cooling responses, indicating sensitization, were 'reinforced' by a predefined temperature decrease; heating responses, indicating habituation, were 'punished' by a predefined tem-

perature increase according to experimental reinforcement conditions (c.f. [104], for basic concepts).

(c) *Intensity Rating:* subsequent to the heat-pain titration interval, participants performed an absolute magnitude rating of perceived stimulus intensity with the VAS described above (see (a) above). While the cursor was moved along the scale automatically in the reference interval, the participants now had to move the cursor themselves with the heating and cooling buttons of the response unit according to their sensation. This rating was used to ensure that the temperature was still judged as painful after the heat-pain titration. Due to software error, the intensity ratings of trials 3 and 4 were lost. Perceived stimulus intensities could only be evaluated for trials 1 and 2 of operant heat-pain titration.

The participants were first informed about the number of trials and their duration. The first trial was then instructed as follows: ‘‘At the beginning of each trial, the temperature increases up to a value slightly above your pain threshold measured before. When this temperature is reached, the so-called reference interval of 6 s duration starts. In this reference interval, you should memorize the current temperature. Concurrently, a scale is displayed on the screen, which shows you the current temperature in relation to your pain threshold. With the end of the reference interval, this scale disappears and the instruction ‘‘please keep constant” appears on the screen. Now, you should keep the temperature, as you have memorized it before, constant. That means if you sense changes in temperature you should immediately readjust it back to the memorized temperature. You should keep adjusting the temperature continuously for 8 min; during this time the corresponding instruction remains on the screen”. Afterwards, the usage of the response keyboard for adjusting the temperature and for giving VAS ratings was explained. For keeping the temperature constant, pressing the red button increased the temperature, while pressing the blue button decreased the temperature. For giving VAS ratings, pressing the red button moved the scale marker upwards, while pressing the blue button moved the cursor downwards.

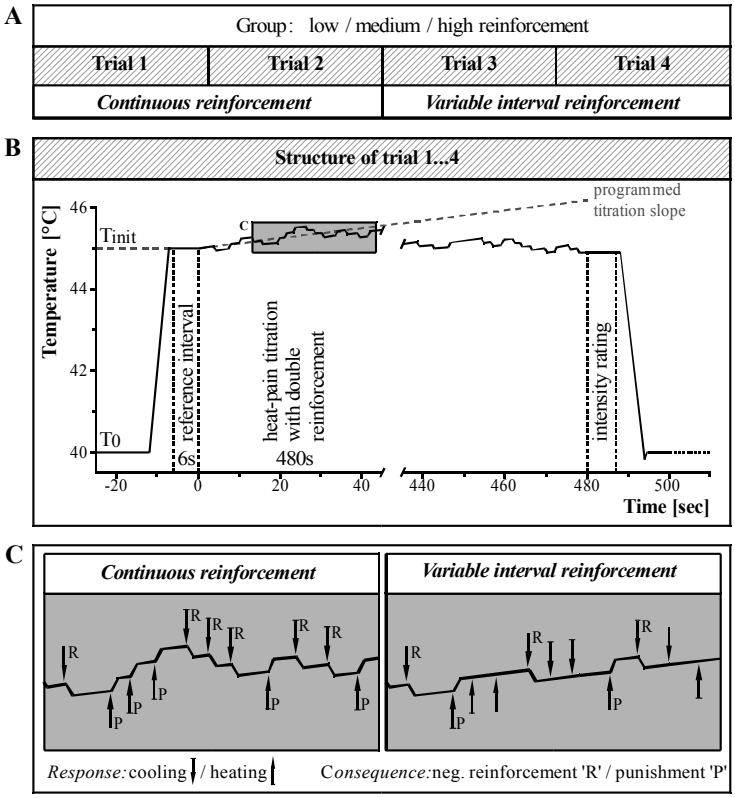

Figure 2: Experimental design, trial structure and schedules of reinforcement of the operant heat-pain titration. (A) Experimental design: each of the three groups exposed to different magnitudes of reinforcement (low/medium/high) performs four trials of operant heat-pain titration, in trials 1 and 2 with continuous reinforcement and in trials 3 and 4 with variable interval reinforcement. (B) Trial structure: stimulation starts from baseline temperature (T_o = 40°C) to a preset initial temperature (T_{init}, individual pain threshold + 0.33°C; slope 0.7°C/s). After reaching this initial temperature, the reference interval (6 s) starts with ongoing stimulation; participants were instructed to memorize the current temperature. Immediately after the reference interval is ended, the heat-pain titration interval with double reinforcement starts (480 s): tonic heat-pain stimulation increases gradually with the programmed titration slope (0.05°C/s); participants were instructed to keep the temperature constant according to the temperature memorized in the reference interval with the use of the cooling and heating buttons of the response unit. Button presses are double reinforced by negatively reinforcing cooling responses with a predefined temperature decrease and concurrently punishing heating responses with a predefined temperature increase. After the heat-pain titration interval, an intensity rating follows, where participant rate stimulus intensity on a VAS. (C) Schedules of reinforcement: with continuous reinforcement (trials 1 and 2) each cooling and heating response is negatively reinforced or punished. With variable interval reinforcement (trials 3 and 4), cooling and heating responses are reinforced or punished only part of the time.

Experimental Conditions and Details of Operant Heat-Pain Titration

Magnitudes of Reinforcement. Within the operant heat-pain titration, the magnitude of reinforcement was defined as the size of the temperature decrease (negative reinforcement) or increase (punishment) contingent on cooling or heating responses. This magnitude of reinforcement was varied between three experimental groups: (a) Group 'low reinforcement': the magnitude of reinforcement was smaller than the suspected just-noticeable-difference (e.g. 0.16°C at 45°C); (b) Group 'medium reinforcement': the magnitude of reinforcement was approximately the suspected just-noticeable-difference (e.g. 0.23°C at 45°C); (c) Group 'high reinforcement': the magnitude of reinforcement was larger than the suspected just noticeable difference (e.g. 0.45°C at 45°C). In addition, magnitudes of reinforcement were adjusted with Weber fractions to account for changes in just-noticeable-difference due to the current absolute temperature. Estimates of these values and just-noticeable-differences were derived from previous studies in humans and monkeys by Bushnell, Maixner and colleagues [35,36,147,148]. For each trial, the cumulated reinforcement temperature was calculated by summing up the temperature decreases and increases due to reinforcement and punishment during the titration trial. Thus, cumulated reinforcement temperature equaled the received negative reinforcement minus the received punishment in total.

Schedules of Reinforcement. With the operant heat-pain titration, the behavior under a continuous schedule of reinforcement was compared to the behavior under a variable interval schedule of reinforcement. With a continuous schedule, every single response is reinforced or punished, while with a variable interval schedule (a special form of a partial schedule) the responses are reinforced or punished only after a variable time interval since the last reinforcement has elapsed. Due to these varying time intervals, participants barely can predict when the next reinforcement will be available. Thus, with a variable interval schedule, the rate of reinforcement (here, rate of contingent temperature decreases and increases) depends only indirectly on the rate of responses (here, rate of cooling and heating responses). This feature permits the dissociation of reinforcement (contingent temperature changes) and reinforced behavior (button presses). This dissociation is particularly important within the operant titration paradigm, because the permanently increasing stimulus intensity (programmed titration slope) sooner or later forces the participants to respond for a short pain relief. The variable interval schedule allows the conclusion that the operant behavior was acquired and that changes in heat-pain sensitivity are not trivially due to the immediate uncondi-

tioned effects of reinforcement, such as acute pain relief. The continuous schedule of reinforcement (CR) was applied during trials 1 and 2, and the variable interval schedule of reinforcement (VI) was applied during the subsequent trials 3 and 4 (Fig. 2A and C). For heating and cooling responses, two concurrent variable interval schedules of reinforcement with the same parameters were implemented. The parameters of the time intervals in the variable interval schedule were adjusted to the three different magnitudes of reinforcement[2]. In the repeated measures analysis, trials were pooled within the schedule of reinforcement (CR: trials 1 and 2; VI: trials 3 and 4) after having ensured that self-adjusted temperatures did not differ between trials (Mixed model analysis, main effect 'Trial', $F(3; 90) = 1.4$, ns). To prevent the conditioning of superstitious or switching behavior [25,230], a short time-out (1s) was activated after each cooling or heating response with continuous as well as with variable interval reinforcement. Within this time span, further responses were not reinforced or punished, and the temperature increased continuously according to the preset titration slope.

Equilibrium Temperature. A typical feature of titration procedures is an initial settling process, resulting in equilibrium between necessary response rate and aversive sensation or pain perception. After the end of the settling process, the training phase follows. In the operant heat-pain titration, the settling process was expressed in a rapid increase and subsequent leveling-off in self-adjusted temperature at the beginning of each individual trial. The equilibrium temperature was defined by the slope changing from positive values to values near zero or negative. (This criterion worked for all trials but one, in which the time of reaching the equilibrium was estimated by the mean time of reaching the equilibrium of all other trials.)

Experimental Design and Statistics

The study was analyzed according to a repeated measures design with Group (low, medium, high magnitude of reinforcement) x Schedule (CR, VI) x Time (0–8 min). Participants (36) were randomly assigned to one of the three groups exposed to different magnitudes of reinforcement (Group 'low reinforcement': $N_1 =$

[2] The variable time intervals (mean duration M ± range) for each of the three groups were: 'low reinforcement': M= 3 ± 2 s, 'medium reinforcement': M = 4 ± 3 s, 'high reinforcement': M = 8 ± 5 s. The mean interval M was calculated according to the amount of cooling responses necessary—at a given reinforcement magnitude—to counteract the temperature change induced by the titration slope. The parameters were tested and optimized in a pilot study.

13, 6 female; Group 'medium reinforcement': N_2 = 11, 6 female; Group 'high reinforcement': N_3 = 12, 6 female). Each participant performed 4 trials of 8 min duration of operant heat-pain titration, with breaks of 5 min between trials. The continuous reinforcement schedule was applied during trials 1 and 2, and the variable interval schedule was applied during trials 3 and 4. For statistical analysis, data were averaged individually per minute. For the analysis of the training phase, individual trials were aligned to the time point of reaching the equilibrium, and the temperature change relative to the equilibrium temperature was calculated. The time span until equilibrium temperature has been different for individual trials. Thus, the alignment resulted in a reduced sample count in the design cells of the late training phase (6–7 min). For further analysis, these decreased cell counts were excluded to avoid a bias of statistics. Repeated measures data were analyzed by Mixed Model Analysis ; significant main effects and interactions are given as adjusted probabilities of approximated F-statistics in Table 1. Non-parametric tests were used to substantiate the effects of Mixed Model Analysis where appropriate. The significance level was set to 5% adjusted with the false discovery rate for multiple testing [15]. All calculations were performed with the SAS® System for Windows®, Release 9.1.

2.3 Results

Operant Learning of Enhanced Perceptual Sensitization with Different Reinforcement Magnitudes

The operant heat-pain titration was effective in producing enhanced perceptual sensitization through operant learning with intrinsic reinforcement. Moreover, changes in perceptual sensitization were directly dependent on the magnitude of reinforcement: the group with the lowest reinforcement magnitude showed the least pain sensitization, and the group with the highest reinforcement magnitude showed the most pain sensitization. Thus, the operant heat-pain titration affected pain sensitivity in a dose-dependent manner (Fig 3A and B).

The self-adjusted temperature during operant heat-pain titration differed between the groups, showing a systematic dependency on the magnitude of reinforcement (Table 1, main effect 'Group', $F(2; 33) = 7.2$, $p < .01$). Self-adjusted temperatures could be approximated linearly over training time (Table 1, linear trend 'Lin (Time)', $F(1; 131) = 61.8$, $p < .0001$). Moreover, this linear trend differed between the groups with different reinforcement magnitudes (linear trend contrast

'Group x Lin(Time)', $F(2; 131) = 4.2$, $p < .05$). The linear trend and the linear trend contrast demonstrated that intrinsic reinforcement resulted in a progressive down-regulation of self-adjusted temperatures in a dose-dependent manner. In addition, even though this temperature drift developed gradually, it differentiated between reinforcement magnitudes already after the first minute in the training phase (Effect slices: Minute 1, $F(2; 131) = 5.3$, $p < .05$, Fig 3B). Specifically, the dose-dependent effect of operant learning was indicated by a significant linear trend difference between the groups with low and high reinforcement (Table 1, linear trend contrast 'Group low/high reinforcement x Lin(Time)', $F(1; 131) = 8.2$, $p < .01$).

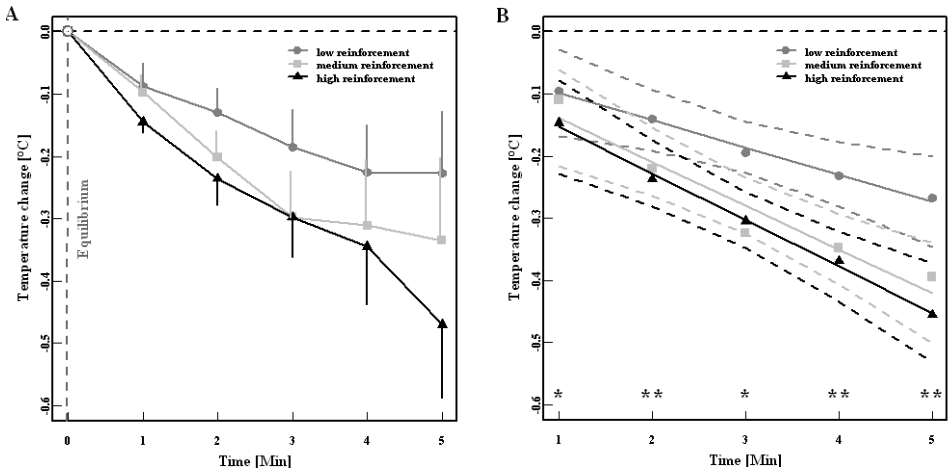

Figure 3: Learning curves during operant heat-pain titration. Learning curves are given as self-adjusted temperature change from individual equilibrium temperature (45.5–46.2°C) for groups receiving different magnitudes of reinforcement (Group 'low reinforcement' $N_1 = 13$; Group 'medium reinforcement' $N_2 = 11$; Group 'high reinforcement' $N_3 = 12$). (A) Minute to minute mean time courses of groups. (B) Linear approximation of minute to minute means for groups. Regression lines (linear trends) with 95% confidence intervals. Self-adjusted temperature changes differ significantly after 1 min (repeated measures analysis effect slices for each minute: * $p < .05$, ** $p < .01$; main effects and interactions in Table 1).

Analysis of the cumulated reinforcement temperature showed that the magnitude of reinforcement was crucial in producing the dose-dependent changes in perceptual sensitization. Although groups differed in the magnitude of reinforcement, the cumulated reinforcement temperature was comparable between these groups (Table 2, column 2, main effect 'Group', $F(2; 62) = 0.5$, ns). Cumulated reinforcement temperature differed neither between the schedules of reinforcement nor between the schedules of reinforcement within each group (see Table 2,

column 2). These results permitted the conclusion that the magnitude of reinforcement was responsible for the dose dependent increase of sensitization.

Table 1: Self-adjusted temperature during training phase of operant heat-pain titration

Effect	Self-adjusted temperature
	F (df num; df den); p[a]
Main effects	
Group [low, medium, high]	7.2(2;33); <.001 **
Schedule [CR, VI]	3.2 (1;29); .08
Time [1-5]	24.9 (4;131); <.001 ***
Interaction	
Group x Schedule	1.4 (2;29); .26
Linear trend	
Lin(Time)	61.8 (1;131); <.001 ***
Linear trend contrasts	
Group x Lin(Time)	4.2 (2;131); .02 *
Schedule x Lin(Time)	0.2 (1;115); .63
Group low/medium x Lin(Time)	3.4 (1;131); .07
Group low/high x Lin(Time)	8.2 (1;131); .01
Group medium/high x Lin(Time)	0.8 (1;131); .37

Results of repeated measures analysis with linear mixed models of the self-adjusted temperatures during training phase (minutes after equilibrium time) of operant heat-pain titration. Group factor 'magnitude of reinforcement' (Group 'low reinforcement' $N_1 = 13$; group 'medium reinforcement' $N_2 = 11$; group 'high reinforcement' $N_3 = 12$); two schedules of reinforcement (Continuous reinforcement (CR): trial 1 and 2 collapsed; variable interval reinforcement (VI): trial 3 and 4 collapsed); 5 Minutes of training (time); approximation of linear trends over 5 Minutes in training (Lin(time)).

[a] Adjusted *F*-ratios, degrees of freedom for denominators (den) and for numerators (num) in brackets and exact probabilities for main effects, interactions, linear trends and linear trend contrasts. Significances given as per false discovery rate adjusted probabilities: t = p < .10 * = p < .05; ** = p < .01; *** = p < .001.

Operant Learning with Different Schedules of Reinforcement

The cumulated reinforcement temperature and response rates showed the successful implementation of the variable interval schedule of reinforcement: the cumulated reinforcement temperature did not differ between the groups and the schedules of reinforcement (see Table 2, column 1), demonstrating that parameters of variable interval schedule of reinforcement were chosen in a way to create comparable conditions for all groups. Although the cumulated reinforcement temperature was identical, the average rate of cooling responses was higher and the average rate of heating responses was lower with the variable interval schedule than

with the continuous reinforcement. While cooling responses were nearly twice as often (170%) within the variable interval schedule than within the continuous schedule, the number of heating responses was halved (53%) with the variable interval schedule. Furthermore, the variable interval schedule was effective as indicated by the reinforcement or punishment not following every single response (average ratio between rate of cooling responses and rate of negative reinforcement was 2; average ratio between rate of heating responses and rate of punishment was 1.3). Self-adjusted temperatures as an indicator for the operant learning of enhanced perceptual sensitization did not differ between the continuous and the variable interval schedule of reinforcement (Table 1, main effect 'Schedule', $F(1; 29) = 3.2$, ns). Since the implementation of the variable interval schedule of reinforcement was successful (as shown above), it could be assumed that the operant heat-pain titration was effective in producing operantly learned behavior. Furthermore, there was no interaction between the groups and the schedules of reinforcement (Table 1, interaction 'Group x Schedule, $F(2; 29) = 1.4$, ns), indicating that the self-regulated temperature did not show schedule-specific effects with different magnitudes of reinforcement. Schedules of reinforcement had no specific effect on self-adjusted temperatures in the course of the training, demonstrated by linear approximations of self-adjusted temperatures that did not differ between the schedules (Table 1, linear trend contrast 'Schedule x Lin(Time)', $F(1; 115) = 0.2$, ns). These results indicated that the operant learning of enhanced perceptual sensitization occurred independent of unconditioned immediate effects of reinforcement that is pain relief.

Characteristics of Operant Heat-Pain Titration

Operant learning of perceptual sensitization could be produced in a dose-dependent manner with the method of heat-pain titration. In order to conclude that these learning effects were not affected by the applied experimental method, some features of the heat-pain titration had to be controlled:

(a) *Initial Temperature:* initial temperatures were individually calculated according to individual pain thresholds (self-adjusted pain threshold + 0.33°C; see Section 2.2). The mean initial temperature was 44.2°C (SD = 1.7). Initial temperatures did not differ between the groups with different magnitudes of reinforcement (Table 2, column 3, main effect 'Group', $F(2;32) = 0.5$, ns). Thus, groups showed no differences in pain threshold previous to operant heat-pain titration.

Table 2: Descriptive statistics and repeated measures analysis of operant heat-pain titration parameters

Effect	Cumulated reinforcement temperature [°C]	Initial temperature [°C]	Equilibrium temperature [°C]	Perceived stimulus intensity [0-110]
Descriptive statistics[a]	*M; SD*	*M; SD*	*M; SD*	*M; SD*
Group: low	16.4; 3.8	43.8; 1.9	45.5; 2.0	52.5; 12.0
Group: medium	15.6; 2.5	44.5, 1.7	46.2; 1.4	55.8; 12.0
Group: high	16.1; 1.2	44.3; 1.6	45.7; 1.1	55.5; 13.4
Repeated measures analysis[b]	*F (df num; df den); p*[c]	*F (df num; df den); p*[c]	*F (df num; df den); p*[c]	*F (df num; df den); p*[c]
Main effects				
Group [low, medium, high]	0.5(2;62); .63	0.5(2;32); .60	2.6(2,129); .08	0.5(2;58); .64
Schedule [CR, VI]	0.0(1;62); .89		2.5(1;129); .12	
Trial [1,2]				0.0(1;58) .89
Contrasts				
Group: low x Schedule	0.0(1;22); .99		0.2(1;46); .63	0.0(1;22); .87
Group: medium x Schedule	0.1(1;18); .77		1.4(1;38); .25	0.0(1;16); .93
Group: high x Schedule	0.0(1;22) .97		2.1(1;45); .15	0.2(1;20); .64

[a] Mean and standard deviation of cumulated reinforcement temperature, initial and equilibrium temperature and perceived stimulus intensity in each group (Group 'low reinforcement' $N_1 = 13$; group 'medium reinforcement' $N_2 = 11$; group 'high reinforcement' $N_3 = 12$).

[b] Results of repeated measures analysis of cumulated reinforcement temperature, initial and equilibrium temperature and perceived stimulus intensity. Group factor 'magnitude of reinforcement' (Group 'low reinforcement' $N_1 = 13$; group 'medium reinforcement' $N_2 = 11$; group 'high reinforcement' $N_3 = 12$); Cumulated reinforcement temperature and equilibrium temperature: two schedules of reinforcement (Continuous reinforcement (CR): trial 1 and 2 collapsed; variable interval reinforcement (VI): trial 3 and 4 collapsed); Initial temperature was equal in each trial (1-4); Perceived stimulus intensity: only trial 1 and 2 were analysed.

[c] Adjusted *F*-ratios, degrees of freedom for denominators (den) and for numerators (num) in brackets and exact probabilities for main effects and contrasts. Significances given as per false discovery rate adjusted probabilities: t = $p < .10$; * = $p < .05$; ** = $p < .01$; *** = $p < .001$

(b) *Equilibrium Temperature:* the equilibrium temperature and the time of reaching this temperature were calculated individually for each trial (see Section 2.2). The mean equilibrium temperature was 45.8°C (SD = 1.6). Equilibrium temperatures did not differ between the groups (Table 2, column 4, main effect 'Group', $F(2; 129) = 2.6$, ns). Moreover, equilibrium temperatures differed neither between

the two schedules of reinforcement nor between the two schedules within each of the three groups (see Table 2, column 4). Thus, the equilibrium temperature and the self-adjusted temperature, respectively, were not affected by the necessary response rate to keep the temperature constant, which was directly dependent on the magnitude of reinforcement. Therefore, the necessary response rate could not explain the dose-dependent differences in operant learning.

(c) *Perceived Stimulus Intensity*: the mean absolute magnitude rating was 54.5 (SD = 12.4) in trials 1 and 2 of the operant heat-pain titration, which was higher than the scale value of 40, that is 'just painful'. Absolute magnitude ratings did not differ between the groups (Table 2, column 6, main effect 'Group', $F(2; 58) = 0.5$, ns). Absolute magnitude ratings also showed no differences between trials 1 and 2, and the ratings in trials 1 and 2 did not differ within each of the three groups (see Table 2, column 6). These results indicated that stimulus intensity was perceived as subjectively painful after the heat-pain titration interval and that participants followed the instruction to keep the temperature constant as anchored in the reference interval.

2.4 Discussion

In this study, implicit operant conditioning of perceptual sensitization by intrinsic reinforcement could be shown. Negative reinforcement by pain decrease or punishment by pain increase applied contingently on discriminative behavior resulted in enhanced sensitization to prolonged heat-pain stimulation. This sensitization was indicated by reductions in stimulus intensity during the operant heat-pain titration, which occurred although the participants were instructed to keep the stimulus intensity constant. In addition, the degree of sensitization was directly dependent on the magnitude of reinforcement. The effect of operant conditioning with operant heat-pain titration resulted in the dose-dependent increase in sensitization to tonic heat-pain stimulation. This systematic dependence on reinforcement magnitude permits the conclusion that changes in perceptual sensitization are the result of operant learning processes, even though within heat-pain titration the implementation of a 'no-reinforcement' control group is not possible. The use of a titration schedule always implies changes in the titration slope, which are at least in part controlled by the participant and accordingly are contingent consequences of behavior (reinforcement).

This study is different from most investigations on operant learning within the framework of pain, due to the application of intrinsic instead of extrinsic reinforcement and the indirect behavioral method for measuring sensory changes. Most studies in this area employ verbal or monetary reinforcement contingent on overt pain reports (e.g. [108,142]). A few exceptions used biofeedback modification of psychophysiological pain responses. There, biofeedback training of increased electrocortical responses related to perceived intensity led to increased pain ratings and vice versa [82,143,166]. Although these studies applied an objective psychophysiological parameter, extrinsic reinforcement and overt pain report as an indicator for pain sensation were used. In contrast, intrinsic reinforcement within a perceptual discrimination paradigm has an immediate effect on pain perception without the risk of merely changing pain reports or overt pain behavior. Intrinsic reinforcement by changes in pain intensity appears directly within the pain system, in contrast to extrinsic reinforcement, which is mediated mainly by social factors. Thus, intrinsic reinforcement may produce a different kind of learning and/or a different motivational state [217]. This can set-off a process of perceptual discrimination learning resulting in sustained hypersensitivity, a prevalent feature in chronic pain. Perceiving pain provokes behavioral responses, e.g. to take up a relieving posture, which results in intrinsic reinforcement by pain relief. Reinforcement would cause the behavioral response to become more likely, if pain is perceived again. The perceived pain thereby becomes a discriminative signal for the performance of the reinforced behavior; the behavior becomes conditioned. In the time course of this process, progressively weaker nociceptive signals might serve as discriminative signals for the performance of the conditioned behavior. Accordingly, the applied paradigm represents a straightforward model of how acute changes in clinical pain can lead to prolonged hypersensitivity and as a result to gradual immobility by learning to avoid pain (cf. [76,269]).

An important feature of this study is the measurement of pain perception, or rather sensitization, by an indirect behavioral discrimination method. Such a mode of pain measurement is not confounded by response biases in contrast to overt reports of pain experience [53,108]. This is the case as long as participants comply with the instruction to keep the temperature constant as realized in this study. In addition, research on implicit perception [72,272] and implicit memory process in pain perception [81] as well as our previous study [106] suggest that perceptual discrimination behavior and reported sensations are dissociable by specific learning. Therefore, it is critical to distinguish between operant conditioning of perception from changing report criteria (c.f. [108]), as overt reporting may not be the ad-

equate representation level of pain information relevant for learning hypersensitivity. The perceptual discrimination paradigm thus addresses high-level pain processing capable of controlling overt behavior, which is not simply reflected in verbal expressions. In addition, these aspects appear to be particularly important in studying chronic pain patients where social variables exert wide influence on different components of pain behavior independent of actual pain perception [84].

The observed perceptual changes developed from rather undramatic stimulus intensities close to the individual pain threshold. Thus, the described operant learning processes do not necessarily have to be triggered by intense noxious events, as stated in previous theories of pain chronicity such as the 'fear-avoidance theory of exaggerated pain perception' [134,268]. This could explain how unspecific chronic musculoskeletal pain might develop from low levels of noxious input, probably caused by subclinical muscle injuries due to lack of physical training and maladaptive body posture [160].

Moreover, the analysis of the cumulated reinforcement temperature revealed that the magnitude of reinforcement is crucial for producing dose-dependent operant learning in heat-pain titration. The cumulated reinforcement temperature did not vary between the groups, thus they cannot explain the observed dose-dependent differences. Few big intrinsic reinforcers appear to produce equal or even stronger effects than various small intrinsic reinforcers or vice versa, possibly explaining relatively fast changes in pain perception in pain that is becoming chronic.

With a variable interval schedule of reinforcement, the rate of reinforcement and the response rate (reinforced behavior) can be dissociated ([74]; see Section 2.2).Within operant heat-pain titration, operant learning effects were comparable between the continuous and the partial schedule of reinforcement. This is indicative of the acquirement of (true) operant behavior, and the observed changes in pain sensitivity cannot be explained plainly by the immediate effects of negative reinforcement, that is a short pain relief. A variable interval schedule of reinforcement also has other specific effects on operant behavior: robust response rates are achieved which are highly resistant to extinction [56,74]. Since reinforcement is typically partial in natural settings, these characteristics are particularly interesting in pain that is becoming chronic, since operantly conditioned hypersensitivity should consequently be very robust and sustained. The high response rate and the

resistance to extinction of hypersensitivity conditioned by a partial schedule of intrinsic reinforcement may explain the persistence of unspecific chronic pain.

Along with the previous study [106], the present results indicate that the operant conditioning of pain perception with intrinsic reinforcement is independent of the applied experimental paradigm. Since the experimental paradigms of these two studies differed in many aspects (e.g. sequential discrete trial procedure vs. Continuous heat-pain titration, percentile schedule vs. Continuous and variable interval schedule), operant learning by intrinsic reinforcement appears to be a powerful mechanism. In addition, this study shows that the operant heat-pain titration is a paradigm that can be used to analyze and operantly modulate pain perception. Titration schedules were originally developed in animal perception studies and behavioral pharmacology, establishing titration as a sensitive method to determine psychophysical thresholds or to study the influence of medication or drugs on perception and behavior (e.g. [26,65-67,130,187,273-275]). However, transfers from animal studies to studies of perception in humans are scarce. Titration in humans was mainly used for optimizing pharmacological treatments (e.g. [99,109]). This study shows the transfer of the titration method to an operant heat-pain titration paradigm in humans. This permits the continuous tracking of pain perception independent of reported subjective pain sensations where intrinsic reinforcement is contained automatically. Furthermore, confounding effects of verbal instruction were widely ruled out since the behavior was shaped by the procedure itself [153].

In summary, intrinsic reinforcement can influence pain perception, and this may explain the development of prolonged hypersensitivity and avoidance of progressively weaker nociceptive stimulation for fear of more pain during the process of pain that is becoming chronic. Moreover, with this learning mechanism, small changes in pain perception are sufficient to act as reinforcers. Therefore, operant learning with intrinsic reinforcement may be the process that links avoidance behavior and changes in pain perception without assuming, e.g. a disuse or physical deconditioning syndrome [31] or cognitive processes like pain catastrophizing [131]. Whether long-term effects of operant conditioning by intrinsic reinforcement can be achieved which are stable enough to account for sustained changes in pain sensitivity, and whether these mechanisms are different in clinical pain patients, remains to be shown in further studies. The paradigm may also be employed to investigate the relation of operant hypersensitivity to current pathophysiological concepts of central sensitization and 'pain memory' [24,210]. In addition, the moderating role of anticipatory fear can be evaluated [268]. For this purpose, studies including func-

tional neuroimaging and EEG measurements are needed that explicitly address operant pain avoidance learning in addition to Pavlovian conditioning of anticipation and fear of pain [189]. Furthermore, the susceptibility to the operant enhancement of sensitization can be evaluated in clinical groups. The paradigm can eventually be employed in a clinical context as a form of therapeutic intervention for pain patients. Through an inverse operant training, a habituation training (c.f. [106]), the development of enhanced hypersensitivity to nociceptive stimuli may be prevented, or already existing enhanced hypersensitivity may be reduced and pain perception might be 'recalibrated'.

3 The Role of Awareness in Operant Conditioning of Heat-Pain Sensitivity

3.1 Introduction

Implicit and explicit learning are different psychological mechanisms dependent on separate memory systems. The conditions of implicit learning, especially in operant (associative) learning, are still discussed. In particular, it has to be clarified whether operant learning of altered pain sensitivity is implicit, because implicit processing would have important implications for the understanding of pain becoming chronic.

Fundamental, declarative and nondeclarative memory is distinguished [68,211,237]. Learning with awareness—recollection of facts and events—is an instance of declarative memory and depends on the integrity of the hippocampus and related structures. Learning without awareness—learning of contents that expresses itself in performance as skills and habits—is an instance of nondeclarative memory and is independent of the medial temporal lobe [68,237]. Thus, implicit and explicit learning are different psychological mechanisms, and awareness during learning indicates the underlying mechanisms and memory systems [48,237]. More generally, the question when awareness in learning is absent, relates to the question of how consciously experience can arise from neural activity [55].

Contemporary learning theories assume that implicit and explicit associative learning processes co-exists and interacts with each other [48,114]. However, it is still discussed when awareness accompanies associative learning or when awareness is even a necessary condition for associative learning [114,222]. In classical eyeblink conditioning, nondeclarative and declarative memory functions have been dissociated by delay and trace conditioning [44,45]. Successful delay conditioning (the conditioned stimulus (CS) begins before and remains until the unconditioned stimulus (US) is presented, overlaps the US and both stimuli co-terminate) needs no awareness of the CS-US contingency—contingency awareness appears to be epiphenomenal in delay conditioning [46,202,232]. In contrast, successful trace conditioning (CS is presented and terminated before the US starts, there is a silent (trace) interval between the two stimuli) requires the awareness of the US-CS contingency [44,150,151]. It has been shown that both delay and trace conditioning in-

volve the cerebellum, but only trace conditioning additionally requires the medial temporal lobe [44,47]. Similar results were obtained in fear and aversive conditioning [39,121,272]. Nevertheless, the unitary view of classical conditioning to be always mediated by cognition is not dismissed [144,223].

In operant learning it is less clear when learning occurs without awareness. Many studies demonstrated operant learning without awareness (e.g. [21,101,135,136,208,250]). However, these studies were frequently criticized and other studies demonstrated the parallel acquisition of awareness as apparently essential for operant learning (e.g. [60,61,180,204,221,222,270]). Successful implicit operant learning was mainly demonstrated by the use of sophisticated experimental methods (e.g. subtle or covered operants; cover stories to distract the subject's attention from the contingency; [21,114,135,136,207,208]). However, the conditions when implicit operant learning exists remain being largely unclear.

One reason for the controversy concerning implicit learning is certainly imprecise definitions and criteria for awareness [48,144]. Different types of awareness have different qualities and significance for learning. In associative learning, awareness of the learning procedure, awareness of the reinforcing stimuli or the US and contingency awareness have to be distinguished. Further, for assessing awareness, subjective and objective methods exist. Subjective methods—e.g. verbal reports or confidence ratings—demand responding according to an internal state and thus introspection [48,260]. Therefore, these methods have been considered as an index for awareness of awareness since they demand second-order discrimination [184,278]. Subjective methods have been criticized to be prone to response biases and lack of sensitivity [53,222]. In contrast, objective methods—e.g. recognition and prediction tests, post-decision wagering—interfere awareness from a test behavior [48,151,184] These methods need no introspection or verbal report and therefore avoid problems such as response biases. However, objective methods indicate (behavioral) first-order discrimination of response accuracy, but this discrimination does not necessarily equal awareness [167,202,278]. Therefore, these methods have been criticized to be insensitive to phenomenal experience [124,219].

Since implicit and explicit learning are qualitatively different mechanisms (c.f. [114,161]), the question if changes in pain sensitivity are learned implicitly is of special interest the context of pain that is becoming chronic: recent studies showed that hypersensitivity can be acquired by operant learning [13,106]. Hyper-

sensitivity involves two things: hyperalgesia—i.e. increased sensitivity to painful stimulation—and allodynia—i.e. sensation of pain as response to non-painful stimulation—and hypersensitivity is a clinical marker of chronic pain [119,288]. Chronic pain is a prominent feature of several clinical pain states where pain outlasts the time of natural healing [139,162]. Nondeclarative memory permits (unnoticed) cumulative changes in perceptual and response systems [45]. Thus, cumulative changes due to implicit operant learning as an instance of nondeclarative memory may explain the gradual development of hypersensitivity without a person's knowledge in pain that is becoming chronic. Further, in implicit learning, contingencies cannot be easily identified and unlearned. Therefore, implicit operant learning of hypersensitivity can explain the persistence of hypersensitivity as well as the resistance of chronic pain to several therapeutic interventions [80].

In order to clarify this question, the role of different types of awareness was tested in an operant learning paradigm to modulate pain sensitivity in the present study. Further, awareness was assessed with both an objective method—a prediction test—and a subjective method—a standardized interview—in order to target different levels of processing. The prediction test required prediction of subsequent reinforcement. Above-chance accuracy in this test indicated first-order discrimination of the contingencies, since participants should be able to perform the task to the extent they discriminated that a specific own behavior predicts reinforcement (c.f. [151]). The interview as a verbal report was used as an indicator of second-order discrimination of contingencies and thus awareness. For the purpose of modulating pain sensitivity, a previously established experimental operant learning task was applied [106]. In order to avoid the risk of solely changing response criteria (c.f. [53]), this operant learning task comprised two special features compared to other studies on operant learning of pain perception (c.f. [108,137,142]): first, pain perception was measured by discriminative behavior [228], that is a behavioral response to a change in nociceptive input and/or a subjectively experienced change in sensation. This discriminative behavior was realized by tonic heat-pain stimulation during which the participant was to keep temperature continuously constant with a response unit. Down-regulations indicated perceptual sensitization while up-regulations indicated perceptual habituation. Further, this discriminative behavior (and not a verbal pain report) was contingently reinforced. The applied paradigm was therefore independent of subjective pain reports. Second, reinforcement was administered intrinsically—i.e. within the pain system—by contingent decreases (negative reinforcement) or increases (punishment) in nociceptive input. Intrinsic reinforcement as a perceptual experience

directly affects pain perception; in contrast, extrinsic reinforcement—external to the pain system e.g. verbal or monetary reinforcement—affects pain perception solely indirectly. Within each conditioning trial, after performance of the discriminative behavior and before reinforcement, the prediction test was done. Immediately after reinforcement, participants were to rate (on a visual analog scale) temperature changes perceived during reinforcement in order to assess awareness of the reinforcing stimuli. The standardized interview was performed after the conditioning. This interview comprised specific questions about possible systematic connections between the different intervals of the conditioning trials, ratings on how well the different tasks were solved, and open questions about the suspected general intention of the experiment, the reasons for temperature regulation and prediction, and if a special strategy was used with prediction. The operant learning task comprised two learning conditions: in the sensitization learning condition, perceptual sensitization was reinforced while perceptual habituation was punished and vice versa in the habituation learning condition.

We hypothesized that neither first- nor second-order discrimination of the contingencies and thus contingency awareness is necessary for modulating heat-pain sensitivity by operant learning. Furthermore, due to the use of discriminative behavior and intrinsic reinforcement, no awareness of the learning procedure was assumed, while stimuli associated with reinforcement could be discriminated, that is, there should be awareness of reinforcing stimuli. In addition, explicit cognitions about own behavior were assumed not to interfere with implicit operant learning of pain sensitivity. Therefore, operant learning in participants who stated the use of an explicit strategy (not necessarily a correct one) in the interview was compared to operant learning of those who did not state a strategy.

3.2 Material and Methods

Participants

33 healthy volunteers (29 female; aged 23-64 years; M=47.4 SD=9.5) participated in the study. Each participant was to attend two experimental sessions on separate days. Participants were included if they reported no pain or pain episodes exceeding one day per month and if they reported no neurological or psychiatric disorders. None of the healthy participants had to be excluded because of thresholds for warm and phasic pain outside a 95% norm range (norm data accord-

ing to [206]). Informed consent according to the revised Declaration of Helsinki was signed by all participants. The study was approved by the local ethics committee.

Apparatus for Stimulus Application

Heat-pain stimuli were applied with a contact heat thermode (SENSELab—MSA Thermotest, SOMEDIC Sales AB, Sweden). Baseline skin temperature was kept constant at 38°C; rate-of-temperature change was 0.7°C/s. All heat stimuli were given to the thenar eminence of the non-dominant hand. The thermode size was 25 x 50 mm. The large stimulation area is known to result in lowered pain thresholds because of spatial summation [206]. For the long-term stimulation during the operant conditioning, specific precautions were taken to avoid skin damage: the maximum thermode temperature was limited to 50°C and total applied thermal energy was controlled by integrating temperature over time, terminating the procedure if a critical value was reached. This value was calculated according to human and animal data on skin burns through contact heat [33,57,126,182]. The experimental procedures were automatized and controlled by a computer. A computer mouse with two buttons and a wheel was used as response unit for the participants. A computer screen placed in front of the participants was used to display instructions, control signals and rating scales.

The Operant Conditioning Procedure

The applied operant conditioning procedure was similar to a previously established discrete-trial operant conditioning procedure [106]. The purpose of the operant conditioning procedure was to enhance perceptual habituation and sensitization to tonic heat-pain stimulation. The entire procedure was applied under the cover instruction of examining heat and pain sensation over time. Participants were not informed about the learning procedure and also not about the specific operant contingencies. Prior to operant conditioning, the individual pain threshold and perceptual sensitization to tonic heat at four temperatures relative to the pain threshold (threshold + k[°C]; k = –1.0, –0.67, +0.67, +1.33) was measured by the method of adjustment and a short form of the 'dual sensitization method', respectively (see [119] for a precise description).

Each session of the operant conditioning procedure consisted of 80 trials, and each trial was composed of five intervals (Fig. 5):

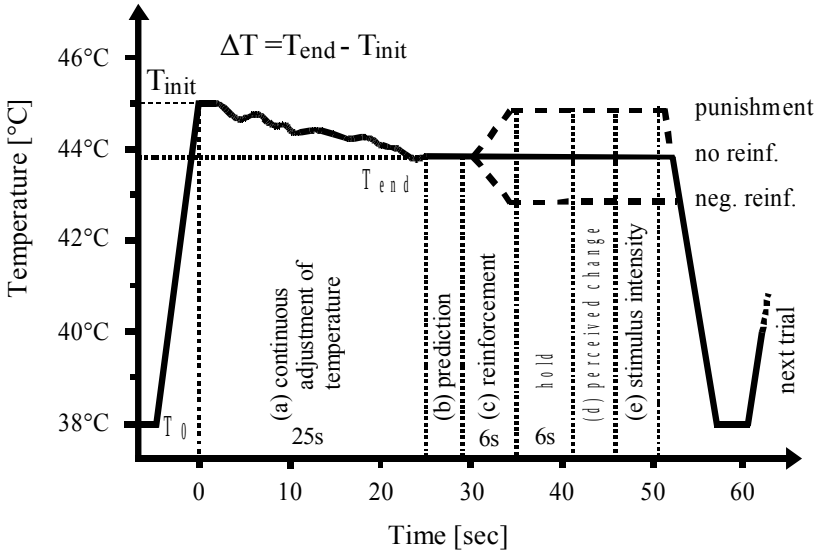

Figure 4: Trial structure of the operant conditioning procedure. Stimulation starts from baseline temperature T_o= 38°C to a preset initial temperature T_{init} (individual pain threshold -1°C; 0.7°C/s). (a) Continuous adjustment of temperature: tonic heat-pain stimulation while participants keep perceived temperature constant by the use of the wheel of a computer mouse for cooling and heating. Adjusted change ΔT: difference of end temperature after 25s of continuous adjustment T_{end} and initial temperature T_{init}. (b) Prediction: participants had to predict temperature changes in the subsequent interval (reinforcement) by selecting one of three alternatives (presumably up/no change/down) by pressing the appropriate mouse button. (c) Reinforcement: a specific temperature decrease (negative reinforcement) or increase (punishment) is made contingent on criterion responses (adjusted change ΔT) to be enhanced or weakened (down-regulation in sensitization learning condition, up-regulation in habituation learning condition). (d) Perceived change: visual analog rating of perceived temperature change during reinforcement. (e) Stimulus intensity: visual analog rating of currently perceived stimulus intensity.

(a) *Continuous Adjustment of Temperature:* The stimulus temperature increased from baseline (38°C) to an initial temperature. During the following 25 seconds of tonic stimulation, participants were instructed to keep the temperature constant by continuous adjustment with the wheel of the response unit. Therefore, up- or down-regulation of temperature indicates perception as a behavioral response to a change in sensation. Thus, by this temperature adjustment a non-verbal, behavioral discrimination task was implemented that measures perceptual changes independent of subjective pain reports. Under this task, up-regulation re-

flected perceptual habituation, while down-regulation indicated perceptual sensitization. Habituation and sensitization were quantified by the difference between the initial temperature and the self-adjusted temperature at the end of the interval. Perceptual sensitization or habituation quantified by this difference and thus discriminative behavior was the target of operant conditioning (see (c) below).

(b) *Prediction:* After the interval of continuous adjustment, the temperature remained constant at the self-adjusted intensity. Participants were instructed to conjecture how the temperature will change in the next interval. For this purpose, the word 'presumably' was displayed on the screen, together with three alternative choices 'up', 'no change', and 'down' below it. Participants selected the appropriate choice by pressing either the left mouse button (up), the middle mouse button (no change), or the right mouse button (down).

(c) *Reinforcement:* After the prediction, the reinforcement interval started. For the participants, this interval was termed 'observation interval' since participants should not be informed about the learning procedure. Participants were instructed—via the computer screen in front of them—to observe the temperature in order to rate perceived changes in the subsequent interval (see (d) below). Operant reinforcement was realized by the connection of the participants' temperature regulation in the adjustment interval with the changes in stimulus intensity in the reinforcement interval—i.e. changes in stimulus intensity for reinforcement were dependent on temperature regulation and thus on discriminative behavior. Up- and down-regulation of temperature indicating perceptual habituation and sensitization was double reinforced, that is, target and opponent behavior were reinforced and punished concurrently [104]: under the sensitization learning condition, perceptual sensitization (down-regulation of temperature) was 'rewarded' negatively reinforced by a decrease in temperature (negative reinforcement) while perceptual habituation (up-regulation of temperature) was 'punished' by an increase in temperature (punishment) and vice versa under the habituation learning condition within the reinforcement interval. For the purpose of achieving a shaping of behavior—i.e. gradually modifying a specific property of behavior by reinforcing successive approximations to the target behavior—towards larger temperature regulations, a percentile schedule of reinforcement was applied, reinforcing only the largest 25% of down- and up-regulations [87]. Under the condition of no reinforcement, temperature was kept constant at the self-adjusted temperature at the end of the adjustment interval. The reinforcement magnitude was predefined slightly greater than just-noticeable differences, i.e. 0.37°C above and 0.54°C below indi-

vidual pain threshold in order to account for different Weber fractions in painful and non-painful regions. The values were derived from previous studies in humans and animals [35,36,147,148].

(d) *Rating of Temperature Change during Reinforcement:* Participants were to rate temperature changes perceived in the reinforcement (observation) interval on a vertically oriented visual analogue scale (VAS) with numerical labels '-1.0°C' and '+1.0°C' as endpoint anchors and subdivisions every 0.5°C at the right of the scale bar. The VAS was open at the upper and lower ends to avoid ceiling effects. Verbal descriptors 'has grown colder' and 'has grown warmer' were added at the endpoint anchors at the left of the scale bar.

(e) *Rating of Stimulus Intensity:* At the end of each trial, the temperature was held constant at the value after reinforcement. Meanwhile, participants performed a magnitude estimation of the currently perceived stimulus intensity on a combined heat and pain VAS. The same display as with the rating of temperature changes during reinforcement in the interval before was used but with different anchors and descriptors. The lower end of the scale was labeled numerically with '0' and verbally with 'warm sensation'. Pain threshold was labeled 'just painful' at a scale value of 40, and the upper end of the scale with the numerical label '100' was marked with the verbal descriptor 'very strong pain'. The VAS was open at the upper end to avoid ceiling effects. Prior to operant conditioning, participants were familiarized with this and the above scale. Participants responded to both rating scales by moving a marker with the wheel of the response unit and confirming the appropriate value by pressing one of the mouse buttons.

Consecutive Procedure: Initial temperature in the first trial of the operant conditioning procedure was preset 1°C below individual pain threshold. This initial temperature was tested and optimized in a previous pilot study in order to allow for both perceptual sensitization and habituation to tonic stimulation to occur. The temperatures of the subsequent trials were chained by a consecutive procedure: trials started with the self-adjusted temperature achieved at the end of the adjustment interval in the previous trial, in order to amplify learning effects over time. With this consecutive procedure—resembling staircase methods commonly used in psychophysical studies (e.g. [94,167])—initial temperature would increase on average over the session when perceptual habituation prevails and decrease when perceptual sensitization prevails.

Individual Baseline: At the beginning of each operant conditioning session, a baseline with no reinforcement was implemented in the procedure. The purpose of this baseline was to achieve a steady state, which is a pattern of responding that exhibits relatively little variation in its measured dimensional quantities [239]. In the operant conditioning procedure, this steady state was defined as a robust stimulus temperature over time, resulting from the consecutive procedure. This steady stimulus temperature is tantamount to perceptual sensitization and habituation appearing equally often during the adjustment interval. The intention of the baseline was the quantification of the effects of operant learning from an individual steady state. Therefore, the change in temperature—as the result from operantly learned behavior—from the temperature in the baseline was calculated. Since the necessary time for this steady temperature to appear varied individually, the number of trials during the baseline was determined separately in each session. Baseline was terminated and the reinforcement schedule activated when the average of self-adjusted temperatures changes over the last seven trials was smaller than 0.10°C.

Measure of First-Order Discrimination of Contingencies

The accuracy of the prediction of reinforcement during the operant conditioning procedure was used as a measure for first-order discrimination of contingencies. The prediction allows for conclusions whether a participant discriminated the contingencies, i.e. the connection of temperature regulation with changes in stimulus intensity associated with negative reinforcement or punishment. This discrimination was termed first-order discrimination, since it not necessarily equals contingency awareness—behavioral (first-order) discrimination is possible without awareness [53,278]. Accuracy of the predictions should correspond to the extent a participant discriminated that own up- or down-regulations of temperature correspond to subsequent changes in stimulus intensity. In order to determine if the participants used any information available from the reinforcement and their temperature regulations first, mutual information of the predictions and reinforcement as well as of the predictions and temperature regulations was analyzed. Mutual information quantifies the mutual dependence or statistical coherence of two variables [224]. In contrast to linear or rank correlation coefficients, mutual information takes into account all types of dependence. Independence of the variables—indicated by a value of zero—implied that no information from the reinforcement or temperature regulation was used for the prediction. Second, it was tested if the mutual information was further transformed in accurate predictions. This second

analysis was necessary since it is possible that mutual information larger than zero exist although without first-order discrimination of contingencies, e.g. if predictions and temperature regulation or reinforcement correlate negatively. In order to test accuracy of the predictions, the agreement between the frequency distribution of predictions (stimulus intensity will go down/up/not change) and the frequency distribution of negative reinforcement, punishment and no reinforcement as well as the frequency distribution of perceptual sensitization, habituation and no change in sensation (indicated by the down-, up- and no-temperature regulation) was analyzed with Cohen's Kappa[3] [50] for each participant. With regard to the fact that discrimination of contingencies needs some time to develop, only the last third of trials in each conditioning session was analyzed.

Measure of Second-Order Discrimination of Contingencies

After the last conditioning session, a standardized interview was performed. This interview was used to analyze for second-order discrimination of contingencies—i.e. contingency awareness—and additionally for awareness of the learning procedure. By the demanded verbalization of the contingencies, the interview required a higher processing level than the prediction and indicated a sort of awareness of awareness. The participants were asked seven specific yes-no questions about possible systematic connections between the different trial intervals and the reinforcement (observation) interval. Afterwards participants were asked to rate on a numeric scale from 0 to 10 (a) how well they solved the tasks, (b) how well they kept the temperature constant, and (c) how well their prospective judgment (prediction) about stimulus changes was performed. Last, participants were asked their opinion about the suspected intention of the experiment, the reason for keeping temperature constant, the reason for the prediction, and if they used a strategy with the prediction.

Study Design and Statistics

The study design comprised two sessions—one including the sensitization learning condition and one including the habituation learning condition—within each participant. The sessions were performed on separate days in balanced order; each session comprised 80 trials of the conditioning procedure. The time to reach a

[3] Cohen's Kappa is calculated with $\kappa = P_o - P_C / 1 - P_C$, where P_o is relative observed agreement (main diagonal of the contingency table divided by the grand total) and P_C is the hypothetical probability of chance agreement (sum of the product of the line totals and column totals divided by the square of the grand total).

steady state during the baseline phase varied individually, and with it the number of available trials for the learning phase, as the overall trial count was constant. For the statistical analysis of learning effects, blocks of 7 trials each were averaged. For the baseline phase, the last seven trials of the baseline were pooled in the first block and the subsequent trials of the conditioning phase constituted the following blocks. This resulted in a reduced sample count in the design cells of the late learning phase (blocks 10-11). These blocks were therefore excluded from analysis to avoid a bias of statistics by reduced cell counts.

The repeated measures design with Learning condition (Sensitization; Habituation) x Time (blocks 1-9) was analyzed by mixed model procedures for repeated measurements [138]. Significant main effects and interactions are given as adjusted probabilities of approximated *F*-statistics. Non-parametric tests were used to substantiate effects of Mixed Model Analysis where appropriate. The significance level was set to 5%, adjusted with the false discovery rate for multiple testing [15]. All calculations were performed with the SAS® System for Windows®, Release 9.1, and R for Windows, Version 2.8.1 [194].

3.3 Results

Operant Learning of Heat-Pain Sensitivity

The operant conditioning procedure was effective in modulating heat-pain sensitivity. Successful operant conditioning was displayed in a progressive change in temperature over the course of the learning session, which resulted from an accumulation of the operant behavior within each trial (up- or down-regulation of temperature indicating perceptual habituation or sensitization), with a difference in this long-term temperature change between the two learning conditions (Linear trend contrast 'Learning condition x Lin(Time)', $F = 20.0$, $p < .001$). Additionally, average temperatures in the sensitization learning condition were below average temperatures of the habituation learning condition (average change from baseline: habituation condition $M = -0.43$°C; sensitization condition $M = -0.81$°C; Main effect 'learning condition', $F = 13.5$, $p < .001$).

First-Order Discrimination of Contingencies

Successful operant learning of heat-pain sensitivity needed no first-order discrimination of contingencies: the measure of contingency discrimination by a prediction test (prediction of reinforcement) indicated in 6 out of 65 sessions

(9.2%) from 5 participants first-order discrimination of contingencies during the operant conditioning procedure. However, only 2 of these participants showed signs of successful operant conditioning. Thus, first-order discrimination of contingencies can be assumed not to be a necessary condition for operant learning of heat-pain sensitivity.

In a first step, mutual information of the predictions and the reinforcement as well as of the temperature regulation (discriminative behavior) and the predictions was analyzed for each participant in order to quantify the mutual dependence of these variables. This quantification displays whether the participants used any information available from the reinforcement and their own temperature regulation behavior for their predictions—independence of the variables (indicated by a value of zero) implied that no information was used. Mutual information of the predictions and the reinforcement significantly larger than zero was found in 25 conditioning sessions (14 sessions in the sensitization learning condition and 11 in the habituation learning condition). Thus, predictions and reinforcement were dependent in 25 out of 65 (37.9%) sessions. Mutual information of the temperature regulation and the predictions was larger than zero and thus dependent in 24 out of 65 (36.9%) sessions (13 sessions in sensitization learning and 11 in habituation learning). However, in 12 sessions (8 sessions in sensitization learning and 4 in habituation learning from 10 participants), dependency—i.e. mutual information—was present only between predictions and reinforcement or between temperature regulation and predictions. Since information from both temperature regulation and reinforcement must be used for correct first-order discrimination of contingencies, both dependencies must have been shown. Thus, in these 12 sessions from 10 participants no present first-order discrimination of contingencies was assumed. As a result of these analyses, first-order discrimination could be present in 18 out of 65 (27.7%) sessions (9 in each learning condition).

Mutual information larger than zero is possible although without first-order discrimination of contingencies, e.g. if predictions and temperature regulation or reinforcement correlate negatively. This would indicate that the participant used the information from temperature regulation and/or reinforcement for predictions but did not discriminate the contingencies. In order to test for this possibility, accuracy of the predictions was tested with Cohen's Kappa (see Section 3.4, Cohen's Kappa; [50]) for each participant in a second step. Thereby, first, the agreement between the frequency distribution of the predictions and the frequency distribution of negative reinforcement, punishment and no reinforcement, and second, the

agreement between the frequency distribution of the predictions and the frequency distribution of up-, down- and no-temperature regulation were analyzed. Above-chance accuracy in both these analyses then indicated correct first-order discrimination of contingencies. Altogether, in 9 out of 65 (13.8%; 3 in sensitization learning and 6 in habituation learning) sessions an agreement between predictions and reinforcement was observable. Agreement between predictions and temperature regulation was found in 7 out of 65 (10.8%; 3 in sensitization learning and 4 in habituation learning) sessions. However, agreement of predictions and reinforcement as well as predictions and temperature regulation was observable only in 6 out of 65 (9.2%) sessions from 5 participants (Participant 59 in sensitization learning; 23, 51, 76 in habituation learning; 70 in both conditions). This result indicated first-order discrimination in these 6 sessions, though in all but one session only partially, since only in this one session agreement was nearly perfect (indicated by a value near 1) while in the other session the agreement was clearly smaller. In all of these 6 sessions the mutual information of both predictions and reinforcement or temperature regulation was larger than zero. Thus, taken the analyses of mutual information and Cohen's Kappa together, 5 participants in 6 sessions were assumed to correctly discriminate contingencies. Of these 6 participants, signs of successful operant learning were observable in only 2 participants (Participant 59: Linear trend contrast 'Learning condition x Lin(Time)', $F = 5.8$, $p < .05$; 76: Linear trend contrast 'Learning condition x Lin(Time)', $F = 34.4$, $p < .001$; both have average temperatures in sensitization learning significantly below average temperatures in habituation learning). These results support the notion that operant learning of heat-pain sensitivity is independent of first-order discrimination of contingencies. First-order discrimination of contingencies appeared to be an epiphenomenon of this learning.

Second-Order Discrimination of Contingencies

Almost all participants were not aware of the contingencies, as hypothesized. The interview as a subjective method indicated that almost all participants could not discriminate the contingencies in second order and thus were not aware of the contingencies. This result was expected since most participants could not even discriminate the contingencies in first order. In the specific questions of the interview about possible relations of the trial intervals, 3 out of 33 participants (9.1%; participants 20, 36, 79) agreed correctly that temperature changes in the reinforcement interval (termed observation interval for the participants) depended on the preceding interval of temperature regulation. However, all these participants

assumed additional conflicting relations between the trial intervals. Furthermore, the answers of these participants in the open questions of the interview contradict contingency awareness, too: all of them assumed the prediction to be a test whether expectancies affect perception; two of them additionally stated the use of an unprofitable prediction strategy, and one stated no prediction strategy. Thus, these participants could not be assumed to be aware of contingencies.

In the open questions of the interview, none of the participants reported the reason for the prediction correctly. However, 4 out of 33 participants (12.2%; participants 41, 54, 69, 76) reported a general association of the prediction and the preceding interval of temperature regulation, but these participants did not report a correct contingency in the antecedent specific questions. Two of these participants reported prediction strategies that were at least in part correct (Participants 41, 76). In summary, none of the participants discriminated the contingencies correctly in second-order and thus were not aware of the contingencies. Only two participants (41, 76) developed a more general awareness of some relation between the trial intervals, indicated by the open questions. Of these participants, one demonstrated signs of successful operant learning (Participant 76: Linear trend contrast 'Learning condition x Lin(Time)', $F = 34.4$, $p < .001$ with average temperatures in sensitization learning significant below average temperatures in habituation learning). This participant is also the only one who discriminated the contingencies correctly in first- and second-order indicated by the objective and subjective measure.

Influence of an Explicit Predictions Strategy

Against our hypothesis, cognitions concerning the own test behavior affected operant learning of heat-pain sensitivity. 17 out of 33 (51.5%) participants reported an explicit prediction strategy and thus cognitions about their test behavior. However, only three of these participants reported an at least partial successful prediction strategy. In order to test if these cognitions affected operant learning of heat-pain sensitivity, operant learning of participants with and without an explicit prediction strategy were compared: participants who reported a prediction strategy showed, in general, no signs of operant learning (Fig. 4B; linear trend contrast $F = 0.33$, ns; 5 out of 17 participants, i.e. 29.4%, demonstrated successful operant learning), while those who did not report a prediction strategy demonstrated in general successful operant learning of heat-pain sensitivity (Fig. 4A; linear trend contrast $F = 5.04$, $p < .05$; 10 out of 16 participants, i.e. 62.5%, demonstrated successful operant learning). Thus, it can be assumed, that cognitions affect or even

superimpose implicit learning of heat-pain sensitivity with operant learning, apparently being mainly affected in the habituation learning condition (see Fig. 4A, B).

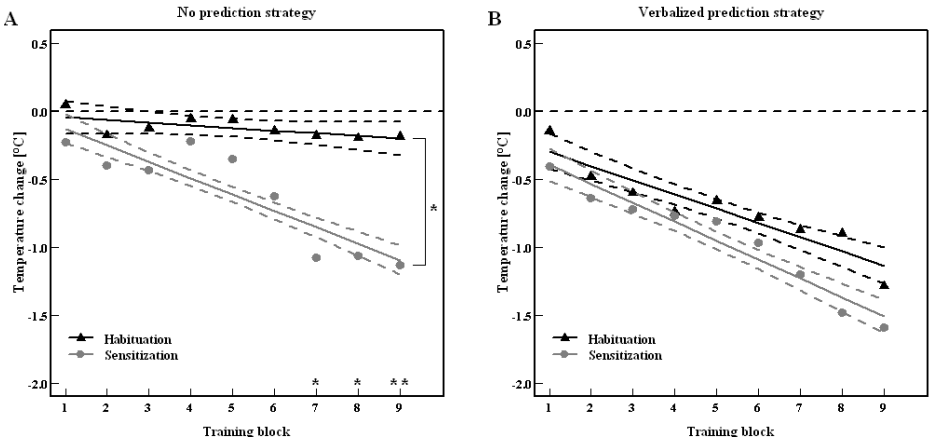

Figure 5: Time course of temperature change during operant conditioning in participants without (A) and with (B) an explicitly stated prediction strategy. Blocks of 7 trials each were averaged (Blocks 10-11 were excluded because of reduced sample count due to individual variance in the number of trial in baseline). Linear approximation of block to block means of temperature change from baseline (block 0). Regression lines (linear trends) with 95% confidence intervals; mixed model analysis effect slices for each block: t = $p < .1$, * = $p < .05$, ** = $p < .01$. (A) Participants without a verbalized prediction strategy: Temperature changes differ significantly after 7 blocks in training between learning conditions. (B) Participants with a verbalized prediction strategy: temperature changes did not differ between learning conditions.

Awareness of Reinforcing Stimuli

Almost all participants were aware of the reinforcing stimuli. Ratings of temperature changes during reinforcement on a visual analog scale indicated that participants discriminated the temperature changes associated with negative reinforcement (M = –0.30°C), punishment (M = –0.36°C), and no reinforcement (M = –0.03°C). Three out of 33 participants (9.1%) in the sensitization learning condition and 4 out of 32 (12.5%) in the habituation learning condition did not discriminate the reinforcing stimuli (Participants 9, 22, 35 in sensitization learning; 22, 23, 25, 70 in habituation learning; Wilcoxon, ns). However, two of these participants in three sessions received only a very small number of negatively reinforcing stimuli (Participant 22, N=5 in sensitization learning and N=4 in habituation learning; 23, N=1 in habituation learning). Two participants (9, 35) rated one or more of the reinforcement classes clearly wrong—e.g. no reinforcement as a temperature decrease

—while the remaining two participants (25, 70) showed ratings of the reinforcing stimuli that, on average, corresponded to the reinforcing stimuli, but mean variation was high. Interestingly, only these latter two participants showed signs of successful operant learning (Participant 25: Main effect 'Learning condition', $F = 11.4$, $p < .01$; 70: Main effect 'Learning condition', $F = 44.6$, $p < .001$). Thus, an at least rough discrimination of the reinforcing stimuli and also more than only a few negative reinforcing stimuli seemed to be a necessary condition for operant learning of heat-pain sensitivity. However, since there were participants who discriminated the reinforcing stimuli but showed no signs of operant learning, awareness of reinforcing stimuli appeared not to be a sufficient condition for operant learning. In addition, all participants unaware of the reinforcing stimuli did not discriminate the contingencies, neither in first- nor in second-order.

Awareness of the Learning Procedure

As hypothesized, almost all participants were not aware of the learning procedure. When asked in the interview about the intention of the experiment, only one participant stated that pain should be learned (Participant 75). However, this participant assumed the different intervals of the procedural trials to be independent and temperature changes in the reinforcement interval to be random. This participant also did not recognize the cause for the prediction and did not state the use of a specific prediction strategy. In addition, 6 out of 33 participants (18.2%) recognized that during the interval of temperature regulation changes in subjective sensation were measured. 23 participants (69.7%) assumed that they corrected with their regulation a computer-controlled change in temperature, while 4 (12.1%) said that they had no idea why they had to regulate temperature. Thus, the learning situation as well as the purpose of the temperature regulation was unapparent for the participants.

3.4 Discussion

Contingency awareness is not a necessary condition for operant learning of altered heat-pain sensitivity. Almost all participants in the present study did not discriminate the contingencies in first-order and also not in second-order when directly asked. Participants who discriminate the contingencies at least partially did not inevitably show signs of operant learning during the conditioning procedure. Thus, it can be assumed, that operant learning of altered heat-pain sensitivity is independent of contingency first- and second-order discrimination and thus contin-

gency awareness. In addition, awareness of the learning procedure is not necessary for successful operant learning in the used paradigm. In contrast, most participants were aware of the reinforcing stimuli, that is, they discriminated stimuli associated with negative reinforcement and punishment. Since participants, who rated reinforcing stimuli wrong, demonstrated no signs of operant learning, awareness of the reinforcing stimuli can be assumed to be a necessary condition for successful operant learning. Nevertheless, awareness of the reinforcing stimuli was not a sufficient condition for operant learning of heat-pain sensitivity since there were participants who discriminated the reinforcing stimuli but showed no signs of operant learning. Altogether, these findings indicate that operant learning of heat-pain sensitivity was implicit and thus is an instance of nondeclarative memory [237]. Thus, this type of learning can be assumed to be independent of the medial temporal lobe, although this assumption has not yet been addressed in studies directly assessing brain systems in operant learning. Studies on reward processing and goal-directed behavior demonstrated the involvement of prefrontal cortex, striatum, amygdale and dopaminergic midbrain [122,177,178]. Although, these studies have not addressed the particular question whether contingency awareness accompanies operant learning, recent findings suggest that brain systems mediating awareness can be differentiated from those mediating operant behavior [252].

In order to address different levels of processing discrimination of contingencies was measured with an objective and a subjective method. The objective method—prediction of reinforcement within each conditioning trial—inferred discrimination of contingencies from the test behavior, that is, first-order discrimination. The subjective method—an interview after the last conditioning session—addressed knowledge by verbalization, that is, second-order discrimination. It must be noted that first-order discrimination is possible without awareness [167,202,278]. Similar to the present study, Reber and Squire (1994) used a prediction test as well as subjective reports of awareness in a serial reaction time task. In their study, amnesic patients learned as well as healthy participants but without subjectively reported awareness. However, these patients scored better in the prediction test than a (random) control group [202]. In contrast, correct second-order discrimination in a subjective test clearly demonstrates the existence of explicit awareness [161,260]. However, conclusions concerning the absence of any information available for accurate discriminations even on an implicit level are possible only from objective tests. Thus, the two methods complement each other and cannot be treated as mutually exclusive or only methodically different (c.f. [222]).

The result that changes in pain sensitivity are learned implicitly is important in the context of pain that is becoming chronic: implicit learning can explain the gradual development of hypersensitivity without the patient's knowledge. Since contingencies are not easily identified and made ineffective in implicit learning, this learning process can also explain the persistence of hypersensitivity and the frequent resistance to therapy [80]. Such a resistance to change of implicitly learned associations is supported by several studies with laboratory animals as well as humans, showing the maintenance of behavior when schedules of reinforcement were changed, magnitude of reinforcement was reduced or reinforcing stimuli were deemphasized or devalued (e.g. [51,73,173]). In addition, implicit learning is assumed to result in automatic, inflexible reactions (c.f. [114,161])—like avoidance behavior in chronic pain—resulting in a vicious circle worsening the pain.

Cognitions concerning the own test behavior affected implicit learning of altered heat-pain sensitivity. Assessed cognitions concerned the strategy used with predicting subsequent reinforcement. About half of the participants (17 out of 33; 51.5%) reported the use of an explicit strategy and thus cognitions about their behavior. However, most of the reported strategies did not correctly mirror the contingencies and thus were not successful (three participants reported a partially successful strategy). In general, participants who stated an explicit strategy showed no signs of learning during the operant conditioning procedure in contrast to those who did not state an explicit strategy. This difference in operant learning appeared to be due to differential behavior in the habituation learning condition. In this condition successful conditioning results in a long-term temperature increase due to the accumulation of operant behavior (up-regulation of temperature) over the whole session (consecutive procedure, see Section 3.4). This increase induces an additional global contingency—between trials—opponent to the local contingency—within trials—and thus reduces power of the habituation conditioning. Such a reduction in power did not occur in the sensitization learning condition, since there, the direction of global (long-term temperature decrease) and local contingency were equal. A reduction in power may make the conditioning more susceptible to faults or interfering factors and thus affected mainly the habituation conditioning. Interactions of implicit and explicit processes in learning were also demonstrated in other studies, where these interactions led to synergistic as well as to diametric effects [114,249].

Fear is known to often accompany pain and also to worsen pain in a chronic condition (e.g. [111,131,189]). The accompanying development of fear during the im-

plicit acquisition of hypersensitivity can be explained by classical conditioning: the experience of pain would be associated with fear of pain, and thus a situation indicating upcoming pain becomes on the one hand a discriminative stimulus for operant behavior and on the other hand a conditioned stimulus triggering conditioned fear (according to [171]). Additionally, fear can also be learned without awareness of contingencies by delay conditioning [121,271]. Since in natural settings the classical conditioning of fear of pain can be assumed to be a kind of delay conditioning, both processes of fear and hypersensitivity conditioning eventually occur without awareness and thus in an automatic, unconscious fashion. These two processes together—the proximal one of operant learning of hypersensitivity and the distal one of the association with fear—may contribute to pain becoming chronic and may explain the interaction of anxiety, fear and fear-avoidance belief with pain sensitivity, clinical pain and disability (c.f. [28,131,227]).

An interview for assessing awareness has some disadvantages compared to other subjective methods, like e.g. confidence ratings. One problem is the fitting-in of the questions: if the question asked does not fit in with the thoughts of the participant, the participant will not report all his/her knowledge [222]. In addition, forcing a participant for introspection about e.g. problem-solving or decision-making can also produce a kind of storytelling because usually there is no conscious access to the psychological process but only to the result of this process [175]. Although subjective methods such as confidence rating were affected by individual response criteria [53,222], they avoid these above-mentioned problems and therefore would be the better choice [58,144].

In summary, altered heat-pain sensitivity was learned implicitly, that is without awareness of contingencies. Neither first- nor second-order discrimination of the contingencies developed in the present study. Moreover, participants who at least partially discriminated the contingencies did not necessarily show signs of operant learning. Thus, operant learning of altered heat-pain sensitivity can be assumed to be independent of contingency awareness and thus to be an instance of nondeclarative memory. In order to prove the latter, studies with functional imaging have to be done. For of a better understanding of the different types of awareness and significance for learning, contingency awareness should be actively manipulated in further studies. Further, the necessity of awareness of the reinforcing stimuli for successful operant learning should be directly tested. Explicit cognitions about the prediction task interfered with operant learning of heat-pain sensitivity. Therefore, further studies should test whether the effect of cognitions was a result

of the particular used method or is a more general effect. This is important, because a general effect of cognitions on learning of pain sensitivity, in particular on habituation learning, would have important implications for therapeutic intervention, since both implicit operant learning and cognitions on potential relationships of behavior and pain sensations have to be regarded.

4 Implicit Operant Learning in Fibromyalgia Patients With and Without Irritable Bowel Syndrome

4.1 Introduction

Recently, implicit operant learning [13,106]—i.e. unintentional learning by the consequences of behavior without a person's knowledge— was demonstrated to change pain sensitivity. Accordingly, hypersensitivity in chronic pain can be assumed to be operantly learned. For the purpose of clarifying the latter, chronic pain patients were tested with an operant conditioning procedure for modulating pain sensitivity in the present study.

The important role of operant learning in the development and maintenance of chronic pain is widely recognized [82,83]. However, the mechanisms mediating between nociceptive processing, environmental consequences, and altered pain perception remain unclear. Enhancement of pain reports by verbal or monetary reinforcement was shown (e.g. [108,137,143]). Whether this reflects changes in pain sensitivity rather than response criteria is debatable (c.f. [53]). However, two studies demonstrated operant conditioning of pain sensitivity with avoiding the risk of changing response criteria [13,106]. These studies used experimental procedures independent of subjective pain report: pain perception was measured by discriminative behavior [228], i.e. a behavioral response to a subjectively experienced change in sensation. This discriminative behavior (not pain reports) was the target of operant conditioning. Further, intrinsic reinforcement was used, i.e. reinforcement within the nociceptive system by decreases or increases in nociceptive input. In contrast, verbal or monetary reinforcement is extrinsic, i.e. outside the nociceptive system. As a perceptual experience, intrinsic reinforcement directly affects pain perception; extrinsic reinforcement affects pain perception indirectly. Involving these features, implicit operant learning changed pain sensitivity [13,106]. Additionally, physical stimulus intensities and pain reports gradually dissociated [106], resembling 'sensory decalibration'—i.e. reported pain experience became disproportional to nociceptive stimulation [134]. Thus, implicit operant learning can provide an explanation for the gradual development of hypersensitivity and sensory decalibration in pain that is becoming chronic.

Fibromyalgia—an unspecific chronic musculoskeletal pain syndrome [284]—comprise somatic hypersensitivity displayed by increased pain sensitivity and enhanced perceptual sensitization (e.g. [216,241,245]). Pathogenesis is being discussed but psychological factors are assumed to facilitate pain [32]. In particular, operant learning is assumed to affect symptom expression and pain perception [23,83,253]. Thus, fibromyalgia patients might be vulnerable to implicit operant learning of enhanced pain sensitivity. In addition, 63-81% of fibromyalgia patients suffer from comorbid irritable bowel syndrome (IBS) [125]—also an unspecific pain syndrome in which psychological pathogenetic factors are assumed [277]—characterized by chronic or recurrent abdominal pain or discomfort [154]. Fibromyalgia patients with IBS display somatic and visceral hypersensitivity [37,170]. Accordingly, fibromyalgia patients with and without IBS are assumed to be differentially vulnerable for implicit operant learning of enhanced pain sensitivity.

The present study aims at clarifying the latter: fibromyalgia patients with and without IBS were tested with an operant conditioning procedure for modulating heat-pain sensitivity. Both groups of patients were expected to be more vulnerable to operant learning than healthy participants and patients with IBS more than patients without. In addition, a gradual dissociation of physical stimulus intensity and subjective pain report was expected, resembling a kind of 'sensory decalibration' [134].

4.2 Methods

Participants

16 fibromyalgia patients with comorbid IBS (FM with IBS; 15 female), 17 fibromyalgia patients without comorbid IBS (FM without IBS; 16 female), and 31 healthy participants matched for sex and age (HP; 28 female) participated in the study. Each participant was to attend two experimental sessions on separate days. The data from 17 of 128 sessions (6 of HP, 4 of FM without IBS, 7 of FM with IBS) was excluded from the statistical analysis because of study dropouts and procedural aspects (reinforcement contingencies were no longer useful because stimulus temperatures were lowered below baseline temperature as a result of the procedure), leading to incomplete datasets. Healthy participants were included if they reported no pain or pain episodes exceeding one day per month and no neurological or psychiatric disorders. Prior to the experimental sessions, quantitative sensory testing was performed with a contact heat thermode (TSA 2001, Medoc Inc., Israel)

—tested were warm detection threshold, heat-pain threshold, and self-adjusted heat-pain threshold and perceptual sensitization to tonic heat (see [119] for a precise description). None of the healthy participants had to be excluded because of thresholds for warm and phasic pain outside a 95% norm range (criteria and norm data according to [206]). Fibromyalgia patients were included in the study if they met the American College of Rheumatology criteria of fibromyalgia [284] and if they reported pain for at least six months. IBS was assessed with a German version of the 'Research diagnostic questions for functional gastrointestinal disorders' [62,63,103]. Depressive symptoms were assessed with the German version of the 'Center for Epidemiologic Studies Depression Scale' (CES-D; [195] German version [100]). Anxiety was assessed with the German version of the 'State Trait Anxiety Inventory' (STAI-X2, trait version; [234], German version [128]). Informed consent according to the revised Declaration of Helsinki was signed by all participants, and the study was approved by the local ethics committee.

Apparatus for Stimulus Application and Operant Conditioning Procedure

The apparatus for stimulus application as well as the applied operant conditioning procedure were the same as in study 2 described above (see Section 3.2).

Standardized Interview

After the last session, a standardized interview with questions about the experiment was presented to the participants. Participants were asked seven specific questions about possible systematic connections between the different trial intervals and the 'observation interval' (reinforcement interval) in order to assess contingency awareness additional to the prediction task within the conditioning procedure (see Section 3.2). These questions were formulated on the basis of a questionnaire by [46], originally used to analyze contingency awareness with classical conditioning procedures. Afterwards participants were asked to rate on a numeric scale from 0 to 10 (a) how well they solved the tasks, (b) how well they kept the temperature constant, and (c) how well their prospective judgment (prediction) about stimulus changes was performed. Last of all, participants were asked their opinion about the suspected general intention of the experiment, the reasons for keeping temperature constant, the reasons for the prediction, and about the accuracy of their predictions.

Study Design

The study design comprised two sessions—one including the sensitization learning condition and one including the habituation learning condition—within each participant. The sessions were performed on separate days in balanced order. In each session, 80 trials of the conditioning procedure were performed. Primary indicator of learning effects was the difference in long-term temperature change between the learning conditions. In addition, average temperatures in the sensitization learning condition were to be below average temperatures of the habituation learning condition in the course of the operant conditioning procedure. Long-term temperature change resulted from the consecutive procedure, chaining subsequent trials and thus leading to a progressive long-term change in temperature relative to baseline.

The time to reach a steady state during the baseline phase varied individually, and with it the number of available trials for the learning phase, as the overall trial count was constant. For the statistical analysis of learning effects, blocks of 7 trials each were averaged. For the baseline phase, the last seven trials of the baseline were pooled in the first block and the subsequent trials of the conditioning phase constituted the following blocks. This resulted in a reduced sample count in the design cells of the late learning phase (blocks 10-11). These blocks were therefore excluded from analysis to avoid a bias of statistics by reduced cell counts, resulting in 9 blocks included in the analysis.

Statistics

The data were analyzed according to a repeated measures design with Group (FM with IBS N_1=13; FM without IBS N_2=16; HP, N_3=29) x Learning condition (Sensitization; Habituation) x Time (blocks 1-9). The data were analyzed by a mixed model procedure for repeated measurements [138]. Significant main effects and interactions are given as adjusted probabilities of approximated *F*-statistics (Table 3, Table 4). Non-parametric tests were used to substantiate effects of Mixed Model Analysis where appropriate. The significance level was set to 5%, adjusted with the false discovery rate for multiple testing [15]. Predictions—as an indirect measure of contingency awareness—were analyzed by comparing the frequency distribution of the predictions ('up', 'no change', 'down') with the frequency distribution of received reinforcement ('punishment', 'no reinforcement', 'negative reinforcement'). Alterations of operant learning in fibromyalgia patients were calculated by devi-

ations from the healthy participants in the slope of the regression line derived by linear approximations of block to block means of temperature change from baseline. These deviations were expressed in Z-values. In order to determine whether altered operant learning was associated with clinical characteristics of the fibromyalgia patients, these Z-values were correlated with duration of chronic pain, maximal pain intensity in the last four weeks, number of tender points, depressive symptoms (assessed with the CES-D), anxiety (assessed with the STAI-X2), self-adjusted pain thresholds, and perceptual sensitization (sensitization gradients received from the 'dual sensitization method'). All calculations were performed with the SAS® System for Windows®, Release 9.1 and R for Windows, Version 2.8.1 [194].

4.3 Results

Operant Learning of Perceptual Sensitization and Habituation

The operant learning procedure was effective in modulating heat-pain sensitivity through intrinsic reinforcement by decreases (negative reinforcement) or increases (punishment) in temperature. Perceptual sensitization and habituation were differentially modulated within 1.5h of operant conditioning. Fibromyalgia patients with and without comorbid IBS differed in operant learning effects from each other as well as from healthy participants (Fig. 7A, C, E).

Up- or down-regulation within a single trial, indicating perceptual sensitization or habituation to ongoing heat stimulation, was the operant behavior to be reinforced. The subsequent trials were chained by the consecutive procedure (see Section .4.2), thus accumulating changes in the operant behavior and leading to a progressive long-term change in temperature despite the instruction to hold the temperature constant during each trial (Fig. 7A, C, E). This long-term change of temperature and its difference between the learning conditions was the primary indicator of learning effects.

Table 3: Effects of operant conditioning on change of temperature and rated stimulus intensity between fibromyalgia patients with and without IBS and healthy participants.

Effect	*Temperature change*	*Rated stimulus intensity*
	F (df num; df den); p[a]	F (df num; df den); p[a]
Main effects and interaction		
Group [HP, FM without IBS, FM with IBS]	4.6(2; 56); .01*	3.7(2; 56); .03*
Learning condition [sensitization, habituation]	0.0 (1; 56); .86	2.4 (1; 56); .13
Time (block) [1-9]	2.0 (8; 56); .14	4.2 (8; 56); <.001***
Group x Learning condition	8.0 (2; 56); <.001***	10.9 (2; 56); <.001***
Contrasts		
Group HP/FM without VHS	7.1 (1; 56); .01	5.8 (1; 56); .02
Group HP/FM with VHS	0.4 (1; 56); .55	3.8 (1; 56); .06
Group FM without/with VHS	6.6 (1; 56); .01	0.0 (1; 56); .90

Results of repeated measures analysis with linear mixed model of change in temperatures and rated stimulus intensities during conditioning phase (blocks after individual baseline without reinforcement) of the operant conditioning procedure between groups. Study design: Group (FM without IBS N_1=16; FM with IBS N_2=13; HP, N_3=29) x Learning condition (Sensitization; Habituation) x Time (Block 1-9).

[a] Adjusted *F*-ratios, degrees of freedom for denominators (den) and for numerators (num) in brackets and exact probabilities for main effects, interactions, and contrasts. Significances given as per false discovery rate adjusted probabilities: t = p < .10; * = p < .05; ** = p < .01; *** = p < .001

(a) *Group Differences in Operant Learning:* Operant learning effects indicated by long-term temperature changes differed between fibromyalgia patients with and without IBS and healthy participants (Table 3, column 2, main effect 'Group', F=4.6, $p < .05$). Post-hoc contrasts between the three groups revealed differences in operant learning between healthy participants and fibromyalgia patients without IBS. Additionally, fibromyalgia patients with and without IBS differed in operant learning (Table 3, column 2, contrast 'Group HP/FM without IBS' $F = 7.1$, $p < .05$; contrast 'Group FM without/with IBS' $F = 6.6$, $p < .05$). Group differences also depended on the learning condition as indicated by the interaction of groups and learning conditions (Table 3, column 2, interaction 'Group x Learning condition' $F = 8.0$, $p < .01$).

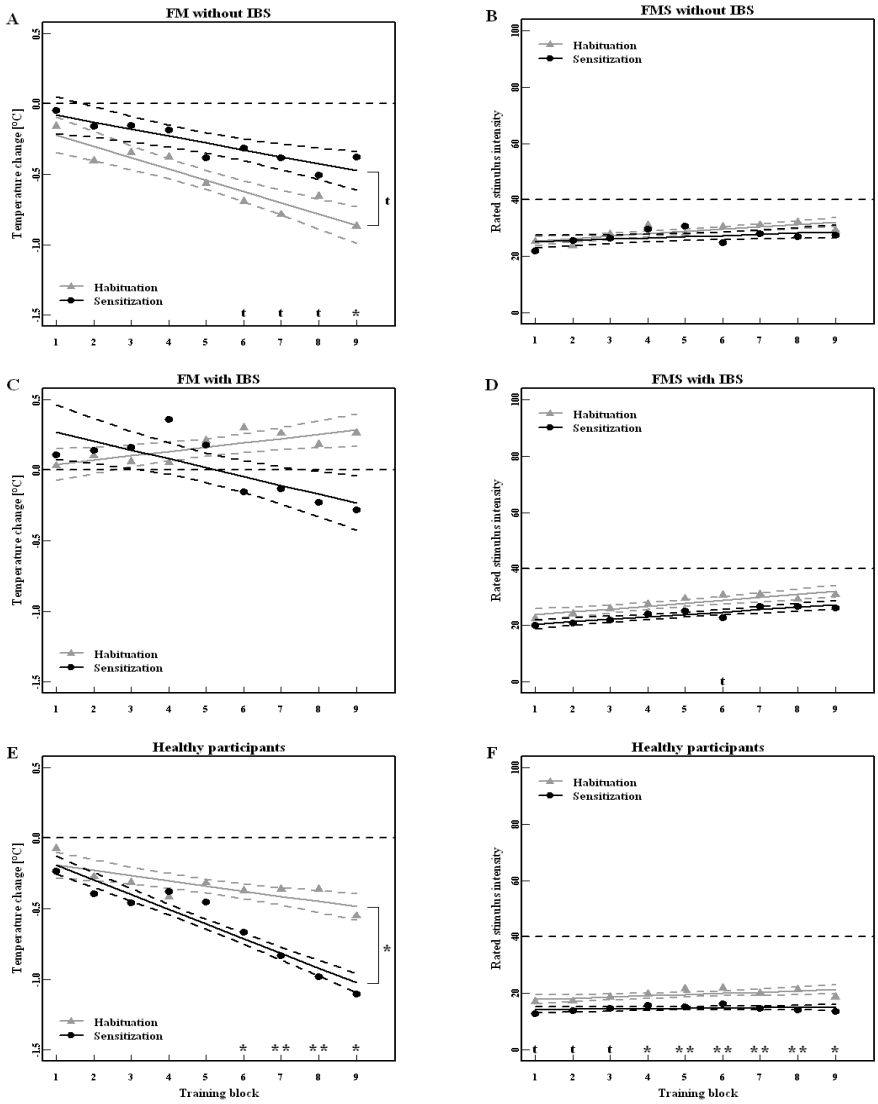

Figure 6: Time course of temperature change and rated stimulus intensities in fibromyalgia patients with and without IBS and healthy participants. Linear approximation of block to block means of (A, C, E; left column) temperature change from baseline (block 0) and (B, D, F; right column) rated stimulus intensities (absolute magnitude estimation on a scale from 0 to 100; 40 indicates the pain threshold). Regression lines (linear trends) with 95% confidence intervals; repeated measures analysis effect slices for each block: t = $p < .1$, * = $p < .05$, ** = $p < .01$. (A-B) Fibromyalgia without IBS: Temperature changes differ significantly after 9 blocks in training. (C-D) Fibromyalgia with IBS: No change in temperature und rated stimulus intensities. (E-F) Healthy participants: Temperature changes differ significantly after 6 blocks in training; Rated stimulus intensities differ significantly after 4 blocks.

(b) *Operant Learning in Fibromyalgia Patients without IBS:* Fibromyalgia patients without IBS tend to responded differentially to the learning conditions (Table 4, column 2, main effect 'Learning condition', $F = 4.1$, $p < .1$), demonstrating a progressive decrease in long-term temperature in the sensitization condition as expected; in the habituation condition, however, long-term temperature progressively decreased even more (Fig 2A). The latter result was not expected and contradicts our hypothesis of heightened vulnerability of fibromyalgia patients to operant learning. The difference in the long-term temperature change between the learning conditions developed gradually and was only observable at late learning stages (Fig. 7A; Table 4, column 2, linear trend contrast 'Learning condition x Lin(Time)', $F = 2.9$, $p < .1$; Effect slices, blocks 6-9 $p < .1$ and .05 resp.).

(c) *Operant Learning in Fibromyalgia Patients with IBS:* Fibromyalgia patients with comorbid IBS showed no signs of operant learning. The temperature changed neither over time (blocks) nor was it different between learning conditions (Table 4, column 3, main effect 'Time' $F = 0.5$, ns; main effect 'Learning condition', $F = 0.1$, ns).

(d) *Operant Learning in Healthy Participants:* The results of the healthy participants demonstrated the effectiveness of the operant conditioning procedure, replicating the results of Hölzl and colleagues (2005). Operant learning was observable according to the learning condition: Long-term temperature change differed between learning conditions, and average temperatures under the sensitization condition were below average temperatures under the habituation condition (Fig. 7E; Table 4, column 4, main effect 'Time' $F = 2.8$, $p < .05$; 'Learning condition', $F = 6.4$, $p < .01$; average change from baseline: habituation condition $M = -0.31$°C; sensitization condition $M = -0.55$°C; Main effect 'learning condition', $F = 8.1$, $p < .01$). The difference in long-term temperature change between the sensitization and habituation learning condition developed gradually and was detectable only at later learning stages (Fig. 7E; Table 4, column 4, linear trend contrast 'Learning condition x Lin(Time)', $F = 4.0$, $p < .05$; Effect slices, block 6-9: $p < .05$ and .01 resp.)

Rating of Stimulus Intensity

During the operant conditioning procedure, physical stimulus intensities and subjective heat-pain reports gradually dissociated in fibromyalgia patients without IBS and healthy participants. In general, all groups displayed either an in-

creased in their rating of stimulus intensities, i.e. in subjective pain reports or ratings changed not in the course of the operant conditioning procedure in both learning conditions (Fig. 7B, D, F).

(a) *Group Differences in Stimulus Intensities Ratings:* The three groups rated stimulus intensities, indicated by magnitude estimations, differentially, (Table 3, column 3, main effect 'Group', $F = 3.7$, $p < .05$): the two patient groups rated stimulus intensities higher than healthy participants (Fig. 7B, D, F). Since the initial physical temperature was higher in healthy participants than in both patient groups (initial temperature of the operant conditioning procedure=self-adjusted pain threshold – 1°C; healthy participants $M = 42.2$°C; FM without IBS $M = 40.4$°C; FM with IBS $M = 41.3$°C), this difference could not be explained by the different physical stimulus temperatures in the groups. Post-hoc contrasts between the three groups revealed that fibromyalgia patients without IBS rated stimulus intensities differently from healthy participants. Furthermore, a tendency to rate stimulus intensities differently was also observable between fibromyalgia patients with IBS and healthy participants (Table 3, column 3, contrast 'Group HP/FM without IBS' $F = 5.8$, $p < .05$; contrast 'Group HP/FM with IBS' $F = 3.8$, $p < .1$). Magnitude estimations depended on the learning conditions, where stimulus intensity was rated in each group higher in the habituation condition than in the sensitization condition (Fig. 7B, D, F; Table 3, column 3, interaction 'Group x Learning condition', $F = 10.9$, $p < .001$).

(b) *Rating of Stimulus Intensities in Fibromyalgia Patients without IBS:* In fibromyalgia patients without IBS, a gradual dissociation of physical stimulus intensities and subjective heat-pain ratings was observed in both learning conditions. Ratings of stimulus intensities remained unchanged in these patients over time in both learning conditions (Fig. 7B; Table 4, column 2, main effect 'Time', $F = 1.1$, ns; main effect 'Learning condition', $F = 0.1$, ns). Since stimulus temperatures decreased in both learning conditions over time in these patients, these results indicated a dissociation with pain ratings becoming unrelated to physical stimulus intensities and thus resembling the a type of sensory decalibration (c.f. Fig. 7A, B).

(c) *Rating of Stimulus Intensities in Fibromyalgia Patients with IBS:* In fibromyalgia patients with IBS ratings of stimulus intensities did not change in the course of operant conditioning in both learning conditions (Fig. 7D; Table 4, column 3, main effect 'Time', $F = 1.8$, $p < .1$, main effect 'Learning condition', $F = 1.6$, ns). Since also physical stimulus intensities remained unchanged during the

operant conditioning in both learning conditions, no dissociation of physical stimulus intensities and subjective heat-pain ratings was observed (c.f. Fig. 7C, D).

Table 4: Effects of operant conditioning on temperature change and rated stimulus intensity within fibromyalgia patients with and without IBS and healthy participants.

Effect		*Change in temperature*	
	FM without IBS F (df num; df den); p[a]	*FM with IBS* F (df num; df den); p[a]	*Healthy participants* F (df num; df den); p[a]
Main effects and interaction			
Learning condition [sensitization, habituation]	4.1 (1; 12); .06[t]	0.1 (1; 11); .76	6.4 (1; 26); .02*
Time (block) [1-9]	2.2 (8; 128); .04[t]	0.5 (8; 96); .82	2.8 (8; 220); .01*
Linear trend and contrast			
Lin(Time)	9.4 (1; 128); .003	0.4 (1; 96); .54	6.72 (1; 220); .01
Learning condition x Lin(Time)	2.9 (1; 94); .09	0.7 (1; 88); .40	4.0 (1; 203); .05
Effect		*Rated stimulus intensity*	
Main effects and interaction			
Learning condition [sensitization, habituation]	0.1 (1; 12); .74	1.6 (1; 11); .24	14.8 (1; 26); < .001**
Time (block) [1-9]	1.1 (8; 128); .39	1.8 (8; 96); .09	2.0 (8; 220); .04[t]
Linear trend and contrast			
Lin(Time)	2.8 (1; 128); .10	8.9 (1; 96); .004	5.8 (1; 220); .02
Learning condition x Lin(Time)	0.1 (1; 94); .83	0.2 (1; 88); .63	2.3 (1; 203); .13

Results of repeated measures analysis with linear mixed model of change in temperature and rated stimulus intensity during conditioning phase (blocks after individual baseline without reinforcement) of the operant conditioning procedure within groups. Study design: Group (FM without IBS N_1=16; FM with IBS N_2=13; HP, N_3=29) x Learning condition (Sensitization; Habituation) x Time (Block 1-9); approximation of linear trends over 9 learning blocks (Lin(Time)).

[a] Adjusted F-ratios, degrees of freedom for denominators (den) and for numerators (num) in brackets and exact probabilities for main effects, interactions, linear trends and linear trend contrasts. Significances given as per false discovery rate adjusted probabilities: t = p < .10; * = p < .05; ** = p < .01; *** = p < .001

(d) *Rating of Stimulus Intensities in Healthy Participants:* In healthy participants, a gradual dissociation of physical stimulus intensities and subjective heat-

pain ratings was observed in both learning conditions. Ratings of stimulus intensities increased over time in the habituation learning condition, while in the sensitization learning condition ratings remained unchanged (Fig. 7E; Table 4, column 4, main effect 'Time', $F = 2.0$, $p < .1$; main effect 'Learning condition', $F = 14.8$, $p < .01$). The difference between learning conditions became more prominent in later blocks of the operant conditioning (Effect slices, blocks 1-3 $p < .1$; block 4-9 $p < .05$ and .01 resp.). Since in both learning conditions physical stimulus intensities decreased over time indicated these results a dissociation with pain ratings becoming unrelated to physical stimulus intensities and thus resembling the a type of sensory decalibration (c.f. Fig. 7E, F).

Rating of Reinforcing Temperature Change

The changes in temperature during the reinforcement interval were detected by the participants. Participants discriminated the changes in temperature associated with negative reinforcement ($M = –0.25$°C), punishment ($M = 0.39$°C), and no reinforcement ($M = –0.004$°C; Main effect "reinforcement' $F(2;112) = 2336.06$, $p < .0001$). These ratings of temperature change during the reinforcement interval were equal in both learning conditions (Main effect 'Learning condition', $F(1;49) = 1.6$, $p = .22$). However, the ratings of reinforcing temperature changes differed between the groups (Mixed model, main effect 'Group', $F(2;56) = 6.8$, $p < .01$). Fibromyalgia patients without IBS rated negative reinforcement as a lesser decrease in temperature ($M = –0.15$°C) than the healthy participants ($M = –.31$°C; contrast 'Group HP/FM without IBS' $F(1;56) = 8.8$, $p < .01$).

Awareness of Contingencies

Despite the detection of reinforcing temperature changes, participants did not recognize the contingency, that is, the dependence of changes in temperature in the reinforcement interval on their operant behavior (up- and down-regulation of temperature in the interval of continuous adjustment). In the standardized interview after the last session (see Section 4.2), none of the participants reported a systematic connection between these two intervals. 70% of the participants stated that they mastered the task of keeping the temperature constant well, and 59% stated that their predictions were passably correct (for both questions: ratings between 0 and 5 on a numeric scale from 0 (very well) to 10 (very badly)).

In addition, the indirect measurement of contingency awareness by the prediction revealed no implicitly existing awareness of contingencies. With regard to

the fact that awareness of contingencies needs some time to develop, only the predictions in the last two blocks of the operant conditioning procedure were analyzed. The predictions of the participants within each trial of the operant conditioning procedure seemed to be random, indicated by an even frequency distribution of responses over the three alternative answers. Beyond that, the comparison of the frequency distribution of predictions with the frequency distribution of actual received reinforcement demonstrated clear differences between these distributions ($\chi^2 = 173.5$, $p < .0001$).

Relation of Altered Operant Learning to Clinical Characteristics

Duration of chronic pain, depressive symptoms (CES-D), anxiety (STAI-X2), maximal pain intensity in the last four weeks, and perceptual sensitization (sensitization gradients) as clinical characteristics of the fibromyalgia patients displayed no relationships to alterations in operant learning in these patients in both learning conditions. Only in the sensitization learning condition numbers of tender points (Spearman, $r = .46$, $p = .02$) and self-adjusted pain thresholds (Spearman, $r = -.55$, $p = .003$) were related to altered operant learning. These correlations indicated that, first, higher numbers of tender points and, second, lower pain thresholds were associated with impaired operant learning of enhanced perceptual sensitization, compared to healthy participants. High numbers of tender points and low pain thresholds both indicate heightened pain sensitivity and, thus, deficiencies in operant learning can be suggested to be associated with heightened pain sensitivity. These numbers of tender points and self-adjusted pain thresholds showed no relation to altered operant learning in the habituation learning condition. Since no association between self-adjusted pain threshold and operant learning was found, these results cannot be explained the absolute initial temperature (self-adjusted pain threshold minus 1°C).

Fibromyalgia patients with and without IBS were pooled for this latter analysis. However, when separated according to present IBS the only relation to altered operant learning that could be found, was to self-adjusted pain threshold in fibromyalgia patients with IBS in the habituation learning condition. Further, the two patient groups did not differ in duration of chronic pain, number of tender points, maximal pain intensity in the last four weeks, depressive symptoms, anxiety, and perceptual sensitization (Table 5). Self-adjusted pain thresholds also were comparable in fibromyalgia patients with and without IBS. Only self-adjusted pain

threshold of fibromyalgia patients without IBS differed from that of healthy participants, resulting in a significant difference over all groups (Table 5).

Table 5: Demographic, psychometric, and psychophysical data for the fibromyalgia patients with and without IBS and the healthy participants.

	FM without IBS (N=17)	*FM with IBS (N=13)*	*Healthy participants (N=29)*	*Test of group differences*
Gender [male, female][a]	1, 12	1, 16	3, 26	
	M (SD)[b]	M (SD)[b]	M (SD)[b]	F(df num; df den)[c]; p[d]
Age [years]	53.3 (8.8)	49.1 (8.9)	47.9 (10.1)	1.8 (2;59); 0.17
Duration of chronic pain [month]	198.3 (157.9)	156.8 (152.7)	--	0.5 (1;27); 0.48
Number of tender points	14.7 (2.4)	15.8 (2.5)	--	1.4 (1;26); 0.25
Max. clinical pain	8.2 (1.7)	8.2 (1.2)	--	0.0 (1;26); 0.96
CES-D [%]	64.4 (27.7)	69.3 (23.7)	--	0.3 (1;27); 0.62
STAI-X2 [%]	73.2 (23.5)	71.8 (27.9)	--	0.0 (1;23); 0.89
Self-adjusted pain threshold [°C]	41.4 (1.6)	42.3 (2.7)	43.2 (2.3)	6.6 (2;118); 0.01*[f]
Sensitization gradient[e] [°C]	$-0.21 \times T_{init}$ -0.02	$-0.14 \times T_{init}$ -0.10	$-0.21 \times T_{init}$ -0.03	0.9 (2;59); 0.42

[a] Number of males and females in each group (FM without IBS N_1=13; FM with IBS N_2=17; HP N_3=29)

[b] Mean and standard deviation of age, duration of chronic pain, depressive symptoms measured by the ADS, anxiety measured by the STAI, and pain threshold in each group.

[c] Results of mixed model analysis of age, duration of chronic pain, depressive symptoms measured by the ADS, anxiety measured by the STAI, and self-adjusted pain threshold; Sensitization gradient: linear trend differences between groups in repeated measures analysis; Factor 'Group' (FM without IBS N_1=13; FM with IBS N_2=17; HP N_3=29).

[d] Adjusted F-ratios, degrees of freedom for denominators (den) and for numerators (num) in brackets and exact probabilities for main effect. Significances given as per false discovery rate adjusted probabilities: t = p < .10; * = p < .05; ** = p < .01; *** = p < .001

[e] Linear regression of perceptual sensitization measure on relative stimulus temperature T_{init} = self-adjusted pain threshold + k*[°C]; k = –1.0, –0.67, +0.67, +1.33.

[f] Post-hoc tests revealed that only healthy participants and fibromyalgia patients without IBS differed in their self-adjusted pain threshold.

4.4 Discussion

The present study demonstrates altered implicit operant learning of heat-pain sensitivity in fibromyalgia patients with and without comorbid IBS, compared to healthy participants. Fibromyalgia patients without IBS show an enhancement of heat-pain sensitivity during sensitization and habituation learning, but this enhancement was more pronounced during habituation learning. Fibromyalgia patients with comorbid IBS demonstrated no changes in heat-pain sensitivity in both learning conditions. Healthy participants learned enhanced perceptual sensitization and habituation according to the learning conditions. Thus, the hypothesis expecting that fibromyalgia patients and particularly patients with IBS would be more vulnerable to operant learning was not confirmed.

Implicit operant learning of pain sensitivity was impaired in fibromyalgia patients with and without IBS, though the groups responded differentially to the operant conditioning. Comparable attempts to investigate operant learning in pain patients are scarce, but impairments in operant learning have been reported for chronic back pain patients tested by an emotional decision task [5,9]. Emotional decision behavior was assessed with the Iowa gambling task, capable of detecting operant learning deficiencies [11]. The behavior of the pain patients in this task was comparable to patients with lesions in orbitofrontal brain regions [11,12], i.e. they do not learn to choose the most profitable outcome. These findings were confirmed by an equivalent study in rats with chronic pain [181]. In these rats, cerebral changes were found, compared to rats without chronic pain. Thus, cerebral changes can be suggested in chronic pain patients (c.f. [77]). In chronic pain and in particular in fibromyalgia, functional and structural cerebral changes have been found [5,123,214,216]. Interestingly, changes were present in brain regions associated with learning—the hippocampus and related structures—and with processing of reward—prefrontal areas. Thus, cerebral changes might explain deficiencies in operant learning in the fibromyalgia patients.

Further, deficient operant learning is in line with the deteriorating influence of chronic stress on learning and memory in animals and humans (e.g. [115,284]). Chronic pain, as chronic stressor, leads to long-term changes in the stress system, particularly in the hypothalamic-pituitary-adrenal (HPA) axis [22,266]. Accordingly, alterations in HPA axis functions have been found in fibromyalgia (e.g. [90,96,263,282]). In the present study, HPA axis functioning was assessed by measuring diurnal saliva cortisol prior to and on the day of the experiments. Hypo-

cortisolism (attenuated awakening response compared to healthy participants) has been found in both patient groups (unpublished data). This alteration of the HPA axis might mediate at least partially impaired implicit operant learning in fibromyalgia.

The differential responding of the two groups of patients is somehow difficult to explain. Conceivable is a mediating effect of additional visceral nociceptive input in patients with IBS. Thus, patients with fibromyalgia and IBS were found to be more sensitive to somatic stimuli than patients with IBS alone (e.g. [37,41,170]). Further, some IBS patients (without fibromyalgia) display a somatic hypersensitivity extending up to cervical levels [30,170]. Such a somatic hypersensitivity is being explained by the convergence of visceral and somatic nociceptive afferents on spinal cord neurons. Tonic visceral and/or somatic nociceptive input sensitizes these neurons, facilitating both visceral and somatic input. An extension of this hyperexcitability to cervical levels is assumed through long ascending propriospinal interactions [170,265]. In contrast to this explanation, fibromyalgia patients with IBS showed less perceptual sensitization than patients without IBS in the present study. A ceiling effect can explain this contradiction: due to the hyperexcitability of spinal neurons, possible extent of windup—as the neuronal basis of perceptual sensitization [69]—is limited and perceptual sensitization therefore attenuated [266]. In such a sensitized system, perceptual habituation occurs, but less likely. This explanation assumes a reduced power of operant conditioning due to attenuated perceptual sensitization and habituation in response to the tonic heat-pain stimulation—eventually in addition to the above-mentioned operant learning deficiencies in pain patients. Other possible mechanisms also resulting in attenuated pain perception in fibromyalgia with IBS and thus possibly impaired operant learning are: (1) attentional effects—pain in different body parts may compete for attentional resources and cause a distraction (2) the diffuse noxious inhibitory control (DNIC) phenomenon—pain in one body part can inhibit another pain even in faraway body parts [129]. In addition, the differential responding of fibromyalgia patients with and without IBS cannot be explained by different absolute initial temperatures: initial temperatures of both groups of patients were comparable.

Perceptual sensitization in fibromyalgia patients without IBS was enhanced rather than attenuated. Although these patients respond to the operant conditioning, their behavior was unexpected. The proposed implicit operant learning mechanism assumes that by perceptual discrimination learning progressively weaker nociceptive signals serve as discriminative stimuli—i.e. stimuli that acquired the

function of a signal for a specific behavior to occur [228]. Such discriminative stimuli trigger the performance of learned behavior, resulting in hypersensitivity and avoidance of gradually weaker noxious and even innocuous stimuli (c.f. [76,106]). Increases in stimulus intensity during the reinforcement interval (punishment) might serve as such discriminative stimuli, triggering avoidance of further aversive stimulation in the following trial displayed by down-regulation of temperature. In habituation learning, down-regulations were punished, resulting in a circle of down-regulation and punishment. In sensitization learning, down-regulations were reinforced by decreasing stimulus intensity, and thus such a circle does not establish. This process can explain the appearance of enhanced sensitization in habituation learning, compared with sensitization learning. Since even innocuous stimulus can become discriminative stimuli, stimulus intensities below pain threshold—as it was largely the case in the present study—are sufficient for triggering previously learned behavior. However, nociceptive activation can be assumed although stimulus intensities were largely rated non-painful: Polymodal and silent C-nociceptors are known to be activated at non-painful temperatures [255,258,259]. The same can be assumed for (nociceptive) AMH-II-fibers [120,259]. Additionally, nociceptor activation might occur without being perceived as painful (c.f. [139,262]). In fibromyalgia, also a generalized heightened responsiveness to various, also innocuous, sensory stimuli is assumed [92].

Altered operant learning in fibromyalgia patients was associated with numbers of tender points and pain thresholds but only in sensitization learning. Thus, impaired sensitization learning seems to be related to heightened sensitivity, probably displaying a ceiling effect. Other clinical characteristics—depressive symptoms, anxiety, duration of pain, maximal clinical pain and perceptual sensitization—showed no relationship to altered operant learning. Moreover, the differential responding of fibromyalgia patients with and without IBS cannot be explained by clinical characteristics, since these groups did not differ in all of the mentioned characteristics. However, implicit operant learning of altered pain sensitivity appears to have some pathogenetic relevance, since it distinguishes between healthy participants and pain patients as well as between pain patients with different manifestations of a pain syndrome.

A dissociation of physical stimulus intensities and subjective pain reports—displaying a kind of 'sensory decalibration' [106,134]—was found in fibromyalgia patients with IBS and healthy participant. These groups, ratings of stimulus intensities increase or remained unchanged during the conditioning sessions, while phys-

ical stimulus intensities decreased. Thus, heat-pain experience appears to be disproportional to sensory input. It was not tested if sensory decalibration was actually present in the fibromyalgia patients, but the gradual dissociation of subjective pain ratings from physical stimulus intensities. However, these results demonstrate first that subjective reports do not necessary have to correspond with behaviorally indicated perception (c.f. [53]) and second that implicit operant learning can be the mechanism leading to sensory decalibration.

Healthy participants learned enhanced perceptual sensitization or habituation according to the learning condition, replicating previous results [106]. However, operant conditioning was less effective compared to the former study. This attenuation might be explained by the additional prediction interval: Thereby the optimal delay of reinforcement—i.e. the time between behavior and reinforcement—was exceeded [156,228]. Additionally, attention is directed away from pain perception to a cognitive task by the prediction.

In summary, implicit operant learning in fibromyalgia patients with and without IBS is altered. Whether this alteration develops with pain becoming chronic or is a particular characteristic of fibromyalgia must be tested in patients at different chronic pain stages and with other pain syndromes. In order to analyze the influence of the IBS, patients suffering solely from IBS have to be assessed. In order to understand the processing of intrinsic reinforcement and the relation to central sensitization and pain memories, studies which employ operant extinction and functional imaging have to be done in healthy participants as well as in pain patients. The finding of altered operant learning by intrinsic reinforcement in fibromyalgia patients with and without IBS is also of relevance for pain therapy: It may explain why some chronic pain patients respond to pain therapy e.g. therapeutic (physical) exercise and other not [1]. The paradigm can probably be used to develop a therapeutic intervention that targets directly at nociceptive processing and pain sensitivity.

5 General Discussion

Implicit operant learning of pain sensitivity with intrinsic reinforcement appears to be a powerful mechanism that provides a psychological explanation for the gradual development of hypersensitivity in chronic pain. However, implicit operant learning of pain sensitivity is impaired in fibromyalgia patients with long durations of pain. Although the studies shed some light on the characteristics of operant learning in pain perception, many details of the above results require further considerations.

5.1 Implicit Operant Learning in Pain Perception

In two different experimental paradigms it was demonstrated that pain sensitivity can be altered by intrinsic operant reinforcement of discriminative behavior. Discriminative behavior was used as an indicator for pain perception and therefore, the learning paradigms are independent of subjective pain report. This independency is crucial for the assessment of the perceptive-discriminative component of pain, since reported experience does not equal perception. Covert, indirect measurement methods of psychophysical parameters of pain perception have been proven before to be useful and stable. Furthermore, these parameters turned out to be pathogenetically relevant, since their characteristics distinguish healthy persons from pain patients [116,119]. Subjective pain reports do not have such a diagnostic quality since they are prone to response biases and changes in response criteria are common and difficult to control (c.f. [53,145]). In the context of operant conditioning, the use of discriminative behavior permits the conclusion that pain perception is the target of the conditioning and operant effects on response criteria are excluded (c.f. [53,108,272]). Thus, in the present studies pain sensitivity and not overt pain behavior was modulated by operant learning, in contrast to most other studies on operant learning in pain (c.f. [108,137,143]). This feature is particularly important because operant learning can explain changes in pain sensitivity, and thus this type of learning can be assumed to contribute to pain becoming chronic. Further, in a previous study [106] and study 3 of this thesis, a gradual dissociation of physical stimulus intensities and subjective pain reports was demonstrated. On the one hand, this dissociation show that behavioral discrimination measures of pain perception indeed be dissociable from subjective sensation report and thus resembles the condition of ‘sensory decalibration’ described in the

fear-avoidance model [143]. In this model, a precise description of the mechanism leading to this sensory decalibration is lacking; however, the above results suggest that implicit operant learning might be this mechanism. On the other hand and maybe more important, the gradual dissociation of physical stimulus intensity as a result of behaviorally measured pain perception and subjective pain report demonstrate that reported experience is not the adequate representation level of pain information relevant for learning of altered pain sensitivity. This supports the necessity of behavioral discrimination paradigms that do not depend on subjective measures of pain experience in the first place but rather address earlier stages of high-level processing of pain signals competent to control overt behavior but not easily reflected in verbal expression.

In addition, it has be demonstrated that successful operant learning of pain sensitivity does not require awareness, neither awareness of the operant contingencies nor a more general awareness of the learning situation. Generally, it is controversially discussed whether implicit learning and in particular implicit operant learning exists. Originally, operant learning was assumed to be automatic, unconscious learning of simple stimulus-response associations [34,229]. Later, the role of cognitions was emphasized and some authors even assumed that learning is always mediated by cognitions, i.e. that there is no implicit learning [34,221]. Contemporary learning theories assume that learning with and without awareness—i.e. explicit and implicit learning processes—co-exists and interacts [48,114,249]. However, it is still discussed when awareness accompanies operant learning or when awareness is even a necessary condition for operant learning [114,222]. This question was addressed in the present study 2 (Chapter 3) by specifying and assessing different types of awareness. Further, awareness was assessed with objective as well as subjective methods. The results demonstrate that when the purpose of the experiment is unobvious, pain perception is measured indirectly and reinforcement is administered intrinsically, awareness is not necessary for successful operant learning. Further, neither behavioral nor verbal discrimination of correct responses—i.e. first and second-order discrimination indicated by objective and subjective methods—is necessary for successful operant learning. Thus, the important role of implicit processing in pain perception was confirmed in two ways: first, by the applied covert and indirect measurement of psychophysical parameters of pain perception demonstrating the dissociation between perception and subjective experience, and second, by demonstrating implicit learning processes to produce gross changes in pain sensitivity.

Despite the influential role of implicit processes in pain perception, the role of cognitions should not be underestimated. One of the present studies (Study 2, chapter 3) demonstrated that cognitions concerning the own test behavior crucially affect operant learning. Persons reporting an explicit response strategy (not necessarily a correct or successful one) showed no signs of operant learning during the operant conditioning. In general, it is assumed that in most learning situations both implicit and explicit processes are involved with varying amounts of contributions from each [218,249,280]. Such an involvement was frequently demonstrated in learning tasks typically used for the investigation of implicit learning, e.g. serial reaction time tasks [176], dynamic control tasks [17], and artificial grammar learning tasks [201]. Synergistic as well as diametric effects of the interaction of implicit and explicit processes have been found: Concurrent verbalization und therefore explicit knowledge has been demonstrated on the one hand to improve the participants' performance in different tasks (e.g. [3,200,239]); on the other hand verbalization could also hamper (implicit) learning (e.g. [64,199,248]). Explicit knowledge appears to overbalance implicit processes when it induces an overtly explicit learning mode in a task that is originally designed for implicit learning. However, implicit and explicit learning can be assumed to develop independently [44,184,249,280]. The interaction of these two processes is of particular relevance in the context of pain and especially in the context of chronic pain: Explicit processes can be assumed to improve as well as inhibit implicit operant learning of altered pain sensitivity. As demonstrated in study 2, in particular learning of enhanced perceptual habituation seems to be inhibited by cognitions concerning the own behavior. This finding suggests that the unlearning of enhanced perceptual sensitization by contradictory learning of enhanced perceptual habituation is aggravated by cognitions. Since many chronic pain patients express activity- and health behavior-related cognitions as well as catastrophizing [131], it can be hypothesized that such cognitions facilitate implicit operant learning of sensitization and in contrast hinder implicit operant learning of habituation. Thus, due to their possible synergistic as well as diametric interaction effects, behavior-related cognitions but also implicit learning processes by intrinsic reinforcement have to be considered in pain therapy.

Implicit operant learning provides a psychological explanation for the development and maintenance of hypersensitivity in chronic pain: The discrimination of a change in nociceptive input and/or in subjective sensation (e.g. perceptual sensitization) is often followed by a behavioral response eventually entailing intrinsic reinforcement. For example, a (small) change in body posture in response to per-

ceived pain can lead to pain relief and thus to intrinsic reinforcement (c.f. [132]). This reinforcement causes the behavioral response—e.g. the change in body posture—to become more likely if a change in nociceptive input or subjective sensation and thus pain is perceived again. The perception of pain thereby becomes a discriminative signal for the performance of the antecedently reinforced behavior—the behavior becomes conditioned. By the process of perceptual discrimination learning, progressively weaker nociceptive signals can serve as discriminative stimuli, resulting in hypersensitivity. The applied learning paradigms therefore represent a model of how acute changes in clinical pain can lead to prolonged hypersensitivity. Learning to avoid pain can also result in a gradual immobility through avoiding potentially painful movements (c.f. [76,231]). Furthermore, the proposed mechanism is independent of mediating fear and thus may provide the proximal mechanism leading to hypersensitivity, which is lacking in the current fear-avoidance theory of musculoskeletal pain [131,268]. However, more distal mechanisms of anticipation of pain and fear may build on this proximal process, leading to sensory decalibration. These suggestions are supported by studies demonstrating that disability in pain patients could not be predicted by pain-related fear in early stages of chronicity and that pain-related fear is associated with pain and disability only at late stages of chronic pain (e.g. [27,226,227]). Furthermore, the fear-avoidance theory states an initial intense noxious event to be a necessary condition for the development of hypersensitivity and sensory decalibration. In contrast, implicit operant learning of hypersensitivity can develop from rather undramatic stimulus intensities close to individual pain threshold as demonstrated in the above studies. This provides an explanation of how chronic pain might develop from small noxious stimuli, caused for example by subclinical muscle injuries due to lack of physical training and maladaptive body posture [160]. In addition, very small reinforcing stimuli—near the just noticeable difference—suffice for successful operant conditioning and a dose-dependency of operant learning on the magnitude of reinforcement was demonstrated.

Intrinsic reinforcement by reductions in nociceptive input, as a perceptual experience, directly affects pain perception in contrast to extrinsic reinforcement. Extrinsic reinforcement is delivered externally to the nociceptive system and thus, modulation of pain perception can only occur indirectly. In contrast, intrinsic reinforcement can be assumed to have an immediate effect and thereby possibly even a larger impact on pain perception than extrinsic reinforcement. The rewarding effect and thus the affective component of pain relief has recently been demonstrated, indicating that pain relief encompasses more than a mere reduction in pain

intensity [132]. Additionally, similarities in brain activity in response to pain relief and reward as well as opioid activation after pain—indicating an opioid-driven pain relief—have been reported [10,220,236]. Studies that show extensive similarities in the anatomical substrates of painful and pleasant sensations also suggest the high impact of intrinsic reinforcement by reductions in nociceptive input [133]. Besides high overlap in brain regions implicated in pain and reward processing, also opioid and dopamine systems are important in modulating both pain and pleasure. These findings suggest functional interactions between these systems where pain decreases pleasure and reward induces analgesia (c.f. [75]). Interactions in the dopamine systems appear also to have clinical relevance: Prolonged stress or pain changes tonic dopamine levels resulting in reduced phasic dopamine signals [285,286]. These phasic signals seem to be associated with analgetic effects of dopamine as well as a reduced responsiveness to pleasure [133,285].

In summary, implicit operant learning of enhanced perceptual sensitivity and habituation by intrinsic reinforcement appears to be a stable and powerful mechanism. This conclusion is supported by the present studies together with a previous study [106], since operant learning is comparable in different experimental paradigms. Two experimental paradigms were applied that differ in many aspects: e.g. continuous heat-pain titration vs. sequential discrete trials, continuous and variable interval vs. percentile schedule of reinforcement, programmed increase in tonic stimulation during titration vs. constant stimulation in discrete trials. Furthermore, the paradigm used in studies 2 and 3 is similar to the one employed by Hölzl (2005), but also differing in some aspects, e.g. a preceding baseline with no reinforcement and the implementation of an additional interval (prediction of reinforcement for the behavioral assessment of discrimination of contingencies) in the later studies.

5.2 Altered Implicit Operant Learning of Pain Sensitivity in Fibromyalgia

Implicit operant learning of enhanced perceptual sensitization and habituation is altered in fibromyalgia patients: Fibromyalgia patients with comorbid irritable bowel syndrome showed no signs of operant learning, while fibromyalgia patients without comorbid irritable bowel syndrome demonstrated paradoxical learning—enhanced perceptual sensitization in both learning conditions but even more pronounced in habituation learning—in study 3 (Chapter 4). Impaired operant learning in chronic pain patients have also been found by others [4,9]. In these studies, impairments in operant learning have been reported for chronic pain pa-

tients tested by the Iowa gambling task, an emotional decision task [11]. The chronic pain patients did not learn to choose the most profitable outcome in this task and their behavior was comparable to patients with lesions in orbitofrontal brain regions [11,12]. These results have been confirmed recently by a study in rats with chronic pain in which also altered brain functioning has been found [181]. These results suggest similar alterations in chronic pain patients that might explain the learning deficiencies (c.f. [5,77,82,123]). Compared to healthy persons, cerebral changes have been found in fibromyalgia patients: Cerebral hypoperfusion—especially in the thalamus—and disturbances in neurotransmitters—especially in the dopamine and opioidergic systems—have been reported [216]. In addition, structural cerebral changes as regional gray matter loss in regions associated with pain modulation such as the cingulate, insular and medial frontal cortices, parahippocampal gyri, and thalamus, have been observed [123,214]. Equivalent gray matter loss in prefrontal areas and the thalamus was also reported in chronic back pain patients [5]. The hippocampus and related structures are associated with learning [68]; prefrontal areas are involved in the coding and updating of reward value and in the anticipation of future reward [178,252]. Further, Kuchniad and colleagues showed an association between the extent of gray matter loss and duration of chronic pain in fibromyalgia patients: The longer the patients have had fibromyalgia, the greater the gray matter loss was, whereas each year in chronic pain was equivalent to 9.5 times the loss in normal aging [123]. Thus, cerebral changes might permit an explanation for the deficiencies in operant learning in the fibromyalgia patients in the present study in particular since these patients already have had very long durations of pain.

Fibromyalgia is often described as a stress-related disorder [263]. Thus, the reported gray matter loss in parahippocampal gyri is in line with this assumption: Increased glucocorticoid levels are assumed to cause atrophy of the hippocampus and other brain areas, such as the amygdale and prefrontal cortex [157]. In fibromyalgia, alterations in the stress-system particularly in the HPA axis—associated with altered glucocorticoid levels—have been found (e.g. [90,96,242,263]). In the present study, hypocortisolism (attenuated awakening response compared to participants) has been found in the fibromyalgia groups[4]. HPA axis function was assessed by measuring diurnal saliva cortisol prior to and on the day of the operant conditioning experiment. Hypocortisolism actually contradicts the assumption of increased glucocorticoid levels. However, some authors assume that there is a

[4] Presentation of these cortisol data is beyond the scope of this thesis and therefore has not been reported.

switch from hyperactivity to hypoactivity of the HPA axis with long durations of pain [86,263]. Thus, hyperactivity of the HPA axis causing atrophy of gray matter in brain areas may occur only in early stages of chronic pain. Functional relevance of such alterations in the HPA axis and brain structure atrophy might include impaired cognitive functioning, which is in line with findings on the deteriorating effect of chronic stress on learning and memory in animals and humans (e.g. [115,283]). Thus, the deficiencies in operant learning in fibromyalgia patients in the present study might be mediated by chronic stress and alterations in HPA axis function.

The finding that operant learning is deficient in fibromyalgia patients is also in line with the above-mentioned changes in tonic dopamine levels in chronic pain patients, particularly in fibromyalgia patients [285,286]. These changed tonic levels collocate with decreased phasic signals, which seemed to be associated with decreased analgesic effects of dopamine and a reduced responsiveness to pleasure [133,285]. Such alterations in the dopamine system would be represented twofoldly in the implicit operant learning paradigm with intrinsic reinforcement: Decreased phasic dopamine responses to changes in nociceptive input, first, would result only in small analgesic effects and, second, would attenuate the rewarding effect of pain relief.

Fibromyalgia patients with and without comorbid IBS differed in operant learning during the operant conditioning procedure in study 3 of this thesis (see chapter 4). A difference in operant learning between these two groups of patients was hypothesized, but fibromyalgia patients with IBS were assumed to be more vulnerable to implicit operant learning of altered pain sensitivity and thus to demonstrate more operant learning than fibromyalgia patients without IBS (see Section 1.4 and chapter 4). In contrast, fibromyalgia patients with IBS showed no signs of operant learning while fibromyalgia patients without IBS responded to the operant conditioning although in an unexpected way: This latter group demonstrated a gradual enhancement of perceptual sensitization in both learning conditions, but the learning effect was more pronounced in the habituation condition than in the sensitization condition. This somehow paradoxical effect might be explained by the previous pain experiences and past (implicit) operant learning: By perceptual discrimination learning progressively weaker nociceptive signals acquire the function of discriminative stimuli—i.e. the function of signaling a specific behavior to be performed [228]—triggering the performance of previously learned behavior. This learned behavior comprises perceptual responses as sensitization to gradually weaker noxious and even innocuous stimuli and also behavioral avoid-

ance of these stimuli. Thus, punishment by increases in stimulus intensity during the operant conditioning procedure might serve as discriminative stimuli, triggering perceptual sensitization and/or avoidance of further aversive stimulation through down-regulation of temperature in the following trial. In the habituation learning condition down-regulations of temperature were punished, resulting in a circle of down-regulation and punishment. Contingencies were reversed in sensitization learning—i.e. down-regulations were reinforced by a decrease in stimulus intensity—and therefore such a circle does not establish. Thus, previously learned perceptual sensitization and avoidance behavior can explain the more pronounced sensitization in habituation learning, probably in addition to the deficiencies in operant learning mentioned above.

However, the differences in responding between the two groups are not easy to explain. Studies with IBS patients have shown that IBS patients with comorbid fibromyalgia are more sensitive to somatic stimuli than patients with IBS alone (e.g. [37,41,170]). Further, some IBS patients (without fibromyalgia) also display somatic hypersensitivity extending up to cervical levels [30,170]. This hypersensitivity is explained by the convergence of visceral and somatic nociceptive afferents on spinal cord neurons. By the tonic visceral and/or somatic nociceptive input, these neurons sensitize, resulting in a facilitation of both visceral and somatic input. Since the somatic hypersensitivity is not limited to lumbosacral levels but extends even to cervical levels, a spatial radiation of the hyperexcitability of spinal neurons through long ascending propriospinal interactions is assumed [170,265]. In spite of these assumptions, patients with both fibromyalgia and IBS showed less perceptual sensitization than patients with fibromyalgia alone during the operant conditioning in the present study. One possible explanation for this attenuation in perceptual sensitization is a ceiling effect: due to the heightened excitability of the spinal neurons caused by the convergent processing of visceral and somatic nociceptive afferents, windup—i.e. an activity-dependent increase in sensitivity—is limited and thus only possible to an attenuated extent (c.f. [266]). Further, in such a sensitized system, perceptual habituation occurs, but less likely. This explanation assumes a reduce power of operant conditioning due to attenuated perceptual sensitization and habituation in response to the tonic heat-pain stimulation —eventually in addition to the above-mentioned operant learning deficiencies in pain patients.

As an alternative explanation, attentional effects are conceivable: Pain in different parts of the body may compete for attentional resources and therefore

fibromyalgia patients may be distracted by additional visceral pain from somatic pain in another body area. Another possible explanation for the differences in operant learning in the two fibromyalgia groups is the diffuse noxious inhibitory control (DNIC) phenomenon: Convergent neurons in the dorsal horn of the spinal cord are inhibited through nociceptive stimulation applied at any part of the body, distinct form their excitatory receptive fields. Thus, nociceptive input in one body part can inhibit pain perception in other even faraway body parts [129]. Thus, the additional visceral pain in fibromyalgia patients with comorbid IBS might have inhibited the perception of the heat-pain stimuli during the conditioning. This explanation seems plausible even though stimulation in the present study was mostly below pain threshold (see Section 4.3), since nociception activation is known to occur also at innocuous temperatures. Polymodal and silent C-nociceptors are activated at non-painful temperatures [255,258,259] and the same can be assumed for (nociceptive) AMH-II-fibers [120,259]. Further, facilitating convergent processing of warmth and nociceptive afferent input has been shown [188] and an effect of this convergent processing on perceptual sensitization cannot be excluded. Additionally, nociceptor activation might occur without being perceived as painful (c.f. [139,262]). In contrast, perceptual sensitization in fibromyalgia patients without IBS was not attenuated but rather enhanced. Thus, a reduction in power of the operant conditioning, as assumed in the fibromyalgia patients with IBS, appeared not to be present. However, fibromyalgia patients respond in an unexpected way to the operant conditioning, as mentioned above.

5.3 Clinical Relevance

The aim of clinical usage of the implicit operant learning paradigms described in this thesis is twofold: first, the use of these paradigms for diagnosis purposes and second, the employment as a type of therapeutical intervention:

The implicit operant learning paradigms applied in the above studies appear to have some diagnostic validity. Operant learning differentiated on the one hand between chronic pain patients and healthy persons and on the other hand also between chronic pain patients with different syndromes or comorbidities. Thus, this parameter seems to be pathogenetically relevant in chronic pain. It can be assumed that deficiencies in operant learning are present only in late states of chronic pain. Thus, it is conceivable to use the implicit operant learning paradigms for the evaluation of vulnerability for operant learning of altered pain sensitivity in early states of chronic pain or even in acute pain. Thereby, the potential contribu-

tion of operant learning mechanisms to the development of hypersensitivity might be estimated individually and therapeutic interventions can be adapted accordingly. However, besides their use as a diagnostic tool, implicit operant learning paradigms also permit the increase of our knowledge about the contribution of implicit procession to the development and maintenance of chronic pain in different syndromes.

In a clinical context, it can be suggested to employ implicit operant learning paradigms of altered pain sensitivity as a therapeutic intervention method for pain patients. The development of hypersensitivity may be prevented through a type of habituation or desensitization training—like the operant conditioning procedure of enhance perceptual habituation used in study 2 and 3 and similar in the previous study by Hölzl and colleagues [106]. Further, by such training an already existing hypersensitivity can be reduced or even entirely undone. Thus, pain perception would be 'recalibrated' by psychophysical methods. Long-term effects of implicit operant learning of changes in pain sensitivity that are stable enough to account for sustained changes in nociceptive sensitivity and pain remain to be demonstrated in further studies including operant extinction and forgetting with clinical groups. However, since the used implicit learning paradigms ensure that pain perception and not solely overt pain report or behavior is target, these methods are very attractive in a clinical and therapeutical context.

6 Conclusion and Outlook

Implicit operant learning of altered pain sensitivity by intrinsic reinforcement was assessed in a number of experiments. It has been demonstrated that enhanced perceptual sensitization as well as habituation to tonic heat-pain stimulation can be learned and that this learning was implicit—i.e. awareness was not a necessary condition for successful operant learning. Implicit operant learning of altered pain sensitivity showed a dose-dependency on reinforcement magnitude. Further, this learning was independent of the schedule of reinforcement and also of the implemented experimental method. In total, a robust and powerful implicit operant learning mechanism capable of producing gross changes in pain sensitivity has been shown. By the analysis of fibromyalgia patients with and without comorbid IBS, the pathogenic relevance of this mechanism was proved. Our results show that implicit operant learning can deliver descriptions of the relation between nociceptive stimuli and consequences of (overt and covert) pain behavior as well as descriptions of altered learning, providing several advantages for the future assessment of operant learning in pain:

- Implicit operant learning paradigms can be employed to clarify the mechanisms between nociceptive processing and altered pain sensitivity. Further, the contribution of operant learning mechanisms to pathophysiological concepts of central sensitization and 'pain memory' [77,210] and also the role of cannabinoid receptors system in extinction of aversive conditioning [152] can be resolved.

- The fear-avoidance theory assumes an essential role of fear and fear-avoidance in pain that is becoming chronic, but experimental support is being lacking. The role of fear and fear-avoidance in pain that is becoming chronic can be directly addressed with implicit operant learning paradigms in addition to classical conditioning of anticipation and fear of pain [189,190].

- The rewarding effect of pain relief as well as the overlap in processing of pain and pleasure has been demonstrated. The implicit operant learning paradigms provide a possibility to directly assess the interaction of intrinsic reward through pain relief and pain perception just as the sensation of pleasure [132]. Further, in order to unravel the differential effect of extrins-

ic (as applied in behavioral pain therapy) and intrinsic reinforcement on pain sensitivity and subjective pain report extrinsic reinforcement can be additionally implemented in the operant conditioning procedure in healthy participants and chronic pain patients [29,113,178].

– By the assessment of chronic pain patients other than fibromyalgia patients—e.g. back pain or complex regional pain syndrome patients—and pain patients at different stages of chronicity with the proposed paradigms, the contribution of implicit operant learning to pain becoming chronic in different pain syndromes would be clarified [4,146]. Thereby, the assumption that implicit operant learning is a distinct feature in the development of chronic pain, independent of a specific syndrome, can be tested.

– Since in most unspecific pain syndromes a dysfunction of the HPA axis is assumed, implicit operant learning paradigms can be applied in addition to stress reactivity tests to clarify the role of acute stress in pain that is becoming chronic. Further, by assessing perceived chronic stress and its relation to a dysfunctional HPA axis, the influence of chronic stress on acute and chronic pain can also be resolved [115,225,283].

Taken together, the plans for future applications and development of the approach are fourfold: (1) Systemic assessment of factors—e.g. physiological, emotional, and cognitive—affecting implicit operant learning of pain sensitivity; (2) analysis of chronic pain patients suffering from different syndromes and at different stages of chronicity in order to contribute to the understanding of alterations in operant learning; (3) development of an easier-to-use method that can also be applied in diagnostic settings; (4) assessment of long-term effects of implicit operant learning on pain perception building a basis for the development of a therapeutic intervention for chronic pain in order to 're-calibrate' pain perception.

Summary

The important role of operant learning in chronic pain is widely recognized. However, the precise mechanisms mediating between nociceptive processing, operant consequences and altered pain perception remain being unclear. The general aim of the three studies contained in this thesis was to clarify the latter. For this purpose, experimental operant learning tasks were employed that were independent of subjective pain report, in order to avoid the risk of solely changing response criteria. Further, intrinsic reinforcement—within the nociceptive system by reductions in nociceptive input—was applied. In contrast to extrinsic reinforcement—external to the nociceptive system e.g. by monetary reinforcement—intrinsic reinforcement directly affects pain perception.

In study 1, a continuous operant conditioning procedure for enhancing pain sensitivity with different magnitudes of reinforcement and different schedules of reinforcement was implemented in healthy participants. The results indicated a dose-dependency of the operant learning. Further, enhanced pain sensitivity was the result of underlying learning rather than immediate (unconditioned) effects of reinforcement (pain relief). Together with a previous study , the independence of the operant learning mechanism from the experimental procedure was demonstrated. Thus, operant learning of pain sensitivity was demonstrated to be a valid and robust mechanism.

In order to demonstrate operant learning to be implicit—i.e. learning without awareness—study 2 employed a discrete-trial operant learning procedure in healthy participants similar to a previously implemented operant learning procedure . Awareness was tested with a behavioral task (prediction of reinforcement) and a standardized interview, addressing different levels of processing. The results demonstrated that operant learning of altered pain sensitivity was implicit; neither verbalization of the operant contingencies (the relationships between behavior and stimuli associated with reinforcement) nor behavioral discrimination was necessary for successful operant learning.

Study 3 repeated the same paradigm as study 2 in chronic pain patients with fibromyalgia with and without comorbid irritable bowel syndrome for testing the vulnerability of these patients to operant learning of altered pain sensitivity. In contrast to a hypothesized heightened vulnerability, operant learning was impaired

in these patients compared to healthy participants. Moreover, fibromyalgia patients with and without irritable bowel syndrome respond differentially to the operant conditioning: While fibromyalgia patients with irritable bowel syndrome showed no signs of operant learning, fibromyalgia patients without irritable bowel syndrome displayed enhanced perceptual sensitization, but this enhancement was paradoxically more pronounced in the habituation learning condition than in the sensitization learning condition. Thus, parameters of operant learning of altered pain sensitivity differentiated between healthy participants and chronic pain patients as well as between different groups of chronic pain patients. In addition, a dissociation of physical stimulus intensities and subjective pain reports was observed, indicating that overt reporting is not the adequate representation level of pain perception relevant for learning altered pain sensitivity.

Taken together, these studies demonstrated (1) operant learning to a be powerful, pathogenetically relevant mechanism, producing gross changes in pain sensitivity without the persons' knowledge and (2) the necessity of behavioral discrimination paradigms that do not depend on subjective measures of pain experience in the first place. The proposed implicit operant learning mechanism of altered pain sensitivity with intrinsic reinforcement provides an explanation for the gradual development of hypersensitivity in pain that is becoming chronic. These results have implications for a wide range of applications ranging from diagnostic procedures to therapeutical interventions in chronic pain.

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Ehrenwörtliche Erklärung

Ich versichere hiermit ehrenwörtlich, dass ich die vorliegende Dissertation selbstständig verfasst und alle benutzten Hilfsmittel angegeben habe. Stellen, die anderen Werken dem Wortlaut oder dem Sinn nach entnommen sind, habe ich in jedem einzelnen Fall durch Angabe der Quelle kenntlich gemacht.

Mannheim, den 15. Mai 2009 Susanne Becker