Aus der Neurologischen Klinik und Poliklinik des Klinikums rechts der Isar

Direktor: Professor B. Hemmer

# Behavioral and neurophysiological investigations of the attentional effects of pain in health and fibromyalgia syndrome

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Laura Tiemann

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| **Referent:** | **Prof. Dr. Josef Zihl** |
| **Korreferent:** | **PD Dr. Markus Ploner** |
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# Inhaltsverzeichnis

# ONE

**Abstract (Zusammenfassung)**

# 1 Abstract (Zusammenfassung)

Successful behavior requires the attentional selection and preferred processing of sensory information. Painful stimuli in particular are of utmost behavioral relevance and therefore capable of affecting attentional resources. In health, these attentional modulations are functionally relevant to maintain physical integrity, as pain fulfills a protective warning function. In chronic pain syndromes, dysfunctional attentional processes have been implicated in its pathogenesis. As yet, the neuronal mechanisms which mediate the attentional effects of pain in health and disease are largely unknown. Hence, the present study investigated the attentional effects of pain in health and fibromyalgia syndrome (FMS) by recording electroencephalography during a visual attention task with concurrent painful stimulation. The results indicate that pain modulates the attentional performance in healthy subjects. The attentional effects of pain were highly variable between subjects, yielding an increase of reaction times in some subjects, as well as a decrease of reaction times in others. Importantly, pain-related changes in visual task performance were paralleled by individual changes in visual gamma oscillations. With regard to patients with FMS, the results of self-assessment questionnaires indicate that patients perceive themselves as hypervigilant towards pain. However, the experimental findings indicate that the effect of painful stimulation on attentional performance and neuronal gamma oscillations does not differ significantly between patients and healthy controls. These findings demonstrate that pain yields variable attentional modulations which most probably correspond to the interaction of alerting and distracting effects of pain. In the human brain, the variable attentional effects of pain are closely related to changes in neuronal gamma oscillations. Moreover, the findings demonstrate that behavioral and neuronal effects of pain on attention are comparable in health and FMS, and do thus not provide evidence for a behavioral or neuronal manifestation of hypervigilance in patients with FMS.

(Effizientes Verhalten erfordert die aufmerksamkeitsgesteuerte Auswahl und bevorzugte Weiterverarbeitung verhaltensrelevanter sensorischer Information. Insbesondere schmerzhafte Reize beeinflussen aufgrund ihrer außerordentlichen Verhaltensrelevanz die Verteilung unserer Aufmerksamkeitsressourcen. Soweit es sich um

Schmerz in seiner physiologischen Form handelt, erfüllt diese schmerzassoziierte Modulation der Aufmerksamkeit eine wichtige Warnfunktion und ist relevant für den Erhalt physischer Unversehrtheit. Im Rahmen chronischer Schmerzsyndrome hingegen sind möglicherweise dysfunktionale Aufmerksamkeitsprozesse an der Entstehung und Aufrechterhaltung der Erkrankung beteiligt. Weiterhin sind die neuronalen Mechanismen, welche den schmerzassoziierten Aufmerksamkeitsmodulationen in Gesundheit und Krankheit zugrunde liegen, zum gegenwärtigen Zeitpunkt weitgehend unbekannt. In der vorliegenden Studie wurden daher die behavioralen und neuronalen Effekte von Schmerz auf Aufmerksamkeit näher charakterisiert. Dazu wurden sowohl gesunde Probanden als auch Patienten mit Fibromyalgie-Syndrom (FMS) während der Bearbeitung einer visuellen Aufmerksamkeitsaufgabe mit gleichzeitiger Schmerzstimulation elektroenzephalographisch untersucht. Die Ergebnisse belegen, dass Schmerz die Aufmerksamkeitsleistung gesunder Probanden beeinflusst. Die Effekte von Schmerz auf Aufmerksamkeit zeigten hierbei eine große interindividuelle Variabilität. Während einige Probanden nach schmerzhafter Stimulation langsamer reagierten, zeigten andere Probanden verkürzte Reaktionszeiten nach einem Schmerzreiz. Diese schmerzinduzierten Modulationen der Reaktionszeit spiegelten sich auf neuronaler Ebene in Modulationen visueller Gamma-Oszillationen wider. Weiterhin belegen die Ergebnisse, dass Patienten mit FMS sich in Selbstbeurteilungsfragebögen als hypervigilant gegenüber Schmerz einschätzen. Die experimentellen Ergebnisse zeigen jedoch, dass sich weder der Effekt von Schmerz auf die Aufmerksamkeitsleistung noch der Effekt von Schmerz auf Gamma-Oszillationen zwischen Patienten und gesunden Probanden unterscheidet. Diese Ergebnisse veranschaulichen, dass Schmerz zu differentiellen Modulationen der Aufmerksamkeitsleistung führt, welche am ehesten durch das Zusammenspiel von aufmerksamkeitsaktivierenden und -störenden Komponenten des Schmerzes zu erklären sind. Neuronale Gamma-Oszillationen spiegeln die Aufmerksamkeitseffekte von Schmerz auf neuronaler Ebene wider und können somit als neurophysiologisches Korrelat der schmerzbezogenen selektiven Aufmerksamkeit interpretiert werden. Weiterhin liefert die vorliegende Untersuchung bei vergleichbaren Effekten von Schmerz auf Aufmerksamkeit in der Patienten- und Kontrollstichprobe keinen Hinweis auf ein verhaltensrelevantes oder neuronales Korrelat von Hypervigilanz bei Patienten mit FMS.)

# TWO

## General Introduction

# 2 General Introduction

In health, pain fulfills a vitally protective warning function. It indicates that action is required to prevent further bodily harm. Accordingly, in its physiological form pain is indispensable for the maintenance of our physical integrity (Mannes and Iadarola, 2007). Due to this biological salience, painful stimuli are probably never completely unattended and affect the allocation of our attentional resources (Eccleston and Crombez, 1999; Seminowicz and Davis, 2007b). The consequences of pain on attentional performance are manifold. On the one hand, the perception of pain may elevate the global excitation level and may thus be associated with alerting effects on attention and behavior (Ploner et al., 2004; Ploner et al., 2006a). On the other hand, the perception of pain may demand the limited resources of selective attention, disturb the processing of competing non-painful stimuli and interfere with ongoing behavior (Crombez et al., 1996, 1997, 1998b; for review see Eccleston and Crombez, 1999). Only recently, neuroimaging studies have begun to visualize the brain structures and neuronal processes involved in pain-related alertness (Ploner et al., 2006a) and involuntary attentional capture (Legrain et al., 2009a; for review see Legrain et al., 2009b). Still, the specific mechanisms which form the neuronal basis of the pain-attention interaction in health are largely unknown and remain to be explored.

In chronic pain states, pain does no longer fulfill a protective function but persists uncoupled of noxious stimuli without obvious physiological purpose (Millan, 1999). In its chronic form, pain has devastating effects on the quality of life of chronic pain sufferers and their families. Moreover, with approximately 17% of the German population being affected (Wolff et al., 2011), chronic pain poses a problem of immense importance even in economic and social terms. Still, the knowledge on the physiological basis of chronic pain syndromes is incomplete, and their treatment often unsatisfactory (Dunajcik, 1999). A large proportion of patients reporting chronic pain are affected by fibromyalgia syndrome (FMS; Hauser et al., 2009c; Branco et al., 2010). FMS is a functional somatic syndrome which is characterized by widespread musculosceletal pain and allodynia (Wolfe et al., 1990; Hauser et al., 2009b). Another characteristic feature is the presence of specific areas of localized tenderness, referred to as tender points (Wolfe et al., 1990). The symptoms of FMS are not restricted to pain, but frequently include joint stiffness,

fatigue, sleep disturbance (Wolfe et al., 1990), and cognitive dysfunction (Glass, 2008, 2009). While pain-related and other clinical symptoms of FMS have been thoroughly described, the primary origin of this pain syndrome remains as yet elusive. There is evidence that alterations in central processing of sensory input, as well as deficits in the endogenous inhibition of pain may play a role in the pathogenesis, exacerbation and persistence of the disease (Bradley, 2009; Staud, 2009). One factor that may be involved particularly in pain exacerbation is heightened attention to pain and other sensory stimuli. According to this *hypervigilance hypothesis*, patients with FMS show a "perceptual style of amplification" (McDermid et al., 1996; Rollman, 2009), which is characterized by increased attention to external stimulation and a preoccupation with painful sensations (Chapman, 1986; Rollman and Lautenbacher, 1993). Although the notion of heightened attention as a determining factor of exacerbated pain perception appears feasible, it is as yet unknown if and what role hypervigilance plays in the pathophysiology of chronic benign pain disorders such as FMS.

Thus, the objective of the present investigation is the characterization of the attentional effects of pain on attention-related behavior and neuronal processing in healthy subjects and patients with FMS. In particular, the study aims to experimentally explore the behavioral and neuronal correlates of the *hypervigilance hypothesis* in FMS.

Chapter 2 of this thesis is intended to give an overview of the neuronal basis of pain perception and the interplay between pain and attention. Subsequently the definition, epidemiology and pathophysiology of FMS as well as studies on hypervigilance in FMS will be reviewed. Based on this review, the objective and hypotheses of the study will be inferred. Chapters 3 and 4 of this thesis are intended to present the methods and results of the present investigation. Chapter 5 is intended to discuss these results in the context of the literature and to provide a perspective on unsolved issues and future work.

# THREE

## Background

# 3 Background

## 3.1 Neuronal fundamentals of pain perception

### 3.1.1 From sensory receptors to the cerebral cortex - pathways of nociception

Nociception refers to the neuronal process of encoding and processing potentially tissue-damaging (noxious) stimuli in the peripheral and central nervous system (Loeser and Treede, 2008). Mechanical, thermal, and chemical stimuli above a certain threshold are detected by peripheral nerve endings referred to as nociceptors. Whenever a nociceptor is activated, the nociceptive signal is transmitted via Aδ and C fibers to terminate on the dorsal horn of the spinal cord. In the dorsal horn, nociceptive fibers synapse to second-order neurons which predominantly project to the lateral and medial nuclei of the thalamus via the spinothalamic tract (Dostrovsky and Craig, 2006). As a main relay site for nociceptive inputs, the thalamus sends third-order neurons to various cortical and subcortical structures, including the primary somatosensory cortex (Apkarian et al., 2005; Bushnell and Apkarian, 2006). The main ascending pathways of nociceptive processing are depicted in figure 1A.

The mere processing of peripheral nociceptive input is complemented by endogenous mechanisms of pain control (Gebhart, 2004). That is, the processing of nociceptive signals can be modulated at all levels of the ascending nociceptive system by descending projections, which adjust and regulate our conscious pain percept (Millan, 2002; Bingel and Tracey, 2008; Heinricher et al., 2009). These modulatory projections originate in various cortical areas, the hypothalamus, the periaqueductal gray (PAG) of the midbrain as well as the raphe nuclei and other nuclei of the rostral ventral medulla. Complex modulatory effects occur at each of these sites, as well as in the dorsal horn (Purves et al., 2001). The main descending pathways of nociceptive processing are depicted in figure 1B.

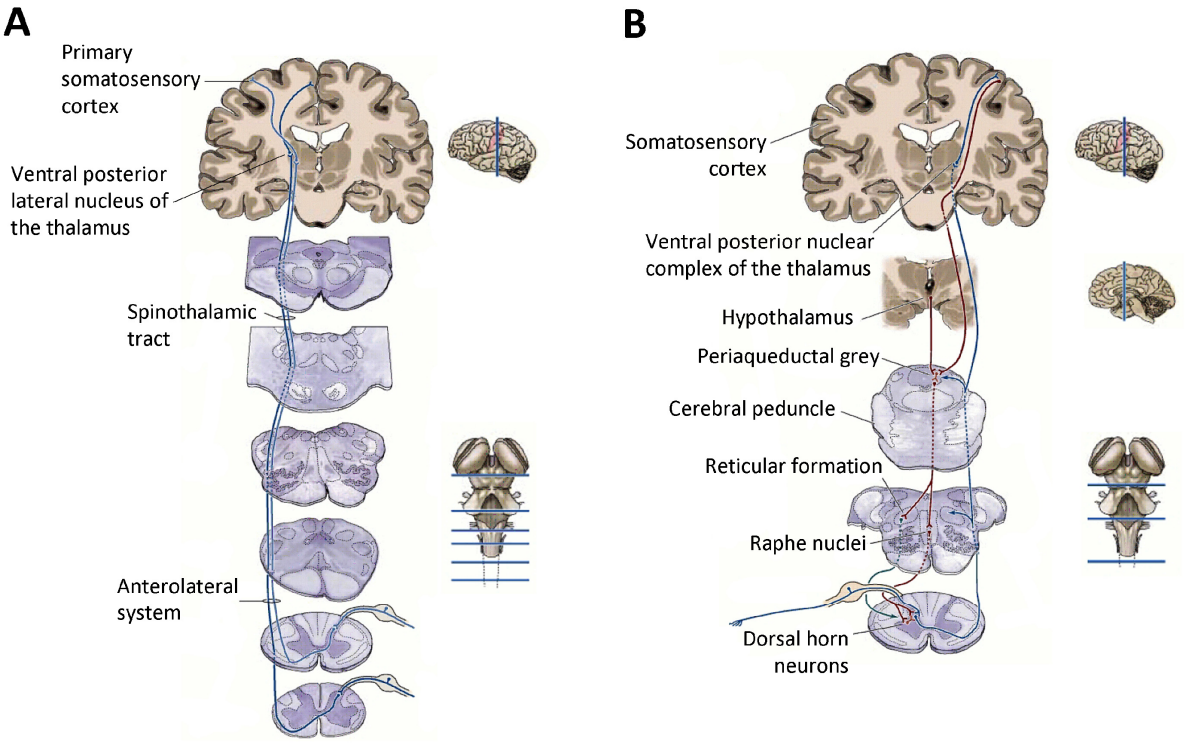



**Figure 1**. **Ascending and descending nociceptive pathways. A** Depicted is the spinothalamic system which carries information about pain and temperature from the lower and upper body parts (excluding the face). **B** Depicted are the descending systems which modulate the transmission of ascending nociceptive signals. These modulatory systems originate in various cortical areas, the hypothalamus, the periaqueductal gray matter of the midbrain, the raphe nuclei, and other nuclei of the rostral ventral medulla (modified according to: Purves et al., 2001).

### 3.1.2 From nociception to perception - pain in the brain

Pain is a complex and multisensory experience. More than any other sensory percept, pain is determined by the interaction between sensory, affective and cognitive factors. It may be attributable to this complexity that painful stimuli activate a widely distributed network of brain areas, which has been referred to as the "pain matrix" (Peyron et al., 2000; Tracey and Mantyh, 2007; figure 2). Although what comprises the pain matrix is not unequivocally defined in the literature (Tracey and Mantyh, 2007), cortical areas frequently activated during pain processing include the primary (SI) and secondary somatosensory cortex (SII), the insular cortex, and the anterior cingulate cortex (ACC; Apkarian et al., 2005). Experimental studies in humans suggest that these different cerebral structures contribute differentially to the various dimensions of the pain experience (Schnitzler and Ploner, 2000).

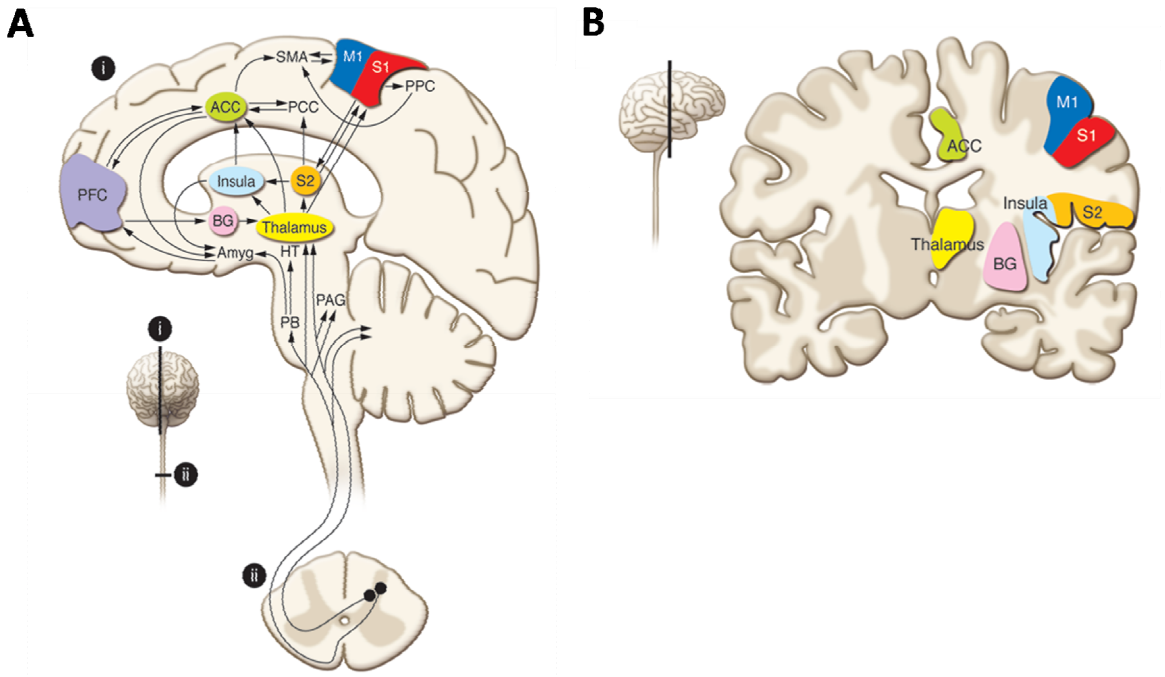



**Figure 2. The pain matrix.** ***A*** Schematic representation of brain regions involved in pain processing. ***B*** Color-coded regions show locations of brain regions involved in pain perception superimposed on an anatomical MRI (coronal slice). Red, S1; orange, S2; green, ACC; light blue, insula; yellow, thalamus; purple, PFC; dark blue, primary motor cortex (M1). SMA, supplemental motor area; PCC, posterior cingulate cortex; BG, basal ganglia; HT, hypothalamus; Amyg, amygdala, PB, parabrachial nuclei. (modified according to: Schweinhardt and Bushnell, 2010).

#### *3.1.2.1 Primary and secondary somatosensory cortices*

SI is activated in merely half of the studies investigating pain-induced cortical activation (Peyron et al., 2000). Hence, the literature concerned with the relevance of SI in pain processing has previously been described as “notoriously inconclusive” (Peyron et al., 2000). However, there is growing evidence that the probability of obtaining SI activation depends on several factors and may thus be increased under certain conditions (Bushnell et al., 1999). Beneficial factors include a higher amount of body surface stimulated (for review see Peyron et al., 2000) or the direction of selective attention towards the painful stimulus (Mima et al., 1998). Beyond the general involvement of SI in pain processing, the role of SI for the pain experience has been further delineated by neurophysiological studies. These investigations confirm the importance of SI for sensory-discriminative aspects of pain perception, e.g. spatial discrimination (Tarkka and Treede, 1993; Andersson et al., 1997; Bingel et al., 2004), intensity coding (Coghill et al., 1999; Timmermann et al., 2001; Bornhovd et al., 2002; Moulton et al., 2005) and temporal coding (Porro et al., 1998; Chen et al., 2002) of nociceptive information.

Moreover, several clinical and experimental observations clearly indicate the involvement of SII in human pain processing. Functionally, pain-induced activity in SII cortex appears to be related to various cognitive (Caselli, 1993; Dong et al., 1994) and sensorimotor functions (Ledberg et al., 1995; Huttunen et al., 1996; Forss and Jousmaki, 1998).

#### *3.1.2.2 Insular cortex*

The insular cortex is implicated in a wide range of conditions and behaviors. Among other things, the insula plays a key role in interoception, which refers to the monitoring of internal bodily perceptions (Craig, 2002, 2003; Critchley, 2005). Moreover, the insular cortex constitutes a multisensory integrative area which is widely connected to systems which are important for affective and cognitive-evaluative processes (Singer et al., 2009; Berntson et al., 2011). Pain-related activation of the insular cortex has been consistently confirmed by functional imaging studies (Coghill et al., 1994; Coghill et al., 1999; Bornhovd et al., 2002; Brooks et al., 2005; Schreckenberger et al., 2005). Studies with brain-injured patients have shown that selective damage to the insular cortex yields deficits in the affective dimension of pain processing, but leaves certain sensory functions intact (Berthier et al., 1988; Greenspan et al., 1999; Starr et al., 2009). Moreover, activation of the insular cortex has been shown to vary with regard to the subjective intensity rating of painful stimuli (Baliki et al., 2009). These findings argue for the notion that insular activity reflects the subjective experience of sensory input rather than objective stimulus features. Additionally, it has recently been shown that the degree to which an impending stimulus is interpreted as threatening biases perceptual decisions about pain (Wiech et al., 2010). The context-dependent evaluation of a painful stimulus was predicted by activity in the insular cortex, suggesting that the insular cortex integrates information about the stimulus saliency into perceptual decision-making in the context of pain. Complementing these results, another recent study investigated how attentional and emotional modulations of pain are subserved in the brain (Ploner et al., 2011). This study revealed that susceptibility of the pain experience to contextual modulations is mediated by flexible functional connectivity patterns of the anterior insula to other functional systems of the brain. Conclusively, the insular cortex is thought to be

involved in generating appropriate, particularly autonomic, responses to sensory stimuli including pain (Craig, 2003; Ploner and Schnitzler, 2004; Starr et al., 2009).

#### *3.1.2.3 Anterior cingulate cortex*

Both anatomically and functionally, the cingulate cortex is a heterogeneous area (Brodmann, 1909; Vogt et al., 1992). The anterior part in particular receives nociceptive input (Vogt et al., 1979; Vogt et al., 1987) and appears to be involved in pain processing. Neuroimaging studies in humans have consistently reported pain-related activations of the ACC (Tolle et al., 1999; Kwan et al., 2000; Buchel et al., 2002). Because of wide and overlapping receptor fields in the ACC region, its activity does not provide relevant information on the sensory-discriminative aspect of pain perception (Sikes and Vogt, 1992; Dostrovsky et al., 1995). Instead, both lesion studies (Foltz and White, 1962; Hurt and Ballantine, 1974) as well as experimental investigations in humans (Rainville et al., 1997; Kulkarni et al., 2005) suggest an involvement of the ACC in the coding of pain-related affect. In fact, recent evidence indivates that negative affect, pain, and cognitive control activate an overlapping region of the ACC (for review see Shackman et al., 2011). Thus, the ACC may be considered as a hub where information about pain as well as other, more abstract kinds of punishment (e.g. negative feedback) is linked to motor centres responsible for affect- and goal-related behavior. Beyond, the ACC appears to exert substantial impact on the endogenous modulation of pain (Wager et al., 2004; Bingel et al., 2006) and play a role in non-pain-related cognitive, attentional and motor functions (Davis et al., 1997; Derbyshire et al., 1998; for review see Bush et al., 2000; Vogt, 2005). Thus, the diversity of nociceptive, motor, and cognitive functions of the ACC and their spatial proximity in terms of neuroanatomy may allow for behavioral reactions, which are motivated by pain as well as modulated by cognitive factors (Vogt, 2005).

### 3.1.3 From pain perception to pain imaging – The electroencephalogram as a method to assess pain processing in humans

Pain is a highly subjective experience. More than any other sensory experience, the perception of pain varies between persons and situations. Accordingly, the search for an objective measure of this subjective percept is not new and still continues today. A

final goal of pain research is to understand the mechanisms of pain perception in the human brain. Eventually, such basic knowledge would be directly related to treatment of pathological pain conditions. In the last decades, pain research has made substantial progress. At least partially, this may be due to recent developments in non-invasive imaging and neurophysiological techniques, such as electroencephalography (EEG), magnetencephalography (MEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS). As an elaborate review of these imaging methods lies beyond the scope of this thesis, the following remarks will focus on the use of the electroencephalogram (EEG) as a neurophysiological measure of pain processing in humans. Figure 3 compares the different approaches to analyze pain-evoked and pain-induced electrical brain activity.

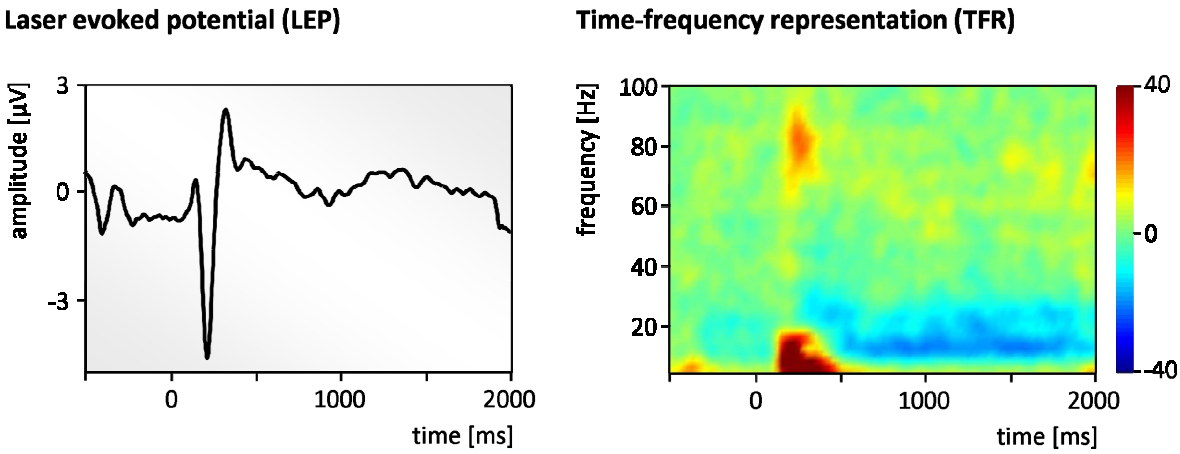



**Figure 3**. **Different approaches to analyze pain-related brain activity.** Both plots show the grand averages of pain-related brain activity of 22 healthy subjects. Approximately 60 painful laser stimuli have been applied to each subject's hand. The left panel shows the classical pain-evoked potential recorded at electrode FCz, displaying the well-known N2 (~250 ms) and P2 (~390 ms) components. The right plot shows the time-frequency transformation of the same data. Here, increases (yellow to red) and decreases (green to blue) of neuronal oscillations in different frequency bands can be distinguished. It becomes evident that the processing of pain is associated with changes in neuronal oscillations at theta, alpha and gamma frequencies, respectively (see paragraphs 3.1.3.1 and 3.1.3.2 for details).

### *3.1.3.1 Laser evoked potentials*

Most EEG studies in pain research have adopted the method of evoked potentials to study the amplitude and temporal characteristics of pain-related neuronal responses (for review see Kakigi et al., 2005; Plaghki and Mouraux, 2005). Evoked potentials are

transient deflections of the EEG that systematically follow the presentation of a sensory stimulus. They result from a synchronized increase of postsynaptic activity in large populations of neurons (Lopes da Silva and Van Rotterdam, 2005). To extract evoked responses from the ongoing EEG activity, the sensory stimulus is presented repeatedly in order to increase the signal-to-noise-ratio. Afterwards, the peristimulus neuronal activity is averaged. The averaging procedure causes random brain activity to be successively cancelled out. On the contrary, stimulus-evoked activity is time-locked to stimulus presentation and is thus preserved during averaging (Handy, 2004). Various stimulation methods have been employed with the objective of recording pain-related evoked potentials (Hari et al., 1983; Hari et al., 1997; Arendt-Nielsen et al., 1999; Wang et al., 2004). At present, there are two methods which meet the requirements of being nociceptive-specific, controllable, safe and reproducible (Kakigi et al., 2005). These comprise the measurement of pain-evoked potentials following painful electrical stimulation (Bromm and Scharein, 1982; Valeriani et al., 2000) and painful laser stimulation (for review see Kakigi et al., 2000). Among these, painful laser stimulation represents the most commonly used method (Cruccu et al., 2004). The resulting laser evoked potentials (LEPs) are mainly composed of three components. A small negative deflection (N1) is reliably followed by a large negative-positive complex (N2 - P2), which has its maximum at vertex electrodes (Plaghki and Mouraux, 2005). Depending on measurement parameters and experimental conditions, the latencies of these components may vary (Chen et al., 1998), but can be estimated to occur at about 150 ms (N1), 250 ms (N2), and 390 ms (P2; Miyazaki et al., 1994; Plaghki and Mouraux, 2005; Kanda, 2006). Investigations using source analysis techniques consistently show that LEPs can be modeled by a combination of generators within the pain matrix, including SI, SII, the insular cortex, and the ACC (Garcia-Larrea et al., 2003). In functional terms, LEPs are modulated by both exogenous factors such as the intensity (Carmon et al., 1978; Carmon et al., 1980) and number (Valeriani et al., 2003; de Tommaso et al., 2011) of the painful stimuli, as well as by endogenous factors such as attentional and cognitive parameters (Beydoun et al., 1993; Garcia-Larrea et al., 1997; Legrain et al., 2002; for review see Kakigi et al., 2000; Lorenz and Garcia-Larrea, 2003).

### *3.1.3.2 Pain-induced oscillatory activity*

Recently, *induced* neuronal oscillations have been suggested to play a role in pain processing, and, in particular, subjective pain perception (Gross et al., 2007; Hauck et al., 2007). These induced oscillations differ from pain-evoked potentials in a lack of phase-locking to the painful stimulus and are thus eliminated by classical averaging techniques. This methodological constraint significantly limits the comprehensive evaluation of pain-related neuronal responses by the evoked-potentials-approach. In the last decade, complementary methods have been utilized for the analysis of pain-induced neuronal oscillations. In particular, the time-frequency decomposition of EEG signals represents a promising approach (Hauck et al., 2008). Thus, the current section reviews the role of pain-related oscillatory changes in specific frequency bands.

Neuronal oscillations in the human brain constitute rhythmic modulations of neuronal activity at multiple frequencies, which are thought to allow the integration of distributed neurons into cell assemblies (Buzsaki and Draguhn, 2004). According to this hypothesis, coherently oscillating neurons can interact effectively, because their communication windows for input and output are open at the same time (Fries, 2005; Uhlhaas et al., 2009). Hence, relying on “communication through neuronal coherence” (Fries, 2005), information is transmitted more effectively in the human brain than it would be if the entire network had to solely rely on static anatomical connections.

In order to image oscillatory neuronal activity at multiple frequency bands, EEG data has to be transformed from the time domain into the time-frequency domain. The resulting time-frequency representations (TFRs) thus show frequency-specific neuronal responses while maintaining a high temporal resolution. The various available methods for time-frequency decomposition of EEG signals include sliding-window Fourier-transformation (Muthuswamy and Thakor, 1998), wavelet analysis (Senhadji and Wendling, 2002), and related methods such as the multitaper method (Mitra and Pesaran, 1999). In the last decades, the number of studies applying time-frequency analyses to electrophysiological data has increased substantially, providing important insights regarding the functional relevance of neuronal synchronization in cortical networks. In particular, the functional role of fast oscillatory activity in the gamma-frequency band (30 - 100 Hz) has been extensively characterized. Based on electrophysiological recordings in animals and humans, these studies confirm the

involvement of neuronal gamma band synchronization in perception and various cognitive tasks, such as stimulus configuration (Gray et al., 1989; Gray and Singer, 1989), feature binding (Tallon-Baudry et al., 1997), attention (Fries et al., 2001), and memory (Tallon-Baudry et al., 1998; Osipova et al., 2006; for review see Jensen et al., 2007; Uhlhaas et al., 2009). On the contrary, only few investigations studied the role of neuronal oscillations in human pain processing and perception. These investigations suggest that the cerebral processing of pain is mainly associated with neuronal oscillations at theta, alpha and gamma frequencies, respectively (Schulz et al., 2011a). On the one hand, experimental painful stimuli elicit an increase of neuronal activity in the theta frequency band, which corresponds to the well-known pain-evoked potential (Mouraux and Plaghki, 2004; Iannetti et al., 2008; Schulz et al., 2011a). On the other hand, the application of an experimental painful stimulus is reliably followed by a decrease of neuronal activity in the alpha and beta frequency bands (Mouraux et al., 2003; Ploner et al., 2006a; Schulz et al., 2011a). This stimulus-related desynchronization has been observed as a result of many types of stimulation (Pfurtscheller et al., 1996; Neuper and Pfurtscheller, 2001), and obviously applies to pain as well. It is thought to reflect the transition from an idling state of the brain to more specific processing, which may be the result of changes in thalamocortical circuits controlling the flow of sensory input from the periphery to the cortex (Chang et al., 2002b; Mouraux et al., 2003; Ohara et al., 2004; Ploner et al., 2006a). Speaking in terms of pain processing, alpha and beta desynchronization may be thought of as a neuronal correlate of the alerting function of pain, which opens relevant thalamocortical gates and prepares the individual to react (Ploner et al., 2006b). Finally, the application of experimental painful stimuli induces high-frequency oscillations in the gamma frequency range (Gross et al., 2007; Hauck et al., 2007; Schulz et al., 2011a). These pain-induced gamma oscillations appear to be particularly associated with the subjective perception of pain (Gross et al., 2007), and are thought to represent a neuronal correlate of the attention-related augmentation of pain processing (Hauck et al., 2007; see paragraph 3.2.2 for further details).

## 3.2 Pain and attention

Attention is not a unitary entity in neuropsychological or neurophysiological terms. Modern views of the dimensionality of attention can be summarized by the multi-component model of attention proposed by van Zomeren and Brouwer (Van Zomeren and Brouwer, 1994; figure 4). A key assumption of this model refers to the distinction between intensity and selectivity aspects of attention (Van Zomeren and Brouwer, 1994; Sturm, 1996). Each of these major components of attention can in turn be subdivided into more specific attentional components, which have been thought to be hierarchically organized and interdependent (Sturm et al., 1997).

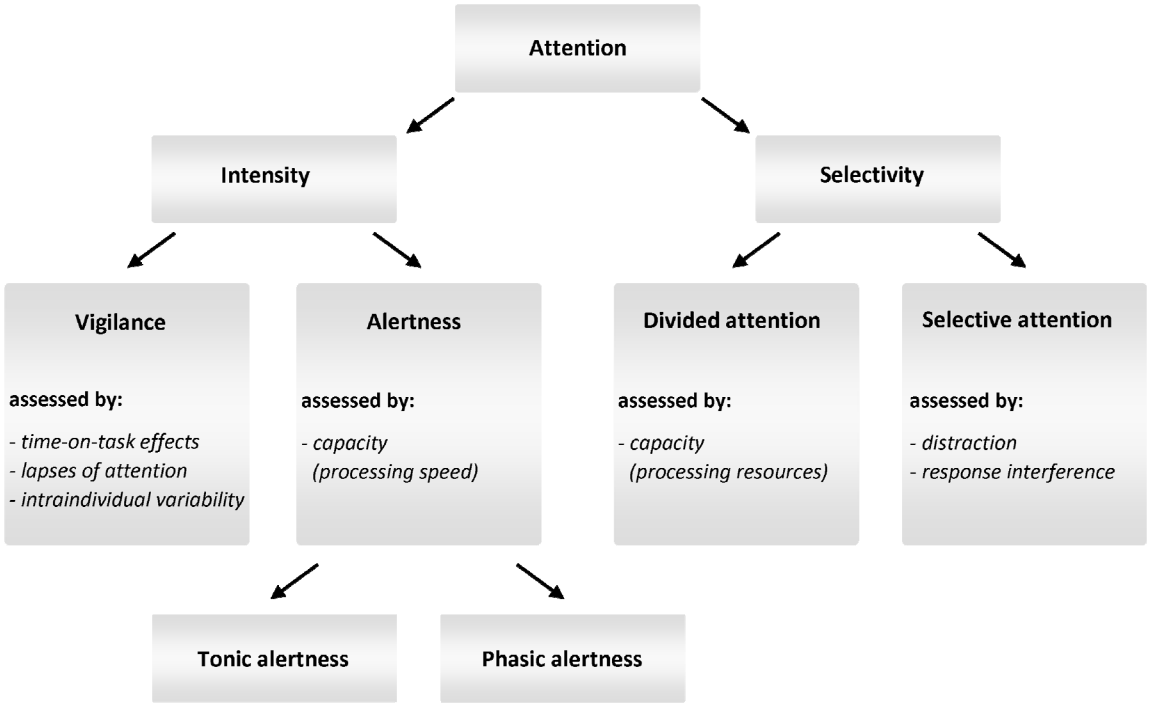



**Figure 4**. **The multi-component model of attention.** The diagram depicts the distinction of selectivity and intensity aspects of attention as proposed in the model by van Zomeren and Brouwer (Van Zomeren and Brouwer, 1994). The intensity aspect of attention can be subdivided into vigilance and alertness, which, in turn, can be further divided into tonic and phasic alertness. The selectivity aspect of attention can be subdivided into divided attention and selective attention.

The intensity aspect of attention comprises two elements: Vigilance and alertness (Van Zomeren and Brouwer, 1994). Vigilance refers to the ability to maintain the attentional focus for a longer period of time (Parasuraman et al., 2000). Alertness is further defined as generalised physical and mental state of arousal and preparedness to

respond (Posner and Boies, 1971; Posner and Petersen, 1990). As the most elementary function of attention, it is considered a prerequisite for the more complex intensity and selectivity aspects of attention. A further distinction is made between two different types of alertness: *Tonic alertness*, which is subject to diurnal fluctuations in wakefulness and can be modulated intrinsically by top-down processes (Posner and Petersen, 1990; Sturm et al., 1997), and *phasic alertness*, which refers to the ability to increase response readiness in consequence of external stimuli (Posner and Petersen, 1990; Sturm et al., 1997).

The selectivity aspect of attention comprises two elements: Selective attention and divided attention. Whereas divided attention refers to the ability to efficiently distribute attentional resources between two or more relevant stimuli, selective attention is thought to involve the ability to focus on relevant features of a task while suppressing responses to irrelevant stimuli at the same time (Posner and Petersen, 1990). The properties of selective attention are often metaphorically referred to as *spotlight,* or *cocktail party effect* (Cherry, 1953; LaBerge, 1983), pointing out that the focus of attention may fluctuate between different locations without overt orientation in terms of eye or head movements. Investigations using neuroimaging techniques have consistently shown that this attentional filtering of sensory input modulates neuronal activity even at very early stages of modalityspecific cortical processing (Desmedt and Tomberg, 1989; Garcia-Larrea et al., 1991; Gandhi et al., 1999; Somers et al., 1999; Eimer and Forster, 2003). There is evidence that attention is preferentially allocated to stimuli which indicate potential danger (Bar-Haim et al., 2007). It can be argued that pain is a prototypical example of evolutionary determined threat (Van Damme et al., 2010), since it fulfills a physiological warning function and is distinguished from other sensory modalities by its invariably high behavioral relevance. Due to this biological salience, painful stimuli are probably never completely unattended and affect the implicit allocation of attention (Eccleston and Crombez, 1999; Seminowicz and Davis, 2007b).

### 3.2.1 Pain-related alertness or distraction? The attentional effects of pain on behavior

Pain can be assumed to exert impact on both intensity as well as selectivity aspects of attention (Lorenz and Bingel, 2008), entailing both beneficial as well as

interruptive effects on simultaneous non-pain-related behavior. On the one hand, it is conceivable that pain increases the global level of alertness, facilitating pain-related and non-pain-related reactions in equal measure. On the other hand, pain may demand the limited resources of selective attention, affect the simultaneous processing of competing non-painful stimuli, and interfere with ongoing non-pain-related behavior. In the literature, both scenarios have been experimentally addressed.

#### *3.2.1.1 Evidence for pain-related alertness*

In the presence of stress, adaptive physiologic and behavioral changes occur, which attempt to maintain and restore our body's homeostasis. Likewise, stressful painful stimuli are thought to increase the global level of alertness. It appears feasible to assume that this pain-induced increase of the global excitation level is accompanied by an enhanced ability to focus on goal-related behavior, and, thus, by an increase of non-modality-specific behavioral efficiency. To some extent, behavioral studies have experimentally confirmed the notion of a pain-related increase of global alertness and non-pain-related behavioral efficiency. However, the effect appears to be subject to certain conditions. That is, a painful stimulus may serve as an efficient wake-up-call whenever reactivity is impaired due to low levels of wakefulness and alertness (Conley et al., 1997). Once the alertness exceeds a certain level, however, the interruptive function of pain predominates. Further empirical evidence for the conditional effects of pain on attentional perfromance has been demonstrated by Patil and colleagues (1995). The study assessed the effect of cold-water-induced pain on the behavioral performance in two different tasks in healthy volunteers. The first task comprised a critical flicker frequency test, which measures a subject's ability to discriminate subtle changes in the frequency of a flickering light and was intended to provide a measure of alertness (Simonson and Brozek, 1952). The second task comprised a test of short-term memory, which was intended to provide a measure of cognitive performance. In conformity with the above-mentioned hypothesis, application of the painful stimulus improved the subjects' performance in the critical flicker frequency test as an expression of a pain-induced increase of alertness. The performance in the short-term memory task, however, was corrupted by the application of the painful stimulus as an expression of the interruptive effects of pain.

#### *3.2.1.2 Evidence for pain-related distraction*

In order to investigate the potential ability of pain to involuntarily capture attention and interfere with ongoing behavior, several studies have made use of the primary task paradigm (Crombez et al., 1994; Eccleston, 1994). In a primary task paradigm, participants are occasionally distracted by painful stimulation while performing an attentionally demanding (primary) task. The rationale of this paradigm states that in a situation of competing sensory input, the attentional selection of the most salient stimulus (e.g. pain) will limit the attentional resources available for the remaining demands. The resulting deterioration in primary task performance is then taken as a measure of pain-related attentional interference. Taken together, these behavioral investigations yielded ambiguous results regarding pain-related attentional capture in healthy volunteers. Some investigators applied painful stimuli during the performance of a perceptual maze test (Petrovic et al., 2000) or a visual search task, respectively (Veldhuijzen et al., 2006). They observed that pain did not significantly affect task performance. On the contrary, there is experimental evidence arguing in favor of pain-related attentional interference. In a series of behavioral studies, Crombez and colleagues demonstrated consistently that the performance in an auditory discrimination task is significantly impaired by electrical painful stimulation (Crombez et al., 1994; Crombez et al., 1996, 1997). Subsequently, further studies have specified the circumstances which are favorable to the occurrence of pain-induced attentional interference. According to these studies, the disruption of ongoing behavior by pain is facilitated whenever the painful stimulus is perceived as particular threatening (Crombez et al., 1998a). Moreover, attentional interference was reported to be enhanced by catastrophic thinking (Crombez et al., 1998b). Interestingly, Seminowicz and colleagues (2004) observed a considerable interindividual variability regarding the effects of pain on attentional performance. Whereas some subjects showed slower reaction times in an attention-demanding task after painful stimulation, others reacted faster after the application of a painful stimulus. According to the authors, the utilization of different cognitive strategies may account for the observed behavioral heterogeneity. Specifically, they propose that subjects with faster reaction times may have focused more efficiently on the attention task during painful stimulation.

Taken together, the existing literature on the attentional effects of pain remains as yet inconclusive. Whereas both facilitating as well as disturbing effects of pain on non-pain-related behavior have been experimentally confirmed by some studies, other investigations have failed to provide evidence for a behaviorally-relevant impact of pain on attention. At least partially, these inconsistencies may be due to the considerable interindividual variability in the effects of pain on behavior. This variability, in turn, suggests a complex interaction of the alerting and distracting effects of pain. Depending on which aspect predominates, the processing of non-pain related sensory information may be supported or disturbed by pain, resulting in pain-induced increased or pain-induced decreased attentional performance. Moreover, the investigations strongly suggest that the extent of pain-related attentional interference may at least partially be determined by top-down regulatory processes (for review see Van Damme et al., 2010).

### 3.2.2 Neuronal correlates of the attentional effects of pain

Functional brain imaging has been adopted to elaborately characterize the neuronal basis of pain processing. More recently, neuroimaging and neurophysiological studies have begun to elucidate the neuronal correlate of the attentional effects of pain.

#### *3.2.2.1 Neuronal correlates of pain-related alertness*

Sensory stimuli in general and painful stimuli in particular may serve as a *wake-up-call*, increasing the alertness and neuronal excitation level. In the human brain, this externally-triggered transition from an awake, but idling state of the brain towards higher excitability has been well characterized. In the resting state, neuronal activity over primary sensory and motor areas is characterized by spontaneous oscillations at frequencies around 10 and 20 Hz (Hari and Salmelin, 1997; Niedermeyer, 2005). These oscillations reflect the functional state of a system, with higher amplitudes of oscillatory activity being related to an idling state, and lower amplitudes being associated with activation (Pfurtscheller, 2005). Alerting sensory stimuli may externally modulate the functional state of a system, resulting in event-related desynchronization of oscillatory neuronal activity (Pfurtscheller, 2005). Thus, the occipital alpha-rhythm is attenuated by visual stimuli, whereas the alpha- and beta-rhythms over sensorimotor cortices are

diminished by touch and / or movements (Hari and Salmelin, 1997; Pfurtscheller, 2005). Likewise, it has been consistently shown that painful stimuli induce a suppression of oscillatory neuronal activity which is thought to reflect the alerting effects of pain (Ohara et al., 2004; Ploner et al., 2006a,b). Being associated with pain-specific changes in the human EEG, this pain-induced suppression can be differentiated from event-related desynchronization induced by other sensory modalities (Chang et al., 2002a). Moreover, pain induces a spatially extensive suppression of cortical oscillatory activity (Ploner et al., 2006a). This global suppression contrasts with the regional suppression induced by other sensory modalities, indicating a more widespread change in cortical excitability which is specific to pain (Ploner et al., 2006a). Functionally, this pain-induced increase in cortical excitability has been related to an opening of thalamocortical gates (Steriade and Llinas, 1988), which appears to prepare the individual for fast and efficient reaction to stimuli of existential relevance (Ploner et al., 2004; Raij et al., 2004; Ploner et al., 2006b).

#### *3.2.2.2 Neuronal correlates of pain-related distraction*

Whereas the distracting effects of pain on behavior have been addressed by several studies, there is hardly any neurobiological evidence on the associated neuronal activity and underlying mechanisms of attentional interference. Investigations using functional magnetic resonance imaging (fMRI) appear to be particularly suited to identify the cerebral regions where the modulatory impact of pain on attention takes effect. In order to reveal how pain interferes with visual object processing, Bingel and colleagues (2007) presented visual objects with and without concomitant painful stimuli during fMRI scanning. Impaired recognition memory after painful stimulation was paralleled by a pain-induced modulation of neuronal activity in the lateral occipital complex, a cerebral region in the ventral visual stream important for visual object processing (Grill-Spector et al., 2001). Moreover, the source of this modulatory influence could be located in the rostral anterior cingulate cortex (rACC), which most probably serves as a link between pain perception and attentional control (Bingel et al., 2007). This notion is supported by an earlier investigation by Bantick and colleagues (2002), who demonstrated that the anterior cingulate cortex (ACC) showed increased activation whenever subjects got distracted from a primary task as a result of painful stimulation. Two other studies

investigated the neuronal correlate of attentional interference using fMRI (Seminowicz et al., 2004; Seminowicz and Davis, 2007a). During painful stimulation, the successful engagement in a cognitive task was paralleled by a modest attenuation of pain-related brain activity in primary and secondary sensorimotor cortex, insular cortex and cingulate cortex. Hence, these findings shed light on the neuronal correlates of efficient attentional engagement in spite of concomitant painful stimulation.

Whereas these studies provide evidence on the cerebral sites of pain-related modulatory effects, the neuronal mechanisms of pain-related attentional interference remain as yet widely unknown. Being able to detect both evoked and induced electrical brain activity, neurophysiological methods such as electro- (EEG) or magnetencephalography (MEG) are particularly suited to complement previous studies and extend the knowledge on underlying neuronal mechanisms of pain-related attentional capture. In an EEG study by Legrain and colleagues (2005) subjects were instructed to engage in a primary visual task, while painful stimuli were applied concurrently. Noteworthy is the finding that performance in the primary visual task was impaired whenever painful stimuli elicited particularly large P2 amplitudes. In contrast, enhancement of the cognitive load in the primary task resulted in decreased amplitudes of the pain-evoked potential, reflecting attenuated orienting of attention to pain.

Besides the evaluation of pain-*evoked* potentials, electrophysiological methods allow for an assessment of pain-*induced* activity as a potential neuronal correlate of the attentional effects of pain. Here, neuronal oscillations in the gamma frequency range (30-100 Hz) appear to be of particular interest. Neuronal gamma oscillations have consistently been related to the attentional selection and enhanced processing of sensory information (Salinas and Sejnowski, 2001; Jensen et al., 2007; Fries, 2009). Recently, gamma oscillations have also been observed in response to painful stimuli (Schulz et al., 2011a,b). These pain-induced gamma oscillations varied with attention to the painful stimuli (Hauck et al., 2007) and their conscious perception (Gross et al., 2007). It can thus be assumed that the attentional effects of pain might be associated with changes of gamma oscillations in the human brain. Still, studies evaluating gamma oscillations as a potential neuronal correlate of pain-related attentional effects remain to be accomplished. Accordingly, a promising approach is to relate pain-induced modulations of attentional performance to pain-induced modulations of neuronal gamma oscillations.

## 3.3 Fibromyalgia syndrome

The fibromyalgia syndrome (FMS) refers to a musculoskeletal disorder which is characterized by chronic widespread pain as a core feature. Besides the painful core symptoms, which are always present, the disorder is associated with characteristic features which are present in more than 75 % of the patients (e.g. morning stiffness, sleep disturbances, or fatigue), and common features that are present in more than 25 % of the patients (e.g. paresthesia or other conditions causing chronic pain; Wolfe, 1989).

The diagnosis of FMS is not a diagnosis of exclusion (Wolfe et al., 1990), but should be based on its particular characteristics. The American College of Rheumatology (ACR) 1990 criteria (Wolfe et al., 1990) are product of the first well-designed, multicenter study and remain a cornerstone for the diagnosis of FMS. They comprise two components: (1) widespread pain involving both sides of the body, present above and below the waist as well as along the axial skeletal system, for at least three months. (2) Pain in 11 of 18 tender points on digital palpation (figure 5).

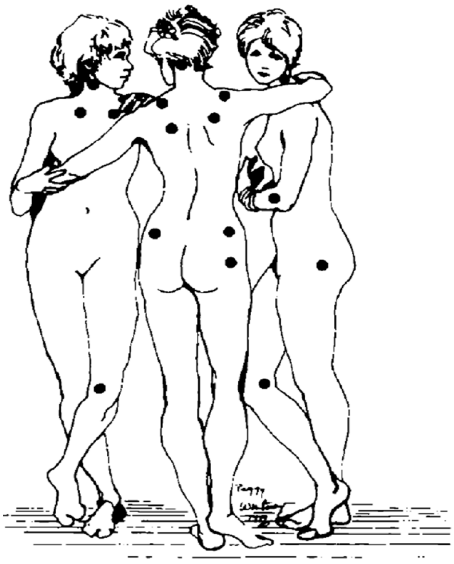


**Figure 5**. **Tender points.** Depicted are the tender point locations as published in the 1990 classification criteria for fibromyalgia (figure taken from: Wolfe et al., 1990).

Using the ACR criteria, the syndrome is commonly diagnosed. The prevalence in the general population of the United States (Wolfe et al., 1995), European countries

(Branco et al., 2010), and Germany (Hauser et al., 2009a) is estimated between 3 and 5 %. Women are 10 times more often affected by FMS than men (Wolfe, 1989). Of all rheumatic disease clinic patients, 10 to 20 % are diagnosed with FMS (Wolfe, 1989).

Recently, the American College of Rheumatology has published the results of a multicenter study, presenting new preliminary diagnostic criteria for fibromyalgia and the measurement of its symptom severity (Wolfe et al., 2010). These criteria are not meant to replace the ACR 1990 criteria, but to provide an alternative method of diagnosis which, more than before, takes non-pain-related symptoms into account. Under these non-pain-related characteristic features, morning stiffness and the subjective feeling of swollen joints are commonly reported symptoms in FMS patients (Mease, 2009). Many patients further experience sleep disturbances and fatigue (Mease, 2009). Moreover, patients frequently complain of cognitive dysfunction, commonly referred to as *fibrofog* (Leavitt et al., 2002). Clinical and experimental evidence suggests that the cognitive functions particularly impaired by FMS include working memory, episodic memory and semantic memory as well as attentional control (for review see Glass, 2008, 2009). Fibromyalgia is frequently comorbid with other psychiatric and painful conditions. Three of the most commonly encountered comorbid psychiatric conditions include anxiety, depression, and the posttraumatic stress disorder (Epstein et al., 1999; Martinez-Lavin, 2001; Buskila and Cohen, 2007). Beyond, a considerable overlap between FMS and other functional somatic syndromes, such as irritable bowel syndrome (Sperber et al., 1999), irritable bladder, atypical facial pain, temporomandibular joint pain or noncardiac chest pain (Wessely et al., 1999; Aaron and Buchwald, 2001; Henningsen et al., 2007), has been empirically confirmed.

Although developments in the understanding of the pathophysiology of the disorder have led to improvements in treatment, FMS is as yet treatable, but not curable. There is evidence that a multidimensional approach including pharmacologic therapy, patient education, cognitive behavioral therapy, exercise, and physical therapy is most effective (Rossy et al., 1999; Carville et al., 2008). As research continues to progress, the pathophysiology of the disorder can be expected to be further elucidated, resulting in more targeted strategies for an efficient treatment of FMS. Current considerations regarding the pathophysiology of the disease are summarized in the following paragraph.

### 3.3.1 Pathophysiology of FMS

Although the causes of FMS remain to be determined, there is strong evidence that the widespread pain as the core symptom of the disorder is due to abnormalities in central nervous system function. Moreover, genetic research has confirmed a familial aggregation of FMS, suggesting a genetic predisposition (Arnold et al., 2004; Buskila and Neumann, 2005; Kato et al., 2006). It has further been hypothesized that the exposure to physical or psychosocial stressors, along with aberrations in the stress response axis, may have a share in symptom expression (Martinez-Lavin, 2007). Finally, it is also thought that psychological and behavioral factors may contribute to the individual manifestation of FMS. As an elaborate review of the genetic and biologic factors associated with the pathophysiology of FMS lies beyond the scope of this thesis, the following remarks will focus on aberrations of central pain processing as well as psycho-behavioral aspects related to the pathophysiology FMS.

A large body of evidence indicates that pain perception and processing in patients with FMS differs from healthy individuals. It appears that, in spite of unaffected detection thresholds for sensory stimuli, patients with FMS display significantly lower pain thresholds in comparison to healthy persons. Several psychophysical studies have consistently demonstrated a reduction of thermal and mechanical pain thresholds (Granges and Littlejohn, 1993; Gibson et al., 1994; Lautenbacher et al., 1994; Hurtig et al., 2001; Desmeules et al., 2003; Petzke et al., 2003; Smith et al., 2008), which appears to be widely independent of stimulation techniques. These subjective indices of pain measurement are complemented by the results of more objective indices, demonstrating a reduced nociceptive reflex threshold in patients with FMS (Desmeules et al., 2003). Moreover, the patients' reports of increased pain perception are corroborated by functional imaging and neurophysiological studies, indicating enhanced pain-related activation in terms of pain evoked potentials (Gibson et al., 1994; Lorenz et al., 1996; Diers et al., 2008) and regional cerebral blood flow (Gracely et al., 2002; Cook et al., 2004; Burgmer et al., 2009; Pujol et al., 2009; for review see Schweinhardt et al., 2008).

To account for the amplified perception and processing of external nociceptive input, both neurobiological as well as psychological factors have been considered. As a neurobiological aberration resulting in temporary or permanent amplification of sensory input, central sensitization has been implicated in the pathophysiology of FMS (for review

see Woolf, 2011). Indeed, mounting evidence suggests that a pathological amplification of pain-related information occurs at the level of the spine in FMS patients (Li et al., 1999; Graven-Nielsen et al., 2000; Staud et al., 2001). However, the underlying mechanisms yielding this amplification have not been sufficiently specified yet. Additionally, but not mutually exclusively, psychological factors may contribute to the pathologically enhanced pain-related sensitivity in patients with FMS. This notion is supported by the observation that FMS is frequently comorbid with psychiatric conditions (Epstein et al., 1999; see paragraph 3.3 for further details). Moreover, somatization as the tendency to develop numerous medically unexplained symptoms is a significant risk factor for the development of chronic widespread pain (McBeth et al., 2001). This finding suggests that widespread pain may be a somatic manifestation of psychological distress (McBeth et al., 2001). Finally, dysfunctional attentional processes in a sense of heightened attention to pain or a failure to disengage from pain have been implicated in the pathogenesis and maintenance of chronic pain (Eccleston and Crombez, 1999; Clauw, 2001; Clauw and Crofford, 2003; Crombez et al., 2005). The hypervigilance hypothesis of FMS is portrayed in the following paragraph.

### 3.3.2 Hypervigilance hypothesis in FMS

Hypervigilance refers to a perceptual style which is characterized by increased attention to external stimuli and a preoccupation with painful sensations (Rollman and Lautenbacher, 1993; Clauw and Crofford, 2003). A hypervigilant style of perception is thought to be associated with impaired cognitive filtering mechanisms as well as an amplification of aversive sensory input (Rollman and Lautenbacher, 1993).

In patients with FMS, hypervigilance has previously been inferred from the fact that patients demonstrate increased sensitivity for various kinds of experimental painful stimuli (see paragraph 3.3.1 for details). Although somewhat controversial (Lautenbacher et al., 1994; Lorenz, 1998; Peters et al., 2000), there is substantial evidence that this heightened sensitivity in patients with FMS does not exclusively apply to pain, but also to a large variety of other sensory signals, including thermal and auditory stimuli (Smythe, 1986; Dohrenbusch et al., 1997; Carrillo-de-la-Pena et al., 2006; Geisser et al., 2008; Hollins et al., 2009). Accordingly, McDermid and colleagues (1996) have proposed their

*generalized hypervigilance hypothesis* of FMS. In their study they compared the perception of both painful and auditory stimuli in patients with FMS, patients with rheumatoid arthritis (RA), and healthy subjects. Besides lower pain thresholds and lower pain tolerance, patients with FMS also displayed lower noise tolerance as compared to patients with RA and healthy subjects. This finding supports the generalized hypervigilance hypothesis put forward by the authors, and suggests that the amplification of incoming sensory information may indeed be a critical factor in FMS.

Importantly however, the heightened sensitivity of patients with FMS to sensory stimuli in general and painful stimuli in particular can not unambiguously be attributed to hypervigilance. Alternatively, a central augmentation of sensory input in terms of central sensitization (Woolf, 2011) or deficient inhibitory control mechanisms (Lautenbacher and Rollman, 1997; Julien et al., 2005) could account for the observed hypersensitivity. This fact makes it necessary to think of alternative approaches to adequately assess hypervigilance. Since hypervigilant persons are by definition “too attentive to their surroundings” (Clauw and Crofford, 2003), it appears feasible to operationalize hypervigilance as the effect of pain on attentional performance. Experimentally, the attentional effects of pain can be adequately assessed using a primary task paradigm (Crombez et al., 1996; see paragraph 3.2.1.2 for further details). While several investigations have applied the primary task paradigm in order to adequately assess hypervigilance in chronic pain disorders, their results remain inconclusive so far.

On the one hand, at least one study reports evidence for behaviorally relevant hypervigilance in patients with chronic pain (Eccleston et al., 1997). In this study, Eccleston and colleagues evaluated the performance of chronic pain patients in an attention-demanding cognitive task. In conformity with the hypervigilance hypothesis, disruption of attentional performance was most pronounced in patients who reported high pain intensity. Importantly, several things need to be considered while interpreting the results of this investigation. First, the study design did not include a control group. Thus, it remains questionable if the observed effects reflect pathological alterations specific to chronic pain disorders. Second, the study sample included patients suffering from chronic pain of various origins. Thus, the observed effects may not be specific to FMS. Finally, the authors applied a modified version of the primary task paradigm: Instead of assessing the distraction due to an experimental painful stimulus, the study

evaluated to what extent the persistent, chronic pain of the patients caused deterioration in task performance. Although this approach might imply enhanced ecological validity, it does not allow for causal reasoning.

On the other hand, several experimental investigations failed to find experimental evidence for hypervigilance in patients with FMS (Peters et al., 2000; Asmundson et al., 2005). Importantly, it has to be noted that these studies evaluated the attentional bias towards innocuous somatosensory (Peters et al., 2000) or threatening linguistic stimuli (Asmundson et al., 2005), but not towards painful sensory stimuli. Thus, based on the results of these studies, it can not be inferred that patients with FMS do not show an attentional bias towards *painful* sensory information.

In summary, the existent literature remains inconclusive, albeit not unsuggestive, of hypervigilance in FMS. It needs to be clarified whether hypervigilance, central sensitization or both phenomena have their share in the development of a heightened sensitivity in patients with FMS. In this context, investigations assessing the pain-related attentional bias and its neuronal correlates in FMS by means of a primary task paradigm with concurrent painful stimulation show particular promise (Crombez et al., 2005).

## 3.4 Aims of the study

In health, pain fulfills a vitally protective warning function. Due to this biological salience, painful stimuli are of utmost behavioral relevance and affect the allocation of attentional resources. Experimental studies have demonstrated both alerting as well as distracting effects of pain on attention, as pain yielded both pain-induced increases as well as decreases of attentional performance. Still, it remains to be determined which neuronal mechanisms mediate these variable attentional effects of pain in health.

In chronic pain states, pain does no longer fulfill a protective warning function, but persists without any obvious physiological purpose. It appears feasible that imbalances in the distracting and alerting effects of pain may contribute to the pathological pain experience. The fibromyalgia syndrome (FMS) is a chronic pain disorder of unknown

origin. Amongst other influencing factors, dysfunctional attentional processes in terms of hypervigilance towards pain have been implicated in its pathogenesis.

In the human brain, neuronal gamma oscillations have been observed in response to painful stimuli. Varying with attention to the painful stimuli, these pain-induced gamma oscillations might represent a neuronal correlate of the attentional effects of pain in health and disease.

Accordingly, the present investigation is intended to characterize the attentional effects of pain in healthy subjects and patients with FMS. In particular, the study aims to verify the following four assumptions:

***1.*** **Painful stimulation modulates the attentional performance in healthy subjects.**

*Subjects will be asked to engage in a primary visual task with concurrent painful stimulation. The changes in visual reaction times following painful stimulation will serve as measure of pain-related attentional modulation.*

**2. Gamma oscillations represent a neuronal correlate of the attentional effects of pain.**

*Specifically, it is hypothesized that visual stimulation will induce gamma oscillations in the primary visual cortex. Painful stimulation will yield pain-induced gamma oscillations in the primary somatosensory cortex. Moreover, painful stimulation will modulate gamma oscillations in the visual cortex. Functionally, these effects of pain on visual gamma oscillations will relate to changes in visual task performance.*

**3. Patients with FMS are hypervigilant towards pain compared to healthy controls.**

*The individual rating in established self-assessment questionnaires will serve as a subjective measure of hypervigilance. The pain-induced modulation of attentional*

*performance in a primary task paradigm as compared to healthy controls will serve as an objective measure of hypervigilance.*

**4. Gamma oscillations represent a neuronal correlate of hypervigilance in FMS.**

*Neuronal gamma oscillations will be differentially modulated by painful stimulation in patients with FMS and healthy controls. Specifically, changes of attentional performance in the primary task paradigm indicative of hypervigilance in FMS will be paralleled by corresponding changes in neuronal gamma oscillations.*

# FOUR

## Methods

# 4 Methods

The present study is intended to characterize the behavioral impact and neuronal mechanisms of the attentional effects of pain in healthy subjects and patients with fibromyalgia syndrome (FMS). Therefore, we recorded EEG from healthy subjects and patients with FMS during an attention-demanding visual reaction time task with concurrent painful stimulation.

It has to be noted that the formulation of the topic evolved as a result of a dynamic process: Initially, the investigation aimed to assess the attentional effects of pain in health. However, the results of the pilot project suggested that maladaptive changes in the attentional effects of pain as well as aberrations in neuronal gamma oscillations might play a role in the pathogenesis of chronic pain syndromes, particularly in FMS. Accordingly, this thesis comprises the results of two subprojects, which were successively performed and differ regarding their subject samples. Whereas the first subproject comprises a sample of healthy subjects, the second subproject compares the attentional effects of pain in patients with FMS and a healthy control group. The subprojects are widely comparable regarding the study design and analysis techniques. In case the adopted methods differ between the subprojects, it will be explicitly stated in the text.

The design, data collection and data analysis for both subprojects covered a three-year period which extended from March 2008 to May 2011.

## 4.1 Subjects

### 4.1.1 Subject sample for subproject 1

30 healthy subjects participated in the experiment. The EEG data from 8 subjects had to be excluded due to poor data quality. The analysis, thus, included data of 22 subjects (11 male, 11 female) with a mean age of 26 years (range 20 - 39 years). All subjects had normal or corrected-to-normal visual acuity. Informed consent was obtained before participation. Subjects were paid 30 Euro for study participation. The procedure

was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

### 4.1.2 Subject sample for subproject 2

#### *4.1.2.1 Patients with FMS*

A total of 22 patients diagnosed with FMS participated in the study. Patients were recruited from the Department of Physical Medicine and Rehabilitation, Klinikum der Universität München and the Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München. The inclusion criterion was fulfilling the American College of Rheumatology (ACR) criteria for FMS (Wolfe et al., 1990). Exclusion criteria comprised neurologic, psychiatric, dermatological or metabolic diseases as well as any disorder causing chronic or acute pain other than FMS. Moreover, patients were excluded from study participation if they were not able to interrupt their pharmacological therapy with centrally active analgesics (opioids) or coanalgesics (antidepressants, anticonvulsants) for a minimum of 7 days. The use of peripherally active rescue analgesics was allowed for up to 24 hours before study participation. Three patients failed to complete either the behavioral or neurophysiological part of the experiments and were excluded from further analyses. Thus, the patient sample comprised data of 19 subjects (5 male, 14 female) with a mean age of 52 years (range 24 – 71 years).

#### *4.1.2.2 Healthy control group*

Additionally, 22 healthy subjects (2 male, 20 female) with a mean age of 47 years (range 25 – 66 years) participated in the study. Control and patient sample were matched for age ($t = 1.4$, $p > 0.1$) and sex ($\chi 2 = 2.1$, $p > 0.1$). All participants had normal or corrected-to-normal visual acuity. Informed consent was obtained from all patients and healthy subjects before participation. Healthy subjects were paid 50 Euro for study participation. The procedure was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki. Table 1 gives an overview of the subject samples of subproject 1 and 2.

**Table 1. Subject samples.** Summarized are the sociodemographic data of the subject samples for subproject 1 and subproject 2.

| | Subproject 1 | Subproject 2 | |
|---|---|---|---|
| | ***Healthy subjects*** | ***Patients with FMS*** | ***Healthy controls*** |
| **n** | 22 | 19 | 22 |
| **Age (M ± SD)** | 26 ± 4 | 52 ± 11 | 47 ± 11 |
| **Age range** | 20 - 39 | 24 - 71 | 25 - 66 |
| **Sex (female / male)** | 11 / 11 | 14 / 5 | 20 / 2 |

*Note:* M = mean; SD = standard deviation.

## 4.2 Procedure

### 4.2.1 Protocol

#### *4.2.1.1 Protocol for subproject 1*

All experiments were performed in a single testing session which took approximately two hours. The process included the completion of forms and self-assessment questionnaires (15 minutes), preparation of the EEG recordings (45 minutes), and EEG recordings during behavioral task performance (60 minutes). Behavioral tasks included the primary task paradigm which is described in paragraph 4.2.2. Moreover, subjects performed a simple pain rating task, which is not covered by this thesis (Schulz et al., 2011a).

#### *4.2.1.2 Protocol for subproject 2*

In order to prevent the effects of fatigue as a confounding factor, experiments were performed on two consecutive days. Testing procedures on day one took approximately 1.5 hours and included the completion of forms and self-assessment questionnaires (30 minutes). Moreover, both patients and healthy controls received quantitative sensory testing (QST, 60 minutes; Rolke et al., 2006), the results of which are not discussed in this thesis. Testing procedures on day two took approximately 2.5 hours and included preparation of the EEG recordings (45 minutes) and EEG recordings during

behavioral task performance (90 minutes plus break). Behavioral tasks included the primary task paradigm which is described in paragraph 4.2.2. Moreover, subjects performed a similar paradigm with concurrent non-painful stimulation as well as two simple rating tasks for painful and non-painful somatosensory stimuli, which are not covered by this thesis (Schulz et al., 2011a).

### 4.2.2 Primary task paradigm

In a primary task paradigm, participants are occasionally distracted by painful stimulation while performing an attentionally demanding task (Crombez et al., 1994; Eccleston, 1994). The resulting deterioration in attentional task performance is then taken as a measure of pain-related attentional interference (Van Damme et al., 2010). Here, participants completed an attention-demanding visual reaction time task with interfering painful laser stimuli (figure 6). The visual task is based on a well-established paradigm which is known to reliably induce gamma oscillations in human visual cortex (Hoogenboom et al., 2006; Scheeringa et al., 2011).

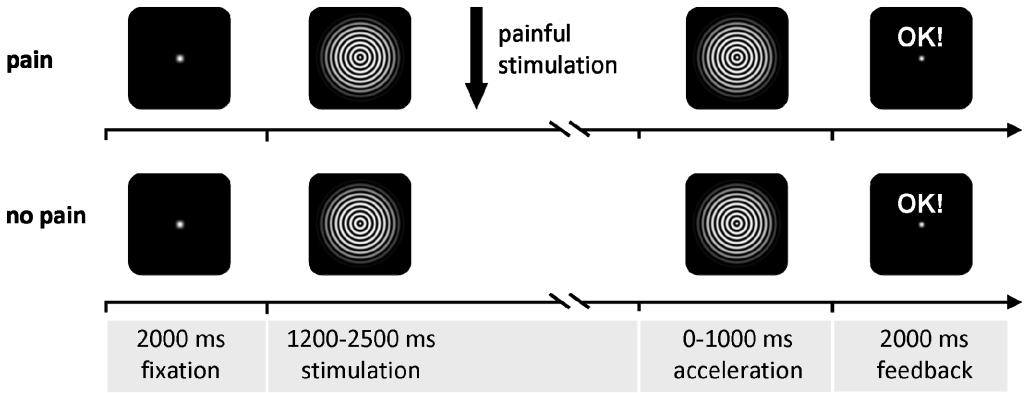



**Figure 6**. **Primary task paradigm.** Subjects were presented a white fixation point against black background. After 2000 ms a circular inward-moving grating was shown. After a pseudorandomly varied duration of 1200 to 2500 ms the contraction accelerated, signaling the subjects to press a button with their right hand as fast as possible. Visual feedback followed the response. In 50 % of the trials painful stimuli were applied to the left hand (*pain* trials).

In this task, subjects attended to circular, inward-moving gratings (diameter: 7°; spatial frequency: 2.5 cycles/degree; contrast: 100%; contraction speed: 1.6 degrees/sec). After a pseudorandomly varied duration of 1200 to 2500 ms, a change of inward-speed

(contraction speed: 2.2 degrees/sec) signaled the subjects to press a button as fast as possible. Visual stimulation was aborted after a response was given or alternatively turned off after 1000 ms. Participants received visual feedback about the correctness of the response.

In 50 % of the trials a painful cutaneous laser stimulus was applied in pseudorandom fashion (*pain trials*, see parapgraph 4.2.3). In the other 50 % of the trials no painful stimulus was applied (*no pain trials*). Time of painful stimuli with respect to the onset of visual stimulation was pseudorandomly varied to avoid predictability of painful stimuli. Apart from the application of painful stimuli, *pain* and *no pain trials* were identical.

The visual task was presented on a personal computer with a 19 inch CRT monitor and a vertical refresh rate of 60 Hz using E-Prime software (release 1.2, Psychology Software Tools Inc., Sharpsburg, USA). Subjects were seated at a distance of approximately 70 cm from the computer screen. The total duration of a trial was between 5200 and 7500 ms. Each subject completed one block consisting of 168 trials with a total duration of approximately 18 minutes. Subjects were instructed to complete the visual task without becoming distracted by the painful stimulation.

### 4.2.3 Cutaneous laser stimulation

Painful stimuli were delivered to the dorsum of the left hand by means of cutaneous laser stimulation. Cutaneous laser stimulation has been extensively used for experimental and clinical investigations of pain pathways (for review see Treede, 2003; Cruccu et al., 2004; Kakigi et al., 2005). A considerable advantage of the method is the fact that it evokes a highly synchronized selective activation of nociceptive afferents without concomitant activation of tactile afferents (Plaghki and Mouraux, 2003). Stimuli yield a mildly to moderately painful pinprick-like sensation. In subproject 1, an Nd:YAP-laser (DEKA, Calenzano, Italy) with a wavelength of 1340 nm, a pulse duration of 3 ms, and spot diameter of 6 mm was used. In subproject 2, a Tm:YAG laser (Starmedtec GmbH, Starnberg, Germany) with a wavelength of 1960 nm, a pulse duration of 1 ms, and a spot diameter of 5 mm was used. Both laser devices induce a painful sensation by emitting light in the infrared spectrum and are thus comparable regarding their modes of

operation. In order to ensure a constant distance between skin surface and laser device, distance pins were mounted on the hand piece of the laser device. To prevent skin irritations, stimulation site was manually varied after each stimulus. In preparation of the testing session, stimulus intensity was individually adjusted to match a rating of 5 on a numerical rating scale ranging from 0 (“no pain”) to 10 (“worst tolerable pain”). During the testing session, subjects were exposed to white noise through headphones to cancel out noise of the laser device.

### 4.2.4 EEG recordings

EEG data were recorded with an electrode cap (Easycap, Herrsching, Germany) and BrainAmp MR plus amplifiers (Brain Products, Munich, Germany) using the BrainVision Recorder software (Brain Products, Munich, Germany). Electrode montage included 64 electrodes comprising the electrode positions Fz/Cz/Pz, FP1/2, F3/4/7/8, C3/4, P3/4, T3/4/5/6, and O1/2 of the 10-20 system and the additional electrode positions FPz, AFz, FCz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, P1/2/5/6, TP7/8/9/10, and PO3/4/7/8/9/10. Two more electrodes were fixed below the outer canthi of the eyes. The EEG was referenced to the FCz electrode, grounded at AFz, sampled at 1000 Hz, and highpass-filtered at 0.1 Hz. The impedance was kept below 20 kΩ.

### 4.2.5 Pain intensity rating and questionnaires

#### *4.2.5.1 Pain intensity rating*

Prior to the EEG testing session, patients with FMS were asked to rate their current pain intensity on a 100 mm visual analogue scale (VAS) anchored with “no pain” and “worst possible pain”, respectively. After the EEG recordings, all participants were asked to rate the mean pain intensity on a 100 mm visual analogue scale anchored with “no pain” and “worst tolerable pain”, respectively.

#### *4.2.5.2 Pain Vigilance and Awareness Questionnaire (PVAQ)*

A German version of the well-established Pain Vigilance and Awareness Questionnaire (PVAQ; McCracken, 1997; appendix A) was used to assess the individual tendency to allocate attention to pain. Examples for included items are: “I focus on sensations of pain”, “I notice pain even if I am busy with another activity”, or “I seem to be more conscious of pain than others”. The 16 items of the PVAQ are answered on a 6-point Likert-scale anchored never (0) and always (5). Total scores range from 0 to 80, with higher values representing greater vigilance to pain. The questionnaire has been extensively used in both clinical (McCracken, 1997; Roelofs et al., 2003) and non-clinical (McWillimas and Asmundson, 2001; Roelofs et al., 2002) samples.

#### *4.2.5.3 Pain Catastrophizing Scale (PCS)*

The Pain Catastrophizing Scale (PCS; Sullivan et al., 1995; appendix B) is a commonly used instrument to assess the individual tendency to catastrophize about pain. The PCS includes 13 items, which are rated in reference to being in pain on a 5-point Likert-scale from 0 (not at all) to 4 (all the time). It consists of three subscales: rumination (e.g. ‘‘When I am in pain, I can’t seem to keep it out of my mind’’), magnification (e.g. ‘‘When I am in pain, I wonder whether something serious may happen’’) and helplessness (e.g. ‘‘When I am in pain, I feel I can’t go on’’). Total scores range from 0 to 52, with higher values representing greater catastrophizing. Catastrophizing in pain is related to physical and emotional health indices, such as pain intensity, pain-related disability, pain-related fear, and psychological distress (Sullivan and Neish, 1998; Sullivan et al., 2000; Sullivan et al., 2001a; Sullivan et al., 2001b). The factor structure, reliability, and validity of the PCS have been repeatedly evaluated (Osman et al., 1997; Osman et al., 2000).

#### *4.2.5.4 Fibromyalgia impact questionnaire (FIQ-G)*

The fibromyalgia impact questionnaire (FIQ; Burckhardt et al., 1991) is a brief self-report questionnaire which measures the overall impact of fibromyalgia with regard to every-day functioning. It is one of the most commonly used instruments in the evaluation of FMS patients (Bennett, 2005). In the present thesis, a German version of the FIQ was used (FIQ-G; Offenbaecher et al., 2000; appendix C). The evaluation of the FIQ-G affirmed

a good internal consistency (Cronbach's α = 0.92) and test-retest reliability (r = 0.95; Offenbaecher et al., 2000). The FIQ-G contains 19 items which are answered in the following fashion: Responses to the first set of items are given on a Likert scale ranging from 0 (“always able to do”) to 3 (“never able to do”). Examples for included items are: “Were you able to make beds?” or “Were you able to walk several blocks?”. Responses to the next two items apply to the number of days in the past week on which patients felt good or were unable to work due to FMS-related symptoms, respectively. Responses to the last set of items are given on a 100 mm anchored visual analogue scale on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Total scores range from 0 to 100, with higher values representing greater disease-specific impairment. While the scores of patients with average FMS-specific impairment are reported to be about 50, severely impaired patients usually reach scores of 70 and above (Bennett, 2005).

## 4.3 Data analysis

### 4.3.1 Behavioral data

To determine the effects of pain on visual task performance, reaction times were registered on a trial-by-trial basis. With regard to nerve conduction velocities, visual reaction times less than 150 ms were considered as false alarms and excluded from further analyses. Likewise, reaction times greater than 500 ms were considered as attentional errors and excluded from the analysis (Iacoboni and Zaidel, 2000; Peiris et al., 2005). With regard to subproject 1, this resulted in a total of 85 excluded trials (~3 %; pain trials: 42, no pain trials: 43). With regard to subproject 2, this resulted in a total of 380 excluded trials (~19 %; pain trials: 222, no pain trials: 161). For each subject, mean reaction times in *pain* and *no pain trials* were calculated. Subsequently, difference values between the reaction time in *pain* and *no pain trials* were calculated, serving as measure of pain-related attentional interference.

Reaction times (Campbell and LaMotte, 1983) and neurophysiological responses (Kakigi et al., 2005) to painful stimuli are mainly observed between 100 and 500 ms after stimulus

application. Therefore, painful stimuli were expected to interfere most profoundly with visual task performance when they occured shortly before a required response. Analysis of behavioral data was therefore focused on *pain trials* where laser stimuli were applied during this time interval (200 or 500 ms before the acceleration of the moving stimulus, n = 24) and compared to otherwise identical *no pain trials* (n = 24).

### 4.3.2 Preprocessing of EEG data

The raw EEG data were preprocessed using the BrainVision Analyzer software (Brain Products, Munich, Germany). Offline analysis included downsampling to 512 Hz for the purpose of data reduction, digital highpass filtering at 0.5 Hz, and recomputation to the average reference (Lehmann and Skrandies, 1980). Downsampling included automatic lowpass filtering at 230 Hz. Independent component analysis was used to correct for vertical and horizontal eye movements (Jung et al., 2000). Trials with artifacts exceeding ±100 µV in any channel were automatically rejected. After preprocessing, the remaining corrected trials were exported for subsequent processing in BESA (BESA GmbH, Gräfelfing, Germany) and Matlab (The Mathworks, Natick, USA).

### 4.3.3 Time-frequency analysis of EEG data

Since reaction times (Campbell and LaMotte, 1983) and neurophysiological responses (Kakigi et al., 2005) to painful stimuli are mainly observed between 100 and 500 ms after stimulus application, analysis of *behavioral* responses focused on this interval. However, these trials are inevitably contaminated by motor activity related to the button press, which occurs shortly after the painful stimulation in these trials. The analysis of *neurophysiological responses* was therefore focused on *pain trials* where a button press occurs at 1800 or 2000 ms after the painful stimulus (n = 60). This procedure ensured a long interval for the neurophysiological analysis, which is not contaminated by motor activity. It is important to note that the trials chosen for behavioral and neurophysiological analysis are identical except for the onset of acceleration of the moving visual stimulus. Since the present study was intended to investigate the neuronal mechanisms *before* the required response, both behavioral and neurophysiological trials

were assumed to be identical concerning the pain-induced neuronal responses prior to the acceleration. The *pain trials* (n = 60) were compared to otherwise identical *no pain trials* (n = 60).

In order to transform the data from the time to the time-frequency domain, the complex demodulation procedure implemented in BESA 5.2 (BESA GmbH, Gräfelfing, Germany) was used. The resulting time-frequency representations (TFRs) show neuronal activity as a function of time and frequency. Unlike evoked potentials, single trial data are first transformed to the time-frequency domain and then averaged. As a result, TFRs include both phase-locked as well as non-phase-locked neuronal responses (see paragraph 3.1.3 for further details). Time-frequency transformation was performed for frequencies from 4 to 100 Hz in a time window from -1000 ms to 4500 ms (or 3500 ms in subproject 2, respectively) with respect to the onset of visual stimulation. Frequencies were sampled in steps of 2 Hz, latencies in steps of 25 ms. Time-frequency representations were calculated as percent signal change with respect to baseline. In the *no pain* condition, baseline was defined as -800 to -100 ms prior to stimulus onset. In the *pain* condition, trials had to be realigned to the laser stimuli that were applied either 500 or 700 ms after onset of the visual stimulation. Thus, the beginning of visual stimulation was preponed for 200 ms in 50 % of the trials, and the baseline was adjusted accordingly. The time-frequency transformed data were then averaged across trials for each condition and each electrode. Subsequently, difference values of visual gamma oscillations in *pain* and *no pain trials* were calculated in order to reveal the attentional effects of pain.

### 4.3.4 Source localization of EEG data

The conversion of the EEG scalp potentials into a source distribution may improve the quality of the recordings, since it compensates for the distortion and smearing effect caused by the rather low conductivity of the skull (He et al., 2002; He, 2004). Here, the Multiple Source Beamformer Tool implemented in BESA 5.2 (BESA GmbH, Gräfelfing, Germany) was used to localize the cerebral sources of the visual and pain-induced gamma oscillations in each subject. The BESA beamformer is a modified version of the linearly constrained minimum variance vector beamformer in the time-frequency domain as described by Gross and colleagues (Gross et al., 2001). It allows localizing evoked and

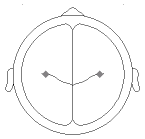
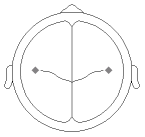
induced oscillatory activity in a user-defined time-frequency window, where time is taken relative to a triggered event.

With regard to subproject 1, strongest gamma responses to visual stimuli were observed at latencies between 100 and 2500 ms and at frequencies between 56 and 64 Hz. Thus, localization of visual gamma oscillations was based on this time-frequency window and compared to a 1000 ms baseline. Strongest gamma responses to painful stimuli were observed at latencies between 200 and 350 ms after application of painful stimuli and at frequencies between 64 and 84 Hz. Thus, localization of pain-induced gamma oscillations was based on this time-frequency window. A 150 ms prestimulus baseline including visual activity was chosen. With regard to subproject 2, strongest gamma responses to visual stimuli were observed at latencies between 150 and 2500 ms and at frequencies between 48 and 54 Hz. Thus, localization of visual gamma oscillations was based on this time-frequency window and compared to a 1000 ms baseline. Strongest gamma responses to painful stimuli were observed at latencies between 75 and 200 ms after application of painful stimuli and at frequencies between 34 and 56 Hz. Thus, localization of pain-induced gamma oscillations was based on this time-frequency window. A 125 ms prestimulus baseline including visual activity was chosen. The resulting individual activation maps were averaged across subjects using BrainVoyager QX 1.9 (Brain Innovation, Maastricht, Netherlands).

With regard to subproject 1, parts of the analyses were conducted in source space. These analyses were based on a model which included the three regional sources which were derived from the localization of visual and pain-induced gamma oscillations. A regional source is a source which describes all activity originating in the vicinity of its location. It can be regarded as a source with three single dipoles at the same location but with orthogonal orientations. In order to ensure that other, potentially overlapping brain activity is effectively separated from the regions derived in the source localization procedure, regional sources in the bilateral secondary somatosensory cortices, the ipsilateral primary somatosensory cortex, and the midcingulate cortex were added (see table 2; Garcia-Larrea et al., 2003; Kakigi et al., 2005). Using this source montage, a time-frequency analysis in source space similar to the time-frequency analysis in electrode space was performed. Since visual gamma oscillations have been consistently localized in lower-level visual cortices in animals and humans (Fries et al., 2001; Rols et al., 2001;

Siegel and Konig, 2003; Adjamian et al., 2004; Hoogenboom et al., 2006; Gruber et al., 2008; Siegel et al., 2008), analyses of visual gamma oscillations were primarily performed in source space.

**Table 2. Coordinates of the seven regional sources of the source montage.** The coordinates of the additional regional sources were chosen in reference to the findings of previous studies, which used intracranial recordings (Frot and Mauguiere, 2003; Frot et al., 2008), functional magnetic resonance imaging, magnetoencephalography (Kanda et al., 2000; Ploner et al., 2002), and EEG (Schlereth et al., 2003) to identify the generators of brain responses to painful laser stimuli in humans.

| Region | Talairach coordinates | | | Location | | |
|---|---|---|---|---|---|---|
| | x | y | z | sagittal left | sagittal right | axial |
| **SI cl** | 36 | -23 | 57 |  |  |  |
| **SI il** | -36 | -23 | 57 | | | |
| **SII cl** | 49 | -16 | 16 |  |  |  |
| **SII il** | -49 | -16 | 16 | | | |
| **ACC** | 2 | -13 | 43 |  |  |  |
| **Vis cl** | 31 | -92 | -2 |  |  |  |
| **Vis il** | -27 | -93 | 0 | | | |

*Note:* SI = primary somatosensory cortex; SII = secondary somatosensory cortex; ACC = anterior cingulate cortex; Vis = visual cortex; cl = contralateral; il = ipsilateral.

However, less evidence has been provided for the cerebral generators of pain-induced gamma oscillations. Thus, pain-induced gamma oscillations were localized as described above but further analyses were performed in electrode space. Moreover, even less evidence has been provided for the cerebral generators of pain-induced gammas oscillations in chronic pain conditions. Since different chronic pain conditions are thought to involve distinct changes in brain activity, which are not fully understood yet (for review see Apkarian et al., 2009), analyses for subproject 2 were performed in electrode space.

## 4.4 Statistical analysis

Statistical analyses were performed using SPSS for windows (release 17 and 18, SPSS Inc., Chicago, USA). Figures and tables were created using MATLAB (The Mathworks, Natick, USA), Microsoft Excel 2003 for windows (Microsoft Corporation, Redmond, USA), and GraphPad (release 5.01, GraphPad Software, Inc., La Jolla, USA). Subsequent image editing was performed using Microsoft Powerpoint 2003 for windows (Microsoft Corporation, Redmond, USA) and Adobe Photoshop (release 9.0, Adobe Systems, San Jose, USA).

$\chi 2$ tests were used for comparisons of categorical sociodemographic factors between the patient and control group.

In order to assess the effect of painful stimulation on attentional performance in health, means of reaction times in the *pain* and *no pain* condition were compared using t-tests for dependent samples. In order to assess the effect of painful stimulation on gamma oscillations in health, means of visual gamma oscillations in the *pain* and *no pain* condition were compared using t-tests for dependent samples.

In order to compare the effects of pain on attentional performance in the patient and control group, means between conditions and groups were compared using a mixed-model analysis of variance (ANOVA). Whereas *group* (healthy / FMS) was considered as between-subject factor, *condition* (pain / no pain) was considered as within-subject factor. Likewise, means between conditions and groups were compared using mixed-model analyses of variance (ANOVAs) to oppose the effects of pain on gamma oscillations in the patient and control group.

Correlations were calculated using Pearson's correlation coefficient. Whenever it was necessary to control for the effect of a third, potentially confounding variable, partial correlations were calculated. Correlation coefficients were compared between the patient and control group by first converting each correlation coefficient into a z-score using Fisher's r-to-z transformation (Fisher, 1921) and then calculating a z-score of the difference between the correlations in question.

For all statistical analyses, the level of significance for hypothesis-testing was set at $p < 0.05$.

# FIVE

## Results

# 5 Results

## 5.1 The attentional effects of pain in health (subproject 1)

### 5.1.1 Pain ratings and questionnaires

Painful laser stimuli elicited at least moderately painful sensations with a mean subjective pain intensity of 5.8 (standard deviation (SD) = 1.7, range 2.2 – 8.1). The mean score in the PCS was 15 ± 8.6 (mean ± SD). The mean score in the PVAQ was 38 ± 11.4.

### 5.1.2 Effects of pain on attention

Mean reaction time across all subjects and conditions was 322 ± 23 ms (mean ± SD). Figure 7A shows reaction times of *pain* and *no pain trials* for each individual. In line with previous studies on pain-cognition interactions (for review see Seminowicz and Davis, 2007b), painful stimuli did not homogeneously affect visual reaction times but yielded an increase of reaction times in some, as well as a decrease of reaction times in other subjects. Consequently, mean reaction times of *pain* (324 ± 21 ms) and *no pain trials* (321 ± 25 ms) did not differ significantly (t = 0.82, p = 0.42; figure 7B).

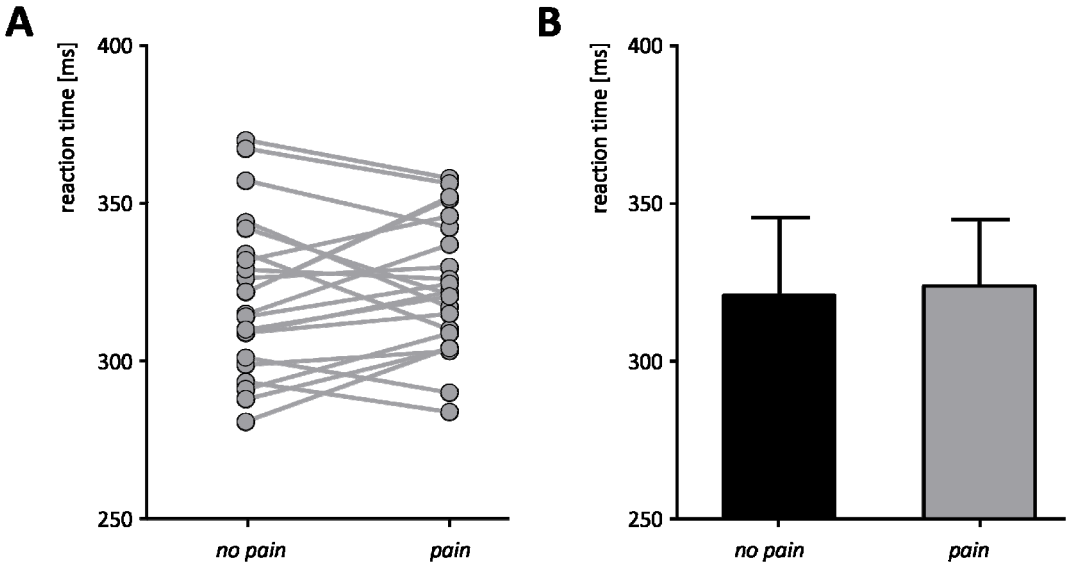



**Figure 7. Behavioral results for subproject 1.** ***A*** Single-subject reaction times for each condition. Please note that ascending lines connecting the *no pain* and *pain* conditions indicate a pain-induced prolongation of reaction times whereas descending lines indicate a reduction of reaction times. ***B*** Mean reaction times for each condition.

Interindividual differences in the effects of pain on visual reaction times were not significantly correlated with differences in pain threshold or differences in stimulus intensity (r = -0.36, p = 0.09; r = -0.32, p = 0.15). Moreover, it was tested whether the effects of pain on attentional performance were correlated with pain vigilance (McCracken, 1997) and pain catastrophizing (Sullivan et al., 1995) as psychological factors which are related to the individual attentional bias towards pain. Pain vigilance did not correlate with the attentional effects of pain (r = 0.04, p = 0.87). The correlation between pain catastrophizing and the attentional effects of pain turned out to be a trend, though not statistically significant (r = 0.39, p = 0.07).

### 5.1.3 Effects of pain on visual and pain-induced gamma oscillations

In a next step, the effects of visual and painful stimulation on neuronal activity in the gamma frequency range were investigated. Figure 8 shows group mean time-frequency representations (TFRs) of neuronal activity averaged across central and occipital electrodes.

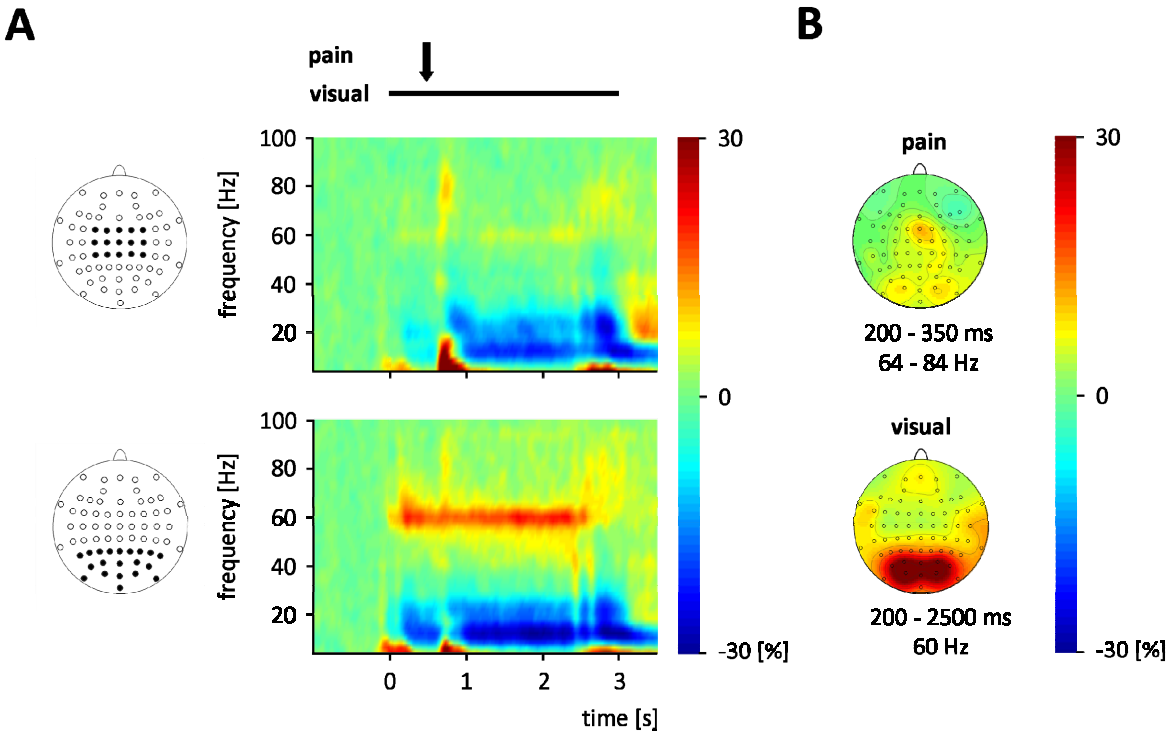



**Figure 8. Visual and pain-induced gamma oscillations.** ***A*** Group mean time-frequency representations of % signal change in *pain trials* used for neurophysiological analysis, averaged across central and occipital electrodes. ***B*** Scalp distribution of gamma oscillations following visual (200 - 2500 ms after onset of visual stimulation, 60 Hz) and painful stimulation (500 - 750 ms after onset of visual stimulation, 200 - 350 ms after painful stimulation, 64-84 Hz) coded as % signal change as compared to baseline.

At occipital electrodes, an increase of gamma oscillations could be noted which started about 100 ms after the onset of visual stimulation and lasted for the whole period of stimulus presentation (up to 2500 ms, figure 8A). Frequency of visual gamma oscillations varied interindividually between 40 and 65 Hz. The signal change was most prominent at electrodes POz, Oz, PO3/4 and O1/2 (figure 8B). At these electrodes, gamma activity during visual stimulation (100 to 2500 ms, 58-64 Hz) was significantly increased compared to the prestimulus baseline ($t = 4.86$, $p < 0.001$).

At central electrodes, an increase of gamma oscillations could be noted between 200 and 350 ms after application of painful laser stimuli and at frequencies between 64 and 84 Hz (figure 8A). The oscillations were most prominent at electrodes Cz and FCz (figure 8B). At these electrodes, gamma activity was significantly increased after painful stimulation (200 to 350 ms, 64-84 Hz) compared to the prestimulus baseline ($t = 4.71$, $p < 0.001$).

Visual gamma oscillations were localized to the left and right occipital cortices (mean Talairach coordinates: left -24, -93, -2; right 23, -93, -3; figure 9). Gamma activity of the left and right visual cortices was significantly increased during visual stimulation compared to the prestimulus baseline ($t = 3.46$ / $4.0$, $p = 0.002$ / $0.001$). Pain-induced gamma oscillations were localized to the right primary somatosensory cortex (mean Talairach coordinates: 36, -23, 61; figure 9). Gamma activity in the right primary somatosensory cortex was significantly increased after painful stimulation compared to the prestimulus baseline ($t = 2.19$, $p = 0.04$). Thus, painful and visual stimuli can induce gamma oscillations in the visual and somatosensory system, respectively.

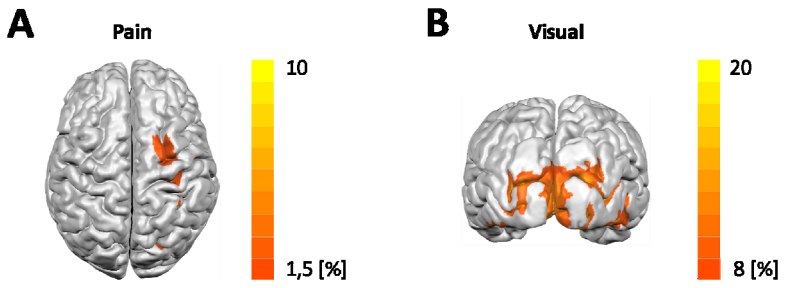



**Figure 9. Cerebral sources of pain-induced and visual gamma oscillations.** ***A*** Location of pain-induced gamma oscillations as seen from the top. ***B*** Location of visual gamma oscillations as seen from the back. All activations are maxima of mean activation maps superimposed on a normalized surface-rendered structural T1-weighted magnetic resonance image. Color-coded is the change of estimated activity in the target interval relative to the baseline in percent.

### 5.1.4 Relationship between the behavioral and neurophysiological effects of pain

In a next step, the behavioral relevance of neuronal gamma oscillations was investigated. If gamma oscillations were functionally relevant for the attentional selection and enhanced processing of visual information, pain-induced changes in gamma oscillations would be correlated with pain-induced changes in behavior. Therefore, it was investigated whether the effects of pain on visual reaction times were correlated with the effects of pain on visual gamma oscillations. The analysis revealed a significant positive correlation between both phenomena. Lower amplitudes of visual gamma oscillations after painful laser stimulation were associated with slower reaction times (left visual cortex: $r = 0.67$, $p = 0.001$; right visual cortex: $r = 0.68$, $p < 0.001$; figure 10). The removal of variance in reaction times due to catastrophizing did not significantly affect the correlation between visual gamma oscillations and reaction times (left visual cortex: $r = 0.67$, $p = 0.001$; right visual cortex: $r = 0.68$, $p = 0.001$). Thus, the involuntary effects of pain on visual gamma oscillations are significantly correlated with the effects of pain on performance in the visual attention task.

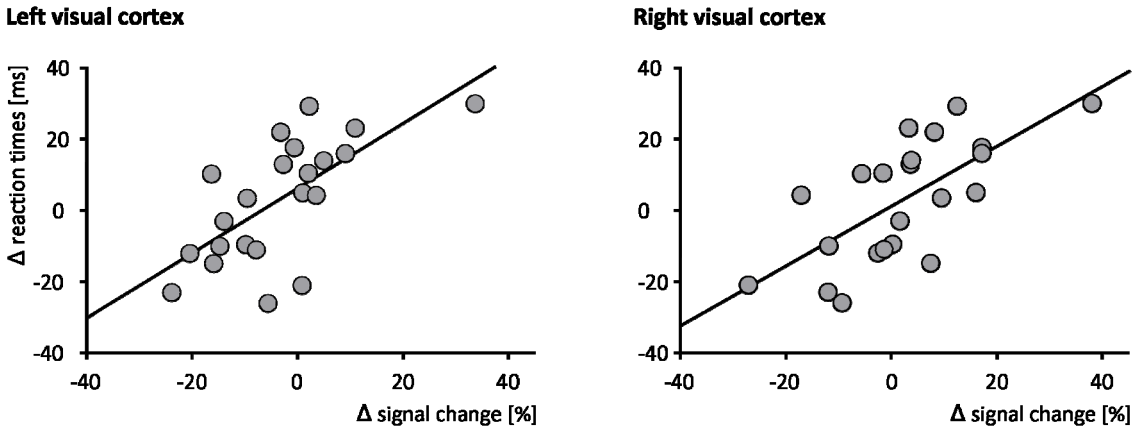



**Figure 10. Relationship between pain-induced changes in visual gamma oscillations and pain-induced changes in visual task performance.** Displayed is the correlation between the signal change of visual gamma oscillations (signal change$_{no\ pain}$ – signal change$_{pain}$) in left and right visual cortex and the change of reaction times after laser application ($RT_{pain}$ – $RT_{no\ pain}$). Stronger pain-related changes of visual gamma oscillations are associated with stronger pain-related changes of reaction times.

To further visualize the effects of pain on neuronal gamma oscillations and their relationship to behavior, a split-half-criterion was applied to assign the subjects to subgroups. Group 1 comprised those subjects, whose reaction times increased after

painful stimulation and were thus indicative of pain-related attentional interference (n = 11). Group 0 comprised those subjects, whose reaction times decreased after painful stimulation (group 0, n = 11). In those subjects susceptible for attentional interference (group 1), a transient pain-induced suppression of gamma oscillations could be noted in the right visual cortex at latencies when pain-induced gamma oscillations were observed (200 - 350 ms after painful stimuli; t = -2.8, p = 0.019; figure 11). No significant suppression of gamma oscillations was observed for those subjects whose reaction times decreased after painful stimulation. In the left hemisphere, no significant pain-induced suppression of visual gamma oscillations was observed for neither group (t = -0.98, p = 0.35).

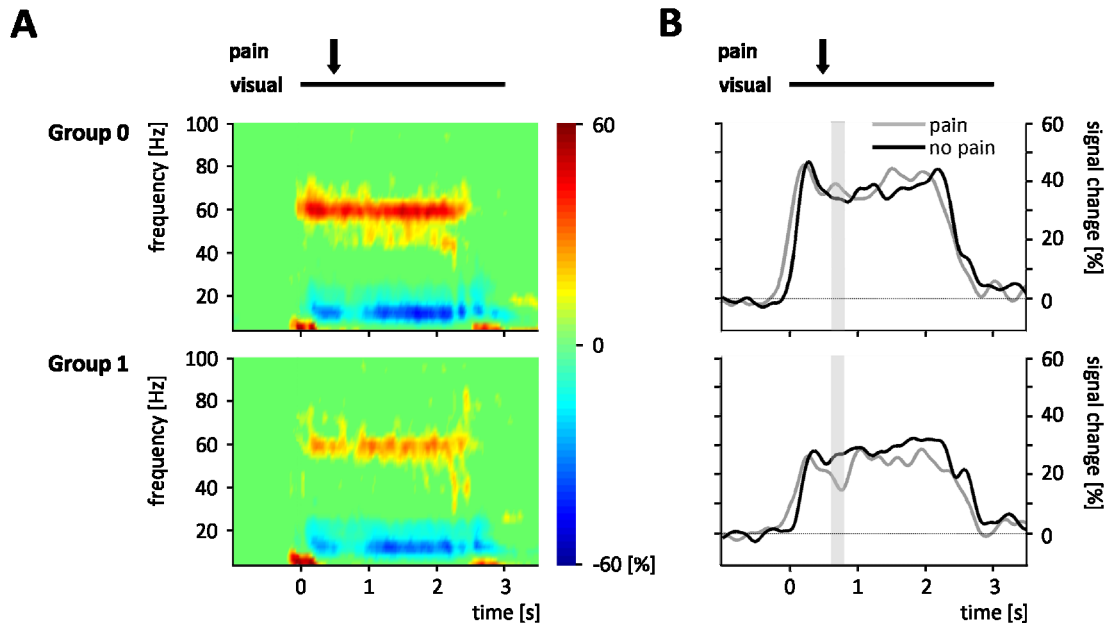



**Figure 11. Effects of painful stimulation on visual gamma oscillations in the right visual cortex.** ***A*** Time-frequency representations of *pain* trials, averaged across subjects of group 0 and 1. A significant decrease of visual gamma activity was evident for group 1. ***B*** Time course of gamma activity (60 Hz) for *pain* and *no pain* trials. Light gray vertical bars mark the interval during which pain-induced gamma oscillations were observed at central electrodes (200 - 350 ms). A significant difference of visual gamma activity between conditions was evident for group 1.

Amplitudes of pain-induced gamma oscillations at central electrodes did not differ between groups (t = 0.02, p = 0.98). Pain catastrophizing and pain vigilance scores did not correlate significantly with pain-induced changes of reaction times for neither group (pain catastrophizing: r = 0.01 / r = 0.29, p > 0.3; pain vigilance: r = 0.04 / r = 0.26, p > 0.4).

## 5.2 Comparison of the attentional effects of pain in health and fibromyalgia syndrome (subproject 2)

### 5.2.1 Pain ratings and questionnaires

Mean objective stimulus intensity of painful laser stimuli across all participants was 528 mJ (SD = 86 mJ, range 320 - 700 mJ). These painful stimuli induced moderately painful sensations with a mean rating of 5.7 (SD = 1.8, range 2.0 - 9.4). Neither stimulus intensity ($t = -1.08$, $p = 0.3$) nor pain ratings ($t = 1.16$, $p = 0.3$) differed significantly between patients and healthy subjects. Mean scores in the PCS were $22 \pm 7.7$ (mean $\pm$ SD) in the patient group and $12 \pm 7.4$ in the control group. Mean scores in the PVAQ were $48 \pm 13$ in the patient group and $32 \pm 8.7$ in the control group. Both pain catastrophizing ($t = 4.53$, $p < 0.001$) as well as pain vigilance ($t = 4.62$, $p < 0.001$) differed significantly between patients with FMS and healthy controls. In the patient group, the FIQ-G was used to assess the impact of FMS on every-day functioning. Mean score in the FIQ-G was 50 (SD = 12, range 36 - 84). Moreover, current pain intensity was specified on a visual analogue scale with possible scores ranging from 0 to 100. Mean current pain intensity was 59 (SD = 21.3, range 18 - 58). Table 3 summarizes the results of the behavioral data.

**Table 3. Behavioral data compared between patients with FMS and healthy controls.**

| | **Patients with FMS** | **Healthy controls** | |
|---|---|---|---|
| | ***M (SD)*** | ***M (SD)*** | ***t*** |
| **stimulus intensity (mJ)** | 512 (103) | 541 (67) | -1.01 |
| **rating** | 6.0 (2.0) | 5.4 (1.6) | 1.16 |
| **PCS** | 22 (7.7) | 12 (7.4) | 4.53*** |
| **PVAQ** | 48 (13) | 32 (8.7) | 4.62*** |
| **FIQ-G** | 50 (12) | | |
| **current pain intensity** | 59 (21.3) | | |

*Note:* M = mean; SD = standard deviation. *** $p < 0.001$.

### 5.2.2 Effects of pain on attention

Mean reaction time across all trials was 361 ± 33 ms (mean ± SD) for healthy subjects and 373 ± 27 ms for patients with FMS. Reaction times across conditions did not differ significantly between groups (t = 1.3, p = 0.2). Differences in reaction times between conditions served as measure of attentional interference. Reaction times in the *pain* vs. *no pain*-condition are displayed in figure 12 for healthy subjects and patients with FMS, respectively. Painful stimuli did not homogeneously affect visual reaction times but yielded an increase of reaction times in some, as well as a decrease of reaction times in other participants. In healthy subjects, these differential effects of pain on behavior have already been noted in previous studies on pain-cognition interactions (Seminowicz et al., 2004; Tiemann et al., 2010; for review see Seminowicz and Davis, 2007b). It was hypothesized a priori that in patients with FMS the effects of pain on visual reaction times would be altered as an expression of disease-specific dysfunctional attentional processes. However, a two-way repeated measures ANOVA with one between-subjects factor and one within-subjects factor demonstrated no significant main effect of group ($F_{[1,39]}$ = 1.73, p = 0.2) or condition ($F_{[1,39]}$ = 1.98, p = 0.17). Moreover, the analysis did not reveal a significant condition x group interaction ($F_{[1,39]}$ = 0.73, p = 0.4). Thus, healthy subjects and patients with FMS do not differ significantly regarding the effects of pain on reaction times as measure of attentional interference.

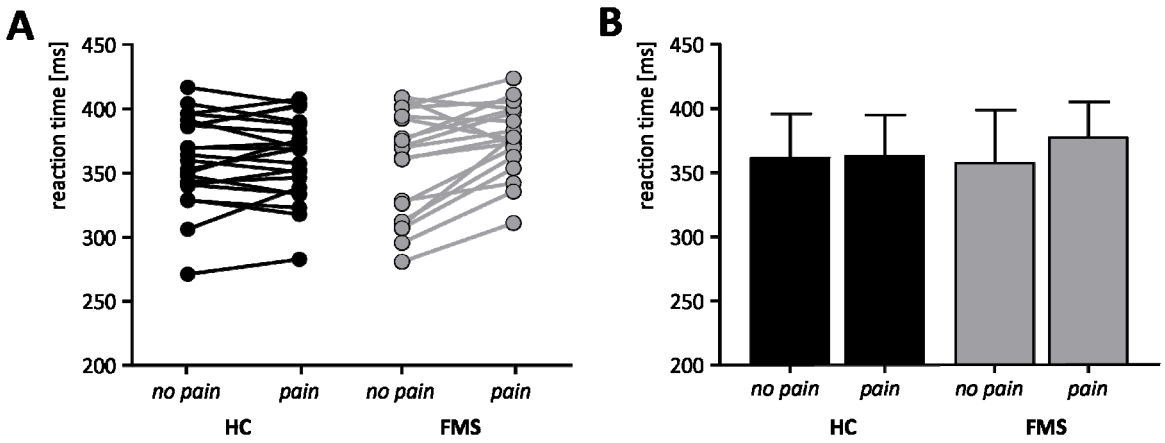



**Figure 12. Behavioral results for subproject 2.** ***A*** Single-subject reaction times for each group and condition. Please note that ascending lines indicate a pain-induced prolongation of reaction times whereas descending lines indicate a reduction of reaction times. ***B*** Mean reaction times for each group and condition. HC = healthy controls; FMS = patients with FMS.

Interindividual differences in the effects of pain on visual reaction times were not significantly correlated with pain threshold ($r = -0.24$, $p = 0.13$) or stimulus intensity ($r = 0.06$, $p = 0.73$). To control for differences in the individual attentional bias towards pain, the individual scores in the PVAQ as a measure of pain vigilance (McCracken, 1997) and the scores in the PCS (Sullivan et al., 1995) as a measure of pain catastrophizing were considered in the analysis. Patients with FMS perceived themselves as significantly more vigilant towards pain ($t = 4.62$, $p < 0.001$) and reported a pronounced tendency for catastrophizing ($t = 4.53$, $p < 0.01$) compared to healthy subjects. However, the correlation between the effects of pain on attentional performance and pain vigilance / pain catastrophizing was not significant ($r = 0.06$ / $-0.16$, $p = 0.71$ / $0.30$). Thus, interindividual differences in the attentional effects of pain can not sufficiently be explained by differences in psychological factors which are related to the individual attentional bias towards pain. In order to control for the influence of relevant disease-specific variables, disease-specific impairment as measured with the FIQ-G as well as current pain intensity were considered in the analysis. However, since neither the FIQ-G ($r = -0.08$, $p = 0.74$) nor the current pain intensity ($r = 0.21$, $p = 0.4$) were significantly correlated with the effects of pain on attention, a relevant influence of these disease-related variables on the individual attentional bias towards pain appears unlikely.

### 5.2.3 Effects of pain on visual and pain-induced gamma oscillations

In a next step, the effects of visual and painful stimuli on neuronal activity in the gamma frequency range were investigated. Figure 13 shows group mean time-frequency representations (TFRs) of neuronal activity at occipital and central electrodes for healthy subjects and patients with FMS, respectively.

At occipital electrodes, an increase in gamma oscillations could be noted, which started about 150 ms after the onset of visual stimulation and lasted for the whole period of stimulus presentation (up to 2500 ms). Frequency of visual gamma oscillations varied interindividually between 40 and 60 Hz. The signal change was most prominent at electrodes POz, Oz, PO3/4 and O1/2 (figure 13, topographical maps). At these electrodes, gamma activity during visual stimulation (150 to 2500 ms, 48-54 Hz) was significantly increased compared to the prestimulus baseline ($F_{[1,39]} = 45.2$, $p < 0.001$). The strength of

visual gamma oscillations did not differ significantly between healthy subjects and patients with FMS ($F_{[1,39]}$ = 0.18, p = 0.7). At central electrodes, an increase in gamma oscillations between 75 and 200 ms after application of painful laser stimuli and at frequencies between 34 and 56 Hz could be noted. The oscillations were most prominent at electrodes Cz and C2 (figure 13, topographical maps). At these electrodes, gamma activity was significantly increased after painful stimulation (75 to 200 ms, 34-56 Hz) compared to the prestimulus baseline ($F_{[1,39]}$ = 7.9, p = 0.008). The strength of pain-induced gamma oscillations did not differ significantly between healthy subjects and patients with FMS ($F_{[1,39]}$ = 0.95, p = 0.34).

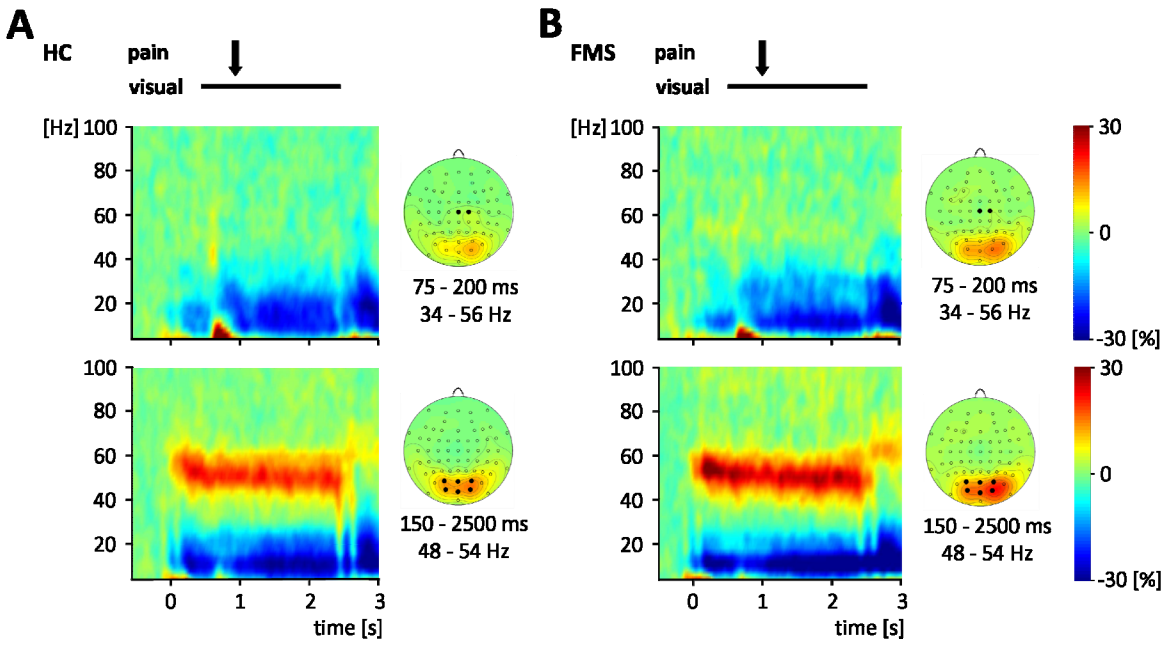



**Figure 13. Visual and pain-induced gamma oscillations.** The time-frequency-representations show group mean neuronal activity (% signal change) in *pain trials* averaged across central (Cz, C2) and occipital (POz, Oz, PO3/PO4, O1/O2) electrodes for the control (***A***) and the patient group (***B***). Data are aligned to the onset of laser stimulation, which occurred 500 or 700 ms after onset of the visual stimulation, respectively. The topographic maps show the scalp distribution of gamma oscillations following visual (150 - 2500 ms after onset of visual stimulation, 48 - 54 Hz) and painful (575 - 700 ms after onset of visual stimulation, 75 - 200 ms after painful stimulation, 34-56 Hz) stimulation coded as % signal change as compared to baseline.

Visual gamma oscillations were localized to the left and right occipital cortices (mean Talairach coordinates: left -25, -93, -4; right 27, -86, -7; figure 14). Gamma activity of the left and right visual cortices was significantly increased during visual stimulation compared to the prestimulus baseline (t = 6.08 / 6.08, p < 0.001). A maximum of pain-

induced gamma oscillations was localized to the right primary somatosensory cortex (mean Talairach coordinates: 32, -20, 35; figure 14). Gamma activity in the right primary somatosensory cortex was significantly increased after painful stimuli compared to the prestimulus baseline (t = 2.29, p = 0.03).

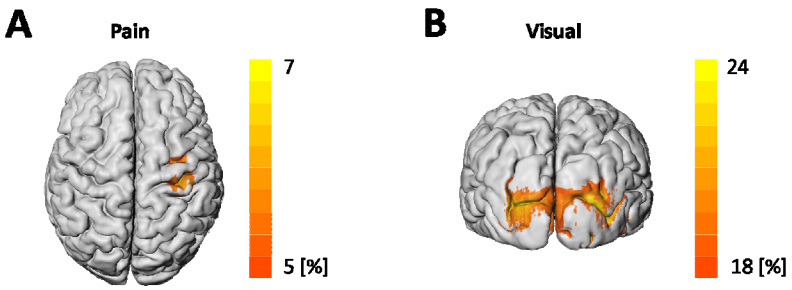



**Figure 14. Cerebral sources of pain-induced and visual gamma oscillations.** ***A*** Location of pain-induced gamma oscillations as seen from the top. ***B*** Location of visual gamma oscillations as seen from the back. All activations are maxima of mean activation maps superimposed on a normalized surface-rendered structural T1-weighted magnetic resonance image. Color-coded is the change of estimated activity in the target interval relative to the baseline in percent.

Thus, painful and visual stimuli can induce gamma oscillations in the somatosensory and visual system, respectively. Healthy subjects and patients with FMS do not differ significantly regarding the strength of these visual and pain-induced gamma oscillations.

### 5.2.4 Relationship between the behavioral and neurophysiological effects of pain

In a next step, the behavioral relevance of neuronal gamma oscillations was investigated. If gamma oscillations were functionally relevant for attentional selection and enhanced processing of visual information, pain-induced changes in gamma oscillations would be correlated with pain-induced changes in behavior. Therefore, it was investigated whether the effects of pain on visual reaction times were correlated with the effects of pain on visual gamma oscillations. The results of subproject 1 indicate that pain-induced modulations of visual gamma oscillations occur in a time window of 200 - 350 ms after painful stimulation (see paragraph 5.1.3; Tiemann et al., 2010). Thus, the correlation

analysis focused on pain-induced modulations of visual gamma oscillations occurring 200 - 350 ms after painful stimulation. The analysis revealed a significant positive correlation. Lower amplitudes of visual gamma oscillations after painful laser stimulation were associated with slower reaction times ($r = 0.32$, $p = 0.04$; figure 15). This finding confirms the expected relationship between the pain-induced modulation of gamma oscillations in the human brain and the pain-induced modulation of attentional performance in a visual attention task.

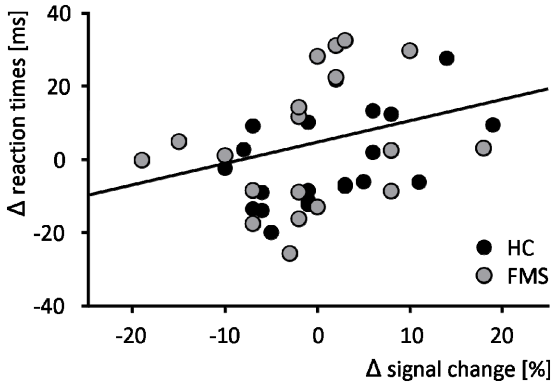



**Figure 15. Relationship between pain-induced changes in visual gamma oscillations and pain-induced changes in visual task performance.** Displayed is the correlation between the signal change of visual gamma oscillations (signal change$_{no\ pain}$ – signal change$_{pain}$) at occipital electrodes and the change of reaction times after painful stimulation ($RT_{pain} – RT_{no\ pain}$). Stronger pain-related modulations of visual gamma oscillations are associated with stronger pain-related modulations of reaction times.

Importantly, the present study further investigated whether the correlation between the behavioral and neuronal effects of pain differed between healthy subjects and patients with FMS. Therefore, the correlations were compared after transforming the correlation coefficients from r to z-scores using Fisher's z transformation. The comparison revealed no significant difference of correlations between the control and patient group ($z = 0.7$, $p = 0.50$). Thus, the relationship between the pain-induced modulation of gamma oscillations and the pain-induced modulation of attentional performance can be regarded as comparable in healthy subjects and patients with FMS.

# SIX

## Discussion

# 6 Discussion

The present study investigated pain-related attentional interference and its neuronal correlates in health and fibromyalgia syndrome (FMS).

Referring to our initial questions, the results demonstrate that painful stimulation modulates visual task performance in healthy subjects as a measure of attention (paragraph 3.4, hypothesis 1). Specifically, pain yielded differential effects of pain on behavioral performance, with painful stimulation resulting in increased reaction times in some, as well as decreased reaction times in other subjects. These pain-induced changes of reaction times were paralleled by pain-induced changes of visual gamma oscillations. This finding substantiates a close association between neuronal gamma oscillations and the involuntary attentional effects of pain in health (hypothesis 2).

Dysfunctional attentional processes have been implicated in chronic pain states, suggesting that both attentional performance and pain-induced gamma oscillations might be altered in patients with FMS as an expression of hypervigilance to pain. However, the results of the present study demonstrate that patients with FMS and healthy subjects do not differ significantly regarding the effects of painful stimulation on reaction times (hypothesis 3). Moreover, patients and healthy subjects do not differ significantly regarding the effects of painful stimulation on visual and pain-induced gamma oscillations (hypothesis 4). Accordingly, the findings of the present investigation do not indicate behavioral or neuronal manifestations of hypervigilance in patients with FMS.

## 6.1 Attentional effects of pain in health

In health, the perception of acute pain is a physiological process of existential relevance, since it protects the body from further injury. As a critical feature of this warning function, pain is particularly capable of affecting our attention. In the literature, variable effects of pain on attention have been described. On the one hand, pain may facilitate pain-related and non-pain-related reactions in equal measure (Patil et al., 1995). This effect is most probably due to the fact that pain enhances the global level of

alertness (Ohara et al., 2004; Ploner et al., 2006a). On the other hand, pain may corrupt the simultaneous processing of competing non-painful stimuli and interfere with ongoing non-pain-related behavior (Crombez et al., 1994; Crombez et al., 1996, 1997). This effect is most probably due to the fact that pain makes demands on the limited capacity of selective attention (Eccleston and Crombez, 1999).

In agreement with these findings, the present study confirms that pain does not uniformly affect attention. Instead, the attentional effects of pain varied considerably between individuals, yielding an increase of reaction times in some, as well as a decrease of reaction times in other subjects. This heterogeneity in observable behavior is well compatible with the assumption that the attentional effects of pain comprise an alerting as well as distracting component, and, thus, exert impact on both intensity as well as selectivity aspects of attention (Van Zomeren and Brouwer, 1994). Moreover, it can be suggested that differences in the balance of alerting and distracting effects of pain on attention may result in a behavioral continuum with varying grades from pain-induced *de*creased to pain-induced *in*creased performance. Still, one can only speculate about the determining factors which account for the individual behavioral consequences of painful stimulation. In the following, potential explanations for the observed individual variability of pain-related attentional effects will be discussed.

The behavioral relevance of pain implies that painful stimuli can not be completely unattended. Still, pain-related attentional capture is not purely automatic, but influenced by attentional top-down modulation (Legrain et al., 2009a). In line with this finding, previous studies have pointed out that certain task characteristics substantially influence the extent of pain-related attentional interference (for review see Eccleston, 1995). Possible influencing factors are the task instructions, the cognitive strategy adopted by the subjects, the task difficulty, or the intensity of painful stimulation. Although instructions are rarely explicitly stated, it can be assumed that experiments differ considerably with regard to the provided instructions (Eccleston, 1995). Accordingly, these differences in task instructions may account for the inconsistent results on pain-related attentional interference which have been reported in the literature (Crombez et al., 1994; Crombez et al., 1996, 1997, vs. Petrovic et al., 2000; Veldhuijzen et al., 2006). In the present investigation, however, instructions have been standardized in order to prevent a manipulation of the mental set to the greatest possible extent. Thus, an

influence of task instructions on the observed behavioral heterogeneity appears unlikely. However, rather than being extrinsically modulated by means of task instructions, the mental set can be intrinsically modulated depending on which cognitive strategy is adopted by an individual (Eccleston, 1995; Seminowicz and Davis, 2007b). Likewise, Seminowicz and colleagues observed a considerable interindividual variability of the attentional performance after painful stimulation and attributed this heterogeneous behavioral effect to the utilization of different cognitive strategies (Seminowicz et al., 2004). Specifically, the authors suggest that a more efficient attentional engagement in the attention task was paralleled by less pain-related distraction. Accordingly, the use of different coping strategies might account for the observed behavioral variability in the present investigation. Still, neither the mentioned study (Seminowicz et al., 2004) nor the present investigation have explicitly controlled for the individual choice of coping strategy (e.g. by means of verbalizing thoughts during task performance, Heyneman et al., 1990; for review see Eccleston, 1995). Thus, future studies might consider to evaluate the impact of individual cognitive strategy on the extent of pain-related attentional interference. Furthermore, it has been suggested that the extent of pain-related distraction is related to the difficulty of the primary task (Seminowicz and Davis, 2007a; Buhle and Wager, 2010; for review see Eccleston and Crombez, 1999). Eccleston (1994) demonstrated that, in order for the attentional performance to be affected by pain, the primary task needs to be highly demanding. This was inferred from the observation that patients suffering from high levels of chronic pain showed a detriment in task performance only if they engaged in the most demanding type of task. Regarding the visual attention paradigm adopted by the present investigation, the cognitive load required to efficiently engage in the task can be regarded as rather low. Hence, it can not be excluded that the choice of paradigm accounts for the observed behavioral heterogeneity in visual task performance. Future studies might consider calibrating task difficulty in order to maximize pain-cognition interference and minimize the variability between subjects (Seminowicz and Davis, 2007b; Buhle and Wager, 2010). Moreover, behavioral studies have revealed that the capture of attention by pain is enhanced whenever pain is perceived as particularly intense (Eccleston, 1994) or threatening (Crombez et al., 1998a; for review see Eccleston and Crombez, 1999). In the present investigation, both objective as well as subjective stimulus intensity has been

demonstrated to be comparable across subjects. Further, neither objective nor subjective pain intensity did correlate with the effects of painful stimulation on behavior. Thus, an influence of pain intensity on the observed interindividual variability appears to be unlikely. However, the individually perceived level of threat of the painful stimulation has not been experimentally monitored and / or manipulated in the present study. Hence, it can not be excluded that extent of individually perceived pain-related threat varied between subjects. Accordingly, pain-related threat may account for the observed behavioral heterogeneity in visual task performance. Future studies might consider to experimentally vary pain-related threat in order to minimize behavioral variability between subjects (Eccleston and Crombez, 1999).

Besides the influence of these contextual factors, it remains debatable which psychological factors might be predictive for the extent of pain-related attentional interference in healthy subjects. Therefore, vigilance to pain and pain catastrophizing were assessed as psychological variables which relate to the individual tendency to allocate attention to pain (Eccleston and Crombez, 1999; Sullivan et al., 2001a). However, pain vigilance and pain catastrophizing scores did not correlate significantly with pain-related effects on behavior. Accordingly, an influence of these pain-related psychological traits appears to be unlikely. Still, the influence of further psychological variables which might have an impact on pain-related attentional processing (e.g. state and trait anxiety) has not been addressed in the present study and can thus not be conclusively determined.

Considered as a whole it can be concluded that the findings of the present study corroborate the first hypothesis. Painful stimulation modulated the attentional performance of healthy subjects, yielding decreased reaction times in some, as well as increased reaction times in other subjects. These differential behavioral effects suggest that the attentional effects of pain in health comprise an alerting as well as distracting component, the balance of which determines the individual behavioral outcome. Still, the regulating factors which define if an individual tends towards one pole of the continuum or the other can not be conclusively identified and need to be elucidated in future studies.

## 6.2 Gamma oscillations as a neuronal correlate of the attentional effects of pain in health

### 6.2.1 Visual and pain-induced gamma oscillations

Neuronal gamma oscillations have been related to the attentional selection and enhanced processing of sensory information (Kastner and Ungerleider, 2000; Fries et al., 2001; Jensen et al., 2007). In the present study, visual and pain-induced gamma oscillations were considered as potential neuronal correlates of visual and pain-related selective attention.

In healthy subjects, visual stimulation induced neuronal gamma oscillations which varied interindividually in a frequency range from 40 - 65 Hz and could be specified to originate in the primary visual cortices. This finding is in good agreement with results from intracranial recordings in monkeys (Fries et al., 2001; Rols et al., 2001; Siegel and Konig, 2003) as well as electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings in humans (Gruber et al., 1999; Adjamian et al., 2004; Hoogenboom et al., 2006; Siegel et al., 2008; Scheeringa et al.). The observed gamma band response shows all characteristics of visual gamma band synchronization in the human brain (Fries et al., 2008). Thus, it can be considered unlikely that the observed visual gamma response reflects brief miniature saccades (Yuval-Greenberg et al., 2008).

Moreover, painful stimulation induced neuronal gamma oscillations which varied interindividually in a frequency range from 64 - 84 Hz. This finding corresponds with results from previous EEG and MEG studies in humans (Babiloni et al., 2002; Gross et al., 2007; Hauck et al., 2007). The suggestion that pain-induced gamma oscillations originate from the contralateral primary somatosensory cortex is in line with results from studies using MEG (Gross et al., 2007; Hauck et al., 2007) which has a higher spatial resolution than EEG. However, since localizations of EEG responses are inherently vague, the present findings do not preclude pain-induced gamma oscillations to originate from other brain areas.

### 6.2.2 Gamma oscillations, attention, and pain

The results of the present investigation suggest a significant correlation between the pain-induced modulation of gamma oscillations and reaction times. This finding corroborates a close relationship between gamma oscillations and reaction times as a measure of attentional performance (Gonzalez Andino et al., 2005; Womelsdorf et al., 2006; Frund et al., 2007; Bauer et al., 2009).

In the visual attention task with concurrent painful stimulation, visual gamma oscillations are likely to reflect attentional engagement in the visual task which may be involuntarily and transiently interrupted by brief painful stimuli. Since gamma-band synchronization is thought to enhance the impact of neuronal activity on other groups of neurons (Fries, 2009), pain-induced gamma oscillations may be instrumental in amplifying pain-related signals and in enhancing their further processing in downstream cortical areas. Pain-induced changes of gamma oscillations are therefore likely to mediate the involuntary attentional effects of pain which can result in an amplification of pain-related signals at the expense of other ongoing sensory processes.

The observations of the present investigation complement a recent EEG study which showed interactions between visual- and pain-evoked potentials (Legrain et al., 2005). In their study, Legrain and colleagues demonstrated that the performance in a primary visual task was impaired whenever painful stimuli elicited particularly large P2 amplitudes. The results of the present study extend these findings by correlating the behavioral and neurophysiological effects of pain, revealing a close association between pain and neuronal gamma oscillations. The present findings further complement a recent fMRI study on the modulatory effects of pain on visual processing (Bingel et al., 2007). The study showed that pain interferes with visual object processing and modulates underlying brain activity in the ventral visual stream. A connectivity analysis suggested the rostral anterior cingulate cortex (rACC) as a possible source of these modulatory effects of pain. Other cerebral sources which are thought to exert attentional modulations on sensory processes include brain areas of the fronto-parietal attention network (Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002). The results of the present EEG study extend these findings by revealing a neuronal mechanism which may underlie the modulatory effects of pain at the level of sensory processing. Thus, the ACC and / or brain areas of the frontoparietal attention

network are likely to represent superordinate sources of the involuntary modulatory effects of pain. These brain areas may allocate processing resources from ongoing, less relevant processes to painful events. The present data suggest that, at the level of sensory cortices, this pain-induced reallocation of processing resources may be mechanistically subserved by a modulation of neuronal gamma oscillations.

Conclusively it can be stated that the findings of the present investigation corroborate the second hypothesis. Whereas visual stimulation yielded gamma oscillations in the primary visual cortex, painful stimulation yielded gamma oscillations in the primary somatosensory cortex. Most importantly, pain-induced changes of reaction times were paralleled by pain-induced changes of visual gamma oscillations. Thus, gamma oscillations can be regarded as a neuronal correlate of the attentional effects of pain.

## 6.3 Attentional effects of pain in fibromyalgia syndrome – evidence for hypervigilance?

Dysfunctional attentional processing of sensory and, in particular, pain-related information has been implicated in the pathogenesis of chronic pain syndromes (Eccleston and Crombez, 1999; Crombez et al., 2004; Crombez et al., 2005). The concept of hypervigilance in FMS gives reason to expect that patients are more easily distracted by painful stimulation and perform worse than healthy subjects in a behavioral paradigm inducing attentional interference. Accordingly, the primary task paradigm utilized in the present study can be considered to be well suited to study FMS-associated alterations of pain-related attentional processes.

The present findings confirm that patients perceive themselves as hypervigilant towards pain as compared to healthy subjects. However, behavioral performance could not confirm an attentional bias towards pain in patients with FMS. In both the patient and the control group, differential effects of pain on visual reaction times were observed, yielding an increase of reaction times in some participants, as well as a decrease of reaction times in others. Although patients showed slightly prolonged reaction times after painful stimulation as compared to healthy subjects, this difference was non-significant

and thus unsuggestive of dysfunctional attentional processing of pain in patients with FMS. In the following, these findings will be discussed and evaluated in the context of the literature in more detail.

In health, variable effects of pain on behavior have been repeatedly described both by the present investigation (Tiemann et al., 2010) as well as previous studies (Seminowicz et al., 2004). This interindividual variability in the reaction to pain could not be attributed to differences in stimulus intensity or to differences in psychological factors (Tiemann et al., 2010). Instead, it was suggested that the behavioral heterogeneity may result from individual differences in the balance of distracting and alerting effects of pain on attention (Tiemann et al., 2010). In conformity with this hypothesis, maladaptive attentional processes in FMS might correspond to a shift in the balance of distracting and alerting effects of pain towards the hypervigilant pole of this continuum. Here, however, a comparable variability in the attentional effects of pain was observed in the patient and the control group. Thus, the results do not provide evidence for a behavioral relevance of dysfunctional attentional processes in patients with FMS.

On the contrary, the results of the present investigation confirm that FMS patients consider themselves as hypervigilant towards pain in self-assessment questionnaires. This finding is in good agreement with the literature (McDermid et al., 1996; Crombez et al., 2004; Hollins et al., 2009). However, self-reported hypervigilance did not manifest itself in behavioral performance or neuronal processing. Likewise, the literature reports inconsistent results when hypervigilance in FMS is tested experimentally. On the one hand, at least one study reports evidence for behaviorally relevant attentional interference in patients with chronic pain (Eccleston et al., 1997). On the other hand, several experimental investigations failed to find evidence for behaviorally relevant hypervigilance in patients with FMS (Peters et al., 2000; Asmundson et al., 2005; for review see Dohrenbusch, 2001). Whereas those studies evaluated the attentional bias regarding innocuous somatosensory (Peters et al., 2000) or threatening linguistic stimuli (Asmundson et al., 2005), the present study is the first to assess the pain-related attentional bias in FMS using a behavioral paradigm with concurrent painful stimulation. Still, the results do not argue in favor of a behavioral or neuronal correlate of self-reported hypervigilance. Accordingly, one might argue that perceived hypervigilance to

pain may be a consequence of the disease rather than a causal element in its pathogenesis.

Decreased heat and pressure pain thresholds in FMS have been consistently reported by investigations using sensory testing methods (Granges and Littlejohn, 1993; Gibson et al., 1994; Lautenbacher et al., 1994; Kosek et al., 1996; Hurtig et al., 2001; Desmeules et al., 2003; Klauenberg et al., 2008; Smith et al., 2008). One possible explanation for this heightened sensitivity in FMS could be a hypervigilant style of pain-related processing (Rollman and Lautenbacher, 1993). However, taking into account the results of the present investigation, this assumption appears rather unlikely. Alternatively, but not mutually exclusively, central sensitization has been implicated in the pathophysiology of FMS (for review see Woolf, 2011). In particular, pathological alterations of diffuse noxious inhibitory control (DNIC) mechanisms have been suggested to underlie the development of widespread pain (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Marchand and Arsenault, 2002; Julien et al., 2005). DNIC relates to an endogenous pain modulating mechanism, which occurs when the response to a painful stimulus is inhibited by another painful sensation ("pain inhibits pain"-phenomenon; Le Bars et al., 1979) and prevents a localized painful sensation from spreading to other body parts (Lautenbacher and Rollman, 1997). In conformity with the present results, it thus appears likely that central sensitization rather than hypervigilance plays a critical role in the chronic pain experience as observed in FMS (Graven-Nielsen and Arendt-Nielsen, 2010).

Conclusively it can be stated that the findings of the present investigation do not corroborate the third hypothesis. Whereas self-assessment questionnaires as a subjective measure of attention to pain are suggestive of dysfunctional attentional processes in FMS, objective measures do not indicate a behavioral manifestation of hypervigilance. Thus, the present findings do not argue in favor of a hypervigilant processing style of pain-related information in patients with FMS as compared to healthy controls.

## 6.4 Gamma oscillations as a neuronal correlate of the attentional effects of pain in FMS

### 6.4.1 Visual and pain-induced gamma oscillations in FMS

In the present investigation it could be demonstrated that pain modulates attention in healthy subjects, and that these pain-related attentional changes are paralleled by modulations of neuronal gamma oscillations. Consequently, it was hypothesized that patients with FMS are characterized by a hypervigilant style of pain processing, which would manifest both behaviorally as well as in a pathological variation of neuronal gamma oscillations. Behaviorally, no manifestation of hypervigilance in FMS could be noted. Still, it remains conceivable that pathological aberrations of neuronal gamma oscillations without significant functional relevance might be present in FMS.

To the best of knowledge, the present investigation is the first to compare gamma oscillations as a neuronal signature of selective attention in healthy subjects and patients with FMS. In conformity with the present findings in healthy subjects the results confirm that visual stimulation induces sustained gamma oscillations. These visual gamma oscillations were strongest at occipital electrodes and varied interindividually in a frequency range from 40 - 60 Hz (Tiemann et al., 2010). Moreover, the results confirm that painful stimulation yields pain-induced gamma oscillations, which were maximal at central electrodes and varied interindividually in a frequency range from 30 - 60 Hz. Subtle distinctions in frequency peaks between different investigations are most probably due to interindividual variability in the frequency of pain-induced gamma oscillations (Gross et al., 2007).

Further, using a multiple source beamformer approach, visual gamma oscillations were found to originate from the primary visual cortex. Pain-induced gamma oscillations were confirmed to originate from the contralateral primary sensory cortex, respectively. This suggestion is in line with the results of subproject 1, which have been obtained in a sample of healthy subjects (Tiemann et al., 2010). However, localizations of EEG responses in both health and disease are inherently vague. Thus, the present findings do not preclude pain-induced gamma oscillations to originate from other brain areas and may be regarded as preliminary.

Most importantly however, healthy subjects and patients with FMS did not differ significantly with regard to the strength of visual or pain-induced gamma oscillations. This finding argues against the notion that gamma oscillations might represent a neuronal correlate of hypervigilance in patients with FMS.

### 6.4.2 Gamma oscillations, attention, and pain in FMS

In the present study a significant correlation between the pain-induced effects on gamma oscillations and reaction times could be observed in patients with FMS. This finding corroborates a close relationship between gamma oscillations and reaction times as a measure of attentional performance (Gonzalez Andino et al., 2005; Womelsdorf et al., 2006; Frund et al., 2007; Bauer et al., 2009). Moreover, it confirms the relationship between pain-induced effects on gamma oscillations and pain-induced effects on reaction times which has been observed in a sample of healthy subjects (Tiemann et al., 2010). In addition, the study was designed to elucidate whether the relationship between gamma oscillations and behavioral performance differed between patients with FMS and healthy subjects as an expression of altered attentional processing in FMS. The results indicate that the relationship between neuronal gamma oscillations and behavioral performance can be regarded as comparable in patients and healthy subjects. Accordingly, abnormalities in this relationship do not appear to be involved in the pathology of FMS.

Considered as a whole it can thus be concluded that the findings of the present investigation do not corroborate the fourth hypothesis.

## 6.5 Limitations and perspectives

In consequence of two main reasons, the degree to which the findings of the present investigation can be generalized is limited. First, the present study investigated the effect of *painful* stimulation on attention and neuronal processing. The advantage of this approach is the fact that pain represents an exceptionally well suited vehicle to study attentional interference due to its outstanding biological salience and behavioral

relevance. However, the present study does not comprise a control condition with a non-painful sensory stimulus. The observed effects on reaction times and gamma oscillations can thus not be specifically attributed to pain, or, vice versa, do not necessarily generalize to other alerting stimuli. The comparison with the effects of non-painful stimuli could add significant information to the present findings and should therefore be included in future studies. Second, the generalizability of the present findings is considerably limited by the rather small sample sizes. Inherently, small sample sizes result in a rather heterogeneous composition of groups. A common problem which then arises is a lack of statistical power, which prevents the detection of actual effects (Ellis, 2010). In accordance with these statistical fundamentals, it was intended to minimize the heterogeneity in the patient group by adopting rather strict exclusion criteria. Thus, patients with FMS were excluded from study participation if they suffered from additional medical disorders, particularly any disorder causing chronic or acute pain other than FMS, or if they were not able to interrupt their pharmacological therapy with centrally active drugs for a minimum of 7 days prior to study participation. Whereas this approach ensures a rather homogenous sample, it gives rise to another potential concern which has to be considered in the interpretation of the results. In real life, a large proportion of patients with FMS is suffering from various comorbid conditions (Aaron and Buchwald, 2001; Martinez-Lavin, 2001; Buskila and Cohen, 2007) and / or is taking centrally active medication (Smith et al., 2011). Thus, the patient sample of the present investigation does not necessarily reflect the factual reality of the population of patients with FMS. Conclusively it can be stated that future studies would benefit from larger sample sizes both in relation to statistical power as well as in relation to a better representation of the actual collective of patients with FMS.

Moreover, several aspects regarding the study design and stimulation modalities need to be considered in the interpretation. In the present investigation, a primary task paradigm with concurrent painful stimulation was adopted to study the attentional effects of pain. The primary visual task is based on a well-established paradigm and was intentionally chosen as it is known to reliably induce gamma oscillations in human visual cortex (Hoogenboom et al., 2006; Scheeringa et al., 2011). However, it can be regarded as only moderately challenging in terms of task difficulty and cognitive load. Since these factors are known to have an impact on the extent of attentional interference (for details

see paragraph 6.1), the results obtained with the present paradigm do not necessarily generalize to other, cognitively more demanding tasks.

Furthermore, pain in the present study was induced by means of cutaneous laser stimulation, which produces phasic painful stimuli of short duration and pinprick-like quality. Laser stimulation was intentionally chosen as method of pain application since stimuli of short duration are best suited to adequately image pain-related changes of neuronal activity by means of EEG. However, experimentally induced phasic pain contrasts with the chronic pain experienced by patients with FMS. Thus, the ecological validity of the present results might be limited. In other words, the extent of attentional interference induced by experimental painful stimulation may not necessarily correspond to the extent of attentional interference induced by persistent pain experienced in chronic pain disorders.

Finally, the present study does not account for whether the observed effects of pain on attention can be considered as reliable upon re-examination. After one-time testing, a considerable interindividual heterogeneity of the attentional effects of pain was observed in both the patient and the control group. It appears feasible that, upon repeated re-examination, the individual extent of pain-related attentional interference might vary from one point in time to another. Such finding would argue in favor of *state*-like fluctuations of the balance between alerting and distracting effects of pain on attention. On the other hand, the interindividual variability might be temporally stable across individuals upon re-examination. Such finding would argue in favor of a *trait*-like organization of alerting and distracting effects of pain on attention. Rather than constituting a limitation of the present study, the investigation of the reliability of the present results can be considered as a promising and appealing approach for future studies.

## 6.6 Conclusions

Using a behavioral paradigm to study attentional interference, the results of the present investigation indicate a comparable task performance in patients and healthy controls. The attentional effects of pain varied considerably between individuals, yielding

an increase of reaction times in some, as well as a decrease of reaction times in other subjects. This variability in observable behavior is well compatible with the assumption that the overall attentional effect of pain is determined by the individual balance of alerting and distracting components.

In both the patient and the control group, attentional effects of pain on behavioral performance were closely related to gamma oscillations in the human brain. However, since these effects did not differ between patients and healthy subjects, the results do not confirm gamma oscillations as a neuronal correlate of perceived hypervigilance in FMS.

The fact that perceived hypervigilance in patients with FMS does not manifest itself in behavioral performance and / or neuronal processing argues against a critical role of hypervigilance in the pathogenesis of the disease. Rather, one may speculate that central sensitization caused by deficient inhibitory mechanisms may account for the observed hypersensitivity in patients with FMS.

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# List of figures

# List of tables

# List of abbreviations

| | |
|---|---|
| ACC / rACC | Anterior cingulate cortex / rostral anterior cingulate cortex |
| ACR | American College of Rheumatology |
| Amyg | Amygdala |
| ANOVA | Analysis of variance |
| BG | Basal ganglia |
| cl | Contralateral |
| DNIC | Diffuse Noxious Inhibitory Controls |
| EEG | Electroencephalography |
| fMRI | Functional magnetic resonance imaging |
| FMS | Fibromyalgia syndrome |
| HC | Healthy controls |
| HT | Hypothalamus |
| il | Ipsilateral |
| LEP | Laser evoked potential |
| M | Mean |
| M1 | Primary motor cortex |
| MEG | Magnetencephalography |
| N1 | Negative deflection of the laser evoked potential (~150 ms) |
| N2 | Negative deflection of the laser evoked potential (~250 ms) |
| P2 | Positive deflection of the laser evoked potential (~390 ms) |
| PAG | Periaqueductal gray |
| PB | Parabrachial nuclei |
| PCC | Posterior cingulate cortex |
| PCS | Pain catastrophizing scale |
| PET | Positron emission topography |
| PFC | Prefrontal cortex |
| PVAQ | Pain vigilance and awareness questionnaire |
| RT | Reaction times |
| SI / S1 | Primary somatosensory cortex |
| SII / S2 | Secondary somatosensory cortex |
| SD | Standard deviation |
| SMA | Supplementary motor area |
| TFR | Time-frequency representation |
| TMS | Transcranial magnetic stimulation |
| VAS | Visual analogue scale |
| Vis | Visual cortex |

# Appendix A (PVAQ)

# PVAQ

**NAME:**

**INSTRUKTIONEN:** Bitte beantworten Sie jede Frage, indem Sie auf der Skala markieren, wie stark die einzelnen Aussagen auf Sie zutreffen.

| | | **nie** | | | | | **immer** |
|---|---|---|---|---|---|---|---|
| | | **0** | **1** | **2** | **3** | **4** | **5** |
| 1. | Ich bin sehr schmerzempfindlich. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | Ich nehme plötzliche oder vorübergehende Veränderungen von Schmerzen bewusst wahr. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | Unterschiede in der Stärke von Schmerzen bemerke ich sofort. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | Die Wirkung von Medikamenten auf Schmerzen fällt mir sofort auf. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. | Veränderungen von Ort oder Stärke der Schmerzen fallen mir schnell auf. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. | Ich konzentriere mich vollkommen auf schmerzhafte Empfindungen. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. | Mir fallen Schmerzen auch dann auf, wenn ich mit anderen Dingen beschäftigt bin. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. | Mir fällt es leicht, Schmerzen zu ignorieren. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. | Wenn Schmerzen beginnen oder stärker werden, fällt mir das sofort auf. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. | Wenn ich etwas mache, das die Schmerzen verstärkt, dann achte ich als erstes darauf, wie sehr die Schmerzen zugenommen haben. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. | Mir fällt sofort auf, wenn sich Schmerzen verringern. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. | Mir scheinen Schmerzen leichter aufzufallen als anderen. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. | Ich achte sehr auf Schmerzen. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. | Ich achte genauestens auf die Stärke von Schmerzen. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. | Schmerzen beschäftigen mich überaus stark. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. | Ich beschäftige mich nicht mit Schmerzen. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**BITTE PRüFEN SIE, OB SIE ALLE FRAGEN BEANTWORTET HABEN!**

# Appendix B (PCS)

# PCS

**NAME:**

**INSTRUKTIONEN:** Die folgenden dreizehn Sätze beschreiben verschiedene Gedanken und Gefühle, die bei Schmerzen auftreten können. Bitte markieren Sie auf der folgenden Skala, wie stark diese Gedanken und Gefühle auf Sie zutreffen, wenn Sie Schmerzen haben.

| **Wenn ich Schmerzen habe…** | **trifft überhaupt nicht zu** | **trifft eher nicht zu** | **Teils-teils** | **trifft eher zu** | **trifft immer zu** |
|---|---|---|---|---|---|
| 1. … mache ich mir ständig Sorgen, ob die Schmerzen wohl jemals wieder aufhören werden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. … denke ich, ich kann nicht mehr. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. … ist es ein schrecklicher Zustand und ich denke, dass es nie mehr besser wird. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. … ist es ein furchtbarer Zustand und droht mich zu überwältigen. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. … habe ich das Gefühl, es nicht mehr auszuhalten. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. … bekomme ich Angst, dass die Schmerzen noch stärker werden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. … denke ich ständig an andere Situationen, in denen ich Schmerzen hatte. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. … wünsche ich mir verzweifelt, dass die Schmerzen weggehen. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. … kann ich nicht aufhören, an die Schmerzen zu denken. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. … denke ich ständig daran, wie sehr es schmerzt. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. … denke ich ständig daran, wie sehr ich mir ein Ende der Schmerzen herbeiwünsche. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. … gibt es nichts, was ich tun kann, um die Schmerzen zu lindern. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. … mache ich mir Sorgen, dass die Schmerzen auf etwas Schlimmes hindeuten. | ☐ | ☐ | ☐ | ☐ | ☐ |

**BITTE PRÜFEN SIE, OB SIE ALLE FRAGEN BEANTWORTET HABEN!**

# Appendix C (FIQ-G)

# FIQ-G

**NAME:**

**INSTRUKTIONEN:** Vorgehensweise: Für die Fragen 1-10 bitte jeweils die Nummer mit einem Kreis markieren, die am besten Ihren Zustand in der letzten Woche beschreibt. Falls Sie irgendeine der aufgeführten Tätigkeiten normalerweise nicht ausführen, streichen Sie die Frage bitte.

| **Waren Sie in der Lage:** | | **immer** | **meistens** | **gelegentlich** | **nie** |
|---|---|---|---|---|---|
| 1. | Einkaufen zu gehen | ☐ | ☐ | ☐ | ☐ |
| 2. | Wäsche mit Waschmaschine und Trockner zu erledigen | ☐ | ☐ | ☐ | ☐ |
| 3. | Essen vorzubereiten | ☐ | ☐ | ☐ | ☐ |
| 4. | Geschirr mit der Hand zu waschen | ☐ | ☐ | ☐ | ☐ |
| 5. | Teppichvorleger staubzusaugen | ☐ | ☐ | ☐ | ☐ |
| 6. | Betten zu machen | ☐ | ☐ | ☐ | ☐ |
| 7. | Um einige Häuserblocks zu gehen | ☐ | ☐ | ☐ | ☐ |
| 8. | Freunde oder Verwandte zu besuchen | ☐ | ☐ | ☐ | ☐ |
| 9. | Hof- oder Gartenarbeit zu erledigen | ☐ | ☐ | ☐ | ☐ |
| 10. | Auto zu fahren | ☐ | ☐ | ☐ | ☐ |

**2. Von den 7 Tagen der letzten Woche: an wievielen Tagen haben Sie sich wohl gefühlt?**

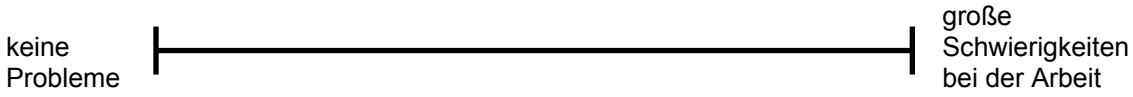
0 1 2 3 4 5 6 7

**3. An wievielen Tagen der letzten Woche konnten Sie aufgrund Ihrer Erkrankung nicht Ihrer Arbeit nachgehen? Falls Sie nicht außerhalb des Hauses arbeiten, bitte diese Frage unbeantwortet lassen.**

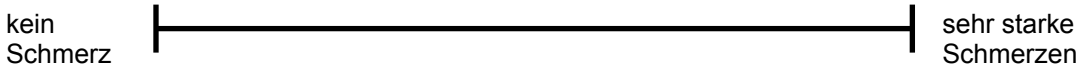
0 1 2 3 4 5

**Vorgehensweise: Für die verbleibenden Punkte, bitte die Stelle auf der Linie markieren, die am besten Ihren Zustand in der vergangenen Woche beschreibt.**

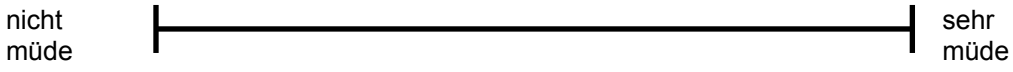
**4. Als Sie während der vergangenen Woche arbeiteten, wie stark haben Schmerzen oder andere Symptome Ihrer Erkrankung Ihre Arbeitsfähigkeit eingeschränkt?**



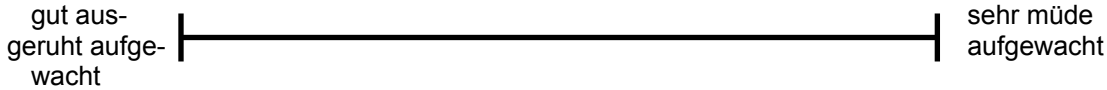

**5. Wie ausgeprägt waren Ihre Schmerzen?**




**6. Wie müde sind Sie gewesen?**

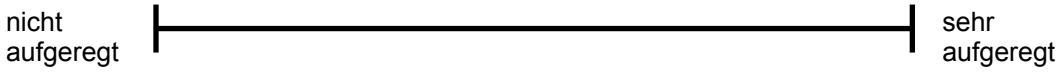



**7. Wie müde haben Sie sich am Morgen nach dem Aufstehen gefühlt?**

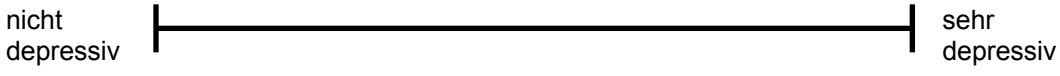



**8. Wie schlimm war Ihre Steifigkeit?**


**9. Wie nervös oder aufgeregt haben Sie sich gefühlt?**




**10. Wie depressiv haben Sie sich gefühlt?**



# Appendix D (Curriculum Vitae)

**Persönliche Daten**

**Laura Tiemann**, geboren am 12. 10.1983 in Recklinghausen

**Promotion**

| | |
|---|---|
| 03/08 – 02/12 | **Thema:** Behavioral and neurophysiological investigations of the attentional effects of pain in health and fibromyalgia syndrome |

**Berufstätigkeit**

| | |
|---|---|
| Seit 03/08 | **Wissenschaftliche Mitarbeiterin**<br>Klinikum rechts der Isar, München |

**Hochschulstudium**

| | |
|---|---|
| 10/03 – 02/08 | **Studium der Psychologie**<br>Ruhr-Universität Bochum |

**Schulausbildung**

| | |
|---|---|
| 08/94 - 06/2003 | Willy-Brandt-Gymnasium, Oer-Erkenschwick, Abitur |
| 08/90 – 06/94 | Westerbachgrundschule, Oer-Erkenschwick |

# Appendix E (Publications)

**Tiemann L**, Schulz E, Gross J, Ploner M (2010) Gamma oscillations as a neuronal correlate of the attentional effects of pain. Pain 150:302-308.

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PAIN®

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# Gamma oscillations as a neuronal correlate of the attentional effects of pain

Laura Tiemann [a,*], Enrico Schulz [a], Joachim Gross [b], Markus Ploner [a]

[a] Department of Neurology, Technische Universität München, 81675 Munich, Germany
[b] Centre for Cognitive Neuroimaging, Department of Psychology, University of Glasgow, G12 8QB Glasgow, UK

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ABSTRACT

Successful behavior requires the attentional selection and preferred processing of behaviorally relevant sensory information. Painful stimuli are of utmost behavioral relevance and can therefore involuntarily affect attentional resources and interfere with ongoing behavior. However, the neuronal mechanisms which subserve the involuntary attentional effects of pain are largely unknown yet. Here, we therefore investigated the neuronal mechanisms of the attentional effects of pain by using electroencephalography during a visual attention task with the concurrent presentation of painful stimuli. Our results confirm that painful and visual stimuli induce gamma oscillations over central and occipital areas, respectively. Pain-induced gamma oscillations were correlated with pain-induced changes in visual gamma oscillations. Behaviorally, we observed variable effects of pain on visual reaction times, yielding an increase of reaction times for some subjects, as well as a decrease of reaction times for others. Most importantly, however, these changes in visual task performance were significantly related to pain-induced changes of visual gamma oscillations. These findings demonstrate that the variable attentional effects of pain are closely related to changes in neuronal gamma oscillations in the human brain. In the hypervigilant state of chronic pain, maladaptive changes in the attentional effects of pain may be associated with abnormal changes in neuronal gamma oscillations. Our findings may thus contribute to the understanding of the neuronal substrates of pain in health and may open a new window towards the understanding of pathological alterations of the pain experience in chronic pain syndromes.



## 1. Introduction

The perception of pain fulfills a vitally protective function, as it signals threat to the organism and urges the individual to react. In a potentially harmful situation, fast and effective behavioral responses need to be ensured. Painful stimuli are therefore processed preferentially in the human brain and thus affect the allocation of attentional resources [12]. On the one hand, painful stimulation induces a widespread increase of cortical excitability, which most probably reflects the alerting function of pain and facilitates a fast reaction to stimuli of existential relevance [31,33]. On the other hand, the preferred processing of pain affects the simultaneous processing of competing non-painful stimuli. That is, pain demands the limited resources of selective attention involuntarily and thereby interferes with ongoing behavior [12]. Abnormalities of this attentional bias towards pain have been implicated in the development and maintenance of chronic pain disorders [10,29]. The neurophysiological processes, however, which underlie the involuntary attentional effects of pain, cause interference with ongoing behavior, and mediate the preferred processing of pain, remain largely unclear.

Here, we aimed to investigate the neuronal mechanisms of the attentional effects of pain by using electroencephalography (EEG) during a visual attention task with the concurrent presentation of painful stimuli. We were specifically interested in the effects of pain on neuronal oscillations in the gamma frequency range (30–100 Hz), since gamma oscillations have been related to the attentional selection and enhanced processing of visual, auditory and tactile information [13,23,36]. Recently, gamma oscillations have also been observed in response to painful stimuli [19,21]. These pain-induced gamma oscillations varied with attention to the painful stimuli [21] and their conscious perception [19]. We thus hypothesized that the attentional effects of pain are associated with changes of gamma oscillations in the human brain. We particularly speculated that during a visual attention task, painful stimuli would induce gamma oscillations in the somatosensory system and simultaneously influence gamma oscillations in the visual system. Furthermore, we hypothesized that the involuntary effects of pain on neuronal gamma oscillations would relate to changes in visual task performance. If so, this would support the hypothesis that gamma oscillations represent a neuronal correlate of the attentional effects of pain.

* Corresponding author. Address: Department of Neurology, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany. Tel.: +49 89 4140 7664; fax: +49 89 4140 7681.
*E-mail addresses:* tiemann@lrz.tum.de, tiemann@lrz.tu-muenchen.de (L. Tiemann).

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## 2. Materials and methods

### 2.1. Subjects

We recorded EEG data from 30 healthy subjects. The data from eight subjects were excluded due to poor data quality. The analysis, thus, included data of 22 subjects (11 male, 11 female) with a mean age of 26 years (range 20–39 years). All subjects had normal or corrected-to-normal visual acuity. Informed consent was obtained from all subjects before participation. The procedure was approved by the local ethics committee and conducted in conformity with the declaration of Helsinki.

### 2.2. Paradigm

Subjects participated in an attention-demanding visual task with interfering painful stimuli (Fig. 1). The visual attention task was based on a paradigm introduced by Hoogenboom and co-workers [22], which reliably induces gamma oscillations in human visual cortices. To investigate the involuntary attentional effects of pain, painful stimuli were pseudorandomly applied to the dorsum of the left hand.

Subjects were presented a white fixation point against black background. After 500 ms the contrast of the fixation point was reduced to cue the beginning of visual stimulation. After 1500 ms a circular sine wave grating contracting towards its center was shown in foveal position. After a pseudorandomly varied duration of 1200–2500 ms the contraction accelerated, signalling the subjects to press a button with their right hand as fast as possible. Visual stimulation was aborted after a response was given or alternatively turned off after 1000 ms. Visual feedback about the correctness of the response was given for a duration of 4000 ms. Thus, the total duration of a trial was between 7200 and 8500 ms. Each subject completed one block consisting of 168 trials with a total duration of approximately 24 min. In 50% of the trials a painful cutaneous laser stimulus was applied (*pain* trials). In the other 50% of the trials no painful stimuli were applied (*no pain* trials). Time of painful stimuli with respect to the onset of visual stimulation was pseudorandomly varied to avoid predictability of painful stimuli. This resulted in 30 trials with a duration of 2500 ms and painful stimulation after 500 ms of visual stimulation, 30 trials with a duration of 2500 ms and painful stimulation after 700 ms of visual stimulation, 12 trials with a duration between 1200 and 2500 ms and painful stimulation 200 ms before the acceleration of the visual stimulus as well as 12 trials with a duration between 1200 and 2500 ms and painful stimulation 500 ms before the acceleration of the visual stimulus. Apart from the application of painful stimuli, *pain* and *no pain* trials were identical.

Subjects were instructed to complete the visual task without becoming distracted by the painful stimulation. After the EEG recordings the subjects were asked to rate the mean pain intensity on a visual analogue scale. The scale ranged from 0 to 10, with 0 representing "no pain" and 10 representing "worst tolerable pain". In addition, we aimed to assess the individual tendency to allocate attention to pain. Both pain vigilance [12] and pain catastrophizing [43] are psychological factors which are related to the individual attentional bias towards pain and which substantially affect pain perception. We therefore assessed pain vigilance and pain catastrophizing by using German versions of well-established questionnaires (pain vigilance and awareness questionnaire, [29]; pain catastrophizing scale, [42]).

### 2.3. Stimuli

The task was performed on a personal computer with a 19 inch CRT monitor and a vertical refresh rate of 60 Hz using E-Prime software (Version 1.2, Psyc. Tools Inc.) for presentation. Subjects were seated at a distance of approximately 70 cm from the computer screen and were free to place their head on a chin rest.

84 painful cutaneous laser stimuli, which evoke a highly synchronized selective activation of nociceptive afferents without concomitant activation of tactile afferents [30], were delivered to the dorsum of the left hand. The laser device was an Nd:YAP-laser (DEKA, Calenzano, Italy) with a wavelength of 1340 nm, a pulse duration of 3 ms, and a spot diameter of 6 mm. Minimum interstimulus interval of laser stimuli was 8 s. Stimulation site was slightly varied after each stimulus. Stimulus intensity was individual pain threshold intensity plus 0.75 J, inducing moderately painful sensations. Mean stimulus intensity across subjects was 2.8 J (range 2.25–3.5 J). Subjects were exposed to white noise through headphones to cancel out any noise of the laser device.

### 2.4. EEG recordings

EEG data were recorded with an electrode cap (FMS, Munich, Germany) and BrainAmp MR plus amplifiers (Brain Products, Munich, Germany) using the Brain Vision Recorder software (Brain Products, Munich, Germany). Electrode montage included 64 electrodes consisting of the electrodes Fz/Cz/Pz, FP1/2, F3/4/7/8, C3/4, P3/4, T3/4/5/6 and O1/2 of the 10–20 system and the additional electrodes FPz, AFz, FCz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, P1/2/5/6, TP7/8/9/10, and PO3/4/7/8/9/10. Two more electrodes were fixed below the outer canthi of the eyes. The EEG was referenced to the FCz electrode, grounded at AFz, sampled at 1000 Hz and highpass filtered at 0.1 Hz. The impedance was kept below 20 kΩ.

### 2.5. Data analysis

#### 2.5.1. Behavioral data

Reaction times were used to determine the involuntary effects of pain on visual task performance. Reaction times were registered

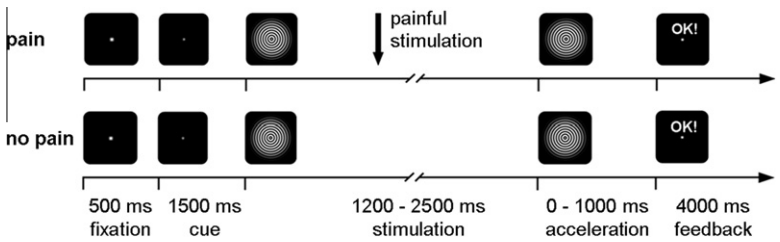


**Fig. 1.** *Paradigm:* Subjects were presented white fixation points against black background. After 1500 ms a circular sine wave grating contracting towards its center was shown. After a pseudorandomly varied duration of 1200–2500 ms the contraction accelerated, signalling the subjects to press a button with their right hand as fast as possible. Visual feedback followed the response. In 50% of the trials painful stimuli were applied to the left hand (*pain* trials). Time of painful stimuli was varied with respect to the onset of visual stimulation to avoid predictability of painful stimuli. Subjects were instructed to complete the visual task without becoming distracted by the painful stimulation.

on a trial-by-trial basis. Reaction times less than 150 ms or greater than 500 ms were excluded from further behavioral analysis. This resulted in a total of 85 excluded trials, which corresponds to 4 (out of 48) excluded trials on average per subject. The number of excluded trials did not differ between *pain* ($n = 42$) and *no pain* ($n = 43$) trials. For each subject, mean reaction times of *pain* and *no pain* trials were calculated and compared. Previous studies showed that reaction times [7] and neurophysiological responses [24] to painful stimuli are mainly observed between 100 and 500 ms after stimulus application. We thus expected the painful stimuli to interfere most profoundly with visual task performance when applied during this interval before a required response. Analysis of behavioral data was therefore focused on *pain* trials where laser stimuli were applied during this time interval (200 or 500 ms before the acceleration, $n = 24$, 30%) and compared to otherwise identical *no pain* trials ($n = 24$).

*2.5.2. Preprocessing of EEG data*

EEG data were preprocessed using the Brain Vision Analyzer software (Brain Products, Munich, Germany) and Brain Electrical Source Analysis 5.2 (BESA, MEGIS Software GmbH, Gräfelfing, Germany). Offline analysis included downsampling to 512 Hz, digital highpass filtering at 0.5 Hz and recomputation to the average reference. Downsampling included automatic lowpass filtering at 230 Hz. Independent component analysis was used to correct for vertical and horizontal eye movements. Trials with artifacts exceeding ±100 μV in any channel were automatically rejected. When recordings were corrupted at single electrodes ($n = 8$), data were interpolated for this subject and electrode.

*2.5.3. Time–frequency analysis of EEG data*

As reaction times [7] and neurophysiological responses [24] to painful stimuli are mainly observed between 100 and 500 ms after stimulus application, we were particularly interested in this interval. However, trials where accelerations occur during this interval are inevitably contaminated by motor activity related to the button press. We therefore focused the analysis of neurophysiological responses on *pain* trials where accelerations of visual stimuli occurred 1800 or 2000 ms after the pain stimuli ($n = 60$, 70%) which ensures a long interval for the neurophysiological analysis not contaminated by motor activity. However, it is important to note that the trials chosen for behavioral and neurophysiological analysis are identical except for the onset of acceleration of the moving visual stimulus. Since we were interested in the neuronal mechanisms *before* the acceleration, we assume both behavioral and neurophysiological trials to be identical concerning the pain-induced neuronal responses prior to the acceleration. The *pain* trials ($n = 60$) were compared to otherwise identical *no pain* trials ($n = 60$). The complex demodulation procedure implemented in BESA 5.2 was used to transform the data to the time–frequency-domain. The resulting time–frequency representations (TFRs) show neuronal activity as a function of time and frequency. Unlike evoked potentials, single trial data are *first* transformed to the time frequency domain and *then* averaged. As a result, TFRs include phase-locked as well as non-phase-locked neuronal responses. Time–frequency transformation was performed for frequencies from 4 to 100 Hz in a time window from −1000 to 4500 ms with respect to the onset of visual stimulation. Frequencies were sampled in steps of 2 Hz, latencies in steps of 25 ms. Time–frequency representations were calculated as % signal change with respect to baseline. In the *no pain* condition, baseline was defined as −800 to −100 ms prior to stimulus onset. In the *pain* condition, trials had to be realigned to the laser stimuli that were applied either 500 or 700 ms after onset of the visual stimulation. Thus, the beginning of visual stimulation was preponed for 200 ms in 50% of the trials, and the baseline was adjusted accordingly. The time–frequency transformed data were averaged across trials for each condition and each electrode.

*2.5.4. Source localization and time frequency analysis in source space*

The Multiple Source Beamformer Tool implemented in BESA was used to localize the cerebral sources of the visual and pain-induced gamma oscillations in each subject. For detailed information on methods and results of the source localization procedure, see Supplementary data. Since visual gamma oscillations have been consistently localized in lower level visual cortices in animals and humans [1,14,20,22,35,39,40], analyses of visual gamma oscillations were primarily performed in source space. Less evidence has been provided for the cerebral generators of pain-induced gamma oscillations. Thus, pain-induced gamma oscillations were localized as described in Supplementary data but further analyses were performed in electrode space.

*2.5.5. Statistical analysis*

Statistical analyses were performed using SPSS for windows (release 16.0.1, SPSS Inc., Chicago). Means were compared using t-tests. Correlations were calculated using Pearson's correlation coefficient. Level of significance for hypothesis testing was $p < 0.05$.

## 3. Results

To investigate the neuronal mechanisms of the attentional effects of pain, we recorded EEG from 22 healthy subjects during an attention-demanding visual reaction time task with interfering painful stimuli (Fig. 1).

*3.1. Behavioral data*

Painful laser stimuli elicited at least moderately painful, "pinprick-like" sensations with a mean subjective pain intensity of 5.8 ± 1.7. Reaction times in the visual task served as a measure of visual attention. Mean reaction time across all subjects and trial types was 317 ± 20 ms (mean ± SD). Fig. 2 shows reaction times of *pain* and *no pain* trials for each individual. In line with previous studies on pain-cognition interactions (for review see [37]), painful stimuli did not homogeneously affect visual reaction times but yielded an increase of reaction times in some as well as a decrease of reaction times in other subjects. Consequently, mean reaction times of *pain* (324 ± 21 ms) and *no pain* trials (321 ± 25 ms) did not differ significantly ($t = 0.82$; $p = 0.42$). Interindividual differences in the effects of pain on visual reaction times were not correlated with differences in pain threshold or differences in stimulus intensity ($r = -0.36$,

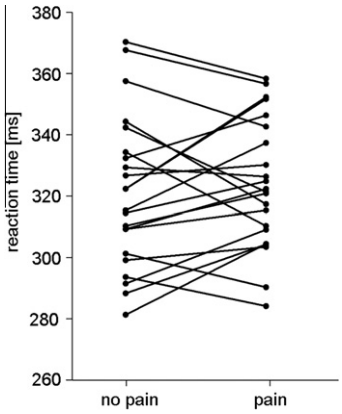


**Fig. 2.** *Behavioral results:* Please note that ascending lines connecting the *no pain* and *pain* conditions indicate a pain-induced prolongation of reaction times whereas descending lines indicate a reduction of reaction times.

$p = 0.09$; $r = -0.32$, $p = 0.15$). Moreover, we correlated the effects of pain on attentional performance with pain vigilance [12] and pain catastrophizing [43] as psychological factors which are related to the individual attentional bias towards pain. Pain vigilance did not correlate with the attentional effects of pain ($r = 0.04$, $p = 0.87$). The correlation between pain catastrophizing and attentional effects of pain turned out to be a trend, though not statistically significant ($r = 0.39$, $p = 0.07$). Furthermore, pain catastrophizing scores did not correlate significantly with pain ratings ($r = 0.26$, $p = 0.25$).

### 3.2. Visual and pain-induced gamma oscillations

We next investigated the effects of visual and painful stimuli on neuronal activity in the gamma frequency range. Fig. 3 shows group mean time–frequency representations (TFRs) of neuronal activity averaged across frontal, central and occipital electrodes, respectively. At occipital electrodes we found an increase in gamma oscillations which started about 100 ms after the onset of visual stimulation and lasted for the whole period of stimulus presentation (up to 2500 ms). Frequency of visual-induced gamma oscillations varied interindividually between 40 and 65 Hz. The signal change was most prominent at electrodes POz, Oz, PO3/4 and O1/2 (Fig. 3B). At these electrodes, gamma activity during visual stimulation (100–2500 ms, 58–64 Hz) was significantly increased compared to a prestimulus baseline ($t = 3.2$–$4.57$; $p < 0.01$). At central electrodes, we found an increase in gamma oscillations between 200 and 350 ms after application of painful laser stimuli and at frequencies between 64 and 84 Hz. The oscillations were most prominent at electrodes Cz and FCz (Fig. 3B). At these electrodes, gamma activity was significantly increased after painful stimulation (200–350 ms, 64–84 Hz) compared to a prestimulus baseline ($t = 3.82$ and 3.61, respectively; $p = 0.001$ and 0.002, respectively). Visual gamma oscillations were localized to the left and right occipital cortices (mean Talairach coordinates: left −24, −93, −2; right 23, −93, −3; Fig. 4). Pain-induced gamma oscillations were localized to the right primary somatosensory cortex (mean Talairach coordinates 36, −23, 61; Fig. 4). These results corroborate that painful and visual stimuli can induce gamma oscillations in the somatosensory and visual system, respectively.

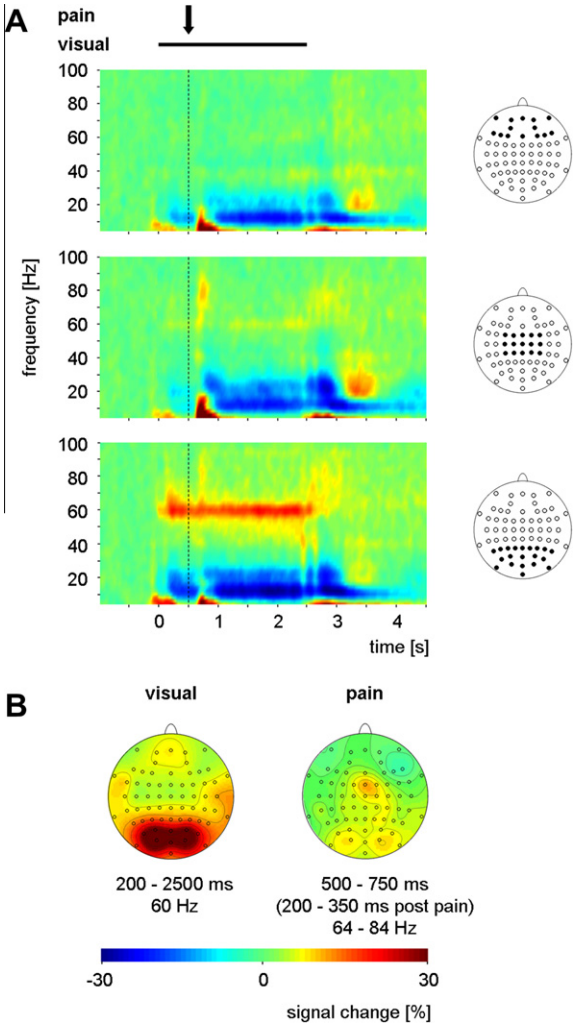


**Fig. 3.** Visual- and pain-induced gamma oscillations. (A) Group mean time–frequency representations of % signal change in *pain* trials used for neurophysiological analysis, averaged across frontal, central and occipital electrodes. In these trials, duration of visual stimulation was 2500 ms. Data are aligned to the onset of laser stimulation, which occurred 500 or 700 ms after onset of the visual stimulation, respectively. (B) Scalp distribution of gamma oscillations following visual (200–2500 ms after onset of visual stimulation, 60 Hz) and painful stimulation (500–750 ms after onset of visual stimulation, 200–350 ms after painful stimulation, 64–84 Hz) coded as % signal change as compared to baseline.

### 3.3. Relationship between pain-induced gamma oscillations and pain-induced changes in visual gamma oscillations

We were next interested in the relationship between the effects of pain on gamma oscillations in the somatosensory and visual system. We therefore correlated pain-induced changes of visual gamma oscillations with pain-induced gamma oscillations over central areas. In a time window from 200 to 350 ms after painful stimuli, we found a significant negative correlation between pain-induced changes of visual gamma oscillations over right visual cortex and pain-induced gamma oscillations over central areas ($r = -0.53$, $p = 0.011$; Fig. 5). No significant correlation between pain-induced changes of visual gamma oscillations over left visual cortex and pain-induced gamma oscillations over central areas could be observed ($r = -0.03$, $p = 0.89$; Fig. 5). Painful stimuli thus proportionally affect neuronal gamma oscillations in the visual and somatosensory system of the contralateral hemisphere.

### 3.4. Relationship between behavioral and neurophysiological effects of painful stimulation

We were next interested in the behavioral relevance of neuronal gamma oscillations. If gamma oscillations are functionally relevant for attentional selection and enhanced processing of visual

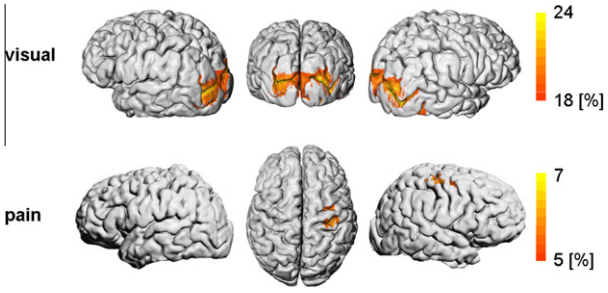


**Fig. 4.** Locations of visual- and pain-induced gamma oscillations. Activations are maxima of mean activation maps superimposed on a normalized surface-rendered structural T1-weighted magnetic resonance image. Color coded is the change of estimated activity in the target interval relative to the baseline in percent. Gamma activity of the left and right visual cortices was significantly increased during visual stimulation compared to the prestimulus baseline ($t = 3.46$ and 4.0, respectively; $p = 0.002$ and 0.001, respectively). Gamma activity in the right primary somatosensory cortex was significantly increased after painful stimuli compared to a prestimulus baseline ($t = 2.19$; $p = 0.04$).

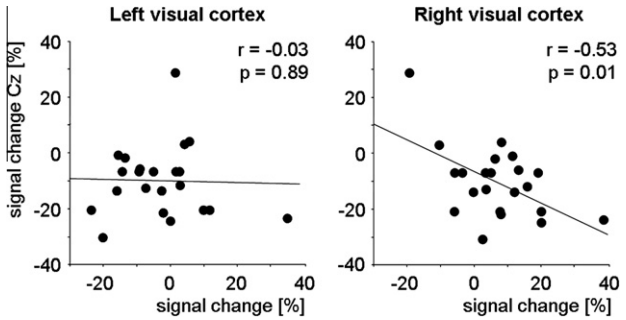


**Fig. 5.** Relationship between pain-induced gamma oscillations and pain-induced changes in visual gamma oscillations. Displayed is the correlation between the signal change of visual gamma oscillations measured 200–350 ms after painful laser stimulation in left and right visual cortex (signal change $Vis_{no\ pain}$ − signal change $Vis_{pain}$), and the signal change of pain-induced gamma oscillations measured 200–350 ms after laser application at Cz (signal change $Cz_{no\ pain}$ − signal change $Cz_{pain}$).

information, pain-induced changes in gamma oscillations should be correlated with pain-induced changes in behavior. We therefore correlated the effects of pain on visual reaction times with the effects of pain on visual gamma oscillations. The analysis revealed a highly significant positive correlation between both phenomena. Lower amplitudes of visual gamma oscillations after painful laser stimulation were associated with slower reaction times (left visual cortex: $r = 0.67$; $p = 0.001$; right visual cortex: $r = 0.68$; $p < 0.001$; Fig. 6). The removal of variance in reaction times due to catastrophizing did not significantly affect the correlation between visual gamma oscillations and reaction times (left visual cortex: $r = 0.67$; $p = 0.001$; right visual cortex: $r = 0.68$; $p = 0.001$). Thus, the involuntary effects of pain on visual gamma oscillations are significantly correlated with the effects of pain on performance in the visual attention task.

To further visualize the effects of pain on neuronal gamma oscillations and their relationship to behavior, we applied a split-half-criterion to divide the subjects into subgroups whose behavioral performance was decreased (group 1; $n = 11$) and increased after painful stimulation (group 0; $n = 11$), respectively. In subjects with a pain-induced decrease in visual task performance (group 1), we found a transient pain-induced suppression of gamma oscillations in the right visual cortex at latencies when pain-induced gamma oscillations were observed (200–350 ms after painful stimuli) ($t = -2.8$; $p = 0.019$, Supplementary Fig. 1). No significant suppression of gamma oscillations was observed for the subjects whose behavioral performance increased after painful stimulation.

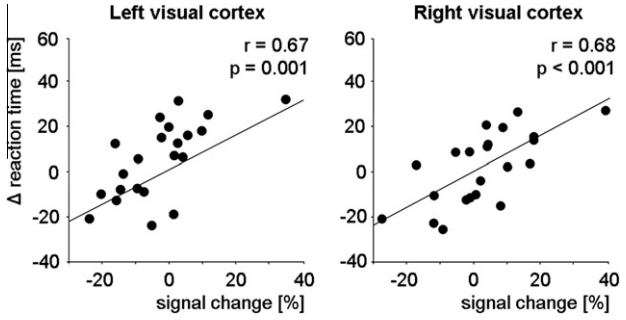


**Fig. 6.** Relationship between pain-induced changes in visual gamma oscillations and pain-induced changes in visual task performance. Displayed is the correlation between the signal change of visual gamma oscillations (signal $change_{no\ pain}$ − signal $change_{pain}$) in left and right visual cortex, and the change of reaction times after laser application ($RT_{pain} - RT_{no\ pain}$). The figure shows that stronger pain-related changes of reaction times are associated with stronger pain-related changes of visual gamma oscillations.

In the left hemisphere, no significant pain-induced suppression of visual gamma oscillations was observed for neither group ($t = -0.98$; $p = 0.35$; Supplementary Fig. 2).

Amplitudes of pain-induced gamma oscillations over central electrodes did not differ between groups ($t = 0.02$, $p = 0.98$). Pain catastrophizing and pain vigilance scores did not correlate significantly with pain-induced changes of reaction times for either group (pain catastrophizing: $r = 0.01$, $p = 0.98$; $r = 0.29$, $p = 0.39$; pain vigilance: $r = 0.04$, $p = 0.9$; $r = 0.26$, $p = 0.44$).

## 4. Discussion

In the present study, we investigated the neuronal mechanisms of the attentional effects of pain. Pain-induced gamma oscillations over central areas were negatively correlated with changes of visual gamma oscillations in the right hemisphere, indicating that pain proportionally affects gamma oscillations in the visual and somatosensory systems. Behaviorally, we observed an inconsistent and non-significant effect of pain on visual task performance, yielding increased reaction times for some, as well as decreased reaction times for other subjects. Most importantly, these pain-induced changes of reaction times were significantly related to the pain-induced change of visual gamma oscillations. This finding substantiates a close association between neuronal gamma oscillations and involuntary attentional effects of pain.

### 4.1. Visual and pain-induced gamma oscillations

Here, we recorded neuronal gamma oscillations over visual cortices during a visual attention task. This finding is in good agreement with results from intracranial recordings in monkeys [14,35,40] and EEG and MEG recordings in humans [1,20,22,39]. The observed gamma-band response shows all characteristics of a visually-induced gamma-band synchronization in the human brain [15]. It is thus unlikely that the observed visual gamma response reflects brief miniature saccades [45]. Moreover, we observed that pain induces gamma oscillations which corresponds to previous EEG and MEG studies [2,19,21]. The suggestion that pain-induced gamma oscillations originate from the contralateral primary somatosensory cortex is in line with the results from studies using MEG [19,21] which has a higher spatial resolution than EEG. However, since localizations of EEG responses are inherently vague, our findings do not preclude pain-induced gamma oscillations from other brain areas.

### 4.2. Transient pain-induced reallocation of gamma oscillations

We observed a transient pain-induced modulation of visual gamma oscillations which correlated with the strength of pain-induced gamma oscillations at central electrodes. Our results thus indicate a proportional pain-related reallocation of gamma oscillations from visual to central areas. Notably, a pain-induced *suppression* of visual gamma oscillations with subsequent decreases in visual task performance was observed in merely half of the subjects. Probable reasons for this inconsistency across subjects are discussed below. It has to be noted further that the suppression of visual gamma oscillations was evident only in the right visual cortex. This lateralization may result from the application of the painful stimuli to the left hand which yields stronger neuronal responses in somatosensory areas of the contralateral hemisphere [4,16,32]. The lateralization may further be attributed to a preponderance of the right hemisphere for attentional processes [8] and/or negative affect including pain [9,11].

We know of only few studies which investigated neuronal gamma oscillations during a shift of attention between modalities [34,41]. These studies revealed that voluntary shifts of attention

between auditory and vibrotactile/visual stimuli were associated with an increase in gamma oscillations in the attended modality and a decrease for the unattended modality. The present study extends these findings by showing that pain can yield an *involuntary* shift of gamma oscillations from the visual system to somatosensory areas, reflecting the effects of pain on the limited attentional resources of the human brain.

### 4.3. Gamma oscillations, attention and pain

Our finding of a significant correlation between the pain-induced effects on gamma oscillations and reaction times corroborates a close relationship between gamma oscillations and reaction times as a measure of attentional performance [3,17,18,44]. In the visual attention task with concurrent painful stimulation of the present study, visual gamma oscillations are likely to reflect attentional engagement in the visual task which can be involuntarily and transiently interrupted by the brief painful stimuli. However, we did not include a control condition with a non-painful sensory stimulus. The observed effects on reaction times and gamma oscillations thus cannot be specifically attributed to pain, or, vice versa, do not necessarily generalize to other alerting stimuli. The comparison with the effects of non-painful stimuli could add significant information to the present findings and should therefore be included in future studies.

Since gamma-band synchronization is thought to enhance the impact of neuronal activity on other groups of neurons [13,36], pain-induced gamma oscillations may be instrumental in amplifying pain-related signals and in enhancing their further processing in downstream cortical areas. Pain-induced changes of gamma oscillations are therefore likely to subserve the involuntary attentional effects of pain which can result in an amplification of pain-related signals at the expense of ongoing sensory processes.

Our observations complement a recent EEG study which showed interactions between visual-evoked and pain-evoked potentials [28]. The present results extend that study by revealing a close association between pain and neuronal gamma oscillations and by relating the neurophysiological effects to the behavioral effects of pain. Our findings further complement a recent fMRI study on the modulatory effects of pain on visual processing [5]. That study showed that pain modulates visual object processing in the ventral visual stream. A connectivity analysis suggested the rostral anterior cingulate cortex as a possible source of the modulatory effects of pain. Other cerebral sources which are thought to exert attentional modulations on sensory processes include brain areas of the fronto-parietal attention network [8,25,26]. The results of the present EEG study extend these findings by revealing a neuronal mechanism which may underlie the modulatory effects of pain at the level of sensory processing. The anterior cingulate cortex and/or brain areas of the fronto-parietal attention network are likely to represent sources of the involuntary modulatory effects of pain. These brain areas may allocate processing resources from ongoing, less relevant processes to painful events. Our data suggest that this pain-induced reallocation of processing resources may be mechanistically subserved by a reallocation of gamma oscillations at the level of sensory cortices.

### 4.4. Variability in the behavioral and physiological effects of pain

Importantly, the effects of pain on visual gamma oscillations and behavior varied between subjects. The involuntary reallocation of attentional resources by pain is a critical feature of its warning function. However, pain-related attentional capture is not purely automatic but influenced by attentional top-down modulation [27]. In line with this finding, previous studies have pointed out that task characteristics and instructions substantially influence the interference with concurrent pain [38]. Differences in tasks and instructions may therefore also account for the inconsistent results on the relationship between pain and cognitive demands (for review see [6]). Thus, future studies might consider to calibrate pain intensity and task difficulty to maximize pain–cognition–interference and minimize the variability between subjects [6]. Moreover, interindividual differences in attentional engagement and behavioral strategy may account for the differences in the behavioral and physiological effects of pain observed in the present study [38]. Here, we calibrated individual pain intensity but not task difficulty. However, an influence of stimulus intensity or subjective pain intensity is unlikely, since these parameters did not correlate with the effects of pain on behavior. Besides the influence of contextual factors, it remains therefore debatable what differentiates between subjects who showed pain-induced interference with visual processing and behavior and those who did not. We assessed vigilance to pain and pain catastrophizing as psychological variables which relate to the individual tendency to allocate attention to pain [12,43]. However, pain vigilance and pain catastrophizing scores did not correlate significantly with pain effects on behavior either. We further noticed a marked but non-significant difference in visual gamma oscillations between subgroups already before application of the painful stimuli (Supplementary Fig. 1), indicating that subjects may differ in their ability to disengage from impending pain. Additionally, the inconsistency of the effects of pain on behavior may also reflect the involvement of other processes than selective attention. The effects of pain on selective attention are possibly complemented by an alerting effect of pain which can enhance response readiness and global cortical excitability and thereby yield faster reaction times [31,33]. Differences in the balance of the alerting effects and the selective attentional effects of pain may account for the considerable interindividual variability in the effects of pain on behavior.

Dysfunctional attentional processes in the sense of a failure to disengage from pain and/or heightened attention to pain have been implicated in the pathogenesis of chronic pain syndromes [10,12]. The present results in healthy human subjects suggest that these maladaptive changes in the attentional effects of pain may be associated with abnormal changes in neuronal gamma oscillations. Accordingly, the paradigm of the present study may be well suited to study pathological alterations of pain-related attentional processes. Moreover, the investigation of gamma oscillations as a neuronal correlate of the attentional effects of pain may contribute to our understanding of attentional dysfunctions in chronic pain syndromes.

## 5. Conclusions and outlook

Here, we show that the involuntary attentional effects of pain are closely related to changes in neuronal gamma oscillations. In healthy human subjects, the complementary alerting and interruptive functions of pain may yield variable and adaptive changes of neuronal gamma oscillations and behavior. In chronic pain, abnormal effects of pain on neuronal gamma oscillations may be involved in the hypervigilant state of the disorder. Thus, our findings may open a new window towards the understanding of the neural substrates of pain in health and disease.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.05.014.

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