Pavlovian Conditioning of Muscular Responses in Chronic Pain Patients

An Experimental Study

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“The Greatest Thing Then, Is to Make the Nervous System Our Ally Instead of Our Enemy.”

-William James

Abstract

Objectives: Muscular tension is assigned an important role in the development, enhancement and maintenance of chronic pain syndromes. It is seen as a psychophysiological correlate of learned fear and avoidance behaviour. While theories like the concept of response stereotypy within the biopsychosocial model of musculoskeletal disorders (Flor et al., 1992) and the theory of myogenic headache with its approach of dysfunctional increased muscle effort (Bischof & Traue, 1983) stress the aspect of respondent learning for the chronification process, multidisciplinary pain therapy focuses on a “muscular unlearning”, although empirical evidence has not as yet satisfactorily proved that respondent learning processes are the meditative variable between muscular tension and chronic pain.

Design & methods: An experimental study using a differential Classical conditioning paradigm was undertaken. 18 patients with chronic back pain or tension-type headache, respectively, and 18 healthy controls were examined. A high, aversive tone served as CS+ which was paired with an intra-cutaneous electric pain stimulus (US), while a neutral tone was used as CS-. Simultaneously, integrated surface electromyograms (EMG) were recorded from erector spinae, (lumbar, bilateral), musculus trapezius (bilateral), musculus corrugator supercilii and biceps brachii (bilateral). It was hypothesised that the pain patients would demonstrate an enhanced conditionability and symptom-specific learning.

Results: Learning occurred in both patient groups. During the two acquisition phases there were significantly more muscular reactions to the CS+ than CS- in terms of the number of reactions across all muscle sites. As this learning was enhanced to the CS+ and the difference between CS+ and CS- reached significance in four sites (lumbar right, trapezius right, right and left arm), the differential conditioning design was verified. Furthermore, the question of augmented conditionability of the patient groups compared to the healthy controls could be supported. The back pain and tension-type headache patients demonstrated significantly more and stronger conditioned responses to the CS+. This also applied to the unconditioned muscular responses as well as to the symptom-specific sites of the back pain patients.

Conclusions: The findings supported the idea of a response stereotypy in the group of back pain patients. The response pattern of the tension-type headache patients, though, questioned the current definition of symptom-specificity of this pain syndrome and approved the inclusion of the lower back muscles in future studies.

This study has clinical relevance in that the findings support the approach of “muscular unlearning” in multidisciplinary pain therapy.

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CONTENTS

LIST OF ABBREVIATIONS

ADS	Affective Depression Scale
ANOVA	Analysis of variance
AL	Arm left
AR	Arm right
ARV	Averaged rectified value
BP	Back pain
CNA	Central nucleus of the amygdala
CNS	Central nervous system
CR	conditioned response
CS+/ CS-	conditioned stimulus
DSP	Digital signal processor
ECG	Electrocardiogramm
EMG	Electromyography
EMN	Excitatory motoneuron
FH	Forehead
FTA	Frontotemporal amygdala
HC	Healthy controls
iEMG	integrated electromyographic activity
IHS	International headache society
IMN	Inhibitory motoneuron
LBP	Low back pain
LL	Lumbar left
LNA	Lateral nucleus of the amygdala
LR	Lumbar right
LTP	Long-term potentiation
m	Musculus
MATLAB	MATrix LABoratory
mm	millimeter
ms	milliseconds
NMDA-receptor	N-methyl-d-aspartate
NRS	Numeric rating scale
n.s.	not significant
PAG	Periaqueductal grey
PC	Personal Computer
SCL-90-R	Symptom-Checklist 90-Revised
SEMG	Surface electromyography
TENS	Transcutaneous electrical nerve stimulation device
TR	Trapezius right
TL	Trapezius left
TTH	Tension-type headache
UR	unconditioned response
US	unconditioned stimulus
VAS	Visual analogue scale
VRS	Verbal rating scale
µm	mikrovolt

LIST OF FIGURES

LIST OF TABLES

1 Introduction

The work in hand focuses on Pavlovian conditioning of muscular responses and its significance in the development, reinforcement and chronification of pain. To illustrate the interrelations between learning, muscular tension and chronic pain, it is essential to consider the process of Pavlovian conditioning from various perspectives. Hence, the paradigm of Pavlovian conditioning, its neuroscientific basis as well as its impact on the development of theoretical models of chronic myogenic pain will be outlined in this chapter. A description of the relevant neurobiological and psychophysiological fundamentals of chronic pain and muscular activity will be given whilst at the same time continuing to place emphasis on respondent learning.

1.1 Pavlovian Conditioning

Pavlovian or classical conditioning describes how organisms learn about pairs of stimuli. Such learning is called associative learning (Domjan, 2000). The concept of associative learning is based upon the research of Pavlov (1927), who as a physiologist pursued investigations of classical conditioning to better understand complex neural functions (Babkin, 1949).

1.1.1 Paradigm

In associative learning it is assumed that a neutral stimulus (e.g., a tone) is repeatedly paired with an unconditioned stimulus (US, e.g., food powder) that elicits a reflex reaction (unconditioned response, UR, e.g., salivation). Through this the unconditioned response (now called conditioned response, CR) also is elicited by the neutral stimulus (conditioned stimulus, CS).

Encouraged by the fact that Pavlovian conditioning has been demonstrated in a wide range of species and response systems, a functional perspective has been developed (Turkkan, 1989). The key assumptions of this view are that the prevalence of Pavlovian conditioning suggests it is an adaptive trait that readily occurs under natural circumstances and serves to promote reproductive fitness (Domjan, 2005). Pavlovian conditioning can control and modify both open behaviour and vegetative, physiological processes (Pauli, Rau, & Birbaumer, 2000).

Classical conditioning is often presented as a mechanism for the learning of new responses. A more appropriate interpretation is that classical conditioning involves

the learning of an association between the conditioned and unconditioned stimulus (Rescorla, 1988).

1.1.2 Neuroscience of Pavlovian Conditioning

The experimental analysis of Pavlovian conditioning can be undertaken at different levels. These range from the behavioural to the molecular level (Aguado, 2003; Fanselow & Poulos, 2005). The three levels regarding the neuroscience of associative learning are

- the level of neuronal systems = brain network circuits that mediate between environmental stimuli and acquired behaviour
- the cellular level = synapses within those network circuits that undergo modification mediated by functional or structural changes in neurons for learning to occur
- the molecular level = molecular mechanisms of neuronal plasticity

Pavlovian conditioning and neuronal plasticity in aplysia:

The core of learning-induced neuronal plasticity is alteration of the strength of synaptic transmission. Many studies in both, vertebrates and invertebrates, have been conducted to reveal the underlying neuro-physiological processes of Pavlovian conditioning. The best studied example is that of the defensive learning of the marine molluske aplysia led by Kandel and associates (Castellucci & Kandel, 1974; Pittenger & Kandel, 2003). The authors showed for the first time how the strength of synaptic transmission in the hippocampus changes: they stimulated neurons to the hippocampus electrically and recorded a potentiation of post-synaptic activity. Single neurons and their input fibres were isolated and the intensity of the electric stimulation varied. At first, a weak pre-synaptic stimulation of the cell led to a weak post-synaptic activation. If, however, this weak input was applied simultaneously with a strong stimulation of a second input fibre, a subsequent weak pre-synaptic activation released an enhanced post-synaptic activation (cf. Figure 1):

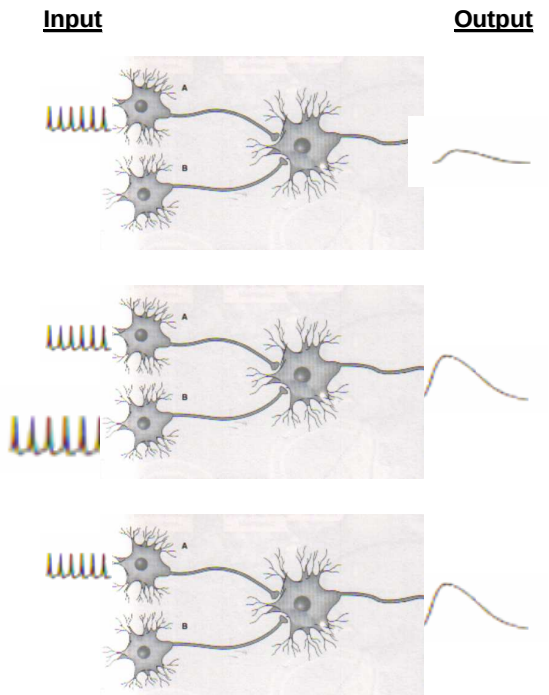

Figure 1: Stimulation of hippocampal neurons in aplysia (illustration taken from Spitzer, 2000)

This mechanism is called associative long-term potentiation (LTP) and is mediated by a subclass of the receptors of glutamate (N-methyl-d-aspartate, NMDA-receptors) (Gazzaniga, Ivry, & Mangun, 2002). LTP is consistent with Hebb´s learning rule, according to which strengthening of synaptic connections is produced when the pre- and post-synaptic cells fire simultaneously (Hebb, 1949). Activation of the NMDA receptor, hence, requires the simultaneous occurrence of two events: membrane depolarization and binding of glutamate, released at the terminals of the pre-synaptic neuron to the NMDA receptor at the post-synaptic neuron. The activation of NMDA receptors starts a complex chain of molecular events finally leading to a lasting increase of synaptic efficacy. This is an attractive model for Pavlovian conditioning because an originally CS- generated glutamatergic input with an initial weak activation of a synapse will be potentiated if the US causes the cell to fire within a limited window of time. The cells that participate in this plasticity thusly receive both, CS and US inputs (cf. Gazzaniga et al., 2002; Lieberman, 2004). The possibility to achieve such plastic changes in cellular activity caused by Pavlovian conditioning is the basic requirement as well as the starting point for the present study.

Pavlovian conditioning and neuronal plasticity in vertebrates:

Associative learning in vertebrates is organized into separate anatomically defined functional systems. The two best studied functional systems and exemplars of Pavlovian conditioning are defensive eyelid conditioning (a tone (CS) is paired with

an airpuff to the eye (US)) and fear conditioning (a tone (CS) is paired with a footshock (US)). In fear conditioning it is possible to measure a wide range of behavioural, physiological and hormonal changes in response to the CS (Fanselow & Kim, 1994). While in eyelid conditioning the cerebellum serves as the neuroanatomical hub, the amygdala is the decisive brain system in the acquisition of conditioned fear (cf. LeDoux, 2000). Thus there is more than a single mechanism for associative learning: the US and the type of reaction it causes determine which neural circuits and sites of plasticity mediate particular changes in behaviour.

The amygdala is composed of several nuclei in the anterior part of the medial temporal lobe. Sensory information, e.g., from the thalamus corresponding to potential CSs, arrive at the frontotemperal amygdala (FTA) (almond-shaped region that interconnects frontal and temporal cortices) via glutamatergic projections. Pain information arrives at the FTA directly from the posterior thalamus as well as from the insular cortex (Brunzell & Kim, 2001; Jasmin, Burkey, Granato, & Ohara, 2004; Lanuza, Nader, & LeDoux, 2004; Shi & Davis, 1999). Pain information from subcortical structures such as the dorsal horn of the spine reach the central nucleus of the amygdala (Benarroch, 2001; Gauriau & Bernard, 2002). In auditory delay conditioning, auditory and somatosensory pathways transmitting CS and US information, respectively, converge onto the lateral nucleus of the amygdala (LNA). While studies show that lesions to the LNA interfere with CR acquisition (e.g., Maren, 2001), lesions to the central nucleus of the amygdala (CNA) affect the expression of learning measured by different behavioural, physiological and hormonal indexes. Hence, a popular view is that the LNA is the hub of associative plasticity underlying Pavlovian fear conditioning and that, from there, information is sent to the CNA which acts as a system for the control and organization of the complex set of changes which constitute the anticipatory fear response. Such changes affect the brainstem as well as the hypothalamus which control the reflexes, autonomic arousal and stress hormones. Another structure that plays an important role in the descending modulation of pain and in defensive behaviour is the periaqueductal grey (PAG) of the midbrain. Its stimulation results in the release of serotonin and noradrenaline in the dorsal horn of the spinal cord, profound analgesia and activation of interneurons containing enkephalin.

In this respect as LTP is the plasticity mechanism on which the tone-shock association is based, the mentioned results would suggest that plasticity in the LNA codes the associative relationship between the danger signal and the aversive US.

LTP might then constitute the mechanisms by which the response of LNA neurons to danger signals is strengthened. Functionally, this would amount to an amygdalar representation of the affective value acquired by the CS.

Figure 2 illustrates the basic circuit for Pavlovian fear conditioning:

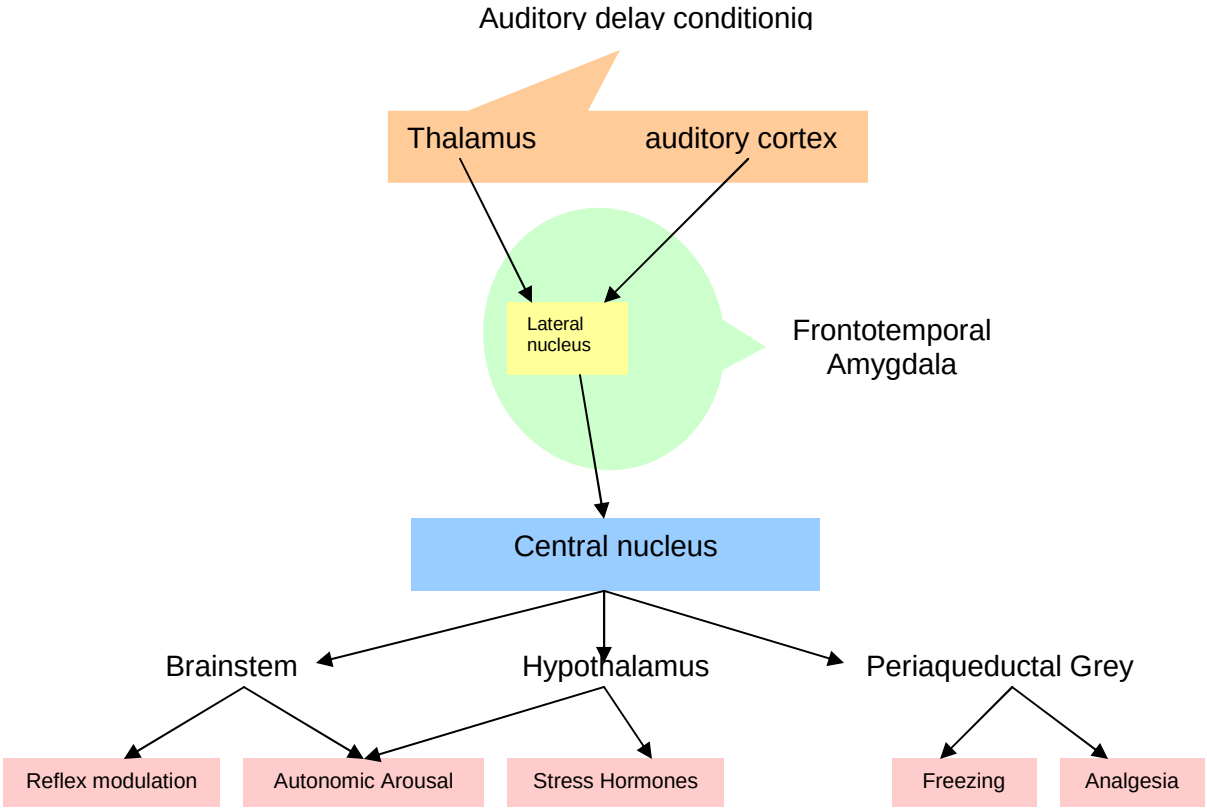

Figure 2: Amygdala circuit for Pavlovian fear conditioning (cf. Fanselow & Poulos, 2005)

The stated findings for associative learning in vertebrates in respect of Pavlovian fear conditioning illustrate how painful sensory input may change the autonomic arousal. This condition is of major importance for the subject matter of this study.

1.1.3 Pavlovian Conditioning and Chronic pain

The traditional specificity theory of pain perception by Descartes (1664) held that pain involves a direct transmission system from somatic receptors to the brain. The perceived extent of pain was assumed to be directly proportional to the extent of injury. Hence, for a long time only organic causes played a role in the development of chronic pain, psychological mechanisms were mostly ignored. In 1965 the gate control theory of pain was proposed (Melzack & Wall, 1965). The emphasis of this theory on the modulation of inputs in the spinal dorsal horns and the dynamic role of the brain in pain processes had a clinical as well as a scientific impact. Psychological

factors such as learning processes were now seen to be an integral part of pain processing (Flor, 2001):

Aversive conditioning circumscribes the learning process in which an unpleasant, or aversive, event serves as the unconditioned stimulus (Domjan, 2000). Nociceptive stimuli can be considered as aversive events which play a central role in the development, reinforcement and chronification of pain. Gentry & Bernal (1977) were the first authors that postulated a “respondent” model of chronic pain by focusing on a vicious circle of pain and tension. Lethem, Slade, Troup & Bentley (1983) suggested that chronic pain patients develop a fear of pain and avoid activities in order to escape anticipated pain. This leads to a reduction of physical and social activities and leads eventually to muscle atrophy, invalidity and depression. A detailed description of the role of classical conditioning in chronic pain was given by Linton & Gotestam (1985). They view pain as an unconditioned stimulus that elicits an unconditioned response such as sympathic activation and muscular tension. The association of pain and neutral stimuli (e.g., hospital) causes fear, sympathic activation and enhanced muscular tension as conditioned responses that can lead to pain if frequency, duration and intensity are sufficient. Thusly, any event that occurs in combination with the experience of pain like a certain movement, a visual image, a sound or thought may become a signal for upcoming pain and might elicit an anticipatory muscular response (Schneider, Palomba, & Flor, 2004).

Two theoretical models come from the perspective of behavioural medicine based upon these assumptions: The biopsychosocial model of musculoskeletal disorders (Flor, 1991) and the theory of myogenic headache (Bischoff & Traue, 1983). Both models emphasise, amongst others, the role of respondent learning in the development, reinforcement and chronification of pain.

1.2 Theoretical Models of Chronic Myogenic Pain

The perspective of behavioural medicine on chronic myogenic pain basis on the assumptions that pain involves reactions to the subjective, the motor-behavioural and the organic dimension (Birbaumer, 1984). Therefore, theoretical models of chronic pain focus on this complex definition of pain and consider somatic as well as psychological factors:

1.2.1 Theory of Myogenic Headache

In the classification system of the International Headache Society (IHS) a distinction is drawn between episodic and chronic tension-type headache (TTH) (IHS, 1988). Episodic TTH (IHS-Code 2.1) is characterised by recurrent episodes of headache lasting from minutes to days. The pain is typically pressing or tightening in quality, of mild to moderate intensity, bilateral in location, which does not worsen with routine physical activity. Nausea is absent, but photophobia or phonophobia may occur. Patients with episodic TTH suffer from headache on less than 15 days per month. In chronic TTH (IHS-Code 2.2) the average headache frequency is more than 15 days per month.

Additionally, the IHS differentiates between TTH associated with and not associated with coexisting pericranial muscle tenderness[1]. For the former, it is assumed that central as well as peripheral mechanisms (anchored in the metabolism of the muscles) are responsible for the development of headache. With the accentuation of such peripheral mechanisms, the TTH associated with coexisting pericranial muscle tenderness is considered as myogenic headache by Bischoff & Traue (Bischoff & Traue, 1983; Bischoff, Traue, & Zenz, 2004).

In their theory of myogenic headache, Bischoff & Traue focus on a dysfunctional increased muscle effort. Their hypothesis states that individuals develop a myogenic headache when, in situations of stress or relief, muscle effort in certain muscles in the head and neck is increased to a critical point within a certain period of time. In the individual case, the “critical increase” might occur in several different ways:

- Immoderate tension increase in stressful situations
- Prolonged recession of tension following a stressful situation
- Muscle tension in a situation of relief
- Muscle tension due to an accumulation or persistence of stressful situations

The authors assume that the various dysfunctions in muscular effort are learned. They interpret increased muscle effort as resulting from classical and operant conditioning of muscle contractions, i.e. certain stress or relief situations have become conditioned stimuli or discriminative stimuli for dysfunctional muscle activity. As Bischoff & Traue postulate a diathesis-stress model of myogenic headache, dysfunctional increased muscle effort is a necessary but not sufficient condition for the development of myogenic headache.

[1] Diagnosed by manual palpation or electromyographic studies

1.2.2 Biopsychosocial Model of Musculoskeletal Disorders

Another theoretical model that originates from the perspective of behavioural medicine is the biopsychosocial model of musculoskeletal disorders (Flor, 1991). In the context of Flor´s diathesis-stress model of chronic back pain four components that interact during the development and maintenance of chronic pain are stated:

- **Eliciting stimuli**: potentially stressful environmental events like aversive external or internal unconditioned or conditioned stimuli that may activate the sympathetic nervous system, the nociceptive system and muscular processes.
- **Eliciting reactions**: e.g., inadequate coping resources or abilities such as the immoderate perception of muscle tension.
- **Predisposing factors**: a predisposing organic or psychological condition is the central component of this model. If aversive stimulation is very intense or recurrent and the individual lacks adequate coping skills, a response stereotypy may develop in an unfavourably disposed physiological system. In musculoskeletal pain syndromes, this unfavourable disposition may be due to over-utilization of a certain muscle group, a structural problem, an acute pain problem or observational learning. This individual response stereotypy may manifest itself as a local muscular hyperreaction that may become prolonged the more the individual's physiological system will be deregulated (Flor, Birbaumer, Schugens, & Lutzenberger, 1992).
- **Processes of maintenance**: Learning processes like operant and classical conditioning of fear of activities or muscular hyperactivity may contribute to the chronification process.

In this theoretical model the concept of a response stereotypy is a necessary but not sufficient condition for the chronification of back pain. Depending on the existence of this response stereotypy psychophysiological variables may play a critical role for the development and maintenance process of chronic back pain. In both theories learning processes such as classical conditioning are part of these mediating variables.

1.3 Neuroscience of Chronic Pain

The leg flexion withdrawal reflex (cf. Figure 3) illustrates how a noxious stimulus activates nociceptors in the sole of the foot, triggers the pain pathway to the dorsal horn of the spinal cord and eventually results in a muscular response (knee flexion

and withdrawal of the leg). This reflex reaction represents non-associative learning and is functional as it protects the individual from further harm.

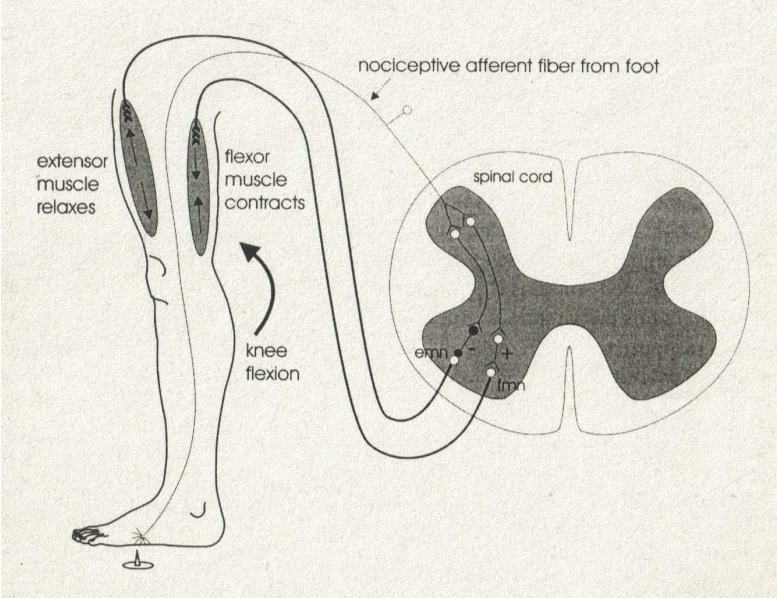

Figure 3: The reflex arc of the leg flexion withdrawal reflex (illustration and description taken from Hesslow & Yeo, 2002 p. 87)
A painful stimulus to the sole of the foot activates cutaneous nociceptors and their Aδ afferent fibres to the spinal cord. The Aδ fibres terminate upon neurons in the dorsal horn of the spinal cord. These dorsal horn neurons project to a further set of interneurons within the ventral horn of the spinal cord. Note that the same sensory input activates both excitatory (emn (+)) and inhibitory (imn (-)) interneurons that project to the leg flexor and extensor muscle motoneurons, respectively. This activation results in a knee flexion and withdrawal of the leg.

The primary nociceptive neurons not only activate interneurons within the ventral horn of the spinal cord to cause the reflex reaction but also project to spinothalamic neurons which cross over in front of the central canal and connect the dorsal horn with the thalamus. From here thalamo-cortical neurons terminate in the "pain centres" of the cerebral cortex and elicit the pain perception process.

Associative learning, as conditioning, helps to avoid acute pain situations. Muscular tension is essential for this act of avoidance (e.g., withdrawal of the leg). Nociception can hence be seen as an early warning system. On the other hand, as mentioned in section 1.1.2 and 1.1.3, pain responses being dysfunctional can be developed by associative learning. If acts of avoidance based on muscular tension occur frequently and automatically (generalisation to other stimuli), the muscular tension contributes to the acquisition of chronic pain states. Exaggerated muscular activity can hereby be seen as a „learned“ relict of the former adverse-effects reflex.

Such learning elicited by a painful stimulus is reflected in line with plasticity: The gate control theory of pain (Melzack & Wall, 1965) has been concentrated upon central nervous system (CNS) plasticity, in which neuronal and synaptic functions are

capable of being shaped so that they influence subsequent perceptual experience. Plasticity related to pain represents persistent functional and structural changes, or somatic memories, produced in the nervous system by injuries or other pathological events (Melzack, Coderre, Katz, & Vaccarino, 2001). These changes are triggered by action potentials generated in nociceptors and injured nerve fibres that release excitatory neurotransmitters at their synaptic terminals such as L-glutamate and substance P (Zieglgänsberger, Berthele, & Tölle, 2005). Empirical evidence indicates noxious stimulus induced changes in CNS functions: Kenshalo, Leonard, Chung & Willis (1982) demonstrated that noxious peripheral stimuli produce changes in the sensitivity of dorsal horn neurons to further stimulation. Woolf & Wall (1986) provided empirical evidence for a primary afferent input triggering sustained increases in central excitability. Furthermore, recent experimental research indicates that noxious stimulation can produce dramatic alterations in spinal cord functions including sensitization, LTP or the expansion of the receptive fields of spinal neurons (Ikeda et al., 2006; Sandkühler, 2000; Schadrack & Zieglgänsberger, 2000; Woolf & Salter, 2000). Similar alterations of the receptive field of neurons and response properties of the CNS have been observed in various other brain regions such as the thalamus (Vos, Benoist, Gautron, & Guilbaud, 2000) and the cortex (Benoist, Gautron, & Guilbaud, 1999; Diesch & Flor, 2007; Skrandies & Jedynak, 2000).

Several researchers have proposed detailed theories of how noxious stimuli produce these changes in CNS function. These state that in addition to a contribution of neuronal hyperactivity to pathological pain, cellular and molecular changes affect membrane excitability and induce new gene expression (Azad & Zieglgänsberger, 2003; Coderre & Katz, 1997; Ji & Woolf, 2001). These changes allow for enhanced responses to future stimulation and could be maintained without further noxious peripheral input.

Phantom limb pain in amputees is a striking clinical example of persistent central sensitizations triggered by noxious stimuli. It is characterized by the persistence or recurrence of a previous pain, has the same qualities and is experienced in the same area of the limb as the pre-amputation pain. Numerous studies show evidence of functional as well as structural reorganization of the somato-sensory cortex following amputation (Davis et al., 1998; Flor, 2002; Florence, Taub, & Kaas, 1998). These studies stress that the sensory representation changes are activity dependent and that after an amputation neurons are probably activated by information from adjacent receptive fields.

The described cortical alterations may correspond to what Katz & Meltzack (1990) have termed a somatosensory pain memory. Implicit pain memories are based on changes in the brain that are not conscious but lead to perceptual changes (such as hyperalgesia and allodynia) and behavioural changes (muscular tension) which the patient is not aware of.

1.3.1 Neuroscience of Chronic Tension-Type Headache

The represented aspects of the neuroscience of chronic pain can be adapted to the development of chronic TTH. As stated above it is assumed that for chronic TTH associated with coexisting pericranial muscle tenderness and myogenic headache respectively the central as well as peripheral mechanisms are responsible for the development of headache. The current literature suggests that a sensitization of peripheral sensory afferents precedes a sensitization of neurons in the CNS (Bendtsen, 2003; Bischoff et al., 2004; Houy-Schäfer & Grotemeyer, 2004). A simplified theoretical model states that the main problem in chronic TTH is sensitization of dorsal horn neurons due to increased nociceptive inputs from pericranial myofascial tissues (Ashina, Bendtsen, Jensen, Sakai, & Olesen, 1999; Bendtsen, 2000). The nociceptive input from myofascial Aδ- and C-fibres increases as a consequence of the activation or sensitization (e.g., caused by ischemia) leading to plastic changes in the spinal dorsal horn (e.g., an expansion of the receptive fields (Hoheisel, Mense, Simons, & X-M, 1993)). As a result, the normally inhibitory effect of Aβ-fibres on pain transmission in the spinal dorsal horn is altered, and the response to nociceptive Aδ- and C-fibres is potentiated. The increased nociceptive stimulation of supraspinal structures may result in increased facilitation and decreased inhibition of pain transmission at the level of the spinal dorsal horn and in increased pericranial muscle activity. Together these mechanisms may induce and maintain the chronic pain condition (Bendtsen, 2000).

On the basis of these findings the presence of allodynia and hyperalgesia in patients with chronic TTH (Ashina et al., 2005; Ashina, Bendtsen, Ashina, Magerl, & Jensen, 2006; Jensen, 1999; Jensen, Bendtsen, & Olesen, 1998; Marlowe, 1992) is seen as a concomitant of this disturbed balance between peripheral input and central modulation. Jensen et al. (1998) compared, for example, the thermal pain sensitivity in patients with chronic TTH and healthy controls. Their results strongly indicate that prolonged nociceptive stimuli from the pericranial myofascial tissue sensitize the central nervous system and, thereby, lead to an increase in the general pain

sensitivity. This sensitization process can be interpreted as a Pavlovian conditioning process similar to the observed potentiation of synaptic activity in aplysia by Kandel and associates (Castellucci & Kandel, 1974; Pittenger & Kandel, 2003). Muscular factors may, therefore, be of major importance for the conversion of episodic into chronic tension-type headache. As TTH patients were hypersensitive to several types of stimuli at symptomatic as well as at non-symptomatic locations, it can be concluded that the general pain sensitivity is affected at the supra-spinal levels and that this responsiveness to pain is enhanced in patients with chronic TTH.

1.3.2 Neuroscience of Chronic Back Pain

Similar observations were made in patients with chronic back pain (BP) with regards to the mechanisms involved in the development of the pain state. Functional reorganisation was found on spinal (Boal & Gillette, 2004; Mense, 2001) as well as on supra-spinal (Flor, 2003; Giesecke et al., 2006) levels caused by long lasting or intense pain conditions.

Flor, Braun, Elbert & Birbaumer (1997) adopted functional brain imaging techniques during which an intra-cutaneous electric stimulation of the lower back and the index finger was applied in chronic low back pain (LBP) patients, a sub-chronic group and healthy controls. The resulting magnetic fields in the range from 40-500 ms post stimulus as well as magnetic source imaging were assessed in order to detect the localization of the neural activity, specifically in the primary somato-sensory cortex (S1). Whilst an elevated response specific for the pain region was observed in an early time window (before 100 ms) for the patients with chronic LBP, an unspecific increase at both sites of stimulation occurred in a later time window (200-300 ms). The authors accounted for this late non-specific increase in activation as a sign of a general sensitization of the cortex. Furthermore, their study revealed a shift of the back representation towards the leg area which they interpreted as an expansion of the back representation. The amount of this expansion was found to be directly proportional to the chronicity suggesting that this pain related cortical reorganization develops over time. As previously mentioned, the basic mechanism for this cortical reorganization can finally be seen in Pavlovian conditioning with muscular tension as behavioural correlative.

Allodynia and hyperalgesia are, as stated above, often found in patients with TTH. Analogically, these observations apply for patients with chronic LBP caused by

cortical alterations. For example, Giesecke et al. (2004) examined chronic LBP patients (n = 11), patients with widespread pain (n = 16) and healthy controls (n = 11). The authors performed an experimental pain testing at a neutral site to assess the pain threshold in all participants. Both groups of patients showed hyperalgesia; the pressure required to produce slightly intense pain was significantly higher in the controls than in the patients. Other studies also report significantly lower perception and pain thresholds as well as pain tolerance levels in patients with chronic LBP (Flor, Diers, & Birbaumer, 2004; Kleinböhl, Gortelmeyer, Bender, & Holzl, 2006; Kleinböhl et al., 1999; Lorenz, Grasedyck, & Bromm, 1996). These thresholds were found to be directly proportional to the chronicity, i.e. the greater the chronicity, the lower the respective thresholds.

1.4 Psychophysiology of Chronic Myogenic Pain

In chronic pain patients general physiological hyperactivity associated with high levels of sympathetic activation might lead to the development, exacerbation and maintenance of pain symptoms (Flor & Turk, 1989). Such responses would be most likely to persist if the individual encountered frequent emotionally demanding stress episodes that induce, among other physiological responses, prolonged muscular contractions. It is the aim of surface electromyography (SEMG) assessment to register the activity of muscles under different conditions. Electromyography (EMG) reveals objectively the fine interplay or coordination of muscles during movements and postures (Basmajian & De Luca, 1985). One of several objectives of current psychophysiological research and the main purpose of the present study is to gain objective data about states of muscle tension and relaxation in the context of clinical psychological examinations (for further potentials of EMG research see Roesler (2001)).

Different SEMG conditions (namely static, dynamic and a combination of these), different postures (sitting, standing) and different methods (multi-site versus single muscle recording, bilateral versus unilateral SEMG) produce different data and the bio-signal obtained by SEMG is complex as it not only indicates the status of a muscle region but also gives information about the nervous system serving the muscle. These aspects have to be considered in the evaluation of the received signal. Static evaluation may be divided into resting and isometric evaluation (Donaldson, Donaldson, & Snelling, 2003). Resting evaluation, which examines the

activity of the muscle while at rest (i.e. sitting) is usually conducted in order to determine which muscles are hyperactive during various sorts of manipulations. This technique was appropriate for the intention of the work in hand. Hence, for reasons of comparability only SEMG studies based on resting evaluation and corresponding to the methodological features of the present study are taken into account in the following review of literature.

1.4.1 Physiological Basis of Surface Electromyographic Activity

Skeletal muscles like the musculus biceps brachii represent an anatomical entity. Each skeletal muscle consists of up to about a thousand muscle fibres or muscle cells (Basmajian & De Luca, 1985). Each muscle fibre is like a fine thread and has a length ranging from a few millimetres up to many centimetres with a diameter of 0.01 to 0.1 centimetres (Roesler, 2001). These merge at their ends into tendons.

Muscle fibres resemble in their structure the other cells of the body and can be characterized by excitability, just like a neuron (action potential, depolarization etc.) (Birbaumer & Schmidt, 2005). A more specific characteristic, however, is that each muscle cell consists of a high number of myofibrils (protein structures (myosin and actin)). They give the skeletal muscle the striated appearance and contract when the muscle is excited. The functional unit of a contraction is the motor unit (cf. Figure 4):

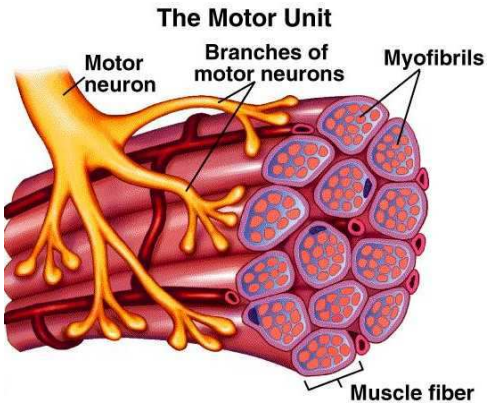

Figure 4: Motor unit
(Illustration taken from http://academic.wsc.edu/faculty/jatodd1/351/ch6outline.html)

A motor unit incorporates a single motor neuron (coming from the anterior horn of the spinal cord) and all of the muscle fibres which it innervates. The area where the motor neuron terminates is defined as motor endplate (neuromuscular junction) and is mostly located near the middle of the muscle fibres. An impulse descending the motoneuron causes all the muscle fibres in one motor unit to contract almost simultaneously (Basmajian & De Luca, 1985). On contracting, they will shorten to

about 57% of their resting length and, thereby, tension develops. The level of contraction determines the muscle tonus or state of tension. A certain tonicity is registered even at rest due to a continuous asynchronic activation of motor units. The strength of tonicity can be influenced by different conditions such as stress or attention which may often lead to an enhanced muscle tonus (Roesler, 2001). As TTH and chronic BP have been viewed as having a musculoskeletal etiology, researchers have focused on characteristic muscular activity employing EMG recordings.

1.4.2 Surface Electromyography and Chronic Tension-Type Headache

According to the hypothesis of increased muscle effort (cf. section 1.2.1), excessive contractions and hyper-reactivity to emotional stressors are seen as relevant mechanisms underlying TTH and should become apparent in abnormally elevated levels of muscle tension. The empirical evidence for the hypothesis of increased muscle effort is based upon only a few experimental studies. These studies examined triggers for increased muscle tension and individual pain ratings. A review of psycho-physiological studies published from 1969 to 1989 including SEMG studies in chronic TTH patients can be found in Flor & Turk (1989). Despite many methodological problems of the reviewed studies the authors conclude that the data on recurrent headaches suggest the presence of symptom-specific responding in EMG levels in TTH patients during stress and pain related situations. In chronic BP patients stress related increases in EMG activity have been observed in paraspinal muscles. Another more recent review presented by Wittrock & Myers (1998) also provides evidence of enhanced physiological responses such as higher SEMG activation in TTH patients compared to controls to experienced as well as to expected stressful events.

The first evidence for the hypothesis of increased muscle effort was provided by Borgeat, Hade, Elie & Larouche (1984) who showed that headache could be induced by volitional contractions of the facial frontalis muscle.

Schoenen, Gerard, De Pasqua & Juprelle (1991) recorded EMG activity over frontalis, temporalis and trapezius muscles during a mental task in 32 female patients suffering from chronic tension-type headache and in 20 healthy volunteers. All EMG levels were on average significantly higher in patients than in controls.

In another study light flashes caused a significant increase in muscle tension in the frontalis muscle (Traue & Lösch-Pötzsch, 1993), 95% of the patients with TTH reacted to the visual stressors with tension feelings, 50% with headache. The healthy controls did not reveal any discomfort. As no enhanced muscle activity was found in the neck region of the healthy controls, these results indicate a differential muscle activation in stress situations of both groups.

Bansevicius, Westgaard & Sjaastad (1999) examined twenty patients with tension-type headache (14 chronic and 6 episodic) and 20 group-matched controls. They participated in a 1-hour reaction-time test, as well as in 5-minute pre-test and 20-minute posttest periods. SEMG was recorded from positions representing the frontal and temporal muscles, neck and trapezius muscles. The test involved provoking pain in the forehead, neck, and shoulders of patients. For patients, the EMG response of the trapezius (first 10 minutes of the test) was elevated relative to pre-test. For controls, only the frontal muscles showed an EMG test response. Patients showed significantly higher EMG responses than controls in the neck (whole test period) and trapezius (first 10 minutes of the test period).

A study by Harnphadungkit, Senanarong & Poungvarin (2001) also revealed increased EMG activity indexed by a sum of scores for eight muscles (right and left frontalis muscles, temporal muscles, occipital muscles and cervical trapezius muscles) during mental stress in a group of 20 patients with chronic TTH compared to a group of healthy participants.

The most recent study by Leistad, Sand, Westgaard, Nilsen & Stovner (2006) presents contradictory findings. They recorded SEMG responses to stress in 22 migraineurs during headache-free periods, 18 patients with TTH, and 44 healthy controls. Sixty minutes of cognitive stress was followed by 30 min relaxation. EMG and pain in the trapezius, neck, temporalis and frontalis areas were recorded. Higher pain responses were observed for the TTH patients in the temporalis and frontalis (with similar trends for trapezius and splenius) and more potentiation of pain during the test than the controls. The EMG responses for headache patients, however, were not different from the controls and the EMG responses did not correlate with pain responses.

Except the last one, studies predominantly present homogeneous results and support the important role of muscular tension in TTH during stressful situations. Enhanced EMG activity in symptom-specific muscle sites seems to be a common phenomenon.

By focusing on EMG activity under different conditions, e.g., standing, at rest, during maximal voluntary contraction or acute headache, more heterogeneous empirical findings emerge. Muscular activity was normal or only slightly increased, being hardly sufficient to explain pain in TTH. Some authors hence question the relationship between chronic TTH and muscular tension (Hatch et al., 1991; Köhler, 2003; Pikoff, 1984). Such results confirm on the one hand that there probably is not a general EMG activity pattern in patients with chronic TTH that applies for all SEMG evaluations, on the other hand, it indicates that the patho-physiological role of muscle activity in headache has not been fully established.

1.4.3 Surface Electromyography and Chronic Back Pain

This section focuses only on those studies which were concerned with SEMG activity in chronic back pain patients during sitting and stress exposure. The muscular reactivity to pain and stress in patients with chronic BP was among other SEMG conditions reviewed by Flor & Turk (1989). Until that time, one study did not find significant paraspinal SEMG changes during mental arithmetic and cold pressure test between 11 chronic LBP patients and 11 healthy controls (Collins, Cohen, Naliboff, & Schandler, 1982), whereas a study by Flor, Turk & Birbaumer (1985) reported significant stress related SEMG changes in BP patients in comparison with other pain patients and healthy controls. The pain patients had to verbally describe self selected personal stress and pain episodes, and only the BP patients showed significant increases in paraspinal SEMG levels in response to this task. The researchers confirmed similar results in two later studies (Flor, 1991; Flor et al., 1992).

A recent meta-analytic review of SEMG among participants with LBP and healthy controls by Geisser et al. (2005) included only one study that examined SEMG in a sitting posture while undergoing various mental stressors (DeGood, Stewart, Adams, & Dale, 1994). The authors of this last study contrasted the reactivity of surface paraspinal EMG among groups of (1) patients seeking treatment for chronic back pain, (2) nonpatients reporting chronic back pain and (3) healthy controls. During brief 1 min. tasks (counting backwards, reciting the alphabet, recalling a recent pain episode, a recent stressful event and a recent enjoyable experience, respectively) the EMG response to the personally relevant stressor task was greater for the patient group relative to the other two groups. Geisser et al. computed a moderate mean effect size (d = .53) between the patient group and the healthy controls.

Although the empirical basis is still weak, most studies have reported a positive relationship between stress and symptom-specific reactivity in the relevant muscle group in chronic BP patients.

1.5 Pavlovian Conditioning, Muscular Tension and Chronic Myogenic Pain

According to the two represented theoretical models of chronic myogenic pain, the significance of operant and respondent approaches concerning the development, reinforcing and maintenance of chronic pain is still emphasised in the behavioural medicine literature (Birbaumer & Schmidt, 2005). Surprisingly, many psychological treatments of chronic pain are based upon these concepts although their validity has not yet been sufficiently proven by empirical evidence.

Just one recent study by Schneider, Palomba & Flor (2004) examined the postulated contribution of respondent learning to the development of muscular tension and pain in chronic pain patients. The authors tested the hypothesis of augmented aversive conditioning of muscular responses in 11 chronic BP patients and 11 healthy controls (HC). In a differential conditioning design an aversive slide served as CS+ that was followed by an intracutaneous electric stimulus which was applied to the left index finger. A pleasant slide served as CS-. As psychophysiological variables the heart rate, skin conductance levels and SEMG recordings from the left and right musculus flexor digitorum, the right musculus trapezius and bilaterally from the musculus orbicularis oculi were acquired. A four-way repeated measures analysis of variance (ANOVA) included the factors “period” (500 ms prior to US-onset), “group” (BP vs. HC), “CS type” (CS+ vs. CS-) and “block” (one for habituation, four for acquisition and two for extinction).

A significant “CS type x period x group x block” interaction was found during acquisition for the left forearm where the US was applied. While the healthy controls revealed a steady level of responses in the 500 ms prior to US-onset, the chronic BP patients showed a linear increase in muscle tension across this period in the CS+ condition. The right forearm did not display any conditioning effects, but the right trapezius showed a significant “group x CS type x period x block” effect in the acquisition phase indicating elevated responses to the CS+ only by the BP patients in the 500 ms prior to US-onset. Hence, both, the left forearm and the right trapezius, demonstrated a differential conditioning effect. Neither heart rate nor skin conductance revealed a conditioned response. During extinction increased muscular responses were maintained in the left forearm of the patients. The patients also

showed a generally elevated muscle tension level irrespective of CS type. Regarding the US, both groups displayed a significantly accentuated unconditioned response at the left forearm on the CS+ and no response on the CS-.
In summary, the results of this study support the assumption of symptom-specific physiological reactivity and, more specifically, the hypothesis of aversive conditioning of muscular responses in chronic BP patients.

Figure 5 points out the main theoretical aspects considered so far and illustrates the framework for the conducted experiment in the present study. Presented is a diathesis-stress-model of the chronification of myogenic pain that starts from the biopsychosocial model of musculoskeletal disorders (Flor, 1991) and its three components namely predisposing factors, eliciting reactions and eliciting stimuli (cf. section 1.2.2). The interaction of these elements activates the pain process and terminates in a complex pain reaction (the pain pathway and perception process were described in section 1.3). As mentioned in section 1.3 and 1.4, muscular tension is a physiological response to the initial pain stimulus. At this point a vicious circle of dysfunctional pain responses could be elicited if the fear of new pain results in avoidance which in turn leads to muscular tension (cf. section 1.1.2 and 1.1.3). If such acts of avoidance generalize to other stimuli, the muscular tension contributes to the acquisition of chronic pain states. This development is described by the two theoretical models namely the hypothesia of increased muscle effort (Bischoff & Traue, 1983) and the concept of response stereotypy (Flor et al., 1992) (cf. section 1.2.1 and 1.2.2). As these theories implicate an increase of (symptom-specific) muscle activity, section 1.4 explained the physiological basis of muscle tension and how it can be measured by surface electromyography. Section 1.4.2 and 1.4.3 showed empirical evidence for the assumption of enhanced electromyographic activity in chronic TTH and BP. It was clarified that these physiological alterations were based on a potentiation of synaptic activity in terms of neuronal plasticity (the basic principles of the neuroscience of chronic TTH and BP were shown in section 1.3.1 and 1.3.2). The described cortical changes correspond, on the one hand, to a somatosensory pain memory (Katz & Melzack, 1990) and constitute, on the other hand, the crucial impulse for a chronification process. The underlying mechanism serving this neuronal sensitization is Pavlovian conditioning (cf. section 1.1 and its following subsections). Pavlovian conditioning does not however only play a decisive role on the central level, but is an important factor behind every step shown in Figure

5. The previous chapters explained how respondent learning influences the pain reaction, elicits and maintains the vicious circle of muscular tension and avoidance behaviour and hence alters physiological responses. The present study attempted to transfer and to approve these assumptions.

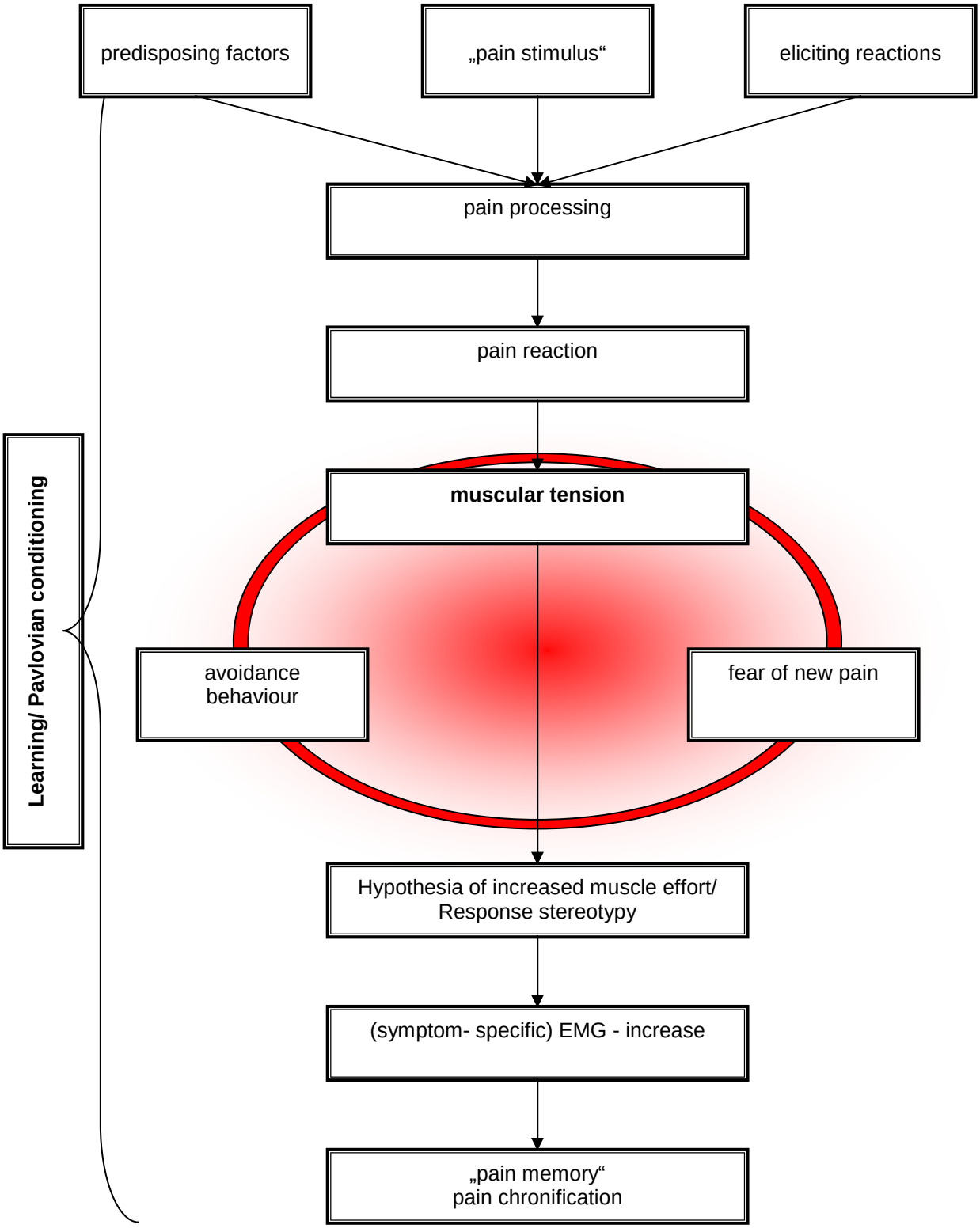

Figure 5: Theoretical framework: diathesis-stress-model of the chronification of myogenic pain

2 Hypotheses

The hypotheses were established in accordance with the presented scientific state of knowledge and mainly based on the two introduced theoretical models of chronic myogenic pain.

Hence, following questions and hypotheses stand in the foreground:

(1) Are muscular responses learnable? (in terms of classical conditioning)

Hypothesis: Chronic pain patients show stronger muscular responses to a given pain stimulus (US) than healthy controls.

(2) Do chronic pain patients differ from healthy controls in their conditioned response?

Hypothesis: Chronic pain patients show stronger muscular responses to a given conditioned stimulus (CS+) than healthy controls.

(3) Do pain patients show a conditioned response in their symptom-specific muscles?

Hypothesis: Chronic back pain and tension-type headache patients show stronger conditioned responses in their symptom-specific muscles.

3 Method

3.1 Participants

A total of 83 participants were recruited over a period of 13 months (August 2004 to September 2005) and subjected to a one-time two hour experimental setting in the clinic for orthopaedy of the University Medical Center Hamburg-Eppendorf.
29 participants had to be excluded due to several reasons. Technical measurement issues accounted for the loss of at least 15 datasets at the beginning of the data acquisition phase such as automatic deactivation of the data acquisition system as a consequence of the summery environmental temperature or an increase in the impedance of the finger electrode. Other deficits such as incomplete questionnaires, the absence of a reflex response to the pain stimulus and withdrawal during the experiment led to further drop outs. 54 participants could be included in the final sample. These were separated into three groups:
Group 1: 18 patients with chronic myogenic back pain (BP)
Group 2: 18 patients with chronic tension-type headache (TTH)
Group 3: 18 healthy controls (HC)

All participants were matched according to age and sex into the three groups to avoid respective influences on the psychophysiological reactions by these factors (Flor, 1991; Tassinary & Cacioppo, 2000). The patients were primarily recruited from the psychotherapeutical outpatient clinic of the Department of Psychology of the University of Hamburg, which has its main focus on behavioural therapy and psychological pain management treatment, and the Clinic Alten Eichen specialising in pain treatment. Both facilities offer treatment for chronic pain patients suffering from different basic diseases of which the majority are back pain and headache patients. The healthy controls were recruited among friends and colleagues of the participants and were paid by an amount of 30 € for participating at the experimental session. The study adhered to the Declaration of Helsinki (World Medical Association, 1984, 2000) and was approved by the local ethics committee[2]. All participants gave informed written consent before participation.

[2] Ethik-Kommission der Ärztekammer Hamburg

3.1.1 In- and Exclusion Criteria

The patients underwent a broad psychological diagnosis and medical examination by the recruiting facilities. To be included, the pain problem of a patient needed to persist for longer than six months confirmed by either the diagnosis of chronic myogenic (without neurological complications) back pain or chronic/ episodic tension-type headache. Furthermore, the existence of an unconditioned muscular response to the intracutaneous stimulus was required for the inclusion of a participant into the sample.

Exclusion criteria were inflammatory cause of pain, indication of a required and/ or upcoming surgery, major psychiatric illness, cardiac pacemaker and intake of centrally acting analgesics (opioids) or psychotropics (the intake of pain reliever was not permitted on the day of examination). The criterion of a Body Mass Index below 30 was applied in order to obtain distinct electromyographic signals.

3.1.2 Demographic and Clinical Data

Table 1 shows demographic characteristics of the participants. The chronic back pain patients´ average age was 48.8 (SD = 11.5, range: 23 – 66), the mean age of the chronic headache patients was 43.2 (SD = 13.6, range: 23 – 66). The healthy controls were on the average 42.5 years old (SD = 12.3, range: 23 – 70). There were no significant differences between the three groups with respect to gender (chi^2 (2; 54) < .01, p = 1.00 n.s.) or age (F (2; 52) = 1.39, p = .26 n.s.).

Table 1: Demographic data

	N = 54		
	Chronic back pain patients	Chronic headache patients	Healthy controls
Age in years M (SD)	48.8 (11.5)	43.2 (13.6)	42.5 (12.3)
Gender (N male/ female)	9/ 9	9/ 9	9/ 9
Family status N			
Single	3	4	4
Married	10	9	8
Divorced	2	0	0
Partnership	2	4	6
Living apart	1	1	0
Education N			
Basic (< 10 years)	5	1	0
Intermediate (< 13 years)	7	5	2
High school (13 years)	2	5	4
University (> 13 years)	4	7	12

The affective mood was assessed using the Affective Depression Scale (Hautzinger & Bailer, 1991), a reliable and valid screening-tool. This commonly deployed 16-item self-report was filled out shortly before the experiment. The participants were also provided with a von Korff Questionaire “Grading the severity of chronic pain” (Von Korff, Ormel, Keefe, & Dworkin, 1992). By this questionnaire, amongst other items, the current pain intensity and the average pain intensity during the last six months were assessed. The questionnaire was translated into German and retranslated into English independently by two native speakers. An additional version for the chronic headache patients was adapted. The Symptom-Checklist 90-R (SCL-90-R) (Derogatis, 1977; Franke, 1995) was applied, a multidimensional self-report inventory to evaluate physical and psychological distress and symptoms of psychopathology. It covers nine primary symptom dimensions and three global indices. This test was sent to the participants together with the information about the experiment approximately one week before its conduction. The three groups did not differ significantly in their affective mood ($F (2; 51) = 2.5$, $p = .09$ n.s.), but for 44% of the back pain patients values above the cut off of 23 ($M = 28.7$, $SD = 3.3$) were observed. Regarding the three global indices of the SCL-90-R, the chronic back pain patients showed a slightly heightened score of 60.4 (Cut off = 60) for overall psychological distress (GSI) while the score of the chronic headache patients revealed a heightened intensity of symptoms (PSDI: 60.6). The healthy controls displayed inconspicuous scores in all three indices as expected. A comparison of the three groups provided evidence about significant differences between the patients and the healthy controls in all three global indices: **GSI**: $F (2;51) = 5.29$, $p = .01$** (Post hoc test: BP > HC: Mean difference = 12.33, 95% CI = 2.50 to 22.17, $p = .01$**; TTH - HC: Mean difference = 9.50, 95% CI = -.34 to 19.34, $p = .06$ n.s.); **PSDI**: $F (2;51) = 7.07$, $p = .01$** (Post hoc test: BP > HC: Mean difference = 9.17, 95% CI = 1.86 to 16.47, $p = .01$**; TTH > HC: Mean difference = 10.00, 95% CI = 2.70 to 17.30, $p < .01$**); **PST**: $F (2;51) = 4.00$, $p = .02$* (Post hoc test: BP > HC: Mean difference = 10.61, 95% CI = 1.03 to 20.20, $p = .03$*; TTH - HC: Mean difference = 7.67, 95% CI = -1.92 to 17.25, $p = .16$ n.s.). These results indicate that the back pain patients in particular suffered significantly more from overall psychological distress and subjectively felt physical and psychological impairment than the healthy control group. These findings were predictable in the context of a chronic pain disease. The two patient groups, though, showed homogeneity regarding the global indices as expected (**GSI**: $F (1;34) = 5.90$, $p = .45$ n.s.; **PSDI**: $F (1;34) = .09$, $p = .77$ n.s.; **PST**: $F (1;34) = .64$, $p = .43$ n.s.).

In respect of the four pain ratings of the patients (average pain of the last 6 months, current pain directly before and after the experiment, pain 24 hours after the experiment) a significant group difference was found. The patients with headache suffered less intense pain at all four assessments than the patients with back pain ($F(1; 34) = 4.33$, $p = .05^*$, $1 - \beta = .53$).

With respect to the perception and pain thresholds of the electric stimulation during the experiment no group differences were found (perception threshold: $F(2; 51) = .25$, $p = .78$ n.s.; pain threshold: $F(2; 51) = 1.32$, $p = .28$ n.s.).

In Table 2 the clinical data of the sample is displayed:

Table 2: Clinical data

	N = 54		
	Chronic back pain patients	Chronic headache patients	Healthy controls
Affective mood N (Affective Depression Scale)			
Depressive (score ≥ 23)	8	3	3
Non-depressive (score < 23)	10	15	15
SCL 90-R M (SD) T-scores (M = 50, SD = 10)			
Global Severity Index (GSI) (overall psychological distress)	60.4 (10.8)	57.6 (11.4)	48.1 (13.4)
Positive Symptom Distress Index (PSDI) (intensity of symptoms)	59.7 (9.1)	60.6 (7.7)	50.6 (9.6)
Positive Symptom Total (PST) (number of self-reported symptoms)	58.4 (10.4)	55.4 (11.6)	47.8 (12.8)
Location of pain N	*Back* 10 *Back & bottom* 3 *Back & thigh* 1 *Back & lower leg* 2 *Neck* 2	*Head* 13 *Back of the head* 2 *Neck* 2 *Temple* 1	-
Duration of current pain N			
0 to 4 weeks	1	1	-
4 weeks to 6 months	2	1	
> 6 months	15	16	
Intensity of pain M (SD) Numeric rating scale (NRS) (min = 0, max = 10)			
average of last 6 months	5.5 (1.7)	5.4 (1.5)	-
current (pre experiment)	4.0 (2.1)	2.9 (2.5)	
current (post experiment)	3.9 (2.8)	2.3 (1.9)	
24h after experiment	4.0 (2.2)	2.3 (2.1)	0.0 (0.0)
Perception threshold of electric stimulation (mA)	0.25	0.22	0.25
Pain threshold of electric stimulation (mA)	0.51	0.50	0.64

Table 3 displays the absolute muscular baseline values for all seven examined muscle sites. The three groups did not differ in the baseline values in any of these

variables before the experiment started. Lower absolute integrated electromyographic (iEMG) mean values were, however, observed for the healthy controls in various muscle sites.

Table 3: Muscular baseline measures

	N = 54		
	Chronic back pain patients	Chronic headache patients	Healthy controls
iEMG of muscle site µV M (SD)			
m. trapezius right	68.3 (86.8)	80.4 (69.8)	32.8 (13.3)
m. trapezius left	47.1 (26.4)	66.9 (75.5)	45.4 (46.5)
m. erector spinae, lumbar right	22.9 (2.4)	30.4 (15.1)	26.1 (13.7)
m. erector spinae, lumbar left	30.1 (11.8)	35.6 (20.5)	26.1 (5.9)
m. biceps brachii right	35.4 (10.1)	29.7 (5.9)	39.6 (58.3)
m. biceps brachii left	21.1 (6.3)	21.3 (10.2)	17.9 (1.7)
m. corrugatur supercilii left	68.9 (27.2)	60.8 (27.5)	56.2 (21.5)

3.2 Design and Experimental Procedure

The experimental design was arranged according to the experimental setup of Schneider et al. (2004), basically constituting a differential Pavlovian conditioning paradigm with a high tone (3500 Hz) as CS+ (to be conditioned stimulus) and a lower tone (500 Hz) as CS-. An intracutaneous electric pain stimulus served as unconditioned stimulus (US) that was individually defined and applied to the index finger of the left hand.

The main difference between the two experimental setups of the Schneider et al. and our study, though, is that we abstained from a habituation phase in the beginning of the experiment. Such a habituation phase of CS+ and CS- is realized by repeated presentation of both stimuli preceeding the conditioning process to avoid eliciting a priori differences in the reactions assessed. A disadvantage of this approach, however, is seen in the latent inhibition: If a stimulus was repeatedly presented (pre-exposed) without any consequences before being paired in terms of a CS with an US in a learning phase, its associability with the US will be weakened (Domjan & Burkhard, 1982; Escobar, Arcediano, & Miller, 2003; Klosterhalfen et al., 2005; Lipp, Siddle, & Arnold, 1994; Lubow & Gewirtz, 1995). A review of studies confirming latent inhibition amongst others in autonomic reactions is given by Lubow & Gewirtz (1995). In the most recent study, Byron & del Carmen (2006) used a computer video game preparation in three experiments to demonstrate latent inhibition in adult humans. These experiments involved having the participants fire torpedoes at a target spaceship by clicking the mouse. Conditioned stimuli (CSs) were presented in the form of coloured "sensors" at the bottom of the screen. Conditioning was conducted

by pairing a sensor with an attack from the target spaceship. The participants learned to suppress their rate of mouse clicking in preparation for an attack. In the first experiment a total of 10 pre-exposures to the sensor CS, prior to conditioning, retarded acquisition of suppression. In experiment 2 the effect of pre-exposure was shown to be context specific. Experiment 3 showed little generalization of the pre-exposure effect from one sensor CS to another. The latent inhibition, hence, describes a blocking or reduction in associative learning in the case of pre-exposure of a stimulus before it serves as a signal for a significant event (Zimmermann, 2002). To avoid this unfavourable effect, the experiment conducted here starts immediately with an acquisition phase. Additionally, this decision was based on the fact that in a preliminary study the high tone was rated more unpleasant than the low tone but did not evoke significant stronger muscular responses (Kleinwort, 2002).

3.2.1 Assessment of the individual pain stimulus

The method of Bromm & Meier (1984) was used to allocate the US. According to this procedure, a small piece of epidermis (with a diameter and a depth of 1 mm) was manually removed from the fingertip with a steel dental drill, and a platinum electrode was inserted into the epidermal opening (cf. Figure 6). The earth electrode and the reference electrodes were mounted on the back of the hand and around the wrist, respectively.

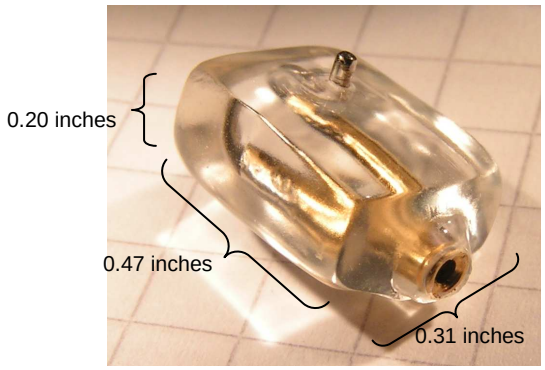

Figure 6: Platinum finger electrode with golden contacts

A verbal rating scale (VRS) was then shown and explained to the participants which served to assess their perception of electrical stimuli (0 = not noticeable; 1 = just perceivable; 2 = clearly perceivable; 3 = strongly perceivable but not painful; 4 = strongly perceivable, noticeably painful; 5 = clearly painful; 6 = strongly painful; 7 = very strongly painful; 8 = immensely painful). The up and down method of psychophysics was applied (Cornsweet, 1962; Dixon, 1965), i.e., subsequent electric stimuli were given to the participant across a period of approximately ten minutes

starting at 0.12 milli amperes (mA) and continuing in three ascending and descending series proceeding stepwise by 0.02 mA within the range from 0.12 mA to 0.20 mA, 0.04 mA within the range from 0.20 mA to 1.00 mA and, finally, by 0.1 mA steps within the range from 1.00 mA to 3.00 mA. Thus, the stimuli ranged from below perception to pain threshold and to pain tolerance. The VRS ratings indicated the levels when participants perceived the stimulus (perception threshold), when they felt pain (pain threshold) and when they felt that the stimulus was unbearable (pain tolerance). The electric stimulus was reduced as soon as the pain tolerance was reached. For the conditioning procedure the average of the six pain thresholds was doubled according to the method of Bromm & Meier and allocated as individual unconditioned stimulus during the conditioning experiment.

3.2.2 Physiological Recordings

The muscular responses were recorded by means of bilateral measurements of the iEMG activity from seven muscle sites (cf. Figure 7):

- Musculus trapezius (right and left)
- Musculus erector spinae, lumbar (right and left)
- Musculus biceps brachii (right and left)
- Musculus corrugator supercilii (left)

The electrodes were placed according to the European recommendations for surface electromyography (Hermens, Freriks, Disselhorst- Klug, & Rau, 2000; Hermens et al., 1999). According to these guidelines, the skin was cleaned with alcohol and an abrasive creme for better skin contact and decreased skin impedance. The recommended disposable surface electrodes were used (Ag/ AgCl- electrodes, type N-00-S – blue sensor from Medicotest®) which relayed the summarized action potential of a muscle and gave information about the muscle tonicity. The signals obtained were bipolar (measuring the voltage difference between a pair of electrodes) with an inter-electrode distance of 10mm.

Furthermore, the electrocardiographic (ECG) activity was derived from the upper and lower portion of the sternum. This derivation primarily served to remove the electrocardiographic artefact from the surface-recorded EMG (cf. section 3.4.1); secondarily, it also provided assessment of the heart rate by identifying the inter-beat-intervals of the peaks within the cardiac signal. As the present study focused on muscular responses, the heart rate was not included in the subsequent analysis (please refer to appendices G and H for detailed computation).

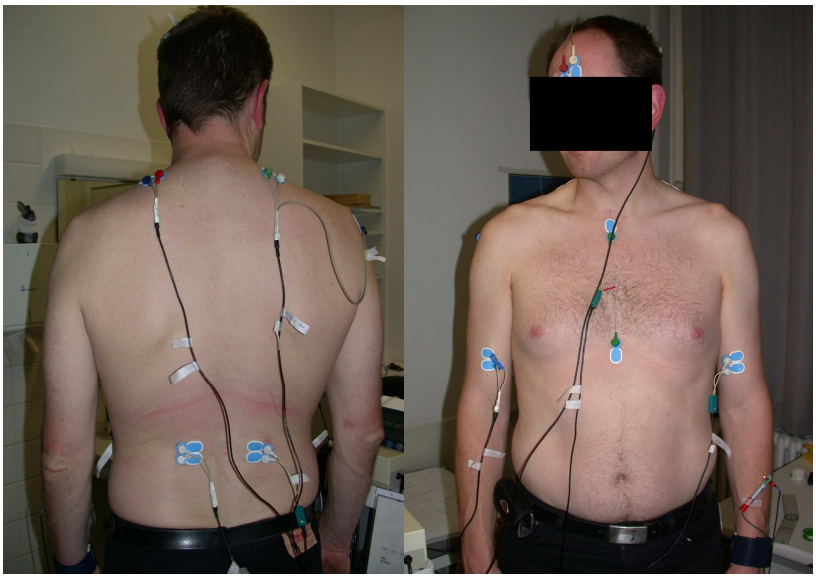

Figure 7: Electrode placements to measure the integrated electromyographic activity; indolent patient

3.2.3 Experimental Course of Events

Assessment of a dynamic EMG preceding the Classical Conditioning Phase

Before the classical conditioning experiment started, the participants had to carry out four movements (dynamic EMG):

(1) they were requested to rise from their chair,

(2) bend forward as far as possible,

(3) straighten up and

(4) sit down again.

The start of the respective movement was indicated by the experimenter´s “now” after muscular relaxation was visible on the screen. The dynamic EMG was recorded as these movements were carried out.

Instructing the Participants

It was then explained to the participants how to rate the pain perception of electric stimuli during the experiment on a visual analogue scale (VAS) from 0 (no pain) to 10 (strongest imaginable pain stimulus). This change from the VRS to the VAS was performed because all of the levels below pain perception (ratings from 0 to 4 on the VRS) were removed, thus, in the following procedure only individual pain stimuli were applied. Then the participants were asked to sit as relaxed as possible and to follow the procedure attentively.

The Classical Conditioning Paradigm

This phase lasted 18 minutes in total and was divided into three blocks: two acquisition or learning phases and one extinction phase. In the acquisition phases three different events could occur: The high tone (CS+) could be followed by an unconditioned stimulus (US) or be applied alone, whereas the low tone (CS-) was always applied alone. While in acquisition phase I all CS+ were coupled with an US, in acquisition phase II an intermittent reinforcement took place (four out of eight CS+ were followed by an US). In the extinction phase only the two tones were applied. The succession of events was pseudo randomized. A long baseline of 30 seconds was measured before and after each block. Each individual event was split up into four seconds pre-baseline, five seconds application of the respective tone (in case of a CS+ coupled with an US the pain stimulus lasted 50 milliseconds and ended exactly with the tone) and 10 seconds post-baseline. Figure 8 gives an overview of the sequence of events.

Ending the Experiment

After the extinction phase and its last baseline, the dynamic EMG of the initial movements already done prior to the conditioning and extinction procedure was repeated. Thereafter all electrodes were removed, and each participant received an individual feedback about his muscular responsiveness as well as a debriefing and explanation of the experiment.

acquisition phase I

event	time
Baseline 1	30 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec

acquisition phase II

event	time
Baseline 2	30 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+ & US	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec

extinction phase

event	time
Baseline 3	30 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
CS+	4 sec
	5 sec
	10 sec
CS-	4 sec
	5 sec
	10 sec
Baseline 4	30 sec

Figure 8: The sequence of events across the three blocks of the experiment; each event was split up into four seconds pre-baseline, five seconds presentation of the respective tone and 10 seconds post-baseline

3.3 Technical Requirements

The surface electrodes were connected to an electrode box by electrode cables with integrated preamplifiers. These preamplifiers were supplied with a 5V current by the electrode box providing a 5000-fold signal amplification. These amplified signals were transmitted to a host system (a personal computer (PC) which was equipped with a Pentium IV processor, a main storage of 512 MB RAM, a 60 GB hard drive and operating system Windows XP). The participants were protected from the power supply by an optocoupler which was incorporated into the electrode box. The general requirements for safety (European safety standard for medical devices EN60601) were adhered to. A digital signal processor (DSP) board from Innovative Integration (M67)[3] with a processor from Texas Instruments was equipped with two analogue/ digital transducer modules (OMNIBUS A4D4) which provided the real time data acquisition of the eight channels. The overall sampling rate was 40 kHz (rate = 5 kHz x eight channels).

The electric pain stimuli were delivered by a transcutaneous electrical nerve stimulation device (TENS) of the type G43 from Bentronic. It was adjusted to the needs of the experiment and attached between the prepared index finger of the participant and the host system. The setting of the individual pain stimulus as well as the experiment was controlled by the specially written program “DAQ Server Tester” (for documentation of this program see Jannasch, 2004) using the programming language of MATrix LABoratory release 7 (MATLAB®) by The MathWorks, Inc.. Figure 9 shows the technical setup:

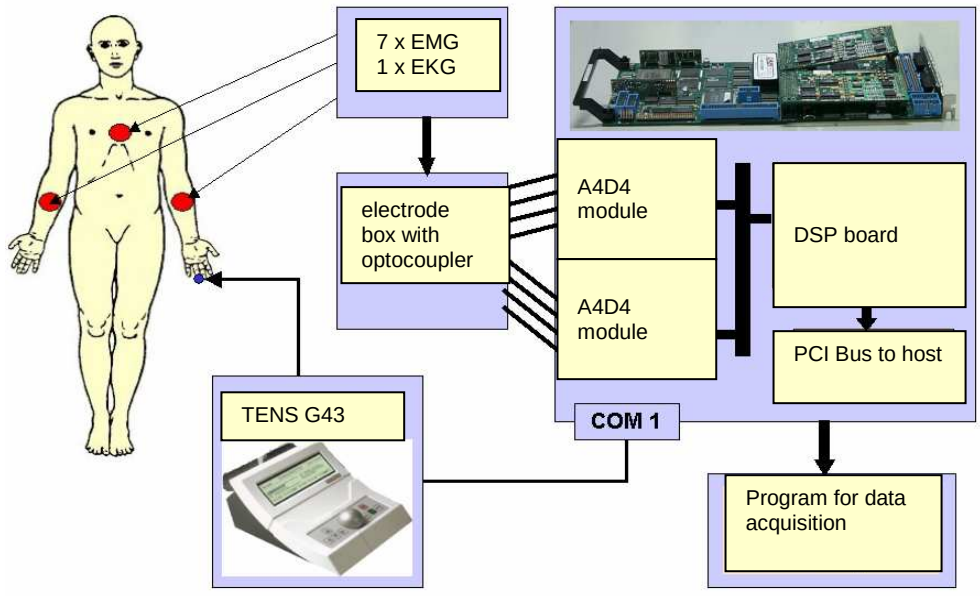

Figure 9: Technical setup

[3] http://www.innovative-dsp.com/products/m6x.htm

3.4 Data Analysis

The long recording time together with a high sampling rate resulted in a dataset of 150 MB for each participant. It was necessary to adjust and reduce each dataset in order to provide an adequate input to the subsequent statistical analysis of the data. The program MATLAB was used for this purpose which allowed the programming of tailored scripts that met the demands of the experiment.

3.4.1 Data Processing

The relevant data was imported into MATLAB in partial sections in order to optimize the performance. Hence, the data processing was achieved in multiple steps. During the data acquisition, the start and the end of each tone given within the experiment was recorded. This interval surrounded by a pre-phase and a post-phase of 15 seconds, respectively, was the relevant event for data analysis. MATLAB was programmed to successively locate the starting and end points of the tone and to import the data for the seven EMG and the one electrocardiographic (ECG) – channels at fixed time windows of 30 seconds around the tones for each event (cf. Figure 10 below).

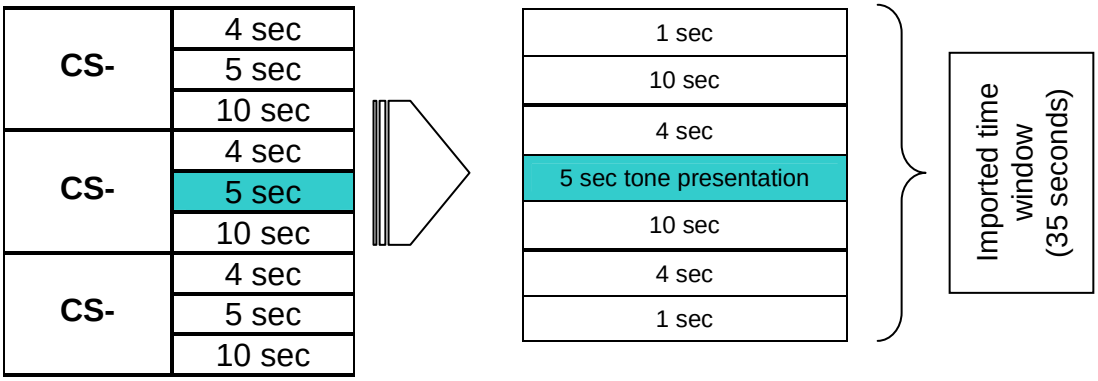

Figure 10: Sample of an into MATLAB imported time window of 35 seconds

Removing Electrocardiographic artefacts:

The heart produces a strong electrical signal that may disturb surface-recorded EMG. The waveforms introduced into an EMG record by cardiac activity are known as electrocardiographic (ECG) artefact. This source of noise is a concern whenever EMG is recorded from muscles in the torso of the body (Spalding, Schleifer, Hatfield, Kerick, & Cram, 2003). This artefact may result in, for example, an over-estimation of absolute EMG levels particularly when muscle activity is low. To avoid this measurement problem, it was necessary to remove the ECG artefact from the EMG

data. The two conventional methods are high-pass filtering of the data or excluding all ECG-contaminated epochs from further analysis. Both methods lead to a loss of information. According to a method first used in respiratory research to remove ECG artefact from diaphragm EMG (Bloch, 1983), Spalding, Kerick, Hatfield, Schleifer & Cram (2001) have adapted this technique to surface–recorded EMG. This "Ensemble-Average-Based Subtraction Method" uses the R-wave peak of the ECG signal of a contaminated segment to gain a waveform that reveals the average shape of the ECG artefact in the EMG record. Values of the ensemble average will be approximately 0 when ECG contamination is absent and non-zero when ECG contamination is present. In the final step a subtraction template which represents the artefact is subtracted from the EMG signal yielding an artefact-corrected data series. This procedure is illustrated in Figure 11 below.

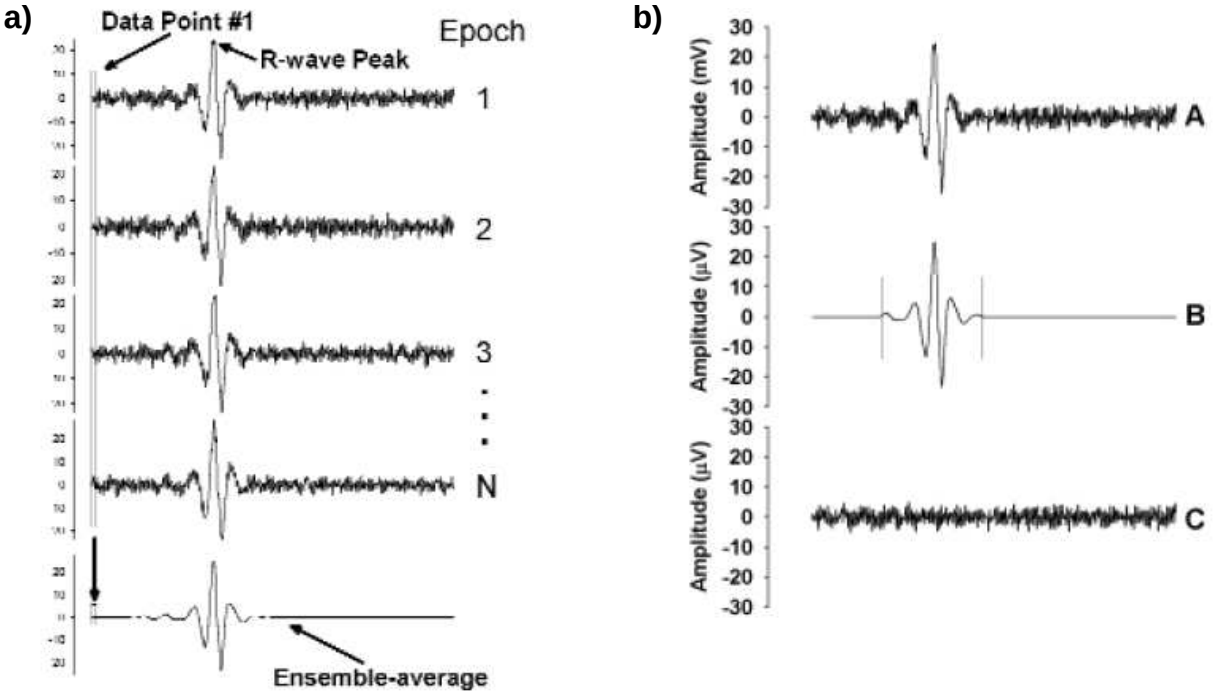

Figure 11: Ensemble-Average-Based Subtraction Method (illustrations and description taken from Spalding et al., 2003, pp.7/8)

a) Segments of upper left trapezius EMG and the associated ensemble-averaged waveform. Each segment consists of 751 data points containing an ECG artefact: 250 points preceding the ECG R-wave peak and 500 points after the R-wave peak. Each segment is aligned on the R-wave peak. Ensemble-averaging proceeds by averaging data points at time 1 across all of the available segments (i.e., segments = 1 to N; N = number of ECG artefacts in the measurement interval) and then repeating the averaging process for each of the remaining data points in the segment (i.e., time = 2 to 751). In this example, the result is an ensemble-averaged waveform with a length of 751 points that represents the average influence of the ECG activity on EMG activity.

b) A segment of upper left-trapezius EMG with a prominent ECG artefact (A), associated ensemble-averaged waveform (B), and corrected EMG series (C). The corrected EMG was obtained by subtracting values of the ensemble average within the subtraction template (indicated by the vertical lines) from the ECG-contaminated EMG. The corrected EMG series (C) shows that the ECG artefact has been completed removed without a loss of data or information.

A MATLAB script was programmed according to this technique using an existing algorithm for MATLAB (Christie, 2003) to detect the R-wave peaks in the relevant segments. The ECG artefact was thus successfully removed from each 35 second time segment in all seven muscle sites (a document of this MATLAB script is attached in appendix J).

Filtering of the EMG signals:

A further source of disturbance of the bio-electric signals was the TENS device that delivered the pain stimulus. Its connection to the power supply system led to an interference of the EMG signals by 50 Hz-noise (as to sources of noise see Basmajian & De Luca, 1985; Tassinary & Cacioppo, 2000). To remove this interference from the respective time segment, MATLAB was used to design a Chebyshev Type II notch filter (10^{th}-order, 120 dB stopband attenuation) that eliminated all frequencies between 48 to 52 Hz (see a document of this MATLAB script in appendix L).

Normalisation of the EMG signals:

To obtain a reference for the muscular responses in the imported time segments, the values of the amplitudes were normalized to the mean of the respective pre-baseline. This was performed separately for each muscle site. It was possible to obtain an intra- and interindividual comparison of muscular responses independent from the offset of the recorded signal by subtracting the pre-baseline mean from the relevant EMG signal section (for concepts of normalisation see Basmajian & De Luca, 1985).

3.4.2 Data Reduction

After a time segment of 30 seconds around each tone event was cleared from disturbing signals and normalised to the pre-baseline as described above, the muscular unconditioned (UR) and conditioned responses (CR) within this time window had to be detected.

As a first step, the procedure of Schneider et al. (2004) was followed. To gain comparability with this study, integrated electromyographic data (iEMG) was chosen as a common parameter for EMG activity (Basmajian & De Luca, 1985; Tassinary & Cacioppo, 2000).

Here the concept of integration is defined as the averaged rectified value (ARV). The metric unit of this parameter is microvolt (µV):

$$iEMG = \frac{1}{N}\sum_{i=1}^{N}|x_i|$$

Unconditioned response (UR):

In analogy to Schneider et al. (2004), the iEMG value of each elicited UR was calculated within a 500 ms window following 50 ms after the offset of the US to avoid shock related artefacts. As twelve pain stimuli were presented during acquisition phase I and II, twelve potential URs were included into the data analysis to get a total UR value for each muscle site.

Conditioned response (CR):

Initially a 500 ms interval, embedding the CS+, prior to US onset was chosen to evaluate potential conditioned muscular responses. In contrast to the UR, however, we supposed that the learning response did not necessarily need to occur at a fixed point in time (e.g., the end of the CS+) as supposed by Schneider et al. (2004). Thus, for the further analysis we used a moving 500 ms lasting time window starting at the beginning of the tone presentation and moving forward in 500 ms steps until the end of the post-baseline to locate the 500 ms interval that could best represent muscular learning. Thus, 30 successive, nonoverlapping intervals were taken into account. These considerations are illustrated in Figure 12 below.

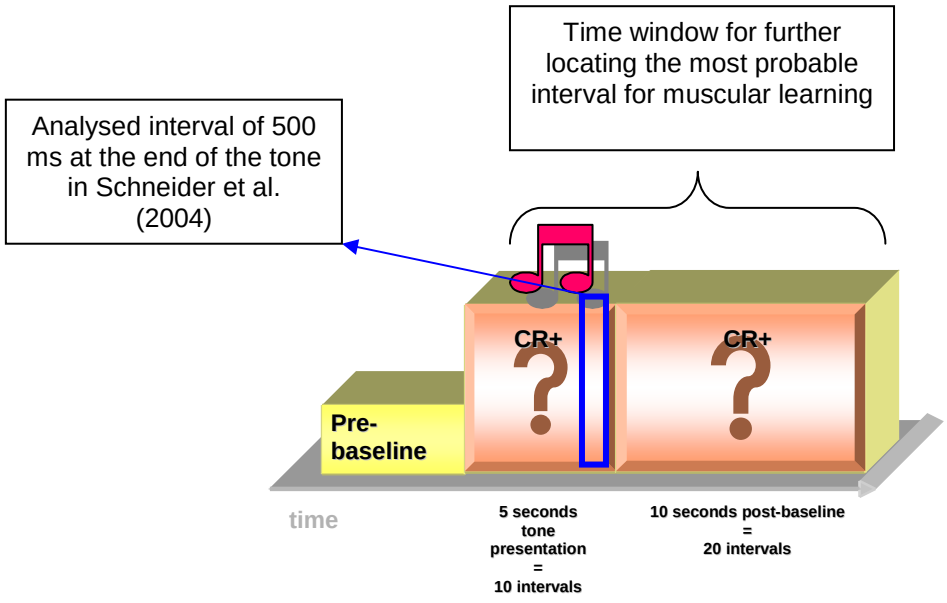

Figure 12: Search for the most relevant interval for muscular learning

Our initial analysis applying the Schneider et al. (2004) interval did not lead to a convincing outcome as shown in Figure 13 below.

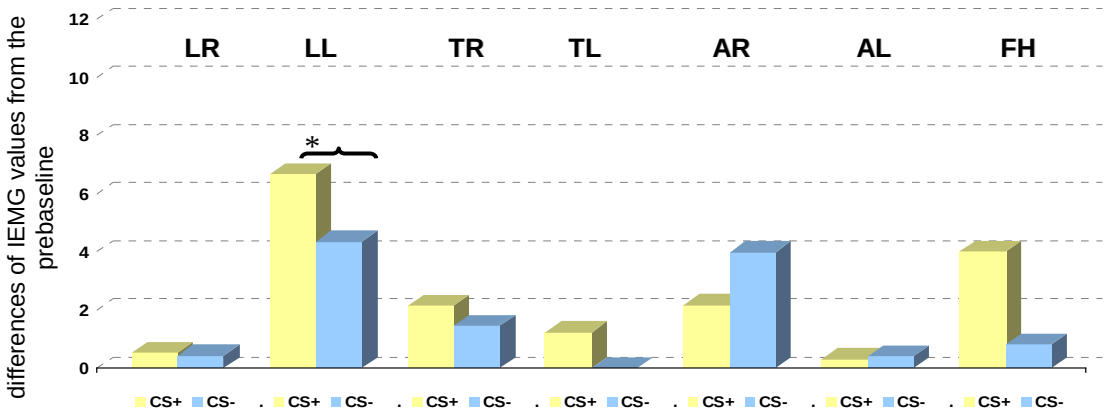

Figure 13: Comparison of conditioned muscular responses (CS+/ CS- -effect) (across groups, acquisition phase I and II combined) for the 500 ms interval prior to US onset according to Schneider et al (2004)
Displayed are the differences of iEMG values from the pre-baseline for each muscle region (LR = lumbar right, LL = lumbar left, TR = trapezius right, TL = trapezius left, AR = arm right, AL = arm left, FH = forehead)

Starting from the assumption that learning in the conducted experiment manifests itself by enhanced muscular responses to the to be conditioned high tone but not to the irrelevant low tone, significant differences between CS+ and CS- should occur. Such a significant “CS type”-effect arose only in the left lumbar region and, therefore, gave reason to broaden the Schneider et al. interval to search for the most relevant interval for muscular learning as mentioned above.

The aim of this search was to locate that interval of 500 ms (within the five seconds of CS+ presentation or its ten seconds post-baseline) in which the two groups of patients showed the most probable conditioned muscular responses. Schneider et al. deployed such a criterion to decide about a conditioned response by defining that the iEMG response must exceed the respective pre-baseline by one standard deviation. In the data analysis, this criterion was *gradually* applied to all successive 500 ms intervals within the relevant time window and made it possible to locate that 500 ms interval that best met the described criterion. The interval of the most probable conditioned muscular responses across all patients was found in the middle of the high tone presentation, starting 2.5 seconds after the CS+ onset. To perform comparisons between CS+ and CS-, the same time window had to serve for the examination of the low tone.

Recapitulating, the following time sections underly all further analysis:

UR : 500 ms window following 50 ms after US offset

CR+: 500 ms window 2.5 seconds after CS+ onset

CR-: analogous to CR+ the 500 ms window following 2.5 seconds after CS- onset

3.5 Statistical Analysis

The statistical analysis was performed with the statistical program SPSS (Statistical Program and Service Solutions, release 12 for Windows).

3.5.1 Operationalisation of the Dependent Variables

The muscular responses in each of the seven muscle sites were considered as dependent variables. Two methods were employed to operationalise a muscular response:

(1) **Criterion: Exceeding one standard deviation of the respective pre- baseline**

The first way was to quantify the global muscular response as **number of substantial iEMG responses** by deploying the criterion of exceeding one standard deviation (SD) of the respective pre-baseline as stated earlier. For this purpose, the respective interval of 500 ms was seperated into 5 x 100 ms sections according to Schneider et al. (2004). If one or more iEMG values of the respective interval oversteped this criterion, the muscular response was considered and counted as a significant learning reaction (either for UR, CS+ or CS-).

e.g.

significant response lumbar left (LL)	=	*iEMG of CS+ interval (LL)* **>** *1 SD of pre-baseline (LL)*

This yielded the frequency of significant muscular responses which were used for the subsequent statistical analysis.

(2) **Criterion: Magnitude of the iEMG response**

The second way was to quantify the muscular response as a **change from pre-baseline** by subtracting the pre-baseline iEMG value from the iEMG value of the respective 500 ms interval (either for UR, CS+ or CS-).

e.g.

change from pre-baseline lumbar left (LL)	=	*iEMG of CS+ interval (LL)* **–** *iEMG of pre-baseline (LL)*

This yielded difference scores which were used for the subsequent statistical analysis.

3.5.2 Statistical Procedure

The dominating parametric test used was the analysis of variance (ANOVA). Depending upon the examined question, one way up to three way ANOVAs with one or two repeated measurement factors were performed separately for each muscle site. The between subject factor “group” is to be distinguished from two within subject factors:

- Factor “Block” (with two stages: acquisition phase I, acquisition phase II)
- Factor “CS type” (with two stages CS+ vs. CS- (variables are averaged over a block/ sections of a block))

As mentioned above, Schneider et al. (2004) subdivided all relevant 500 ms intervals into 5 x 100 ms sections. In their analysis a third within subject factor “period” was introduced as the authors found a constant increase in the muscular reaction within these 5 sections. This effect could not be replicated in this present study. It was therefore decided not to include this factor in the subsequent analysis.

For reasons of clarity the statistical analysis mostly started by taking the **number of substantial iEMG responses (criterion: exceeding one standard deviation of the respective pre-baseline)** into consideration. In a second step the **iEMG change from pre-baseline (criterion: magnitude of the iEMG response)** was analysed. Although these criteria were both deployed in the Schneider et al. study, the authors did not mention any results concerning the number of substantial iEMG responses. They probably favoured the magnitude of iEMG responses as this criterion includes every muscular response into the statistical analysis and is closer to the original physiological data. However, the present study included both criteria in the data analysis as it often seemed appropriate to differentiate between the frequency of substantial responses and the intensity.

The effect size (Cohen´s d) and statistical power (1 – β) were given for significant effects. Post hoc tests were conducted by using the Bonferroni correction method. Greenhouse Geisser epsilons (ε) were used for nonsphericity correction of the degrees of freedom where appropriate (Greenhouse & Geisser, 1959).

To test the hypotheses, the following ANOVAs were calculated:

- a three way repeated measure ANOVA with the between subject factor “group” and the within subject factors “CS type” and “Block”
  - across all muscle sites
  - for each of the seven muscle sites
  - for combined muscle regions

- a two way repeated measure ANOVA for each muscle site (between subject factor “group” and within subject factor “CS type”) for the extinction phase
- Bonferroni corrected simple main effects analyses (two way repeated measure ANOVA separately for each group on the factors “CS type” and “Block” to explore significant interaction effects).

Table 4 shows a summarized depiction of the hypotheses testing.

Additionally, exploratory analyses followed which focused on differences in learning that can be characterised as differences concerning

a) discrimination learning (does each group manage to discriminate between the tones and do the three groups differ in this process (interactiion effect “group x CS type”)),
b) location of learning (in which stage within the experiment does learning occur and do the groups differ in this aspect?) and
c) preconditioning (do the groups reveal differences in their unconditioned muscular responses?).

Hence, the following exploratory analyses were performed:

- a three way repeated measure ANOVA for each muscle site including just the comparison of healthy controls and one group of patients.
- a two way repeated measure ANOVA separately for each group
- a one way ANOVA regarding
  - each tone
  - the second half of acquisition phase I
  - the overall URs across all muscle sites
  - the overall URs for each muscle site
- Pearson´s correlations between overall URs of all muscle sites and between pain intensities

Table 5 gives a summarized depiction of the exploratory analyses.

Table 4: Summarized depiction of the hypotheses testing

	between subject factor	within subject factors	dependent variable			step
ANOVA	group (HC, BP, TTH)	"CS type" (CS+ and CS-) "Block" (acquisition phase I and II)	number of substantial iEMG responses	•	across all muscle sites	(1)
			iEMG change from pre-baseline	•	for each muscle site	(2)
				•	for muscle regions	(3)
		"CS type" (CS+ and CS-) during extinction phase		•	for each muscle site	(4)
simple main effects analysis	separately for each group	"CS type" (CS+ and CS-)		•	for each muscle site	(5)

Table 5: Summarized depiction of the exploratory analyses

	between subject factor	within subject factors	dependent variable		step
ANOVA	group (HC vs. BP) (HC vs. TTH)	"CS type" (CS+ and CS-) "Block" (acquisition phase I and II)	iEMG change from pre-baseline	• for each muscle site	(6)
	separately for each group		number of substantial iEMG responses	• across all muscle sites	(7)
	group (HC, BP, TTH)	----------		• for each tone	(8)
		----------	iEMG change from pre-baseline	• for the mean of the last 4 CS+ of acquisition phase I for each muscle site	(9)
		----------	number of substantial iEMG responses	• for overall URs across all muscle sites	(10)
		----------		• for overall URs for each muscle site	(11)
Pearson´s correlation coefficient r	separately for each group	----------	iEMG change from pre-baseline	• for overall URs between all muscle sites	(12)
		----------		• between pain intensities	(13)

4 Results

4.1 First Question: Are muscular responses learnable? (in terms of classical conditioning)

4.1.1 Criterion: Exceeding one standard deviation of the respective pre-baseline

(Refer to data from step (1) of Table 4)

The existence of an unconditioned muscular response to the intra-cutaneous stimulus was required for the inclusion of a participant into the sample. To detect this unconditioned response (UR), a criterion was deployed. As stated above, this criterion was specified by the exceeding of one standard deviation of the respective pre-baseline for both, unconditioned and conditioned responses. This allowed the counting of all substantial unconditioned as well as all conditioned muscular responses defined by this criterion.

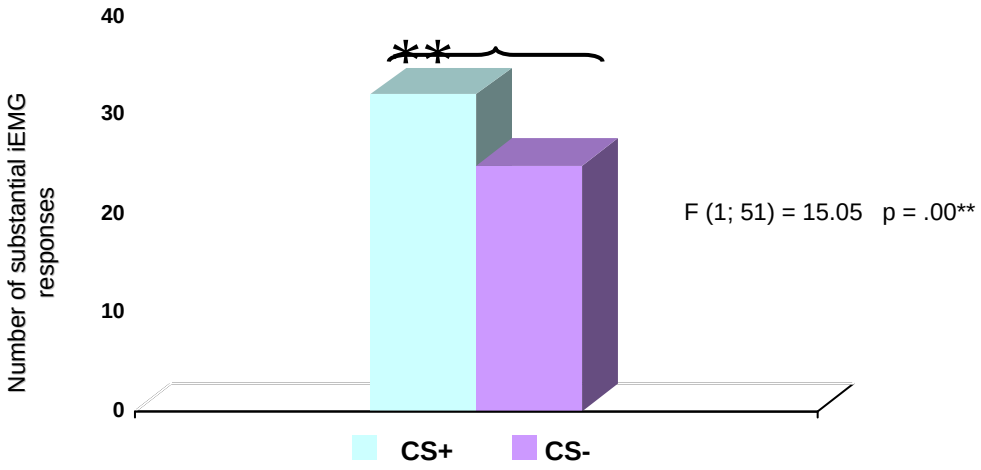

Figure 14: All conditioned responses within the two acquisition phases for „high tone“ (CS+) vs. „low tone“ (CS-) across all groups
Displayed is the mean number of substantial iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values.

Figure 14 shows that for both tones across all seven muscle regions several reactions were strong enough to overstep the criterion and, thus, learning occurred. A comparison of all substantial reactions to the high tone (CS+) and low tone (CS-), respectively, showed a significant main effect “CS type” (F (1; 51) = 15.05, p = .00**). The means and standard deviations are depicted in Table 6:

Table 6: All conditioned responses within the two acquisition phases for „low tone“ (CS-) vs. „high tone“ (CS+)

	all participants (N = 54)	
Type	**M**	**SD**
CS+	31.96	(27.60)
CS-	24.81	(25.29)

Displayed is the mean number of substantial iEMG responses (M) (defined by exceeding one standard deviation of the pre-baseline by the iEMG values) and its standard deviation (SD).

4.1.2 Criterion: Magnitude of the iEMG response

(Refer to data from step (2) to (4) of Table 4)

A different perspective is to look at the iEMG differences (resulting from the subtraction of the iEMG value of the respective interval and the iEMG value of the pre-baseline). This gives a more sophisticated view on each of the seven EMG sites:

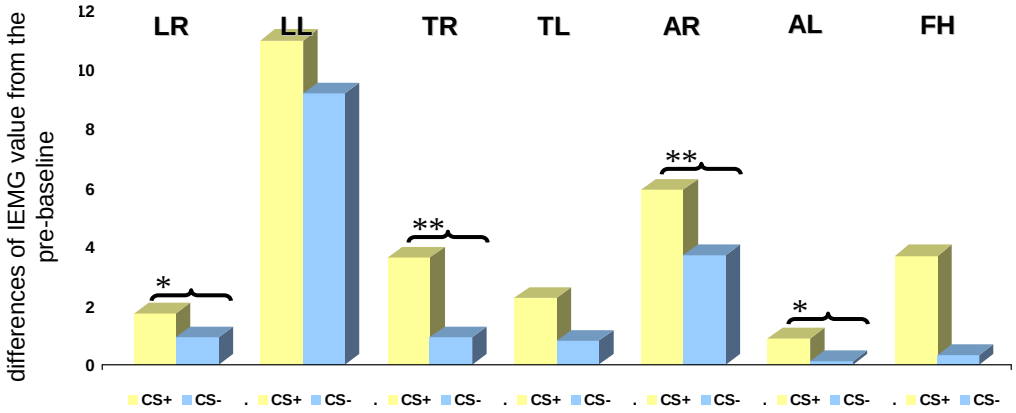

Figure 15: Conditioned muscular responses (CS+/ CS- -effect) (across groups, acquisition phase I and II combined)
Displayed are the differences of iEMG values from the pre-baseline for each muscle region (LR = lumbar right, LL = lumbar left, TR = trapezius right, TL = trapezius left, AR = arm right, AL = arm left, FH = forehead).

For each muscle region all three groups tended to react more enhanced to the high tone (CS+) than to the low tone (CS-). This difference was significant for four muscle sites (cf. Figure 15 and Table 7): lumbar right ($F(1;51) = 4{,}80$, $p = .03$*), trapezius right ($F(1;51) = 9{,}86$, $p = .00$**), right arm ($F(1;51) = 7{,}21$, $p = .01$**) and left arm ($F(1;51) = 5{,}06$, $p = .03$*). This finding confirms the differential conditioning design; differentiated learning between the two tones has taken place in four of the seven muscle sites.

Table 7: Conditioned muscular responses (CS+/ CS- -effect) (across groups, acquisition phase I and II combined)

	(CS+)		(CS-)					
muscle	**M**	**SD**	**M**	**SD**	**F**	**significance**		**1 - β**
LR	1.74	(0.59)	0.93	(0.52)	F(1; 51) = 4.80	p = .03*	CS+ > CS-	.58
LL	10.97	(1.88)	9.21	(1.96)	F(1; 51) = 2.74	p = .10 n.s.	CS+ - CS-	.37
TR	3.62	(0.94)	0.95	(0.78)	F(1; 51) = 9.86	p = .00**	CS+ > CS-	.87
TL	2.28	(1.24)	1.35	(0.83)	F(1; 51) = 2.06	p = .16 n.s.	CS+ - CS-	.29
AR	5.93	(1.79)	3.71	(1.36)	F(1; 51) = 7.21	p = .01**	CS+ > CS-	.75
AL	0.89	(0.27)	0.14	(0.26)	F(1; 51) = 5.06	p = .03*	CS+ > CS-	.60
FH	3.70	(1.98)	0.35	(1.01)	F(1; 51) = 2.36	p = .13 n.s.	CS+ - CS-	.33

Displayed are the mean differences of iEMG values from the pre-baseline (M) for each muscle region, its standard deviation (SD), F and p-values as well as the test-power (1 – β).

The means for each pair of muscle sites (left and right) have been combined as illustrated in Figure 16 (corresponding means and standard deviations are displayed in Table 8). Across the groups this resulted in three significant differences between CS+ and CS- applying for the entire lumbar region (F(1;51) = 4.38, p = .04*), the trapezius region (F(1;51) = 7.93, p = .01**) and in the upper arm region (F(1;51) = 10.19, p = .00**). Thus, for each muscle region enhanced muscular conditioning on the CS+ can be stated.

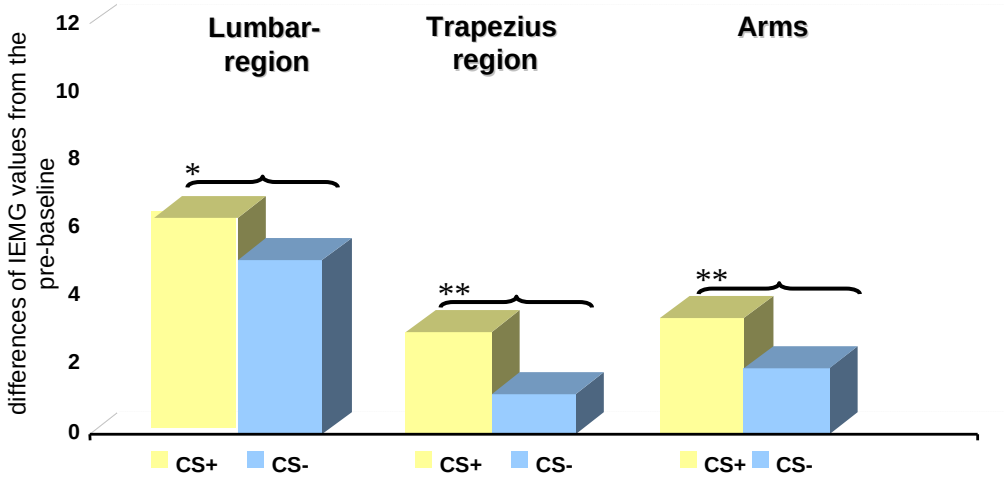

Figure 16: Conditioned muscular responses (CS+/ CS- -effect) (matching muscle sites combined across all groups, acquisition phase I and II combined)
Displayed are the differences of iEMG values from the pre-baseline for each muscle region.

Table 8: Conditioned muscular responses (CS+/ CS- -effect) (matching muscle sites combined across all groups, acquisition phase I and II combined)

	(CS+)		(CS-)					
muscle	**M**	**SD**	**M**	**SD**	**F**	**significance**		**1 - β**
Lumbar region	6.35	(1.11)	5.07	(1.15)	F(1; 51) = 4.38	p = .04*	CS+ > CS-	.54
Trapezius region	2.95	(0.93)	1.15	(0.56)	F(1; 51) = 7.93	p = .01**	CS+ > CS-	.79
Arms	3.41	(0.95)	1.92	(0.76)	F(1; 51) = 10.19	p = .00**	CS+ > CS-	.88

Displayed are the mean differences of iEMG values from the pre-baseline (M) for each muscle region, its standard deviation (SD), F and p-values as well as the test-power (1 – β).

Due to the experimental procedure, a deletion of all conditioned responses should occur in the third phase of the experiment (extinction phase). Thus, there should be no substantial differences between the high and low tones in this phase. Table 9 shows that there were indeed no significant differences between the two tones during this third phase.

Table 9: Conditioned muscular responses (CS+/ CS- -effect) for the extinction phase (across all groups)

	(CS+)		(CS-)			
muscle	**M**	**SD**	**M**	**SD**	**F**	**significance**
LR	0.39	(0.39)	0.72	(0.42)	F(1; 51) = 0.40	p = .53 n.s.
LL	4.13	(1.63)	3.40	(1.12)	F(1; 51) = 0.26	p = .61 n.s.
TR	2.83	(2.06)	1.94	(1.47)	F(1; 51) = 0.12	p = .73 n.s.
TL	0.61	(1.66)	0.45	(1.02)	F(1; 51) = 0.01	p = .93 n.s.
AR	2.42	(1.47)	2.46	(0.85)	F(1; 51) = 0.00	p = .97 n.s.
AL	0.18	(0.35)	0.40	(0.45)	F(1; 51) = 0.24	p = .62 n.s.
FH	4.03	(2.07)	-0.24	(2.26)	F(1; 51) = 1.60	p = .21 n.s.

Displayed are the mean differences of iEMG values from the pre-baseline (M) for each muscle site, its standard deviation (SD), F and p-values.

4.2 Second Question: Do chronic pain patients differ from healthy controls in their conditioned response?

4.2.1 Differential effects between CS+ and CS- in group comparisons

Criterion: Magnitude of the IEMG response

(Refer to data from step (2) and (5) of Table 4)

To answer this question primarily in analogy to the Schneider et al. (2004) study, the first criterion was neglected at this point. The hypothesis testing focused on a significant main effect “group” or an interaction effect “group x CS type”.

The three way ANOVA with repeated measure in two factors only revealed evidence for differences in learning between the three groups in the trapezius region (cf. Figure 17): Here, a significant interaction effect “group x CS type” occurred in the left trapezius (F(2;51) = 4.03, p = .02*). The healthy controls as well as the group of patients with headache reacted similar to both tones during the two acquisition phases while the patients with back pain responded significantly stronger to the high tone, i.e. the CS+ (main effect “CS type”: F(1;17) = 7.12, p = .02*).

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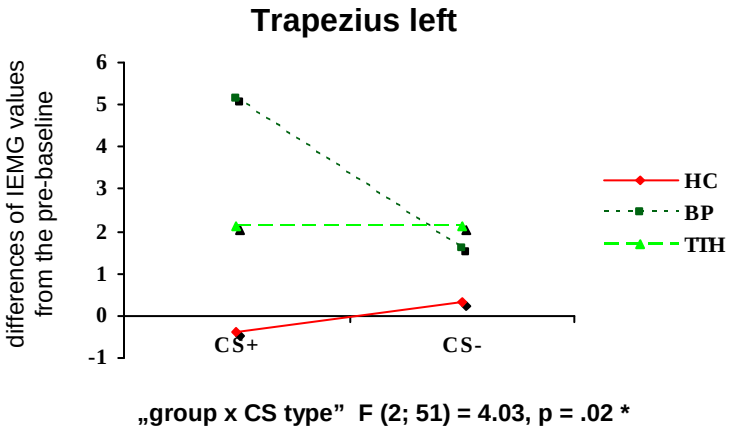

Figure 17: Significant interaction effect „group x CS type“ in the acquisition phases (trapezius left); *Displayed are the differences of iEMG values from the pre-baseline.*

In the other six muscle sites no further significant interaction effects could be found. The relevant statistical values are displayed in Table 10. For p - values below .10 a trend was indicated.

Table 10: Results from the three way repeated measure ANOVA for each muscle site (across acquisition phase I and II)

muscle	effect	F	significance		1 - β
LR	Group	F(2; 51) = 1.03	p = .36 n.s.		.22
	Group x CS type	F(2; 51) = 0.25	p = .78 n.s.		.09
	Group x CS type x Block	F(2; 51) = 1.37	p = .26 n.s.		.28
LL	Group	F(2; 51) = 2.63	p = .08 n.s.	(HC < BP < TTH)	.50
	Group x CS type	F(2; 51) = 0.30	p = .98 n.s.		.05
	Group x CS type x Block	F(2; 51) = 1.03	p = .36 n.s.		.22
TR	Group	F(2; 51) = 1.14	p = .33 n.s.		.24
	Group x CS type	F(2; 51) = 1.06	p = .36 n.s.		.23
	Group x CS type x Block	F(2; 51) = 0.17	p = .84 n.s.		.08
TL	Group	F(2; 51) = 0.98	p = .38 n.s.		.21
	Group x CS type	F(2 51) = 4.03	p = .02*	cf. Figure 17	.69
	Group x CS type x Block	F(2; 51) = 2.73	p = .08 n.s.		.52
AR	Group	F(2; 51) = 0.77	p = .47 n.s.		.17
	Group x CS type	F(2; 51) = 1.78	p = .18 n.s.		.36
	Group x CS type x Block	F(2; 51) = 0.44	p = .65 n.s.		.12
AL	Group	F(2; 51) = 1.52	p = .23 n.s.		.31
	Group x CS type	F(2; 51) = 0.42	p = .66 n.s.		.11
	Group x CS type x Block	F(2; 51) = 1.06	p = .35 n.s.		.23
FH	Group	F(2; 51) = 1.23	p = .30 n.s.		.26
	Group x CS type	F(2; 51) = 0.28	p = .76 n.s.		.09
	Group x CS type x Block	F(2; 51) = 0.26	p = .77 n.s.		.09

Displayed are F and p-values as well as the test-power (1 – β) for each muscle site.

As these findings could not satisfactorily answer the hypothesis of group differences in learning in the first place, additional exploratory analysis followed to reveal references of clinical importance and to give hints for further studies.

4.2.2 Differences between CS+ and CS- within each group

Criterion: Exceeding one standard deviation of the respective pre-baseline

(Refer to data from step (7) of Table 5)

As stated in section 4.1, the participants across the groups discriminated successfully between the CS+ and CS- across all muscles as well as in all specific muscle regions except the forehead (cf. Figure 14 to 16). A separate calculation for each of the three groups revealed differences in the discrimination process within the patients and within the healthy controls (cf. Table 11). Both groups of patients discriminated significantly between high (CS+) and low (CS-) tone across all muscles. The healthy controls narrowly failed to discriminate significantly between these two stimuli ($F(1; 17) = 3.46$, $p = .08$).

Table 11: Conditioned muscular responses within the two acquisition phases for „high tone“ (CS+) vs. „low tone“ (CS-)

	(CS+)		(CS-)					
group	**M**	**SD**	**M**	**SD**	**F**	**significance**		**1 - β**
healthy controls (HC) (N = 18)	19.78	(15.10)	15.33	(12.98)	F(1; 17) = 3.46	p = .08 n.s.	CS+ - CS-	.42
back pain patients (BP) (N = 18)	32.78	(28.92)	25.39	(22.73)	F(1; 17) = 7.54	p = .01**	CS+ > CS-	.74
headache patients (TTH) (N = 18)	43.33	(31.86)	33.72	(33.60)	F(1; 17) = 5.25	p = .04*	CS+ > CS-	.58

Displayed are the mean numbers of substantial iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values (M), their standard deviations (SD), F and p-values as well as the test-power (1 – β).

4.2.3 Group differences for CS+ and CS-

Criterion: Exceeding one standard deviation of the respective pre-baseline

(Refer to data from step (8) of Table 5)

A separate calculation for each tone was made to clarify if the groups differ in their overall muscular responses during each tone (cf. Figure 18). For the low tone (CS-) there were no significant differences between the groups. Regarding the high tone (CS+) a significant group effect could be described (F (2; 51) = 3.62, p = .03*). The post hoc test showed a significant difference between the patients with chronic tension-type headache (TTH) and the healthy controls (HC) (TTH > HC: Mean difference = -23.56, 95% confidence interval (CI) = -45.28 to -1.83, p = .03*, d = .94). The patients with headache responded more often to the high tone (CS+) than the healthy controls. The post hoc test did not reveal a significant difference between the patients with back pain (BP) and the healthy controls (BP – HC: Mean difference = -13.00, 95% CI = -34.76 to 8.73, p = .43 n.s., d = .56).

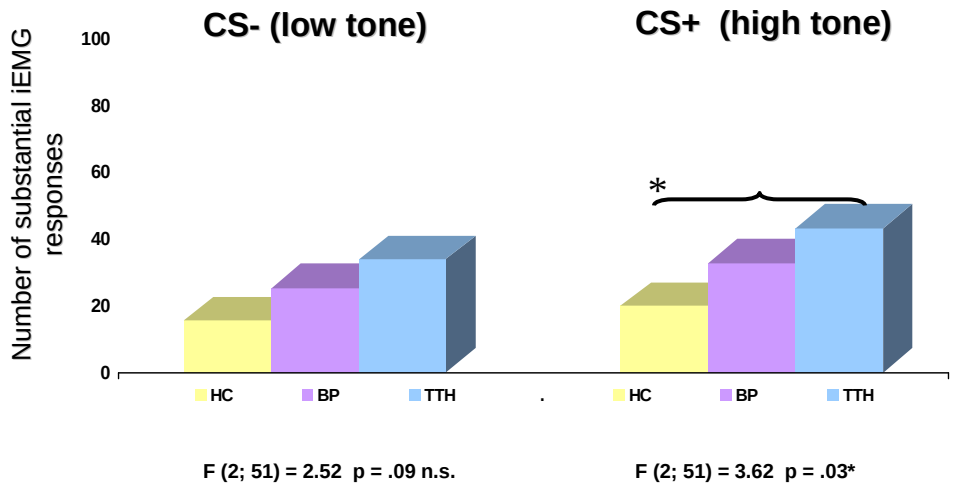

Figure 18: All conditioned responses within the two acquisition phases for „low tone“ (CS-) vs. „high tone“ (CS+)
Displayed is the mean number of substantial iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values.
Post hoc tests (Bonferroni corrected) for condition “high tone”: TTH > HC: Mean difference = -23.56, 95% confidence interval (CI) = -45.28 to -1.83, p = .03, d = .94; BP – HC: Mean difference = -13.00, 95% CI = -34.76 to 8.73, p = .43 n.s..*

Table 12: All conditioned responses within the two acquisition phases for „low tone“ (CS-) vs. „high tone“ (CS+)

	healthy controls (HC) (N = 18)		back pain patients (BP) (N = 18)		headache patients (TTH) (N = 18)	
Type	**M**	**SD**	**M**	**SD**	**M**	**SD**
CS-	15.33	(12.98)	25.39	(22.73)	33,72	(33.60)
CS+	19.78	(15.10)	32.78	(28.92)	43.33	(31.86)

Displayed is the mean number of substantial iEMG responses (M) (defined by exceeding one standard deviation of the pre-baseline by the iEMG values) and its standard deviation (SD).

4.2.4 Differential effects between CS+ and CS- in (pairwise) group comparisons

Criterion: Magnitude of the iEMG response

(Refer to data from step (5) of Table 4 and step (6) and (9) of Table 5)

Trapezius region:

By exploratory analysis another interaction effect „group x CS type“ was observed in the right trapezius (cf. Figure 19) by pairwise testing of the groups (HC vs. TTH: $F(1; 34) = 4.95$, $p = .03$*; HC vs. BP: $F(1; 34) = 1.04$, $p = .32$ n.s., $1 - \beta = .17$) The TTH patients showed a considerably stronger conditioned response to the CS+ than the controls. Within the TTH patients the difference between CS+ and CS- was significant with $F(1;17) = 6.58$, $p = .02$*.

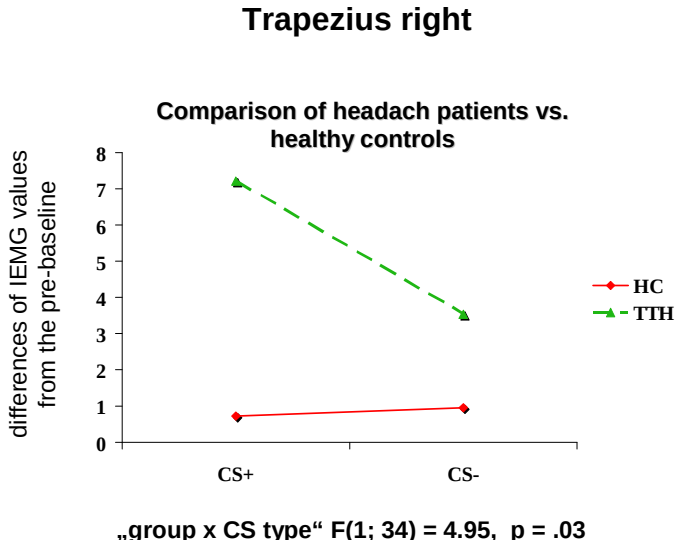

Figure 19: Significant interaction effect „group x CS type“ in the acquisition phases (trapezius right); *Displayed are the differences of iEMG values from the pre-baseline.*

Lumbar region:

According to learning theory, the highest effect in learning should be expected at the end of acquisition phase I and at the beginning of acquisition phase II, respectively. Therefore, differences in the muscular conditioned responses between the groups of patients (BP, TTH) and the control group should occur particularly in these intervals. Such a group difference (F(2;51) = 3.49, p = .04*) arose for the second half of the first acquisition phase in the lumbar area (right and left combined) (cf. Figure 20 and Table 13):

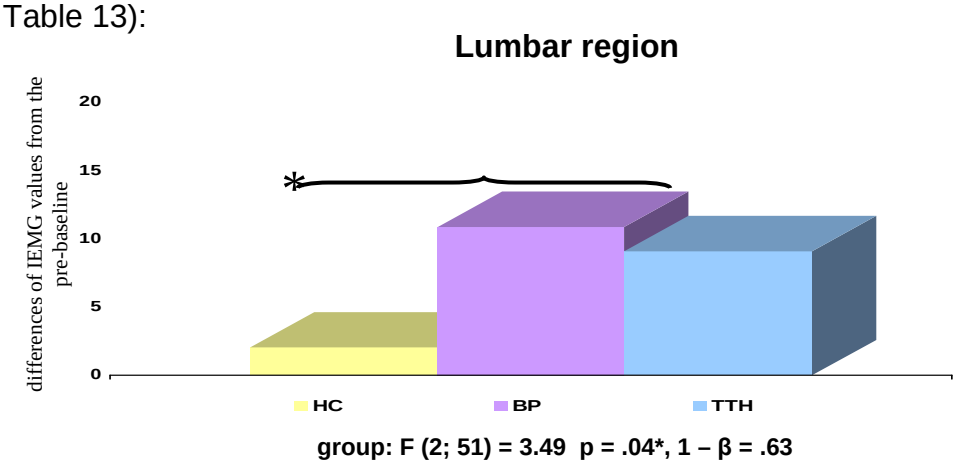

Figure 20: Conditioned muscular responses in the lumbar region on CS+ in the three groups for the second half of acquisition phase I
Displayed are the differences of iEMG values from the pre-baseline.
Post hoc tests (Bonferroni corrected) for condition "high tone": BP > HC: Mean difference = -8.80, 95% CI = -17.49 to -0.09, p = .05, d = .99; TTH - HC: Mean difference = -7.00, 95% CI = -15.70 to 1.70, p = .16 n.s..*

Table 13: Conditioned muscular responses in the lumbar region on CS+ in the three groups for the second half of acquisition phase I.

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	healthy controls (HC) (N = 18)		back pain patients (BP) (N = 18)		headache patients (TTH) (N = 18)	
Muscle	**M**	**SD**	**M**	**SD**	**M**	**SD**
Lumbar region	2.05	(6.00)	10.84	(11.02)	9.05	(13.27)

Displayed are the mean differences of iEMG values from the pre-baseline (M) and their standard deviations (SD).

The post hoc test showed that this main effect "group" is for the most part based on a significant difference between the patients with back pain and the healthy controls. The comparison between the group of headache patients and the healthy controls narrowly failed to become significant in the Bonferroni post hoc test, a less conservative t-test however stated significance (BP > HC: t(34)=-2.97. p=.01**; TTH > HC: t(34)=-2.04. p=.05*).

4.2.5 Group differences in the unconditioned response

Criterion: Exceeding one standard deviation of the respective pre-baseline

(Refer to data from step (10) to (12) of Table 5)

Furthermore, the results of another exploratory analysis showed group differences in the unconditioned response to the painful stimulus, although the three groups did not differ significantly neither in their perception threshold (BP: 0.25 mA, TTH: 0.22 mA, HC: 0.25 mA) nor in their pain threshold (BP: 0.51 mA, TTH: 0.50 mA, HC: 0.64 mA) (thus all groups received an objectively comparable electric stimulus which they all percepted similarly): The number of unconditioned responses across all muscle sites showed a significant main effect “group” with F(2;51) = 4.62, p = .01** (cf. Figure 21/ Table 14). The groups of patients with back pain as well as the group of patients with tension-type headache responded significantly more often to the unconditioned stimulus than the healthy controls (BP > HC: Mean difference = -64.28, 95% CI = -127.70 to -0.86, p = .05*, d = 1.05; TTH > HC: Mean difference = -70.17, 95% CI = -133.58 to -6.75, p = .03*, d = 0.95).

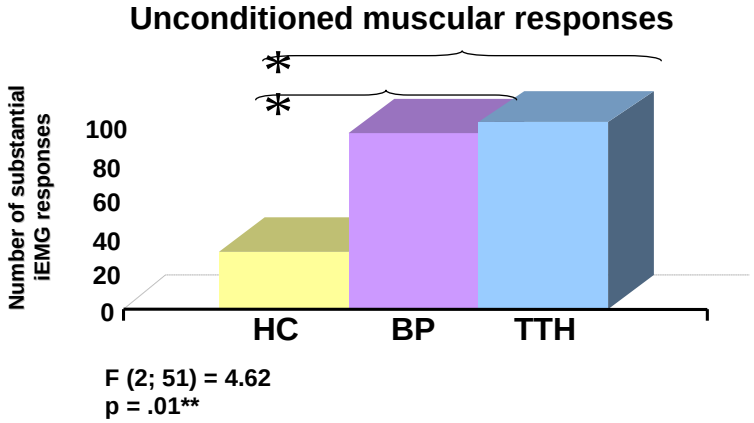

Figure 21: Unconditioned muscular responses across all muscle sites for the three groups (considering acquisition phase I and II)
Displayed is the mean number of substantial iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values.

Table 14: Substantial unconditioned muscular responses across all muscle sites for the three groups (considering acquisition phase I and II)

	healthy controls (HC) (N = 18)		back pain patients (BP) (N = 18)		headache patients (TTH) (N = 18)				
	M	**SD**	**M**	**SD**	**M**	**SD**	**F (2; 51)**	**p-value**	**1 - β**
UR	31.22	(23.88)	95.50	(82.87)	101.39	(101.40)	4.62	.01**	0.76

Displayed is the mean number of substantial unconditioned iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values (M), its standard deviation (SD), F- and p – values as well as the test power (1 – β).

Closer examination of the effects in the single muscle sites showed that these different reflex actions were manifest in the left lumbar region as well as in both trapezius sites (cf. Figure 22/ Table 15). In these three areas the patients responded significantly stronger to the intra-cutaneous pain stimuli than the healthy controls.

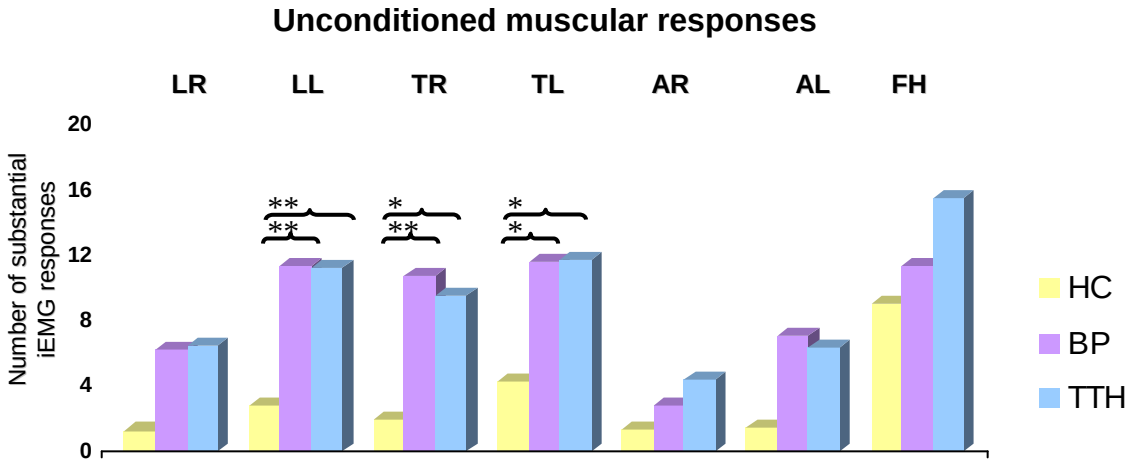

Figure 22: Substantial unconditioned responses within the two acquisition phases for all muscle sites

Displayed is the mean number of substantial iEMG responses defined by exceeding one standard deviation of the pre-baseline by the iEMG values.
*Post hoc tests (Bonferroni corrected) for condition "lumbar left": BP > HC : Mean difference = -8.50, 95% CI = -15.33 to -1.67, p = .01**; TTH > HC : Mean difference = -8.39, 95% CI = -15.22 to -1.56, p = .01**; for condition "trapezius right": BP > HC : Mean difference = -8.72, 95% CI = -15.30 to -2.14, p = .01**; TTH > HC : Mean difference = -7.50, 95% CI = -14.08 to -0.92, p = .02*; for condition "trapezius left": BP > HC : Mean difference = -7.33, 95% CI = -15.21 to 0.54, p = .08 n.s.; TTH > HC : Mean difference = -7.50, 95% CI = -15.37 to 0.37, p = .07 n.s..*

Table 15: Substantial unconditioned responses within the two acquisition phases for all muscle sites for the three groups

	healthy controls (HC) (N = 18)		back pain patients (BP) (N = 18)		headache patients (TTH) (N = 18)				d	
muscle	**M**	**SD**	**M**	**SD**	**M**	**SD**	**F(2; 51)**	**p-value**	**(BP > C)**	**(H > C)**
LR	1.28	(1.93)	6.17	(7.88)	6.50	(9.81)	2.85	.07 n.s.		
LL	2.83	(1.82)	11.33	(9.28)	11.22	(10.78)	6.24	.00**	1.27	1.09
TR	2.00	(2.59)	10.72	(9.54)	9.50	(9.65)	6.31	.00**	1.25	1.06
TL	4.22	(3.41)	11.56	(10.30)	11.72	(12.47)	3.63	.03*	.96	.82
AR	1.33	(2.59)	2.83	(5.00)	4.39	(7.08)	1.54	.22 n.s.		
AL	1.50	(2.87)	7.06	(10.32)	6.39	(9.55)	2.41	.10 n.s.		
FH	9.06	(7.89)	11.33	(9.10)	15.50	(12.20)	1.96	.15 n.s.		

Displayed are the mean number of substantial iEMG responses (M) (defined by exceeding one standard deviation of the pre-baseline by the iEMG values), its standard deviation (SD), F- and p-values as well as the effect size (d).

The existence of an unconditioned response was, as stated above, considered as inclusion criterion. The intra-cutaneous electric stimulus was applied to the left index finger. Correlations of the number of unconditioned responses shown at the left upper arm with the other muscle sites revealed further differences between the three groups (cf. Table 16): In both groups of patients the number of unconditioned responses in the left upper arm correlated significantly with the number of unconditioned responses in the right and left lumbar region as well as in the right and left trapezius region. The more muscular reactions the patients showed in the left arm the more muscular reactions they showed in the lumbar and trapezius sites. This coherence was not significant for the healthy controls. The more unconditioned reactions the healthy controls exhibited in the left arm the more unconditioned reactions they showed in their right upper arm. This interrelation was also observable in the group of patients with headache. Thus the patients did not only differ from the healthy controls in the number of sites correlating with the reflex action of the left arm but also in the locations of intercorrelating unconditioned responses.

Table 16: Correlations of all unconditioned responses (defined by exceeding one standard deviation of the pre-baseline by the iEMG values) within the two acquisition phases for all muscle regions for the three groups

		UR_LR	UR_LL	UR_TR	UR_TL	UR_AR	UR_FH
healthy controls (HC) (N =18)	**UR_AL**	r = .31	r = .33	r = -.02	r = .34	r = .81**	r = .75
back pain patients (BP) (N = 18)	**UR_AL**	r = .81**	r = .50*	r = .82**	r = .88**	r = .37	r = .13
headache patients (TTH) (N = 18)	**UR_AL**	r = .75**	r = .70**	r = .87**	r = .97**	r = .93**	r = .41

** p < .01

* p < .05

4.3 Third Question: Do pain patients show a conditioned response in the symptom-specific muscles?

(Refer to data from step (13) of Table 5)

For patients with chronic back pain the lumbar as well as the trapezius region are regarded as „symptom-specific“ muscles, whereas for patients with chronic tension-type headache the trapezius region and the forehead are considered as „symptom-specific”. A main effect “group” or interaction effect “group x CS type” in these muscles was thus of major interest.

4.3.1 Patients with chronic back pain and symptom-specificity

At a glance, for the group of patients with back pain symptom-specific high CS+ reactions were observed in the left trapezius (cf. Figure 17). Here, a significant interaction effect “group x CS type” was discovered which was due to a significantly stronger muscular response of the patients to the CS+. According to the exploratory analyses, the patients differed significantly from the healthy controls in the lumbar region within the acquisition phase I (cf. Figure 20). In addition these patients showed significantly more unconditioned reactions than the control group in the left lumbar as well as in both trapezius sites (cf. Figure 22).

4.3.2 Patients with tension-type headache and symptom-specificity

In the context of the exploratory calculations, the significantly enhanced muscular response of the headache patients compared to the healthy controls in the right trapezius to the CS+ during acquisition phase I supported the assumption of symptom-specificity (cf. Figure 19). This group also showed significantly more unconditioned reactions in both trapezius sites than the control group (cf. Figure 22). While the TTH patients tended to exhibit stronger muscular reactions than the controls to the CS+ in the lumbar region and revealed significantly more unconditioned responses in the left lumbar, these reactions were so far not considered as symptom-specific (cf. Figure 20 and 22).

In the group of patients with back pain significant correlations between the average pain intensity of the last six months and the pain intensity shortly before, shortly after and 24 hours after the experiment were observed. The number of unconditioned responses they showed during the experiment was independent from these pain ratings (cf. Table 17). By contrast, in the headache group the pain intensity of the last six months was independent from the three pain ratings before and after the

experiment. However, in this headache group significant correlations between the number of substantial unconditioned iEMG responses observed in the experiment and these three pain intensities were demonstrated: The more unconditioned reflex actions the headache patients showed to the electric stimulus the stronger the pain intensity of their headaches which they reported before, immediately after and 24 hours after the experiment.

Table 17: Correlations of all unconditioned responses (defined by exceeding one standard deviation of the pre-baseline by the iEMG values) with the intensity of pain at different times (the average of the last 6 months, right before and right after as well as 24 hours after the experiment) for the two groups of patients

			Intensity of pain			
		average of last 6 months	**unconditioned responses**	**current (pre Experiment)**	**current (post Experiment)**	**24 h after experiment**
back pain patients (BP) (N = 18)	**average of last 6 months**	--	r = -.20	r = .81**	r = .59**	r = .85**
	unconditioned responses	r = -.20	--	r = -.03	r = -.29	r = -.21
headache patients (TTH) (N = 18)	**average of last 6 months**	--	r = .03	r = .17	r = -.22	r = -.15
	unconditioned responses	r = .03	--	r = .60**	r = .59**	r = .47*

** p < .01 * p < .05

5 Summary of results

The statistical analysis of the data provided explicit information in view of the three questions of interest.

The results confirmed the **first question** of muscular learning. During the acquisition phases it was possible to elicit muscular reactions that overstepped the criterion of exceeding one standard deviation of the respective pre-baseline which represents a benchmark for learning. This applied to all three groups as well as to both stimuli in terms of the number of muscular responses across all seven muscle regions. Moreover, this learning occurred enhanced to the CS+ which supports the differential conditioning design. While this difference between high tone (CS+) and low tone (CS-) tended to appear in each muscle region, it reached significance in four out of the seven muscle sites (lumbar right, trapezius right, right and left arm). Enhanced muscular conditioning to the CS+ was also observed for the combined lumbar- and trapezius-region as well as for the arms in both acquisition phases. As expected for the extinction phase, the different reactions to both tones disappeared.

Relating to the **second question**, the hypothesis testing revealed just one out of seven potential interaction effects regarding each muscle site: a significant “group x CS type” effect identified a significant stronger response of the patients with back pain in the left trapezius to the high tone (CS+) compared to the headache patients and healthy controls.

Further exploratory analyses were performed and showed several indications of differences in learning between the chronic pain patients and healthy controls:

1. The comparison of all conditioned muscular responses within the two acquisition phases for CS+ vs. CS- revealed that only the patient groups discriminated significantly between the two tones. So conditioning worked only in the patient groups.
2. It was shown that in line with this finding the mean number of significant muscular reactions of the pain patients to the CS+ exceeded the mean of the healthy controls. This was demonstrated significantly between the headache patients and the control group.
3. A significant interaction effect “group x CS type” occurred between the headache patients and healthy controls in the right trapezius with the patients showing an enhanced conditioned response to the CS+.

4. A closer look at the relevant stages of the experiment according to learning theory also gave evidence of group differences in learning. In the second half of the first acquisition phase a main effect “group’” in the lumbar region revealed significantly stronger conditioned responses of the back pain patients to the high tone (CS+) compared to the healthy controls.
5. The three groups also differed with regards to the unconditioned reaction (UR). Across all muscle regions as well as in the left lumbar region and in both trapezius sites the two groups of patients responded significantly more often to the pain stimulus than the controls. Further, a significant correlation between the number of unconditioned responses in the left arm and the number of unconditioned responses in the lumbar and trapezius sites was only observed in the patient groups. Such an interrelation in the healthy controls was only apparent for the left and right arm.

The **third question** focused on the symptom-specificity of muscular learning. For the back pain patients symptom-specific conditioned responses were measured in the left trapezius site across both acquisition phase I and II.

Over the course of the exploratory data analyses, the BP patients also showed more conditioned responses in the lumbar region during acquisition phase I and more unconditioned responses in the left lumbar and in both trapezius regions. The results for the headache patients revealed, besides an enhanced muscular response in the right trapezius and therefore relevant site, stronger unconditioned muscular reactions than the control group in both trapezius sites and left lumbar, a site that was not considered as symptom-specific. Another finding concerned the relation between back pain or headache and the experiment. While in the group of back pain patients the average pain intensity of the last six months correlated positively with the pain intensity shortly before, shortly after and 24 hours after the experiment, this finding did not apply for the group of headache patients. Instead, in this group the number of unconditioned responses correlated positively with the respective current three pain ratings.

6 Discussion

The interest of the present study centred on the question of muscular learning in terms of Pavlovian conditioning of muscular responses and its impact in the development, enhancement and chronification of pain.

6.1 Muscular learning

The results showed that it is possible to provoke a conditioned response (muscular activity (CR)) by repeatedly pairing a neutral stimulus (tone (CS)) with an unconditioned stimulus (intracutaneous electric pain stimulus (US)). This procedure followed a differential Pavlovian conditioning paradigm in which a high tone served as the CS+ while a low tone was never paired with the pain stimulus and, therefore, served as CS-. Both patient groups associated the high tone with the US over the course of the experiment and responded to the CS+ with an enhanced muscular activity compared to the respective pre-baseline.

6.1.1 Weak stimulus control of behaviour of the CS-

According to learning theory, the CS- should be a reference stimulus that is commonly used to indicate discrimination in learning (cf. Domjan, 2005). Hence, ideally no subject was expected to react to the low tone. This ideal case would demonstrate a strong stimulus control of behaviour which is defined by an altered response to changes in a stimulus (Domjan, 2005), here, the frequency of the tones. In the present study the low tone did not achieve the desired degree of stimulus control and obviously failed to fulfil its function as a signal for safety. The CS- was also able to elicit enhanced muscle activity. Several explanations for this incidence should be taken into consideration:

- One explanation for this finding could be that instead the participants generalized to some extent and, therefore, did not show the intended strength of differential responding. It can be suspected that the chosen tone was not an ideal CS-. Either the two tones were too close in their characteristics (frequencies, intensity or length) for the participants to be able to discriminate between them correctly (this was reported during the standardized short interview by several participants after the experiment) or the modality was too similar.
- Some studies identified a set of characteristics that are relevant for successful differential conditioning like temporal lobe lesions (Daum, Channon, & Gray,

1992), aging (Bellebaum & Daum, 2004) or awareness (Clark & Squire, 2004). However, none of these impairments can be an explanation for the study in hand as no brain lesions existed, the average age was below the assumed critical age range of 51 to 80, and the sense of awareness is irrelevant for delayed fear conditioning in contrast to trace conditioning (Fanselow & Poulos, 2005).

- Another possible reason could be that the time sequence of the two tones was too close. In the present study the events followed each other without an interval in between; there were hence only 14 seconds between the two tones (cf. Figure 8). In the cited study by Schneider et al. (2004) the trials were separated by a variable mean inter-trial interval of 12 seconds (range 6 to 18 seconds). Although the post-baseline after each tone of 4 seconds was shorter, a duration of 14 seconds was the smallest time interval between the two tones. It might have been better to analogically stretch the time between the presentation of the tones to up to 26 seconds to optimize the differential learning and to ensure a potential decrease of muscular tension at the same time.

Future studies might consider extending the intervals between the presentation of the tones or choosing a different CS-. In spite of these considerations, a differential learning within the patient groups can still be assumed since in successful differential conditioning more conditioned responses are elicited by the CS+ than by the CS- (cf. Cheng, Knight, & Smith, 2006; Clark & Squire, 2004): the difference between CS+ and CS- reached significance across all seven muscle regions, in four muscle sites as well as for all relevant combined muscle regions.

6.1.2 Successful extinction

In the last phase of the experiment no US was given, only the presentation of the tones continued. Hereby, it was intended to extinguish the successful differential conditioning effect again and, hence, to diminish the learned muscular reactions to the CS+. The results demonstrated in section 4.1.2 proved that no main effect “CS type” reached significance which supports the assumption that the extinction was achieved.

On the basis of these findings, it can be concluded that muscular responses were changed by Pavlovian conditioning. This conclusion seems to be supported by the successful extinction of the changed responses during the third phase of the

experiment. Therefore, the question of muscular conditioning learning deserves an affirmative answer.

6.2 Group differences in muscular learning and symptom-specific responses

The main focus of the work in hand was based on the two theoretical models of chronic myogenic pain namely the theory of myogenic headache with its hypothesis of increased muscle effort and the biopsychosocial model of musculoskeletal disorders with its concept of a response stereotypy. It was hypothesised that chronic pain patients show stronger muscular responses to the conditioned stimulus (CS+) than healthy controls. The hypotheses testing failed to confirm the hypotheses of group differences in learning and symptom-specific responses in six out of seven muscle sites. Only in the left trapezius was evidence found to the effect that the back pain patients revealed enhanced muscular responsiveness in a symptom-specific site.

Therefore the following remarks also focus on the results of the exploratory analyses, which took several aspects of differences in muscular learning into account. These implications might give valuable hints for further investigations.

6.2.1 Muscular responses of the control group

The healthy controls narrowly failed to discriminate successfully between CS+ and CS- when all conditioned muscular responses were taken into account. Only the patient groups showed a differential learning. Hence, this outcome shows that the conditioning did not work for the healthy participants in our experiment, but that they demonstrate a tendency for muscular conditioning learning. As Pavlovian conditioning was introduced as learning of an association between the conditioned and unconditioned stimulus (Rescorla, 1988) and an adaptive trait that naturally occurs (Domjan, 2005), it is not surprising that potential muscular learning might also be revealed in healthy participants. A successful conditioning of the control group, though, could have caused methodological limitations by levelling differences between patients and healthy controls with regards to the dependent variables such as number of substantial conditioned responses or iEMG change from pre-baseline. The potential interfering impact of learning of the healthy controls might advocate for a different control group in future studies. A control group that does not get anything to learn at all would be ideal. Thus, these participants could, for example, also be

chronic pain patients who pass through the experiment without ever receiving an unconditioned pain stimulus (natural history). Thereby, the comparability in respect of the dependent variables would be increased and the mentioned methodological difficulties decreased.

6.2.2 Specifics in the muscular learning of the pain patients

Corrugator supercilii

An unexpected finding regards the missing significance in the forehead of the TTH patients. The corrugator supercilii left was defined as a symptom-specific muscle, but no learning to the CS+ occurred. The preliminary study revealed significant differences in the forehead between the patients with back pain and the control group (Kleinwort, 2002). The patients responded significantly stronger to the CS+ in their facial expression, as the corrugator supercilii reflects the non-verbal aspects of negative emotions including pain. In the present study the results also showed high differences of iEMG values from the pre-baseline in the forehead to the CS+, but this applied to the mean of all groups together (cf. Figure 15). The comparison of CS+ to the low value regarding the CS- probably failed to reach significance because of the high standard deviations. Furthermore, the results indicated that the corrugator region was the site which actually showed the maximum number of substantial unconditioned responses for all three groups (cf. Figure 22). This finding is surely important to mention and implicates the validity of the corrugator supercilii responsiveness as a measure for non-verbal pain expression. Although the TTH group showed the most substantial unconditioned responses, no group difference was significant. Again, the high standard deviations could be the determining factor for this result. From these aspects it can be concluded that the missing significance in the forehead of the TTH patients is due to the fact that all three groups performed a facial expression during the unconditioned and conditioned stimulus. Additionally, it could be discussed whether the corrugator supercilii is hence not as symptom-specific as assumed for the TTH pain syndrome. These considerations can be taken to recommend that future examinations should focus on the frontalis muscle as a symptom-specific muscle like in most other SEMG studies (Leistad et al., 2006; Schoenen et al., 1991; Traue & Lösch-Pötzsch, 1993).

Muscular responsiveness of the TTH patients in the lower back

Symptom-specific muscular learning cannot be confirmed for the groups of TTH patients. They indeed showed a significantly elevated muscular reactivity in the right trapezius, but another result does not seem to correspond with the concept of response stereotypy. The headache patients showed a high, but not significant level of iEMG responses in the lumbar region (cf. Figure 20). The number of substantial unconditioned responses in the left lumbar was even significant compared to the controls (cf. Figure 22). The lumbar region, though, is not defined as relevant for TTH. None of the SEMG studies with chronic headache patients examined muscle tension in the lumbar region; one main reason for this apparent lack in the literature must certainly be that by definition it would not seem necessary to examine this site by SEMG. In the present study this result was disclosed by coincidence, as back pain patients were examined at the same time. A possible explanation for this unspecific lumbar response could be given by the fact that patients with TTH showed an increased general pain sensitivity (Jensen et al., 1998) and, therefore, increased muscle tension in the whole muscular system. In their study the patients were hypersensitive to several types of stimuli at symptomatic as well as at non-symptomatic locations compared to healthy controls. Hence, the authors concluded that supra-spinal levels were affected by neuronal alterations. Another conceivable explanation for the enhanced muscular tension in the lumbar region might be seen in the fact that the muscles of the upper back are not independent from the muscles in the lower back. Physiotherapy of TTH incorporates this opinion and necessarily includes the lower back into the treatment. So the lumbar region could be seen as a relevant site for the disorder, although rigorous evidence for the effectiveness of manipulation in patients with TTH was not found, yet (Fernandez-de-Las-Penas et al., 2006; Lenssinck et al., 2004).

Based on the results of our study a new question arises: As mentioned above, most studies that examined TTH patients by SEMG during stress exposure revealed an elevated trapezius activity (e.g., Bansevicius et al., 1999; Harnphadungkit et al., 2001). Can these findings still be declared as symptom-specific or was symptom-specificity wrongly assumed as a consequence of the measurement of a priori defined relevant muscles? To answer this question, future investigations should have a closer look on the up to now valid definition of symptom-specificity and, hence, constitute the measurement of the lumbar region as a new control variable.

Symptom-specific learning of the back pain patients

The back pain patients exhibited a significant enhanced learning in the left trapezius for both acquisition phases and in the combined lumbar region in the second half of acquisition phase I. The muscle sites that responded strongest to the CS+ (lumbar and trapezius site) correspond with the relevant sites of pain in chronic back pain. Hence, symptom-specific learning can be postulated. These findings coincide with the state of the art in the literature about SEMG studies with chronic back pain patients. It was stated in subsection 1.4.3 that most studies have reported a positive relationship between stress and symptom-specific reactivity in relevant muscle groups in chronic back pain patients (Flor, 1991; Flor et al., 1992; Flor et al., 1985; Geisser et al., 2005). Hence, the tested patients with chronic back pain did not only learn more effectively than the healthy controls, they also showed heightened conditionability in their already sensitized muscle sites of pain.

Preconditioning concerning the unconditioned responses

From the exploratory results one might speculate that muscular learning took place already before the experiment, probably in terms of a predisposing factor within the chronification process. This preconditioned learning influences the reaction to the US. As shown in section 4.2.3 the two groups of patients displayed significantly more unconditioned responses to the pain stimulus across all muscle regions as well as in the left lumbar and in both trapezius sites compared to the healthy controls. This finding is not a product of the physical intensity of the applied electric stimulation: the three groups did not differ in their perception or pain threshold (cf. Table 2), the applied pain stimulus was objectively comparable high and, indeed, slightly higher for the controls (patients = 0.5 mA, controls = 0.6 mA). From this it can be assumed that the observed differences in the number of UR are based on a central sensitization which determined this alteration in pain processing during the experiment. Furthermore, the conclusion might be drawn that these findings confirm the concept of response stereotypy for the BP patients, as the significant differences were found in the left lumbar and trapezius sites, hence, in regions that were classified as relevant for chronic BP. This is also consistent with the observation in the right arm which is an irrelevant site for the pain syndromes. As expected, this site showed the lowest number of unconditioned responses and, therefore, served its function as a control site.

Another interesting result which is consistent with the often mentioned hyperalgesia of chronic BP and TTH patients was the correlation between the left arm and the other muscle sites. Only in the patient groups was the number of unconditioned responses in the site of pain application found to correlate significantly positive with the number of unconditioned responses in the lumbar and trapezius sites. In the healthy controls such an interrelation was only observable for the left and right arm. While the controls thus exhibited muscular tension to the US in the corresponding limb, the patients showed their maximum of unconditioned pain responses in symptomatic sites.

By looking at the result described in section 4.3.2, a further influence of the unconditioned responses on the patients´ muscular level needs to be mentioned: in the TTH group the number of unconditioned responses correlated positively with the pain ratings before and after the experiment. The more painful reflex actions were provoked the more pain was reported. The BP patients showed a different correlation; their average pain intensity of the past six months correlated positively with the current pain ratings but was independent from the unconditioned responses in the experiment. Although the patients did not differ from the healthy controls in their muscular basic levels, this finding implicates that the TTH patients reveal habitual elevated iEMG responses during events of negative valence like the intra-cutaneous electric stimulation. This aspect corresponds with the described concept of a dysfunctional increased muscle effort (Bischoff & Traue, 1983; Bischoff et al., 2004). To recapitulate, according to this concept, individuals develop a myogenic headache when muscle effort in certain muscles in the head and neck is increased to a critical point within a stressful situation. These excessive contractions and hyper-reactivity to emotional stressors become apparent in abnormally elevated levels of muscle tension. It could be suspected that the unconditioned responses served as stressors that probably caused a critical increase of tension and hence influenced the headache intensity even a day afterwards.

6.3 Comparison of the present results with the results of Schneider, Palomba and Flor (2004)

The work in hand was in many parts based on the mentioned study of Schneider et al (2004) (cf. section 1.5) which also tested the hypothesis of augmented aversive conditioning of muscular responses in chronic back pain patients and healthy controls. Thus, the issue of replication and validation of these former results were of major interest for the present study.

Schneider et al. gave evidence of respondent muscular learning of the patients in the left forearm and right trapezius. The healthy controls did not react with elevated muscular tension to the CS+. The only site tested in both studies was the right trapezius, as it was not measured bilaterally in the Schneider et al. work. In the present study, however, the left trapezius of the BP patients responded significantly stronger to the CS+. Concerning the unconditioned responses, the comparative study by Schneider et al. did not find any significant differences between the group of BP patients and the control group.

During the extinction phase of the Schneider et al. study, the differential conditioning effect persisted in the left forearm of the BP patients, so no extinction occured. This finding differs from the present study in which no more significant responses to the CS+ occurred. The authors argue that this result confirms the assumption of maladaptive muscular conditioning. It cannot be clarified why the two studies differ concerning the extinction process, especially, as the left forearm was not examined in the actual work. A possible reason however could be a greater effect in learning in the Schneider et al. work caused by more learning trials accompanied by stronger extinction resistance.

Hence, although both studies did not show exactly the same results, there are similarities. These two studies complement one another in that they clearly demonstrate significant differences between BP patients and healthy controls in muscular learning. At the same time, the additional muscle sites and group of headache patients tested in the present work extend the findings of Schneider et al. Both works of research implicate that the enhanced muscular conditionability might be a mechanism responsible for chronic hyperreactivity of the muscular system in chronic pain patients.

Restrictions in the comparability of these two investigations should, however, be mentioned. Firstly, the experiment was more comprehensive in the study of Schneider et al., as it consisted two additional habituation phases, two more

acquisition phases and a second extinction phase. There were also more trials within each of these blocks. Secondly, an aversive and a positive slide served as CS+ and CS-, respectively. Thirdly, only 11 BP patients and 11 healthy controls were examined. Lastly, the authors established a high-pass filter that eliminated all frequencies below 90 Hz. The present work used, instead, a notch filter (filtering the frequencies between 48 and 52 Hz), which allowed a bigger amount of relevant information and additional muscle fibres to be analysed. Still, the assumption of Pavlovian conditionability of muscular responses and an augmented aversive conditioning in back pain patients compared to healthy controls seems to be legitimate.

6.4 Limitations of the study and suggestions for further research

The data for the present study was collected in a relatively small sample of patients in an experimental setting. Hence, it needs to be resolved to what extent the results apply to chronic back pain and tension-type headache patients in general and generalize even to other chronic pain states.

The unconditioned response was probably the most critical and limiting variable of the whole study: the existence of an unconditioned muscular response to the intra-cutaneous stimulus was established as inclusion criterion for the participation in the study. This was required as it has a fundamental influence on the outcome parameters of muscular learning. In regard of the classical conditioning paradigm a conditioned response is determined in its occurrence and strength by the quality of the unconditioned response. If the latter is missing or weak, no conditioned response would be acquired. The presented significant results support the hypothesis of different muscular learning in the patient groups, but these findings must be seen in relation to the data that did not reach significance. The group that exhibited the most unconditioned responses was the TTH group with approximately 100 URs. Actually, more than 400 unconditioned responses could have been possible. This implicates that the applied pain stimulus was strong enough to elicit an unconditioned response, but its success rate amounts to only ¼ of all possible URs. From this starting point it soon became clear during the data analysis that even less conditioned responses would be obtained and, consequently, that significant results could be rare. Against this background of methodological and statistical limitations dependent on the UR, it should be highlighted that the demonstrated evidence for enhanced and symptom-related muscular learning in the examined chronic patients gains in importance.

The small sample, the mentioned low success rate of elicited unconditioned responses and, therefore, the minor possible differences in learning and restricted likelihood of conditioned responses led to methodological limitations in terms of little test power. To solve these statistical problems, different options could be considered. Thus, more participants could be examined or the unconditioned stimulus could be increased in intensity to elicit stronger unconditioned and, as a result, conditioned responses. The practicality of these considerations, however, needs to be determined first. Raising the number of participants, for example, has the disadvantage that it would prolong the time of data acquisition which was already long with a high drop out rate. For ethical reasons it is also not recommendable to enhance the electric stimulation drastically. However, one way to increase the

statistical power in future studies could be to choose a control group that does not experience an US and, hence, only listens to the two stimuli (natural history). This would enlarge the range of possible EMG levels to the CS+.

Finally, it is debatable whether SEMG is a suitable method at all for the statistical analysis of groups, as muscular tension is a very sensitive parameter, which is partly a signal of biological coincidence and whose reliability is restricted even intraindividually. Further on, it has to be conceded that this technique, which is very complex and vulnerable to disturbance variables like, e.g., general muscle strength, the extent of fat tissue atop the muscles etc., might not be ideal to detect interindividual differences anyway. The present study coped with these difficulties by an intraindividual normalization of the physiological data before comparing them with the data of the other participants and by following the current state of the art in SEMG.

7 Conclusion

In this work the results clearly indicated that “muscular learning” is as substantial as learning on a molecular, neuronal or behavioural level. It is a phenomenon that can be found in chronic back pain and tension-type headache patients. Although the hypotheses testing primarily failed to give definite evidence for group differences in learning, exploratory analyses could support the existence of such differences. On the basis of the exploratory results, the mechanism responsible for the learning process is Pavlovian conditioning which can hence be viewed as an intermediary variable between muscular tension and chronic pain. Although it was demonstrated that the examined pain patients showed an enhanced conditionability to the conditioned stimulus, no judgement can be made to what extent this heightened muscular conditionability is a cause or a consequence of the chronic pain. It seems to be at least a maintaining factor. As an implication, future studies could, e.g., choose a pre-chronic control group and ideally use a longitudinal study design.

The increased readiness to learn in the patient groups was found to be elevated at symptom-specific sites for the BP patients. This applied to the unconditioned as well as to the conditioned muscular responses. Such a physiological disposition to react more sensibly to pain at the site of pain stresses the importance of the concept of a response stereotypy within the biopsychosocial model of musculoskeletal disorders. According to this, such a predisposing factor for the development and maintenance of the chronification process which develops above all through learning implicates the therapeutic need to prevent and compensate this progression by effective coping skills at an early stage of pain treatment.

Furthermore, the present study revealed lumbar responsiveness in TTH patients. These findings posed the question of the correctness of so far defined symptom-specific sites.

From the position of muscular conditionability the clinical and practical relevance needs to be stressed. As muscular learning was achieved, muscular unlearning must be equally possible. Enhanced muscle tension that was evoked by learning experiences could, hence, be reduced by the implementation of relaxation training and exercises. Such implications support the objectives and methods of a psychological pain therapy which focuses on educating the patient in relaxation techniques, coping with stressful situations that cause and maintain pain, reducing avoidance behaviour, developing activities and so forth. As chronic pain was

described as a multidimensional phenomenon, it is nowadays successfully treated in multididisciplinary settings including the interventions of cognitive behavioural therapy. On the other hand, the significance of operant and respondent approaches concerning the development, reinforcing and maintenance of chronic pain has not yet been sufficiently proven by empirical evidence. One of the most important results of the present study is, therefore, the growing evidence of the impact of respondent learning on the chronification process of back pain and myogenic headache.

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Appendix

Fachbereich Psychologie
Psychologisches Institut III
Arbeitsbereich Verhaltenstherapie

Postanschrift:
Von-Melle-Park 5
20146 Hamburg

UHH • PSYCHOLOGISCHES INSTITUT • VON-MELLE-PARK 5 • 20146 HAMBURG

Universität Hamburg

Aufklärung

Sehr geehrte Damen, sehr geehrte Herren,

Sie haben sich nach einer eingehenden mündlichen Informationsvermittlung entschieden, an einer Untersuchung zur Erforschung von Lernvorgängen bei Schmerzen teilzunehmen.

Die Untersuchung enthält eine Reihe von Abläufen. Wir möchten Sie ausdrücklich auf zwei Dinge, die auf Sie zukommen werden, aufmerksam machen: Zum einen werden Sie während der experimentellen Untersuchung mehrmals einen eher unangenehmen Ton hören. Zum anderen werden Sie durch ein für diese Zwecke zugelassenes Gerät (intracutanes Schmerzreizgerät) mehrere kurze Schmerzreize zugefügt bekommen. Hierfür ist eine geringfügige Abtragung der obersten Hornhautschicht ihres Zeigefingers erforderlich, die mittels eines kleinen Stiftes mit rauher Oberfläche vorgenommen wird. An dieser Hautstelle bleibt für 1-2 Tage durch die Abschürfung bis zum Nachwachsen der Haut eine kleine Blessur bestehen. Die Stärke des an dieser Stelle applizierten elektrischen Reizes werden Sie durch eine vorherige Bestimmung selbst festlegen. Er wird geringer sein als das Ausmaß, das Sie selbst als oberste Grenze der zu tolerierenden Schmerzen angegeben haben. Dieser Reiz wird oft wiederholt. Er kann **keine** bleibenden oder gesundheitlichen Schäden hervorrufen, aber er ist schmerzhaft, da dies für die Untersuchung erforderlich ist.

Sollten Sie zu irgendeiner Zeit der Untersuchung den Wunsch haben, das Vorgehen zu unter- oder abzubrechen, können Sie dies in jedem Fall und unter allen Umständen tun. Ihre Teilnahme ist zu jedem Zeitpunkt völlig freiwillig und unverbindlich. Ein Widerruf Ihrer Einwilligung wird für Sie keinerlei Nachteile bedeuten. Dies gilt auch für den jetztigen Zeitpunkt. Sofern Sie trotz Ihrer Zusage Bedenken an einer Teilnahme haben, können Sie diese jederzeit geltend machen und Ihre Teilnahmeerklärung widerrufen.

Sollten Sie nach dem Lesen dieses Aufklärungsblattes doch noch Fragen haben, können Sie diese bei Ihrem nächsten Termin klären.

Mit freundlichen Grüßen

Dr. R. Klinger

EINVERSTÄNDNISERKLÄRUNG

Ich bin über Wesen, Bedeutung und Tragweite der oben genannten klinisch-experimentellen Untersuchung von den Unterzeichnenden eingehend mündlich und auch schriftlich unterrichtet worden und hatte ausreichend Bedenkzeit für meine Entscheidung der Einverständniserklärung. Zu dem Ablauf, dem voraussichtlichen Nutzen und den Risiken konnte ich Fragen stellen; die Informationen habe ich voll inhaltlich verstanden.

Hiermit erkläre ich, dass ich zur Teilnahme an der experimentellen Untersuchung bereit bin. Mir ist bekannt, dass die Teilnahme freiwillig ist. Entsprechend kann ich meine Einwilligung jederzeit, auch während der laufenden experimentellen Untersuchung, ohne Angabe von Gründen und ohne Nachteile für mich bzw. für meine weitere Behandlung widerrufen.

Ich verpflichte mich, während der Teilnahme an dieser Untersuchung die Untersuchungsleiter über alle Erkrankungen bzw. Gesundheitsstörungen zu unterrichten. Dies tue ich ebenfalls im Falle der Inanspruchnahme ärztlicher Behandlung und der Einnahme zusätzlicher Medikamente.

Dr. R. Klinger	Dr. R. Klinger
Stempel	Ort, Datum, Unterschrift

Name des / der Studienteilnehmers/-in Ort, Datum, Unterschrift

Im Zusammenhang mit dieser klinischen Untersuchung werden meine Daten unter Wahrung des Datenschutzgesetzes zum Zweck der Auswertung auf elektronische Datenspeicher übertragen und statistisch ausgewertet.

Damit erkläre ich mich mit meiner Unterschrift einverstanden:

Name des / der Studienteilnehmers/-in Ort, Datum, Unterschrift

Fragen zur Schmerzintensität

Geben Sie bitte unten an, wie stark Ihre Rückenschmerzen sind. Kreuzen Sie die Zahl an, die Ihren Schmerz am besten beschreibt auf einer Skala von 0 bis 10, wobei 0 keine Schmerzen bedeutet und 10 die stärksten vorstellbaren Schmerzen bedeutet.

Zunächst geben Sie bitte an, wie stark die Schmerzen sind, die Sie jetzt gerade **in diesem Augenblick** erleben (während Sie diesen Fragebogen ausfüllen).

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Geben Sie bitte an, wie stark die **stärksten Schmerzen** waren, die Sie in den **letzten 6 Monaten** erlebt haben:

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Geben Sie bitte an, wie stark Ihre Rückenschmerzen im Durchschnitt waren in den **letzten 6 Monaten**:

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Fragen zur Beeinträchtigung

An wievielen Tagen ungefähr haben Ihre Rückenschmerzen Sie in den **letzten 6 Monaten** davon abgehalten, Ihren üblichen Aktivitäten nachzugehen (Arbeit, Schule, Haushaltsarbeit)?

_____Tage

Wie stark haben Ihre Rückenschmerzen Sie in den **letzten 6 Monaten** daran gehindert, Ihren täglichen Aktivitäten nachzugehen?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Behinderung — unfähig, irgendeiner Aktivität nachzugehen

Wie stark haben Ihre Rückenschmerzen in den **letzten 6 Monaten** Ihre Fähigkeit, sozialen, familiären oder Freizeit- Aktivitäten nachzugehen, verändert?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
kein Veränderung — extreme Veränderung

Wie stark haben Ihre Rückenschmerzen Ihre Fähigkeit zu arbeiten (inclusive Haushaltsarbeit) in den **letzten 6 Monaten** verändert?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Veränderung — extreme Veränderung

Fragen zur Schmerzintensität

Geben Sie bitte unten an, wie stark Ihre Kopfschmerzen sind. Kreuzen Sie die Zahl an, die Ihren Schmerz am besten beschreibt auf einer Skala von 0 bis 10, wobei 0 keine Schmerzen bedeutet und 10 die stärksten vorstellbaren Schmerzen bedeutet.

Zunächst geben Sie bitte an, wie stark die Schmerzen sind, die Sie jetzt gerade **in diesem Augenblick** erleben (während Sie diesen Fragebogen ausfüllen).

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Geben Sie bitte an, wie stark die **stärksten Schmerzen** waren, die Sie in den **letzten 6 Monaten** erlebt haben:

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Geben Sie bitte an, wie stark Ihre Kopfschmerzen im Durchschnitt waren in den **letzten 6 Monaten**:

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Schmerzen — stärkste vorstellbare Schmerzen

Fragen zur Beeinträchtigung

An wievielen Tagen ungefähr haben Ihre Kopfschmerzen Sie in den **letzten 6 Monaten** davon abgehalten, Ihren üblichen Aktivitäten nachzugehen (Arbeit, Schule, Haushaltsarbeit)?

_____Tage

Wie stark haben Ihre Kopfschmerzen Sie in den **letzten 6 Monaten** daran gehindert, Ihren täglichen Aktivitäten nachzugehen?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Behinderung — unfähig, irgendeiner Aktivität nachzugehen

Wie stark haben Ihre Kopfschmerzen in den **letzten 6 Monaten** Ihre Fähigkeit, sozialen, familiären oder Freizeit- Aktivitäten nachzugehen, verändert?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
kein Veränderung — extreme Veränderung

Wie stark haben Ihre Kopfschmerzen Ihre Fähigkeit zu arbeiten (inclusive Haushaltsarbeit) in den **letzten 6 Monaten** verändert?

[0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
keine Veränderung — extreme Veränderung

Einstufung der Schmerzreize während des Konditionierungsexperiments

Name, Vorname _____

Datum der Untersuchung _____

Wahrnehmungsschwelle: _____

Schmerzschwelle: _____

Phase 1	Ereignis	Einstu-fung	Bemerkungen	Phase 2	Ereignis	Einstu-fung	Bemerkungen	Phase 3	Ereignis	Einstu-fung	Bemerkungen
	Baseline				Baseline				Baseline		
	CS+				CS+				CS+		
	CS+				CS-				CS-		
	CS-				CS-				CS-		
	CS+				CS+				CS+		
	CS-				CS+				CS+		
	CS-				CS+				CS-		
	CS+				CS-				CS+		
	CS+				CS-				CS-		
	CS+				CS+				CS-		
	CS-				CS+				CS+		
	CS-				CS-				CS+		
	CS+				CS+				CS+		
	CS-				CS+				CS-		
	CS-				CS-				CS-		
	CS-				CS-				CS+		
	CS+				CS-				CS-		

Einschätzung des Experiments

- Wie haben Sie die Töne empfunden?
  - Hoher Ton:

    sehr unangenehm **unangenehm** **neutral** **angenehm** **sehr angenehm**

  - Tiefer Ton:

    sehr unangenehm **unangenehm** **neutral** **angenehm** **sehr angenehm**

- Wie schätzen Sie den stärksten Reiz der Schwellenwertbestimmung nun auf der Skala von 0 bis 10 ein?

  [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
  kein Schmerz — stärkster vorstellbarer Schmerzreiz

Experiment:

- Wie haben Sie die Töne empfunden?
  - Hoher Ton:

    sehr unangenehm **unangenehm** **neutral** **angenehm** **sehr angenehm**

  - Tiefer Ton:

    sehr unangenehm **unangenehm** **neutral** **angenehm** **sehr angenehm**

- Haben Sie irgendeinen Zusammenhang zwischen Tönen und den Schmerzreizen gesehen?

  Ja **nein**

Falls „ja“, bitte beschreiben Sie kurz diesen Zusammenhang:

_____
_____

- Als ich während des Experiments die hohen Töne hörte,...
  - ... spannte ich an

    überhaupt nicht **ein wenig** **ziemlich** **stark** **sehr stark**

  - ... war ich gestresst

    überhaupt nicht **ein wenig** **ziemlich** **stark** **sehr stark**

  - ... erwartete ich den Schmerzreiz

    überhaupt nicht **ein wenig** **ziemlich** **stark** **sehr stark**

Nach 24 Stunden:

- Wie schätzen Sie Ihre momentanen Schmerzen auf der Skala von 0 bis 10 ein?

  [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
  kein Schmerz — stärkster vorstellbarer Schmerzreiz

MATLAB script (Removing ECG Artefacts)

```
% hier wird nur Kanal 7 ausgelesen = Herz, um die Herzrate rauszurechnen
    'Lade die Daten'
    ecg = read_antwerp(filename, Experiment.ChannelPairCount*2, [7], start, ende);
    'Daten sind geladen'
% Bestimme die Herzrate und die Herzschlag-Abstaende(ibi)
    'Bestimme die Herzrate und co.'
    [rate,ibi,peaks]=QRS(ecg);
    'Bestimmt!'

% Bestimme die Indices der Herzschlaege in peaks und ecg.
    ind = find( peaks~=0 );
    A = 1200;
    B = 600;

    Templiste =zeros(8,l);
    for Tempnr = 1:8
    signal = read_antwerp(filename, Experiment.ChannelPairCount*2, [Tempnr], start, ende);
    'Daten sind geladen'

    temp=template(ende, ecg, ind, A, B, Tempnr, signal);
    'Template bestimmt. Bereinigtes Signal in alle.mat gespeichert'

    load 'Kanal.mat'
    'Bereinigte Daten geladen'

    Templiste(Tempnr,:) = Kanal; % ist jeweils nur ein Kanal nach dem anderen!
    'Bereinigte Signale in Templiste gespeichert'
    end % Ende der For-Schleife

    % Einschalten wenn die 7. Zeile raus soll:
    if 1
    % Indizes der Signale die nicht aus der Liste raus sollen:
    InteressanteSignale= [1;2;3;4;5;6;8];
    % Uebernehme alle Zeilen bis auf die 7.
    Templiste = Templiste(InteressanteSignale,:);
    end
```

MATLAB script (function “QRS(ecg)”)

```
%     [rate, ibi, peaks] = QRS(ecg)
%
% QRS bestimmt die Herzrate aus dem gegebenem Signalabschnitt.
% Eingaben:   ecg   = Signalabschnitt
% Ausgaben:   rate  = die Herzrate
%             ibi   = interbeat interval
%             peaks = Hat die gleiche Form wie der Signalabschnitt.
%                     Enthaelt die Werte der Peaks, an den jeweiligen
%                     Positionen und ist sonst Null.

function [rate, ibi, peaks]=QRS(ecg)

if ischar(ecg)
  file=ecg;
  disp(' ')
  disp(strcat('Loading...',file))
  ecg=load(strcat(file));
  ecg=ecg(:,ecgchannel);
else
  file='output';
end

if (size(ecg,2) ~= 1)
    ecg = ecg';
end

fecg=filtfilt(fir1(width,lp/(fs/2),'low',hamming(width+1)),1,ecg);

decg=[0;diff(fecg)];

for i=1:length(decg)
  if decg(i)>0
    decg(i)=decg(i)^2;
  else
    decg(i)=0;
  end
end
```

```
safe=round(safe/(1000/fs));
search=round(search/(1000/fs));

peak=zeros(length(fecg),1);

for i=search+1:length(fecg)-search
  if i<(safe+1) & fecg(i)>fecg(i-search:i-1) & fecg(i)>fecg(i+1:i+search) & max(decg(i-search:i+search))>(threshold*mean(decg)) & sum(peak(1:i-1))==0
    peak(i)=fecg(i);
    % [i,search,safe]
elseif i > safe & fecg(i)>fecg(i-search:i-1) & fecg(i)>fecg(i+1:i+search) & max(decg(i-search:i+search))>(threshold*mean(decg)) & sum(peak(i-safe:i-
1))==0
        peak(i)=fecg(i);
    % [i,search,safe]
  elseif i>(length(fecg)-safe) & fecg(i)>fecg(i-search:i-1) & fecg(i)>fecg(i+1:i+search) & max(decg(i-search:i+search))>(threshold*mean(decg)) &
sum(peak(1:i-1))==0 & fecg(i)>fecg(i+1:end)
    peak(i)=fecg(i);
  end
end

peaks = peak;
ibi=[diff(find(peak~=0))*1000/fs]';

disp(' ')
disp(strcat('Length of recording...',num2str(length(ecg)/fs)));
disp(strcat('Total IBI time...',num2str(sum(ibi)/1000)));
disp(strcat('Min IBI...',num2str(min(ibi))));
disp(strcat('Max IBI...',num2str(max(ibi))));
disp(strcat('Mean IBI...',num2str(mean(ibi))));

rate = 1000/mean(ibi) * 60; % DAS IST DIE HERZRATE!!!
sdrate = 1000/std(ibi);
disp(strcat('Heart rate ...', num2str(rate)));

if strcmp(saveibi,'yes')
    fid=fopen(strcat(file,'_ibi.txt'),'w');
    fprintf(fid,'%d\n',ibi);
    fclose(fid);
end
% for further functions and definitions refer to Christie (2003)
```

MATLAB script (function “template”)

```
function template = template(ende, ecg, ind, A, B, Tempnr, signal, STILL)
% signal ist der Kanal, aus dem ich die Herzrate rausrechnen will

% Falls STILL nicht angegeben wurde, wird es als 0 angenommen,
% und es werden alle Ausgaben/Bilder produziert.
    if (nargin < 8)
        STILL = 0;
    end

    HerzschlAnz = length(ind);
    HerzschlListe = zeros(HerzschlAnz,A+B+1);

    for i = 2:HerzschlAnz
        % Bestimme die akutelle Position des Herzschlags:
        pos = ind(i);
        % Schneide den Herzschlag aus, und schreibe es in die HerzschlListe:
        if (pos+B < length(signal))
        HerzschlListe(i,:) = signal(  pos-A : pos+B  );
        end
    end


if (~STILL)
    % Zeichnen
    if 1
        'Zeichnen'
        figure(1);
        clf;
        hold on
        for i = 2:HerzschlAnz
            plot( [1:A+B+1],HerzschlListe(i,:),'r'  )
        end
        hold off
        'fertig'
    end
end
```

```
% template bestimmen
    template = mean(HerzschlListe(2:end,:));

    % 'template' sollte den Mittelwert 0 haben, sonst wirkt sich das Abziehen
    % eventuell negativ aus. Durch das abziehen des Mittelwertes des Template wird Mittelwert 0 erreicht:
    template = template - mean(template);

if (~STILL)
    if 1
        %template zeichnen:
        figure(1)
        hold on
        plot( [1:A+B+1],template, 'k' )
        hold off
    end
end

% Nun soll aus dem Signal die Herzrate (also das Template) rausgerechnet werden:
 Kanal = signal;
    for i = 2:HerzschlAnz
        pos = ind(i);
        if (pos+B < length(signal))
        Kanal(pos-A:pos+B) = signal(pos-A:pos+B) - template;
        end
        Kanal;
   % Templiste (Tempnr,ende)= Kanal;
    end

    if (~STILL)
        if 1
            figure(2)
            clf
            hold on
            plot(1:length(ecg),signal)
            plot(1:length(ecg),Kanal,'k')
            hold off
        end
    end
 save 'Kanal.mat' Kanal
```

MATLAB script (filter)

```
% das Signalstueck wollen wir nun filtern, d.h. das 50 Hz Brummen wird
 % rausgefiltert mit einem chebyshew-Filter
    se=[];           % se soll das gefilterte Signalstueck werden
    N      = 10;      % Order
    Fstop1 = 0.0192;  % First Stopband Frequency (48Hz/2500Hz)
    Fstop2 = 0.0208;  % Second Stopband Frequency (52Hz/2500Hz)
    Astop  = 120;     % Stopband Attenuation (dB)
    x=Templiste';

% To be safe you can increase the stop band if your desired frequency
% doesn't fall in the stop-band range.
% as 50Hz can vary practically, I considered the ideal case.

% Obtain filter coefficients
      [b,a] = cheby2(N/2, Astop, [Fstop1 Fstop2], 'stop');

% filter the signal

      y=filtfilt(b,a,x);
      se= y';

   % se ist nun das gefilterte Signalstueck, mit dem wir weiterrechnen
```