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On the neurobiology of somatoform pain:

A functional magnetic resonance imaging investigation

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Abstract

Somatoform pain disorder is characterised by chronic pain without significant peripheral organic pathology. A central dysfunction that disrupts the brain's capacity to process emotions is claimed to be the neural correlate. However, there is little direct experimental evidence to support this hypothesis. The studies presented in this thesis address this question using functional magnetic resonance tomography, a modern non-invasive technique for brain imaging.

First, I examine alterations of the neural correlates of emotional processing. Specifically, I focus on empathy for pain, a fundamental affective behavioural trait in everyday social life. Study I demonstrates that patients show lower activation of the perigenual anterior cingulate cortex during the sharing of other people's pain. This area is involved in constructing affective meaning. This finding suggests that patients with somatoform pain have a disturbed emotional processing owing to decreased activation of empathetic-affective networks.

Second, I test whether alterations in neural circuits related to affective function only appear during a specific emotional behaviour, such as empathy, or if they are more deeply ingrained in the human brain. Study II and III demonstrate that patients suffering from somatoform pain show a shift to higher frequencies of spontaneous oscillations of neural activity in the cingular-insular (i.e. fronto-insular) network and the anterior default mode network even during a resting state without external stimulation. No differences are observed in the functional connectivity, a measure of the spatial extent of resting state networks, or in functional network connectivity, a measure of their interplay. These data suggest that chronic medically unexplained pain is an endogenous process that occurs within neural systems dedicated to emotional processing.

Taken together, these findings may lead to a more specific and detailed neurobiological understanding of the clinical observation of disturbed affect in patients experiencing chronic pain disorder.

Table of contents

1. Introduction

What are the reasons for chronic pain when no significant organic pathology can be located? Is it an “emotional” problem? Is it a “home-made” phenomenon intrinsically produced by the human brain? The imaging studies presented in this thesis aim to elucidate the neurobiology of somatoform pain disorder. Specifically, I address the following questions:

1. Is there neurobiological evidence that somatoform pain mirrors an impaired access to one’s own and other’s emotions?

2. Does the human cerebrum intrinsically – i.e. without external stimulation - produce specific patterns of endogenous activity that are related to chronic pain without sufficient peripheral causes? Is somatoform pain disorder associated with alterations in the spatial and temporal domains of neural networks dedicated to emotional processing during a resting state of the organism?

1.1 Functional somatic syndromes – characteristics and clinical implications

Functional somatic syndromes, symptoms without a significant organic correlate, present a large challenge for modern medicine. These psychosomatic diseases are common throughout the world and are costly for health care systems. Furthermore, these disorders are subject to becoming chronic and leading to severe suffering. Their cause has eluded diagnostics, and even the most advanced therapies cannot offer relief (Wessely et al., 1999, Grabe et al., 2003, Barsky et al., 2005, Henningsen et al., 2007, Fink and Schroder, 2010). Somatoform pain disorder plays an important role among functional syndromes. It is characterised by ongoing pain suggestive of physical illness and injury symptoms that cannot be fully explained by a general medical condition, the direct effect of a substance, or another mental disorder (Kroenke et al., 1997, APA, 2000). Patients often persistently refuse to accept the conclusion that there is no adequate physical cause for their bodily symptoms except for short periods during or immediately after medical investigation (WHO, 2005). As in anxiety disorders and in depression,

patients experience severe impairments in quality of life and have high numbers of sick days and consultations (Kroenke et al., 1997, Jackson and Kroenke, 2008). Therefore, research on the aetiology of somatoform pain is required. However, only a few studies have examined the neurobiology of somatoform pain. These studies support the notion that somatoform pain reflects dysfunction of pain processing in the central nervous system (Stoeter et al., 2007, Gundel et al., 2008, Garcia-Campayo et al., 2009, Valet et al., 2009).

1.2 Pain – dimensions and neuroimaging

As shown by modern imaging methods, such as functional magnetic resonance imaging and positron emission tomography, pain is a multidimensional phenomenon that can be experimentally related to distinct brain regions (Valet et al., 2010):

a) The sensory-discriminative component comprises the detection, localisation and determination of the quality and quantity of a painful stimulus. The noxious information reaches the thalamus via trigemino-thalamic and spino-thalamic fibres. Projections from the (ventro-) lateral nuclei mainly extend to the primary and secondary somatosensory cortex. Therefore, this system is called the “lateral pain system”.

b) The affective dimension of pain perception reflects anxiety, unpleasantness, emotional awareness, and the monitoring of bodily states mediated by the anterior insula and the anterior cingulate cortex (Craig, 2002, 2003, Seeley et al., 2007). The (ventro-) medial nuclei of the thalamus project to these regions and represent the gate of the so-called “medial pain system”. The insular cortex shows a functional organisation following an anterior-posterior axis. Its posterior region mediates somatosensory processing, whereas the anterior insula is responsible for emotional processing (Taylor et al., 2009, Kurth et al., 2010, Cauda et al., 2011). Activity within the posterior insula is associated with pain intensity. Function of the anterior insular cortex is related to anxiety (Lin et al., 2013). The anterior cingulate cortex also underpins affective processing and is associated with the unpleasantness of pain (Peyron et al., 2000).

Activity of the medial prefrontal cortex and the orbitofrontal cortex is associated with anxiety (Ochsner et al., 2006). In addition, the amygdala is a contributor to the affective processing of pain. This region is associated with emotional stimuli and emotional learning (Phelps and LeDoux, 2005, Wiech and Tracey, 2009).

c) The “medial pain system” also subserves the cognitive dimension, which reflects the evaluation of painful stimuli and its effects on the organism. Attention, appraisal and anticipation are highly influential to the subjective experience of pain (Wiech et al., 2008). Anterior cingulate cortex and insula activity are enhanced when high intensities of pain are expected (Koyama et al., 2005). The medial prefrontal cortex shows higher activation during self-referential attention and anticipation of pain (Straube et al., 2009). Moreover, this area is involved in endogenous pain inhibition (Zubieta et al., 2001, Seifert et al., 2009).

d) Another facet of pain-processing is the motor-dimension, which is evident during shortening reactions and relieving postures. Brain regions underlying motor-functions, such as the primary motor cortex, the middle anterior cingulate cortex, the supplementary motor area, the basal ganglia and the cerebellum, show (inconsistent) activation during pain perception (Valet et al., 2010).

e) Autonomous reactions, such as increased pulse, perspiration and vaso-vagal syncopes, represent the vegetative dimension of the experience of pain. Regions related to the processing of stress and vegetative functions, such as the anterior cingulate cortex, the medial prefrontal cortex, the hypothalamus and the amygdala, seem to play an important role (Valet et al., 2010). Interestingly, some of these regions, especially those related to the affective dimension, are also activated during the perception of pain in others.

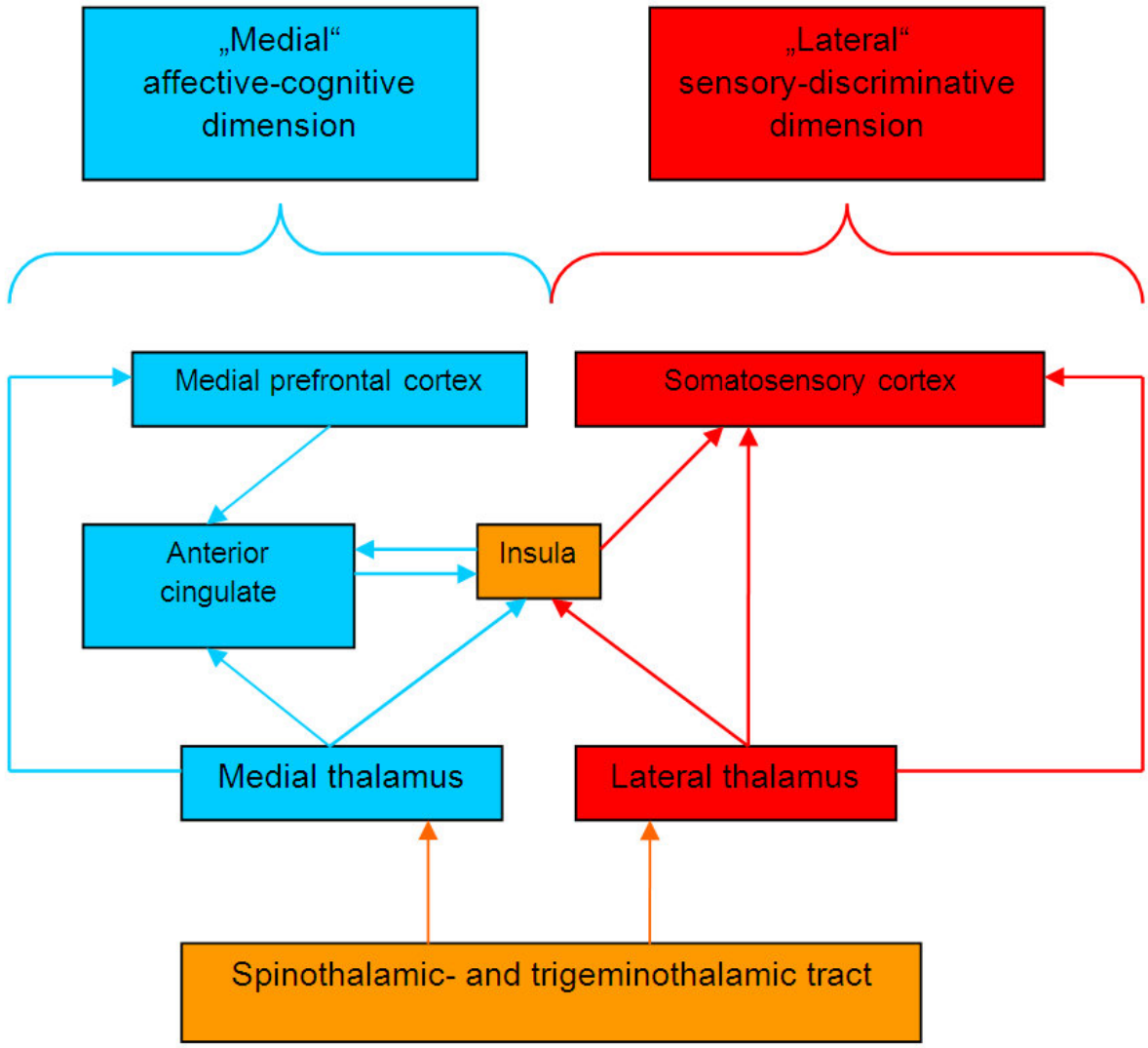

Figure 1: Central pain processing (modified Otti and Noll-Hussong, 2011)

1.3 Empathy for pain – behavioural facets and neural basis

Pain is critical for survival. It not only warns the organism of a physical threat value, but additionally will automatically attract emotional attention leading to high affective contagion and empathy in potential caregivers (Craig, 2004b). The construct of empathy is defined as identifying with and sharing the feelings and thoughts of others. Recent functional imaging studies show that empathy for pain and physical pain share the same neural circuits as proposed by Preston and De Waal (2002) in a neuro-integrative model of human empathy (for review see Fan et al., 2011, Lamm et al., 2011). The mere observation of actions activates the same brain regions as the generation of the very same actions, known as perception-action coupling (Prinz, 1997, Hommel et al., 2001, Decety and Jackson, 2004). The primary overlap between the states of observing or experiencing pain occurs in the anterior insula, anterior cingulate cortex and middle cingulate cortex. Activation of the anterior cingulate cortex is correlated with the subjective intensity of empathically perceived pain (Jackson et al., 2005). The response of the anterior insula is associated with attention to pain in self (Lovero et al., 2009) and others (Craig, 2004a, Moriguchi et al., 2007, Silani et al., 2008, Bird et al., 2010). Interestingly, as demonstrated by Singer et al. (2006), the observer exhibits less activation of the cingulo-insular system if the person suffering from pain displayed unfair behaviour prior to the painful experience. Additionally, social differences between the observer and the person in pain can lead to similar effects (Hein et al., 2010, Azevedo et al., 2012, Bernhardt and Singer, 2012, Sheng and Han, 2012). Furthermore, activation is observed in the supplemental motor area (Decety and Jackson, 2004). The role of the somatosensory cortex in empathy for pain is still under debate (Singer et al., 2004, Cheng et al., 2008). This region seems to be activated if visual stimuli are used (Lamm et al., 2011). Apart from these core regions (Decety and Jackson, 2004, Fan et al., 2011), other brain areas can contribute to empathy, including the medial prefrontal cortex and lateral parietal regions. These regions are not directly involved in the

affective response to another's pain but underlie other functions, such as cognitive processes and emotional regulation.

Empathy requires the ability to access one's own and others' affective states. Recent functional imaging research has demonstrated that less activation within affective-empathetic neural networks while observing the pain of others is associated with impaired recognition of one's own emotions and deficits in empathic abilities (Moriguchi et al., 2006, Moriguchi et al., 2007).

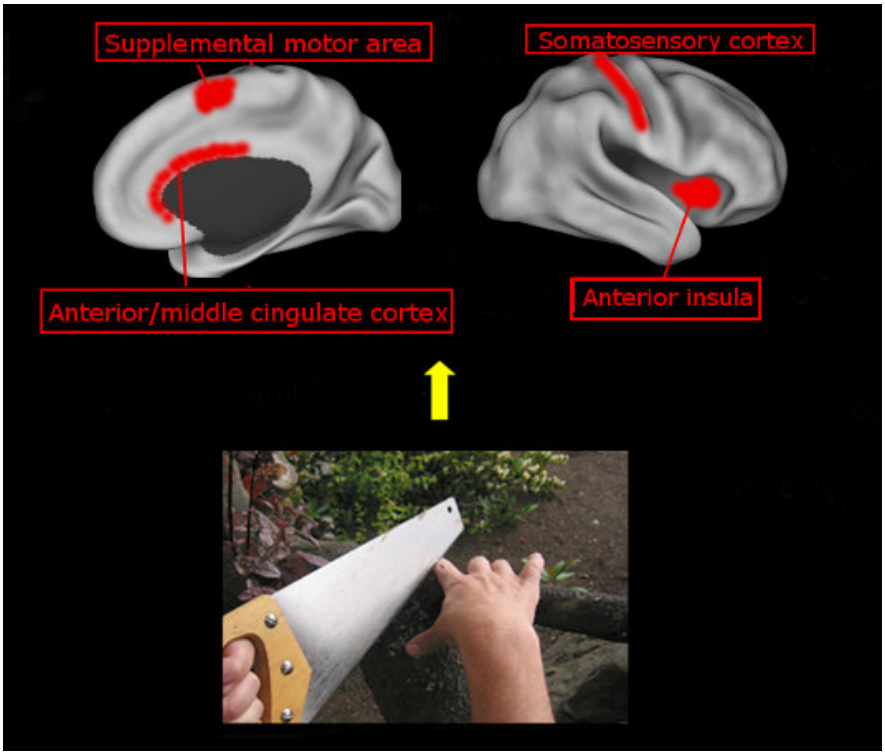

Figure 2: Core-regions of empathy for pain

1.4 The neurobiology of somatoform pain

Patients suffering from somatoform pain show difficulties in realising and interpreting affective signals. They perceive emotions as mere physical sensations (Duddu et al., 2006), a phenomenon that has been conceptualised as alexithymia (Sifneos, 1996). Compared to other psychiatric diseases, somatoform disorders (Wessely et al., 1999) are related to subjective emotional awareness of feelings (Subic-Wrana et al., 2005, Subic-Wrana et al., 2010). Therefore, patients with somatoform pain experience emotional distress more somatically (Mabe et al., 1990, Subic-Wrana et al., 2005, Waller and Scheidt, 2006, Subic-Wrana et al., 2010) in terms of a “bodily distress syndrome” (Silton et al., 2011). This leads to a higher subjective pain perception and pain catastrophising (Petrak et al., 2003). In other words, patients with somatoform pain often are not aware of their own or others’ affective states (Moriguchi et al., 2006, Clore and Pappas, 2007, Pedrosa Gil et al., 2009, de Greck et al., 2011). Thus, from an neurointegrative point of view, it has been suggested that clinical chronic pain and other mental disorders (Apkarian et al., 2011) “might be exacerbated by a reduced capacity to appropriately assign affective meaning to sensory and internal cues” (Roy et al., 2012). Accordingly, there are hints that a lack of emotional awareness, as defined by "difficulty identifying feelings of oneself and others,” is associated with lower back pain (Mehling and Krause, 2005). Biologically, this specific mind-body discrepancy reflects a neural imbalance of sensory-discriminative, affective, cognitive, executive, vegetative and introspective functions (Chaturvedi and Desai, 2006, Beauregard, 2007, Rief and Broadbent, 2007, Verkuil et al., 2007, Browning et al., 2011). The question arises whether somatoform pain is associated with impaired empathetic abilities and altered activity in affective-empathetic systems, such as the anterior cingulate cortex, insula, supplemental motor area, and somatosensory cortex. However, little is known about the neural mechanisms of somatoform pain. Patients show a significant loss of grey matter in the cingular-insular system and in the medial prefrontal cortex (Valet et al., 2009). Furthermore, altered brain function has been reported. Gündel et al. (2008)

demonstrated that the experimental application of heat leads to enhanced activation of the anterior cingulate cortex, insular cortex, amygdala and parahippocampal gyrus, but a reduced response of the ventral medial prefrontal cortex. Stoeter et al. (2007) reported similar findings but showed enhanced activation of the dorsal mPFC in the patient group.

1.5 The human brain's resting state

"The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is… far from restful."

Seneca, ~ 60 A.D.

Our knowledge of the neurobiology of somatoform disorders is primarily based on a handful of imaging studies measuring the neural response to a specific stimulus, such as heat. However, the human brain also produces permanent and spontaneous fluctuations of neural activity even during a resting state without external stimulation. "The brain's dark energy" (Zhang and Raichle, 2010) is approximately 30 times higher than its extrinsic activity. Alterations within this stimulus-independent activity might be associated with chronic pain without sufficient peripheral organic pathology.

The brain's intrinsic energy is highly organised in several intrinsic connectivity networks (Fox et al., 2005), which consist of regions characterised from experiments using external stimulation, such as the direct application of pain or the presentation of visual stimuli depicting others in pain. Even without tactile stimulation, spontaneous activity within the sensorimotor network can be detected. The cingular-insular system, which overlaps with areas dedicated to the affective processing of pain, also shows spontaneous neural oscillations without nociceptive input. Among intrinsic connectivity networks, the so-called default mode network holds a special position. In 1997, a meta-analysis by Shulman et al. demonstrated that not all networks increase their activity during external stimulation. Some areas show an "inverse" activation pattern, with increased activation during rest but relatively decreased activation during goal-directed

behaviour and externally oriented attention (Shulman et al., 1997). Mazoyer et al. (2001) provided further evidence for a task-negative system that was finally described as the “default mode network” by Raichle et al. (2001). The main components of this circuit are shown schematically in Figure 3. The circuit consists of strongly connected hubs (red) and more weakly (blue) integrated associated areas. Both an anterior and a posterior subsystem can be detected depending on the method of analysis and the structure of the data (Mantini et al., 2007, Calhoun et al., 2008, Damoiseaux et al., 2008). The anterior default mode network is composed of the ventromedial and dorsomedial prefrontal cortices (vMPFC, dMPFC), including the orbitofrontal and anterior cingulate cortices, as well as the precuneus (Prec). The precuneus (Prec), the posterior cingulate (PCC), the retrospenial cortex (rspC), the inferior parietal lobule (IPL), the temporal cortex and the hippocampal formation, including the parahippocampus (HF+), represent the posterior part of the default mode network. Whenever the organism focuses on its own inner status, the default mode network shows enhanced activation (Gusnard et al., 2001, D'Argembeau et al., 2005, Kong et al., 2006, Buckner and Carroll, 2007, Schneider et al., 2008, Otti et al., 2010).

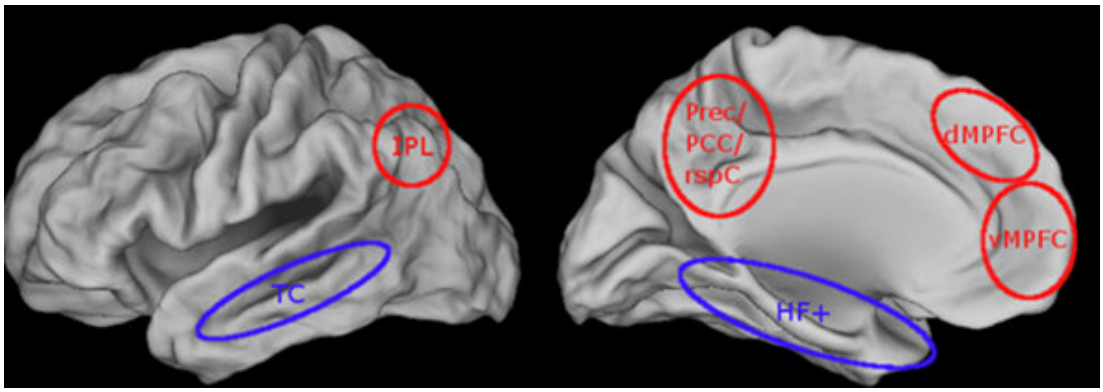

Figure 3: Default Mode Network (Otti et al., 2012).

1.6 Parameters for the description of brain function

Taken together, the following termini are relevant to describe the brain's functional architecture during rest and stimulation by functional magnetic resonance imaging:

1. The terminus "activation" describes the extent of neural activity in brain regions during specific conditions, i.e. the level of excitation and inhibition.

2. As described above, the brain shows endogenous low-frequency oscillations in neural activity even during a resting state. However, different brain regions can have differences in the time-courses of the fluctuations in neural activity. Significant "functional connectivity" between different brain regions represents a significant correlation between the time-courses of the fluctuations of neural activity, which establish a functional neural network (Calhoun et al., 2001).

3. The "power spectra" describe the spectrum of the frequencies of the aforementioned neural oscillations within a network (Garrity et al., 2007, Salvador et al., 2008, Cauda et al., 2009, Malinen et al., 2010). In the current study, six equally spaced frequency bins were used (0 – 0.04 Hz; 0.04 – 0.08 Hz; 0.08 – 0.12 Hz; 0.12 – 0.16 Hz; 0.16 – 0.20 Hz; 0.20 – 0.24 Hz). The main advantage of 6 bins compared to larger numbers is that it reduces the number of multiple comparisons (level of significance $p < 0.0083 = 0.05/6$; Bonferroni correction for 6 frequency bins). A lower number of bins, however, might have led to false-negative results as the spectral changes are rapid as a function of frequency.

4. Recently, "functional network connectivity" has gained attention. This parameter reflects the functional interaction between networks (Jafri et al., 2008).

5. All the aforementioned termini can be summarised as "activity".

1.7 Functional magnetic resonance imaging and electrophysiology

How does functional magnetic resonance imaging directly visualize neural activity? The succinct answer is that it does not! It leads to images of physiological reactions of the brain that are correlated with neuronal activation. The key-concept of functional magnetic resonance imaging is: enhanced activity of neurons increases their metabolic requirements in form of a higher oxygen-extraction which leads, in turn, to an increased blood flow. Oxygenated and deoxygenated hemoglobin show different magnetic susceptibilities (Pauling and Coryell, 1936). Functional magnetic resonance imaging measures changes of the concentration of deoxgenated hemoglobin which indicates the oxygen consumption within a brain region. Therefore, the signal from the scanner does not directly reflect neural activation but an epiphenomenon – the blood-oxygen-level dependent effect (Ogawa and Lee, 1990, Ogawa et al., 1990, Heeger and Ress, 2002).

In a hallmark-report, Logothetis et al. (2001) simultaneously recorded functional magnetic resonance imaging data and electrophysiological activity from the visual cortex of anesthetized monkeys. Three types of electrophysiological data were obtained: single-unit activity (spiking of a single neuron close to the electrode), multi-unit activity (firing rate of smalls groups of neurons) and local field potentials (summations of excitatory/inhibitory postsynaptic potentials as well as dendritic after-hyperpolarizations and intrinsic membrane oscillations). Especially the local field potentials - and to a less extent also the single- and multi-unit recording - can predict the signal change of the blood-oxygen-levels (Logothetis, 2003). The amplitude and timing of the functional magnetic resonance imaging signal is related to the local field potential power (Magri et al., 2012). As shown by Goense and Logothetis (2008) in awake monkeys, a hemodynamic response can even be detected in cases when action potentials are completely absent (for similiar effects see Viswanathan and Freeman, 2007, Rauch et al., 2008). There is a strong correlation between the local field potential and the functional magnetic resonance imaging signal also in human beings as shown by Huettel et al. (2004) in nine patients who had

indwelling subdural electrodes as part of presurgical testing. These findings support the idea that the functional magnetic resonance imaging signal correlates strongly, in many cases, with the underlying local field potential (Huettel et al., 2004, Kayser et al., 2004, Ureshi et al., 2004, Niessing et al., 2005, Shmuel et al., 2006, Devor et al., 2007, Masamoto et al., 2008). Some studies note exceptions to the idea, that the functional magnetic resonance imaging signal typically represents local field potentials, and report strong correlations between blood-oxygen-levels and action potentials (Rees et al., 2000, Kim et al., 2004, Mukamel et al., 2005, Nir et al., 2007, Burns et al., 2010, Bartolo et al., 2011). However, the association between action potentials and local field potentials is dependent on the input into a region due to the heterogeneous nature of the local field potential. Thus, hemodynamic responses and spike rate correlations cannot typically be assumed (Ekstrom, 2010). Furthermore, it might be dependent of the task if action potentials or local field potentials are stronger correlated with the functional magnetic resonance imaging signal (Burns et al., 2010, Bartolo et al., 2011). Taken together, these data suggest a significant link between the blood-oxygen-levels and neural activation.

There is also accumulating experimental evidence for an electrophysiological equivalent of the endogenous fluctuations of the functional magnetic resonance imaging signal during a resting state. As shown recently by Thompson et al. (2013) and Pan et al. (2013), infra-slow local field potentials (<0.5 Hz) have a high spatial and temporal coherence with the endogenous changes of the blood-oxygen-levels. Furthermore, the delta- and gamma frequencies of the local field potentials in the rat-brain seem to be related to spontaneous hemodynamic changes (Pan et al., 2011, Magri et al., 2012). Functional connectivity between different brain regions during rest is associated with the low-frequency oscillations of the local field potential (<20 Hz) (Wang et al., 2012). Shmuel and Leopold (2008) found that fluctuations in the hemodynamic response in widespread areas in visual cortex were significantly correlated with neuronal activity from a single recording site in the visual area 1. They argue that functional connectivity in the resting state can be linked to synchronization of slow oscillations in the underlying neuronal signals.

(However, please note that Logothetis et al. (2009) reanalyzed the data of Shmuel and Leopold (2008) and argue that their results are not due to functional connectivity but local differences in vascularisation).

Resting state networks have a unique electrophysiological signature. Mantini et al. (2007) combined functional magnetic resonance imaging with electroencephalography and demonstrated that the default mode network is associated with a strong beta- and gamma-activity, whereas the contribution of alpha-activity is low. The sensorimotor network shows a high beta-activity but relatively low contribution of theta-activity. (For further studies see Cannon and Baldwin, 2012, Yuan et al., 2012, Chang et al., 2013, Fahoum et al., 2013, Mayhew et al., 2013, Nasrallah et al., 2013, Wong et al., 2013).

Another important aspect of the principle of functional magnetic resonance imaging is the association between neural activity and changes in the vascular system. Neural activity changes the diameter of arterioles significantly (Ngai et al., 1995, Iadecola, 1998, Attwell and Iadecola, 2002, Iadecola, 2002). However, the neurovascular coupling also puts limits on the spatial specificity of the functional magnetic resonance signal because arteriolar dilatation and increased blood flow can also be detected some millimetres distant to the peak of neuronal activity. Here the question arises if there are others factors besides neural activity that influence the functional magnetic resonance imaging signal. There are specific regions in the midbrain that broadly project dopaminergic fibers to small arterioles that can modulate the local flow pattern (Krimer et al., 1998). Furthermore, astrocytes seem to play an important role. Using tow-photon imaging, Takano et al. (2006) showed that a release of calcium-ions from glial cells leads to a significant vasodilatation which might influence functional magnetic resonance imaging measurements (for review of glial effects on cerebral blood flow see Attwell et al., 2010).

The aforementioned studies suggest that neural activity is correlated with the functional magnetic resonance signal. Furthermore, there is electrophysiological evidence that functional

magnetic resonance imaging measures slow-frequency fluctuations of neural activity and functional connectivity between remote brain regions during a resting state. However, the exact physiological source of the resting state signal is still unknown and it remains unclear to which extent the hemodynamic response is influenced by other factors besides neural activity.

2. Aim

The studies presented here provide neurobiological evidence for the hypothesis that somatoform pain reflects a central dysfunction in neural circuits dedicated to emotional processing. Functional magnetic resonance imaging is chosen for these studies as this method visualises brain networks in vivo with a high spatial resolution and does not require the application of contrast agents. The patients and controls participating in the current studies are clinically and psychometrically characterised by instruments such as the Structured Clinical Interview for DSM Disorders (Wittchen et al., 1997, APA, 2000), SF-36 (McHorney et al., 1993, Bullinger, 1995, Keller et al., 1998, Alonso et al., 2004), PHQ-15 (Kroenke et al., 2002, Kroenke et al., 2010), the Wisconsin Brief Pain Questionnaire, (Cleeland and Ryan, 1994), the Beck Depression Inventory I (Hautzinger, 1991, Heinz et al., 2007), and the Trait Anxiety Inventory (Laux et al., 1981).

Study I tests whether somatoform pain is associated with altered neural activation during empathy for pain, a specific and evolutionary fundamental emotional behavioural trait used in everyday social interactions. Using an established picture paradigm (Jackson et al., 2006), I hypothesise that somatoform pain is associated with diminished activation of the core regions of empathic processing, such as the anterior cingulate cortex and the insula, while observing another person's pain.

The objective of Study II is to test whether somatoform pain is associated with alterations in the spatial and temporal domains of pain-related resting state networks. Intrinsic (resting state) activity is approximately 30 times higher than the extrinsically motivated activity (Sokoloff et al., 1955, Fox et al., 2005). Highly organised in resting state networks, "the brain's dark energy" (Zhang and Raichle, 2010) appears without external stimulation and may play an important role for the development of chronic pain. Given the lack of a peripheral organic pathology, the question arises whether the brain is producing patterns of neural activity that are associated with somatoform pain. Specifically, I hypothesise that patients suffering from somatoform pain

show altered frequencies of the spontaneous oscillations (power spectra) of neural activity within pain-related networks, such as the anterior and posterior default mode network, the cingular-insular (i.e. fronto-insular) network, and the sensorimotor network. Furthermore, I postulate that somatoform pain is related to changes in the functional connectivity within these networks. Herein, independent component analysis, a new data-driven approach, is used for the analysis of brain networks (Calhoun et al., 2001, Calhoun et al., 2008). The main advantage of this method is that it requires no a priori assumptions of the intrinsic structure of the data. Its high reliability is remarkable as iterative techniques are based on multiple computational processes that statistically lead to a high variance (Zuo et al., 2010). Moreover, the number of independent components is based on a mere statistical estimation and not on neurophysiological hypotheses (Cole et al., 2010).

Study III expands upon functional network connectivity, a new approach for testing one important facet of the resting state network model to examine the intrinsic functional connectivity between networks active during the resting state. As shown recently in individuals with schizophrenia, differences in inter-network communication in regards to functional network connectivity could be a valid measure reflecting cortical-processing deficits in patients with chronic psychiatric symptoms. Therefore, I aim to test the practical relevance of functional network connectivity for chronic, medically unexplained pain (Jafri et al., 2008). Specifically, given a disconnection of pain-related neural systems, I hypothesise that alterations exist in the functional network connectivity between the anterior and posterior default mode network, the cingular-insular (i.e. fronto-insular) network and the default mode network in patients with somatoform pain disorder.

All three of the studies were published in peer-reviewed journals:

Study I:

Noll-Hussong et al. Neural correlates of deficits in pain-related affective meaning construction in patients with chronic pain disorder. Psychosomatic Medicine. 2013; 75(2):124-36.

Study II:

Otti et al. Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. BMC Psychiatry. 2013; 13:84.

Study III:

Otti et al. Functional network connectivity of pain-related resting state networks in somatoform pain disorder – an exploratory fMRI study. Journal of Psychiatry and Neuroscience. 2013; 38(1):57-65.

3. Study I - Neural correlates of deficits in pain-related affective meaning construction in patients with chronic pain disorder

Published in *Psychosomatic Medicine*. 2013; 75 (2):124-36.

The aim of this study is to investigate the effect of impaired affective regulation in somatoform pain disorder. To test this, I focus on empathy for pain, a fundamental affective behavioural trait. Twenty-one patients suffering from somatoform pain disorder and 19 healthy controls are enrolled in the study. (These participants are also used in Study II and Study III). During functional magnetic resonance imaging, participants are presented with pictures depicting human hands and feet in different painful and nonpainful situations and asked to estimate the perceived pain intensity. The healthy controls show significantly higher activation of the left perigenual anterior cingulate cortex and a trend toward higher subjective pain ratings than the patients. The neuroimaging results are not influenced by the scores on the self-assessment instruments (Beck Depression Inventory I, Interpersonal Reactivity Index, and 20-item Toronto Alexithymia Scale). These findings suggest that altered central pain perception is due to a decreased neural response in affective cerebral systems, which I interpret as a deficit in pain-related affective meaning construction. Furthermore, these results highlight the neurobiological effect of chronic pain on every day social life.

For this study, I independently analysed both the behavioural data and the imaging data Furthermore, I recruited the participants with Dr. med. M. Noll-Hussong, and scanned participants with Dr. rer. nat. A. Wohlschläger and Dr. M. Noll-Hussong. Prof. Dr. C. Zimmer, Prof. Dr. P. Henningsen, PD Dr. C. Lahmann, Dr. J. Ronel, Dr. C. Subic-Wrana, Prof. Dr. J. Decety, Prof. Dr. R. Lane, Prof. Dr. H. Gündel, and Dr. M. Noll-Hussong were responsible for the research design.

4. Study II - Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder

Published in *BMC Psychiatry*. 2013; 13:84.

The aim of this study is to test whether somatoform pain is associated with changes in spatial and temporal properties of endogenous patterns of activity in pain-related neural networks during the resting state. Twenty-one clinically and psychometrically well-characterised patients who suffered from chronic pain disorder and 19 age- and healthy controls undergo 3-Tesla-functional magnetic resonance imaging. (These participants are also used in Study I and Study III). All neuroimaging data are analysed using independent component analysis including power spectra analysis. In patients suffering from chronic pain disorder, the fronto-insular 'salience' network (i.e. cingular-insular network) and the anterior default mode network, which comprises the prefrontal cortex and precuneus, oscillate predominantly at higher frequencies (0.20 - 0.24 Hz). No significant differences in power spectra are observed in the posterior default mode network, which consists of the precuneus as well as lateral parietal regions, and the sensorimotor network. No significant changes are observed in the spatial functional connectivity of the networks. These results indicate that chronic pain disorder may be a self-sustaining and endogenous mental process that affects temporal organisation by causing a frequency shift in the dynamic rhythm of cortical networks associated with emotional homeostasis.

For this study, I independently analysed both the behavioural data and the imaging data using new data-driven techniques. Furthermore, together with Dr. M. Noll-Hussong, I recruited the participants. Together with Dr. A. Wohlschläger and Dr. M. Noll-Hussong, I scanned participants. Prof. Dr. C. Zimmer and Prof. Dr. H. Gündel were responsible for the research design.

5. Study III - Functional network connectivity of pain-related resting state networks in somatoform pain disorder: an exploratory fMRI study

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Whereas Study II is focused on intra-network activity, the purpose of Study III is to visualise the interplay between functional networks in healthy individuals and patients with somatoform pain disorder. I compare 21 patients suffering from somatoform pain and 19 healthy controls using 3-Tesla-functional magnetic resonance imaging. (These participants are also used in Study I and Study II). All neuroimaging data are analysed using independent component analysis. Significant functional network connectivity is detected between the cingular-insular network (i.e. fronto-insular network) and the sensorimotor/anterior default mode network, between the anterior default mode network and the posterior default mode network/sensorimotor network, and between the posterior default mode network and the sensorimotor network. Interestingly, no group differences in functional network connectivity are seen. To my knowledge, these findings are the first to demonstrate resting functional network connectivity among pain-related intrinsic connectivity networks. However, these results suggest that functional network connectivity alone is not sufficient to describe the putative central dysfunction underpinning somatoform pain disorder.

For this study, I independently analysed both the behavioural data and the imaging data using new data-driven techniques. Furthermore, together with Dr. M. Noll-Hussong, I recruited the participants. Together with Dr. A. Wohlschläger and Dr. M. Noll-Hussong, I scanned participants. Prof. Dr. C. Zimmer, Prof. Dr. P. Henningsen, Prof. Dr. H. Gündel, and Dr. M. Noll-Hussong were responsible for the research design.

6. Discussion

Chronic somatoform pain is a severe psychosomatic disease currently diagnosed by exclusion. My thesis addresses this issue and aims to visualise the neural substrates of somatoform pain disorder. First, using the example of empathy for pain, I address the question of whether neurobiological evidence exists for difficulties in accessing one's own or other's emotions. Second, I test whether chronic pain without a significant peripheral organic correlate reflects a specific pattern of endogenous neural activity during a resting state without external stimulation. A reasonably sized group of clinically well-classified patients and healthy controls undergo functional magnetic resonance tomography. In contrast to other techniques, such as positron emission tomography, functional magnetic resonance imaging is a non-invasive method that visualises brain function with high spatial resolution and without the application of radioactive tracers.

While empathizing with pain of another person, patients exhibit a significantly lower activation of the left perigenual anterior cingulate cortex. Furthermore, they show a trend to perceive another's pain as less intense compared to healthy controls. Moreover, patients have less empathy and more difficulties in describing their feelings. These findings suggest that somatoform pain is associated with an impaired access to one's own and other's emotions as the perigenual anterior cingulate cortex plays a role in processing affective information. This role includes assigning emotional valence to internal and external stimuli and conditioned emotional learning, regulating autonomic and endocrine functions, and assessing motivation and empathy for pain (Vogt et al., 1992, Devinsky et al., 1995, Whalen et al., 1998, Roy et al., 2012). Furthermore, the perigenual anterior cingulate cortex was found to be involved in the processing of both somatic (Derbyshire et al., 1997, Lorenz et al., 2003, Lui et al., 2008) and visceral pain (Aziz et al., 2000, Fan et al., 2009). Vogt et al. suggested that the activation of the perigenual anterior cingulate cortex may be involved in affective responses to noxious stimuli, such as the suffering associated with pain (Vogt et al., 1996). Frewen and colleagues observed a correlation

between activation of the perigenual anterior cingulate cortex and emotional awareness in healthy subjects during recall of traumatic experiences (Frewen et al., 2008). Interestingly, this region is also functionally related to the onset of uncertainty of impending, externally applied thermal stimuli at noxious and non-noxious temperatures (Mohr et al., 2005). In summary, the perigenual anterior cingulate cortex is integral for the construction and deployment of affective meaning (Roy et al., 2012), which may be disturbed in somatoform pain disorder.

In contrast to the control subjects, somatoform pain patients are subjectively accustomed to the sensory experience of lasting pain, i.e., they are certain that they will feel persistent pain. Thus, I suggest that in the healthy controls, the experience of pain induced by the visual pain paradigm may be more surprising and, thus, a more intense and differentiable experience, resulting in a higher activation of the perigenual anterior cingulate cortex and a trend corresponding with a higher pain intensity rating. One may speculate that a type of “habituation” is present in chronic pain patients in the affective dimension of the painful experience that is isolated in this study using the visual pain paradigm. Against this background, the prolonged activation of pain-processing areas could potentially diminish stimulus-evoked responses in those areas and thus explain the finding that chronic pain patients exhibit a lower activation of the perigenual anterior cingulate cortex than pain-free controls (Rennefeld et al., 2010).

Furthermore, the functional architecture of the resting state is investigated in this thesis. Neural activity within the fronto-insular network (i. e. cingular-insular network) and the anterior default mode network shows significantly shifted frequencies in patients suffering from somatoform pain disorder compared with healthy controls. Specifically, there is a general trend towards higher spectral power in the 0.20-0.24 kHz frequency bin in patients versus control subjects. However, no significant group differences in spectral power are detected in the sensorimotor network and the posterior default mode network. Although the current study cannot provide causation, several aspects suggest there is a strong relationship between the pain condition and altered patterns of endogenous neural activity during the resting state. The cingular-insular network (i.e.

fronto-insular network) and the anterior default mode network instantiate affective and introspective neuroprocessing (Gusnard et al., 2001, D'Argembeau et al., 2005, Buckner and Carroll, 2007, Mantini et al., 2007, Seeley et al., 2007, Otti et al., 2010). In addition to the activation detected during empathy for pain, these findings could reflect a neurobiological rationale for the strong impression of clinicians that patients who suffer from somatoform pain often show disturbed affective processing in terms of reduced subjective emotional awareness and impaired social understanding (Subic-Wrana et al., 2010). Furthermore, somatoform pain is associated with higher autonomic arousal (Thieme et al., 2006, Stoeter et al., 2007), which, in turn, has been associated with increased activation in the cingulate cortex, the insula, and medial prefrontal regions (Querleux et al., 2008, Cauda et al., 2009). Moreover, the various bodily complaints in patients with somatoform pain have consistently been associated with a high affective component of individual pain, which indicates impaired emotional regulation (Burba et al., 2006, Kirmayer and Looper, 2006, Waller and Scheidt, 2006, Verkuil et al., 2007). The fact that no differences were previously observed in the sensorimotor network underlying sensory-discriminative processing (Biswal et al., 1995) supports this idea that somatoform pain is especially related to emotional processing. Furthermore, these results expand the findings of Malinen et al. (2010) and Cauda et al. (2009), who found similar alterations of power spectra in chronic pain associated with various organic diseases, such as diabetic neuropathic pain or phantom limb pain. Interestingly, as shown by the current study, peripheral organic correlates do not seem to be necessary for these changes in the neurobiology of the brain.

In contrast to Malinen et al. (2010), who reported weaker functional connectivity between the insula and anterior cingulate cortex in predominantly nociceptive chronic pain, and Baliki et al. (2008), who found diminished default mode network connectivity in chronic back pain patients, I do not find changes in spatial functional connectivity. In contrast to chronic pain caused by diverse peripheral causes, I presume that somatoform pain, which cannot be explained fully by

nociceptive input, is not associated with changes in the spatial domain of the functional architecture of the brain's resting state.

In contrast to our hypothesis, the current studies show that persistent non-nociceptive pain does not lead to changes in functional network connectivity among pain-associated networks during a resting state. In patients and healthy controls, significant functional network connectivity is observed between the cingular-insular network (i.e. fronto-insular network) and sensorimotor network/anterior default mode network, the anterior default mode network and the posterior default mode network/sensorimotor network, and the posterior default mode network and the sensorimotor network. The sensorimotor network strongly interacts with the cingular-insular (or fronto-insular) network, the anterior default mode network, and the posterior default mode network. These results suggest that functional network connectivity signatures alone are not sufficient for characterisation of the putative central dysfunction underlying somatoform pain disorder.

However, to my knowledge, this is the first demonstration of the intrinsic interconnection of pain-related connectivity networks in healthy controls at resting state. These interactions again suggest that sensory-discriminative processing is highly related to affective processing, self-referential thoughts and memory functions. Furthermore, the timing of the sensorimotor network is offset from the other intrinsic connectivity networks by some seconds. Emotional and cognitive processing seems to precede the activity of the sensorimotor system during a resting state. This result might explain the influence of the inner world with its various subjective states, such as anxiety, sadness and individual predictions about the future, on the perception of the outer world via sensory systems (Bar, 2009, Coen et al., 2011, Vancleef and Peters, 2011). Because the current analysis does not provide insight into causality, these results encourage further research on putative effects of activity within the default mode network and cingular-insular (or fronto-insular) network on the sensorimotor network.

There is no significant correlation between the imaging data and anxiety (Ochsner et al., 2006), depression (Henningsen et al., 2003, Muller et al., 2008, Hanel et al., 2009) or pain intensity in the patient group of the current studies. Importantly, a similar discrepancy between activation detected by functional magnetic resonance imaging and behavioural measurements was also described in a study investigating the altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder (Gundel et al., 2008). Thus, differences between patients and controls may be more easily detected via neuroimaging methods than through subjective behavioural ratings, in accordance with several other studies (Smolka et al., 2005, Silani et al., 2008, Bird et al., 2010, Noll-Hussong et al., 2010). As a whole, the results of the studies presented in this thesis seem to correspond with some of the clinically relevant emotional challenges confronting patients and their social networks, such as their family and physicians.

The present study is limited due to the lack of measurements of possible sources of physiological artefacts such as respiration, cardiac function or blood pressure. However, in the agreement with previous findings, the current results are unlikely to be confounded by these factors (Cauda et al., 2009, Malinen et al., 2010). Furthermore, functional magnetic resonance imaging relies on the measurement of signals dependent on blood oxygen levels, from which conclusions about neural activity are drawn. However, it is still under debate whether this epiphenomenon is also influenced by other cerebral processes, such as activity-independent changes of the concentration of fast neurotransmitters (Attwell and Iadecola, 2002, Logothetis, 2008). One important limitation of the current studies is medication. More than half of the patients are undergoing treatment with antidepressants and analgesics. The effect of medication of the blood-oxygen-level-dependent effect is poorly understood. It is of note that despite ethical reasons, it is nearly impossible to convince the somatoform pain patients to interrupt their (psychotropic) medication in this intentionally naturalistic study.

7. References

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8. List of publications

8.1 Publications that are part of this thesis (see attachment)

Neural correlates of deficits in pain-related affective meaning construction in patients with chronic pain disorder

Michael Noll-Hussong, **Otti A,** Wohlschlaeger A. M., Zimmer C, Henningsen P, Lahmann C, Ronel J, Subic-Wrana C, Lane RD, Decety J, Guendel H.

Psychosomatic Medicine. 2013 Feb; 75 (2):124-36. Epub 2013 Jan 29.

Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder.

Alexander Otti, Harald Guendel, Afra M. Wohlschlaeger, Claus Zimmer, Micheal Noll-Hussong.

BMC Psychiatry. 2013 Mar 13;13:84.

Functional network connectivity of pain-related resting state networks in somatoform pain disorder – an exploratory fMRI study

Alexander Otti, Harald Guendel, Peter Henningsen, Claus Zimmer, Afra M. Wohlschlaeger, Michael Noll-Hussong.

Journal of Psychiatry and Neuroscience. 2013 Jan; 38(1):57-65.

8.2 Other publications

Aftermath of sexual abuse history on adult patients suffering from chronic functional pain syndromes: an fMRI pilot study.

Noll-Hussong M, **Otti A,** Laeer L, Wohlschlaeger A, Zimmer C, Lahmann C, Henningsen P, Toelle T, Guendel H. Journal of Psychosomatic Research. 2010 May; 68(5):483-7. Epub 2010 Mar 16.

I know the pain you feel-how the human brain's default mode predicts our resonance to another's suffering.

Otti A, Guendel H, Läer L, Wohlschlaeger AM, Lane RD, Decety J, Zimmer C, Henningsen P, Noll-Hussong M. Neuroscience. 2010 Aug 11;169(1):143-8. Epub 2010 May 5.

Acupuncture-Induced Pain Relief and the Human Brain's Default Mode Network - An Extended View of Central Effects of Acupuncture Analgesia

Otti A and Noll-Hussong M. Research in Complementary Medicine (Forschende Komplementärmedizin). 2012; 19(4):197-201. Epub 2012 Aug 3. Review.

Intrinsic brain activity with pain.

Otti A, Noll-Hussong M. Schmerz. 2011 Sep; 25(5):501-7. Review. German.

Default mode network of the brain. Neurobiology and clinical significance.

Otti A, Gündel H, Wohlschläger A, Zimmer C, Sorg C, Noll-Hussong M. Nervenarzt. 2012 Jan; 83(1):16, 18-24. Review. German.

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Study I

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Neural correlates of deficits in pain-related affective meaning construction in patients with chronic pain disorder

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Neural Correlates of Deficits in Pain-Related Affective Meaning Construction in Patients With Chronic Pain Disorder

Michael Noll-Hussong, MD, Alexander Otti, Afra M. Wohlschlaeger, PhD, Claus Zimmer, MD, Peter Henningsen, MD, Claas Lahmann, MD, Joram Ronel, MD, Claudia Subic-Wrana, PhD, Richard D. Lane, MD, PhD, Jean Decety, PhD, and Harald Guendel, MD

Objective: Psychological and neural mechanisms of the affective dimension of pain are known to be disturbed in patients with chronic pain disorder. The aim of this functional magnetic resonance imaging study was to assess the neurofunctional and behavioral measures underlying the ability to construct pain-related affective meaning in a painful situation by comparing 21 clinically and psychometrically well-characterized patients with persistent non-nociceptive somatoform pain with 19 healthy controls. **Methods:** The functional magnetic resonance imaging task involved viewing pictures depicting human hands and feet in different painful and nonpainful situations. Participants were asked to estimate the perceived pain intensity. These data were correlated with behavioral measures of depression, alexithymia, and general cognitive and emotional empathy. **Results:** In a hypothesis-driven region-of-interest analysis, the healthy control group exhibited greater activation of the left perigenual anterior cingulate cortex than patients with pain (Montreal Neurological Institute coordinates ($x\ y\ z$) = −8 38 0; cluster extent = 54 voxels; $T = 4.28$; $p = .006$ corrected for multiple comparisons at cluster level). No group differences in the activation of the anterior insular cortex were found. Scores on self-assessment instruments (Beck Depression Inventory I, Interpersonal Reactivity Index, and 20-item Toronto Alexithymia Scale) did not influence neuroimaging results. **Conclusions:** Our results suggest that patients with chronic medically unexplained pain have an altered neural pain perception process owing to decreased activation of empathetic-affective networks, which we interpret as a deficit in pain-related affective meaning construction. These findings may lead to a more specific and detailed neurobiological understanding of the clinical impression of disturbed affect in patients with chronic pain disorder. **Key words:** pain disorder, somatoform pain disorder, affective meaning, empathy, affective neuroscience, functional magnetic resonance imaging.

ACC = anterior cingulate cortex; **BDI-I** = Beck Depression Inventory I; **BOLD** = blood oxygenation level–dependent; **BPI** = Brief Pain Inventory; **CIP** = congenital insensitivity to pain; **fMRI** = functional magnetic resonance imaging; **pACC** = perigenual ACC; **ROI** = region of interest; **SCID-I** = Structured Clinical Interview for DSM Disorders; **SD** = standard deviation; **SMA** = supplementary motor area.

INTRODUCTION

Pain perception involves psychological (1) and neural mechanisms that represent the affective meaning (2) or dimension (3) of this homeostatic emotion (4). For sensory pain, heightened pain perception has been found in patients with somatoform pain disorder (5). These patients are characterized by ongoing pain suggesting physical illness and injury symptoms that cannot be fully explained by a general medical condition, the direct effect of a substance, or another mental disorder (6). There is often a persistent refusal to accept—except for short periods during or immediately after medical investigation—the medical conclusion that there is no adequate physical cause for the physical symptoms of these patients (7). Individuals with somatoform pain disorder often have difficulties realizing and interpreting emotional signals within themselves and perceive these signals as mere physical sensations (8)—a phenomenon that has been conceptualized as alexithymia (9). More specifically, patients with somatoform disorders (and/or functional somatic syndromes (10)) often show reduced subjective emotional awareness of feelings compared with patients with other psychiatric diagnoses (11,12), thus experiencing emotional distress somatically (11–14) as "bodily distress syndrome" (15). Patients with somatoform disorders often are not aware of and do not understand their own or others' emotional states (16–19); from a neurointegrative point of view, it has been suggested that (among other mental disorders) clinical chronic pain (20) "might be exacerbated by a reduced capacity to appropriately assign affective meaning to sensory and internal cues" (21). Accordingly, there are hints that a lack of emotional awareness ("difficulty identifying feelings of oneself and others") is associated with low back pain (22). Biologically, this specific mind-body discrepancy (23–26) seems to reflect a neural imbalance between sensory-discriminative, affective (27), cognitive, executive, vegetative, and introspective functions, and emotional empathy (i.e., sharing of others' emotions in social contexts; for details, see de Greck et al. (16) and Parr et al. (28)), and—at a higher level—in the construction of conceptual information in the ventromedial prefrontal cortex that drives affective, physiological, and behavioral responses (21) within this mental disorder (13,18,29,30).

Remarkably, it has recently been demonstrated that the observation of body parts in painful situations even results in a pain network–associated blood oxygenation level–dependent (BOLD) activation pattern in patients with congenital insensitivity to pain (CIP; i.e., patients who cannot refer to their own nociceptive experience of pain to understand how the pain of others feels) (31). Interestingly, the behaviors of patients with CIP did not differ significantly in self-rated empathy from the

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behaviors of the control participants. With reference to patients with CIP who have never experienced nociceptive pain, one could question whether—and, if so, which—neural circuits are activated in patients on the other end of the non-nociceptive pain spectrum (i.e., those with persistent non-nociceptive somatoform pain). Thus, how do clinically well-classified patients who exclusively and subjectively perceive their continuing non-nociceptive chronic pain to be a solely physical (sensory) phenomenon in benign chronic pain disorder (32,33) differ, both neurobiologically and psychometrically, from healthy controls with regard to the relative contributions of automatic resonance and perspective taking to understanding their own and others' pain?

In this study, we adopted a functional magnetic resonance imaging (fMRI) paradigm that has been used in previous studies to evaluate empathy for pain in both healthy individuals (34) and patients with CIP (31) but has not yet been applied to patients with persistent pain that has no convincing organic etiology. Self-assessments were used to collect behavioral measures of depression, alexithymia, and both general cognitive and emotional empathy. We hypothesized that the ability to imagine how one would feel in a particular painful situation (sometimes also referred to as "pain empathy") is disturbed in patients with chronic pain disorder. Furthermore, we anticipated that—in contrast to feeling the pain directly, such as with thermal pain experiments—patients with ongoing somatoform pain who are visually confronted with new painful situations and asked to perform "self-perspective" (35) are ultimately less aware of their own emotions than the healthy control population. Relatedly, we would suggest that our patients are more physically somatosensory oriented than healthy controls, thus reflecting a lower differentiation in emotion and a lower awareness of emotional complexity (12,36). Thus, when comparing patients with chronic pain disorder with healthy controls, we would first expect a disturbance in neural response in a core network consisting of the anterior cingulate cortex (ACC) (37) and the insular cortex, which is associated with emotional awareness of and emotional empathy for pain (38,39). Second, we would argue that this disturbance should consequently influence the generation of integrative conceptual information that contributes to the construction of affective meaning (21).

METHOD

This study was approved by the local ethics committee (Klinikum rechts der Isar, Medical Faculty of Technische, Universitaet Muenchen, Muenchen, Germany) and performed in accordance with the Declaration of Helsinki.

Participants

Participants were 19 healthy controls (12 women) and 21 outpatients (17 women) with German-language skills and chronic pain disorder (operationalized as pain-predominant mulisomatoform disorder) (33,40–42). The mean (SD) age was 48.79 (12.25) for the control group and 46.62 (12.49) for the patient group. All participants provided written informed consent. Pain disorder is a form of somatoform disorder (6). Pain-predominant multisomatoform disorder, which is a moderately severe somatoform disorder, was primarily diagnosed by an experienced physician who performed a modified Structured Clinical Interview for DSM Disorders (SCID-I) using the official criteria for somatoform and chronic pain disorder. The main feature of somatoform disorders is the repeated presentation of physical symptoms together with persistent requests for medical examinations despite repeated negative findings and reassurances by doctors that the symptoms have no physical basis. If any physical disorders are present, the disorders do not explain the nature and extent of the symptoms or the distress and preoccupation of the patient (7). Multisomatoform disorder is defined as "three or more medically unexplained, currently bothersome physical symptoms plus a long (≥2 years) history of somatization" (32). It has been shown that, compared with mood and anxiety disorders, multisomatoform disorder is associated with comparable impairments in health-related quality of life, more self-reported disability days and clinic visits, and the highest level of provider frustration (32,43), thus covering the clinical reality of patients with complex overlapping diagnoses (44).

In this context, as first precondition, the physical component summary measure (45) in our patient group had to be at least 1 SD below the population norm (i.e., ≤40), as measured with the 36-item Short-Form Health Survey (SF-36), thus meeting the DSM-IV Criterion B for "significant distress or psychosocial impairment due to the somatoform pain" in patients with pain disorder (6). As second precondition, the scores for the 15-item Patient Health Questionnaire had to be higher than 10, representing medium somatic symptom severity. The German version of the Brief Pain Inventory (BPI) (46) was used to estimate the intensity of the participant's pain. Patients with insufficient cognitive abilities and severe chronic somatic diseases, unambiguous nociceptive pain (e.g., postsurgery pain), hypochondria, posttraumatic stress disorder, a severe comorbid mental disorder that causes a major impairment of social functioning (e.g., schizophrenia or severe substance abuse), or insufficient German-language skills were excluded. All participants were white, of white origin, and right-handed, as assessed by the Edinburgh Handedness Inventory (47). Data were collected from 2006 to 2010.

Psychometric Instruments

The occurrence of somatoform disorders was assessed in a modified structured psychiatric interview (SCID-I, German version) (48) in accordance with DSM-IV criteria (6). The SCID-I evaluates the patient's current (the last 4 weeks before the interview) and lifetime psychiatric status for major Axis I psychiatric disorders with criteria corresponding to the DSM-IV.

The BPI was developed by the Pain Research Group of the World Health Organization Collaborating Center for Symptom Evaluation in Cancer Care to provide information on the intensity of pain (sensory dimension) and the degree to which pain interferes with function (reactive dimension). The BPI used in this study shows front and back body diagrams, four pain severity items, and seven pain interference items rated on 0 to 10 scales, and a question on the percentage of pain relief by analgesics during a 24-hour recall period (49). The validity of the BPI has been demonstrated in the German version (46) and in the measure of pain in patients without cancer (50).

The SF-36 is a by multipurpose short-form health survey with 36 questions (51) that yields an eight-scale profile of functional health and well-being scores, psychometrically based physical and mental health summary measures, and a preference-based health utility index. The SF-36 is a generic measure that differs from questionnaires targeting a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of the general population and specific groups when comparing the relative burden of diseases and when differentiating the health benefits generated by a diverse range of different treatments (52). Its German translation has been validated in a variety of German healthcare settings (53–55).

The 15-item Patient Health Questionnaire is a brief self-administered questionnaire that has proven useful in screening for somatization and in monitoring somatic symptom severity for clinical practice and research purposes. Scores of 5, 10, and 15 represent cutoff points for low, medium, and high somatic symptom severity, respectively (56,57).

The intelligence level of participants was assessed with the Multiple Selection Vocabulary Test (MSVT-B). The MSVT-B, which is an accelerated, objective, and reliable test that measures the general level of intelligence, is only insignificantly influenced by mental disorders (58). The results of the test correlate with the global intelligence quotient in healthy adults and are less sensitive to current disturbances than other tests, such as the Wechsler Adult Intelligence Scale (59).

To measure the level of alexithymia, which is a state of deficiency in understanding, processing, or describing emotions (9), each participant completed the validated German version (60) of the 20-item Toronto Alexithymia Scale (TAS-20), which uses a five-point Likert response scale (61) and cutoff scoring (≤51 = nonalexithymia; 52–60 = possible alexithymia; ≥61 = alexithymia).

The German version of the Interpersonal Reactivity Index (IRI) was also used (62). This 28-item self-report questionnaire consists of four scales, each of which measures a distinct component of empathy. The four scales include empathic concern (feeling emotional concern for others), perspective taking (ability to cognitively take the perspective of others), fantasy (emotional identification with characters in films, books, and so on), and personal distress (tendency to become anxious when witnessing suffering people's need for others' help).

Beck Depression Inventory I (BDI-I) is a 21-item self-reporting instrument that measures cognitive and endogenous aspects of depression on a four-point scale ranging from 0 to 3 (standard cutoffs are as follows: 0–9 = no depression; 10–18 = mild depression; 19–29 = moderate depression; >30 = severe depression). This questionnaire has undergone extensive reliability and validation studies (63,64).

The German version of the State-Trait Anxiety Inventory (STAI-T) is a valid and reliable 20-item questionnaire that measures the general level of anxiety on four-point scales ranging from 1 to 4 (65). Spielberger states that "trait anxiety implies differences between people in the disposition to respond to stressful situations with varying amounts of State-Anxiety. But whether or not people who differ in Trait-Anxiety will show corresponding differences in State-Anxiety depends on the extent to which each of them perceives a specific situation as psychologically dangerous or threatening, and this is greatly influenced by each individual's past experience" (66).

Visual Stimuli

The stimuli were previously developed and validated by Jackson et al. (34) through fMRI experiments evaluating empathy, impact of self, and other perspectives in healthy individuals. The stimuli consisted of a series of photos that show white (67) human feet and hands in various painful and nonpainful situations that occur in everyday life. Pictures were taken from positions implying a first-person perspective (i.e., a mental rotation of the limbs by the observer was not required). The 120 stimuli used in this study were selected from a larger sample and grouped into four levels of pain (no, low, medium, and high pain, with 30 pictures for each level) based on the pain intensity ratings of 20 healthy participants (34). Photographs of limbs were smoothed using a Gaussian filter to avoid any influence related to age and sex.

Scanning Method and Procedure

To become familiar with the stimuli and postscan rating procedure, the participants underwent training outside the scanner immediately before the fMRI experiment. Twelve stimuli that were not used in the fMRI paradigm were presented in random order (three from each of the four aforementioned pain intensity conditions). Participants were instructed to adopt self-perspective when rating the subjective intensity of pain for each stimulus on a scale from 0 (no pain) to 9 (strongest pain imaginable) by pressing the corresponding key on a numeric keypad as quickly and accurately as possible. The presentation of the stimuli was cycled until the participant became acclimated to the rating procedure.

For the fMRI task, the stimuli were projected into the scanner tube by a projector, and the stimuli were grouped into 12 blocks, each of which consisted of nine stimuli from the same pain condition chosen in random order. Each stimulus appeared only once throughout the entire experiment. The presentation of each picture lasted 2 seconds, followed by a 1-second blank screen; thus, the duration of each block was 27 seconds. Four additional blocks of the same length constituted a baseline condition that consisted of a blank screen with a green fixation cross at the center. This resulted in a total set of 16 blocks (three blocks per pain condition plus four baseline blocks). The task consisted of presenting the blocks from this set in random order, resulting in a total task time of 432 seconds.

Immediately after the fMRI procedure, the participants were interviewed outside the scanner. The stimuli were presented to them in the same order as previously shown in the fMRI task. All participants were reminded to adopt self-perspective and to respond as quickly and accurately as possible. Each stimulus was presented for 2 seconds (as in the scanner experiment), followed by a blank screen. After 4 seconds, a sound reminded the participants to rate the pain intensity of the picture by pressing the corresponding target button, as rehearsed in the training phase. The next picture was shown immediately after a numeric button had been pressed. The ratings for each stimulus were recorded. If a participant's response time exceeded 4 seconds, an omission error was recorded.

The stimuli were presented inside and outside the scanner with the use of a computer running the Presentation software (Neurobehavioral Systems Inc., Albany, CA; http://www.neurobs.com).

Data Acquisition and Analysis

Images were acquired using a 3-T Philips Achieva Scanner (Philips Medical Systems, Best, the Netherlands) with a standard eight-channel SENSE head coil. Thirty-two contiguous slices (no gap) with steep angulation (to exclude the eyes) were acquired using a gradient-echo echo-planar sequence with the following parameters: repetition time = 2000 milliseconds; echo time = 35 milliseconds; flip angle = 82°; field of view = 220 mm; slice thickness = 4 mm; matrix = 80 × 80; voxel size = 2.75 × 2.75 mm; SENSE factor = 2. Anatomical images were obtained using a T_1-weighted turbo gradient-echo sequence with the following specifications: repetition time = 9 milliseconds; echo time = 4 milliseconds; flip angle = 8°; field of view = 240 mm; matrix = 240 × 240; voxel size = 1 mm isotropic; slice = 170; gap = 0.

Data analysis was performed using SPM5 (Statistical Parametric Mapping software; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The first three images of each run were discarded to allow longitudinal magnetization to equilibrate. The preprocessing steps included the following: a) realignment and unwarping of images to correct for movement artifacts and related susceptibility artifacts; b) coregistration of anatomical images to functional images; c) segmentation and normalization of anatomical images to standard stereotactic space (Montreal Neurological Institute); d) application of normalization transformation to functional images; and e) smoothing with an 8-mm Gaussian kernel for group analysis.

We modeled the conditions as blocks to capture task-related effects. The blocks were then convolved with the canonical hemodynamic response function. For each participant, the images were subjected to fixed-effects analysis. Random-effects analysis was performed at the group level.

For single-group analyses, we applied an a priori threshold of $p < .001$ uncorrected at the voxel level and $p < .05$ corrected for multiple comparisons at the cluster level. We used a cluster extent threshold of 10 voxels. For group comparison, analysis of variance was performed to test for main effects and Group × Stimulus interaction (F tests) using an a priori threshold of $p < .001$ uncorrected at the voxel level, with a cluster extent threshold of 10 voxels. For post hoc t tests, we again applied an a priori threshold of $p < .001$ uncorrected at the voxel level and $p < .05$ corrected for multiple comparisons at the cluster level, with a cluster extent threshold of 10 voxels. To compare our results with those of previous studies and to prevent any relevant activation from being overlooked, we performed region-of-interest (ROI) analyses (Wake Forest University Pickatlas; http://fmri.wfubmc.edu/cms/software). ROI were derived from the Automated Anatomic Labeling software, which is implemented in the Wake Forest University Pickatlas. In accordance with previous studies, the ROI analyzed included the following: right and left ACC, right and left middle cingulate cortices (MCC), right and left postcentral gyri, right and left supplementary motor areas (SMAs), and right and left insulae (34,38,68,69).

To determine significant group differences in the psychometric data set, we applied t tests and defined $p < .05$ as the threshold for significance.

RESULTS

Pain Ratings

Among participants with chronic pain disorder who rated their own "pain intensity on the average" (Item 5) using the BPI before scanning, the M (SD) value was 7 of 10 (2.24). For comparison, in cancer-induced bone pain, which is the most common cause of pain in patients with cancer, the median average pain as rated with the BPI was found to be 4 of 10 (70).

TABLE 1. Results of the Postscan Psychometrics of the Participants

	Patients	Controls	*p*
Pain rating			
''No pain''	0.65 (1.28)	0.54 (0.88)	.36
''Pain'' (all conditions)	4.31 (1.73)	5.05 (1.12)	.06
Beck Depression Inventory I			
Total score	**17.84 (9.03)**	**4.43 (4.70)**	**<.001**
Somatization	**8.33 (3.43)**	**2.26 (2.49)**	**<.001**
Interpersonal Reactivity Index			
''Perspective taking''	14.83 (3.98)	16.24 (3.96)	.06
''Empathic concern''	**13.92 (3.99)**	**16.53 (4.82)**	**.04**
''Fantasy''	**16.88 (2.93)**	**19.96 (5.52)**	**.02**
''Personal distress''	15.20 (2.74)	14.53 (5.02)	.30
20-Item Toronto Alexithymia Scale	**53.19 (9.18)**	**44.37 (8.56)**	**.003**

Data are expressed as mean (standard deviation).
P values < .05 are presented in boldface.

All patients with chronic pain experienced pain throughout the scanning, whereas none of the control participants reported experiencing any pain during the scanning.

Behavioral Measures

The control group attributed a marginally higher pain intensity to all "pain" pictures than to the patients ($p = .057$) (Table 1).

Compared with the control group, the patients reported significantly higher levels of depression in the total score of the BDI-I, indicating mild depression, on average, (Table 1) and higher trait anxiety (STAI-T) scores. Furthermore, the patients suffered more from the somatic symptoms of depression and showed significantly higher levels of alexithymia in TAS-20 compared with the controls (Table 1). The patients showed significantly lower levels on the "empathic concern"

TABLE 2. Main Effects and Interactions in BOLD Signaling Using Analysis of Variance

Region of Interest	Montreal Neurological Institute Coordinates (*x y z*)	*k*	*F*	*p*
Main effects: Group				
Left anterior cingulate cortex	−4 40 −6	11	15.08	.03
Left middle cingulate cortex	−10 2 42	76	20.28	.005
Right middle cingulate cortex	18 −26 42	96	20.21	.006
	10 −6 44	44	17.14	.02
Left insula	−40 14 6	49	20.69	.004
Right supplemental motor area	10 −6 46	34	17.78	.02
Left postcentral gyrus	−30 −40 72	26	19.52	.01
	−52 −4 40	11	15.69	.06
Right postcentral gyrus	56 −4 32	13	15.43	.06
Main effects: Stimulus				
Left anterior cingulate cortex	−2 32 −4	44	9.70	.03
Right anterior cingulate cortex	0 32 −2	21	8.82	.04
Right middle cingulate cortex	6 18 44	49	17.73	<.001
Left supplemental motor area	−2 16 50	21.81	454	<.001
Right supplemental motor area	4 18 48	21.66	356	<.001
Left postcentral gyrus	−42 −44 60	18.90	109	<.001
	−56 −24 30	16.66	85	<.001
Right postcentral gyrus	60 −22 44	11.76	13	.02
Group × Stimulus interaction				
No suprathreshold voxels				

BOLD = blood oxygenation level–dependent.
The table presents Montreal Neurological Institute coordinates, *F*-scores, and cluster sizes in voxels for pain-related brain areas (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level; extent threshold $k > 10$ voxels; *p* value in the table corrected for familywise error at the voxel level).

and "fantasy" scales of IRI (Table 1). However, the group differences found in IRI and TAS-20 are confounded by the level of depression in the BDI-I, and the differences did not remain significant after the removal of the BDI-I score as an interfering variable.

The pain ratings and the "empathic concern" subscale of IRI ($r = 0.6$; $p = .01$) were positively correlated for patients with chronic pain disorder. Furthermore, TAS-20 score and its three subscores ("difficulty identifying feelings," "difficulty describing feelings," and "externally oriented thinking") were positively correlated with the BDI-I score ($r = 0.524$; $p = .015$) in the patient group. In contrast, TAS-20 scores were positively correlated with the "personal distress" subscale of IRI ($r = 0.535$; $p = .018$) in the control group.

No significant intelligence level differences were detected in our participants using the MSVT-B (patients, M (SD) = 27.47 (5.51); controls, M (SD) = 26.37 (7.85); $p = .612$) (71,72).

fMRI Measurements

- Analysis of variance: main effects and interactions. Main effects of the factor "Group" were seen in the left perigenual ACC (pACC), left and right MCC, left insula, right SMA, and both postcentral gyri. Main effects of the factor "Stimulus" were seen in the left and right pACC, right MCC, left insula, left and right SMA, and both postcentral gyri. No significant group-stimulus interaction was detected (even when at a more lenient threshold of $p < .05$ uncorrected at the voxel level) (Table 2).
- Single-group analyses: "Pain > Baseline." In the control and patient groups, the perception of painful stimuli was associated with increased activation of the ACC, postcentral gyrus, insula, and SMA (Table 3, Fig. 1).
- Single-group analyses: "No Pain > Baseline." In the patient group, nonpainful visual stimuli led to increased activation of the left ACC, left MCC, both insulae, both SMAs, and both postcentral gyri. In the control group, the perception of nonpainful stimuli was associated with increased activation of the right and left SMAs, right and left insulae, and left postcentral gyrus (Table 4).
- Single-group analyses: "Pain > No Pain." In the control group, the perception of painful stimuli was associated with increased activation of the postcentral gyrus, left dorsal ACC, and both insulae (Table 3, Fig. 2). No such signal change was observed in patients when comparing "Pain > No Pain" (Table 5, Fig. 2).
- Group comparison: "Pain > Baseline." No significant group differences were found. After the influence of depression was controlled for, introduction of the BDI-I, TAS-20, IRI scores as confounding variables did not change the comparison results (Table 3, Fig. 1).
- Group comparison: "No Pain > Baseline." No significant group differences were found. After the influence of depression was

TABLE 3. BOLD Signal Differences Between Patients and Controls in the "Pain > Baseline" Contrast

Region of Interest	Pain > Baseline			
	Montreal Neurological Institute Coordinates (*x y z*)	*k*	*T*	*p*
Controls				
Left anterior cingulate cortex	0 4 30	13	4.51	.047
Right middle cingulate cortex	*2 4 30*	*11*	*4.24*	*.8*
Left insula	−28 24 2	355	7.6	<.001
Left supplemental motor area	−8 22 50	1016	8.46	<.001
Right supplemental motor area	2 8 60	472	6.65	<.001
Left postcentral gyrus	−60 −22 30	160	6.85	<.001
	−40 −36 42	65	6.66	.01
Right postcentral gyrus	56 −24 44	46	4.54	.03
Patients				
Left anterior cingulate cortex	0 8 23	21	5.12	.030
Right middle cingulate cortex	*2 6 30*	*17*	*5.19*	*.05*
	4 18 44	*60*	*4.60*	*.08*
Left insula	−28 22 4	461	5.75	<.001
Right insula	42 16 2	42	5.08	.01
Left supplemental motor area	−2 16 50	658	6.43	<.001
Right supplemental motor area	4 10 58	518	7.74	<.001
Left postcentral gyrus	−20 −74 56	1293	6.70	<.001
Right postcentral gyrus	34 −36 44	274	5.59	<.001
Controls > Patients				
No suprathreshold voxels				
Patients > Controls				
No suprathreshold voxels				

BOLD = blood oxygenation level–dependent.

The table presents Montreal Neurological Institute coordinates, *T*-scores, and cluster sizes in voxels for pain-related brain areas that were activated in response to painful picture stimuli (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level; $p < .05$ corrected for multiple comparisons at the cluster level [the actual value of the latter is given in the table]; extent threshold $k > 10$ voxels; nonsignificant activations are presented in italics).

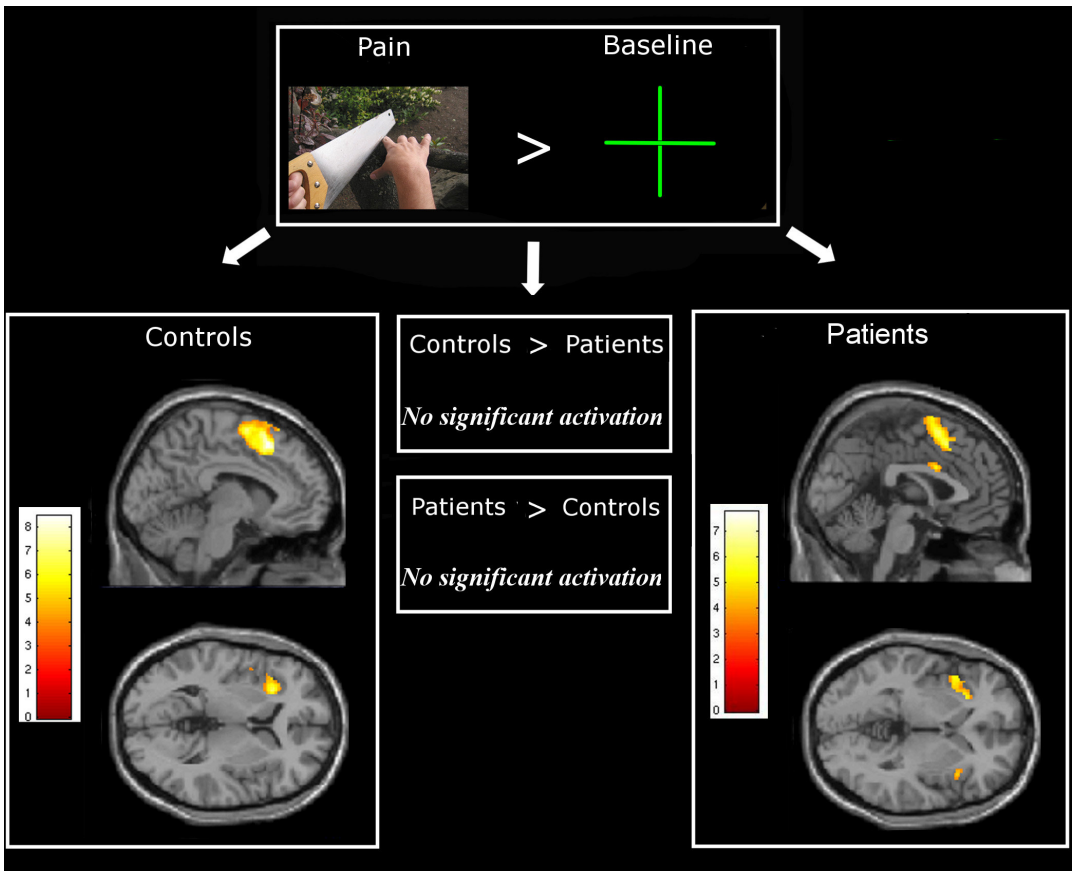

Figure 1. Activation of pain-related brain areas in response to painful picture stimuli computing "Pain > Baseline." Controls showed significant activation of the left insula, both supplementary motor areas, and both postcentral gyri (data not shown). Patients showed significant activation of the left anterior cingulate cortex, both insulae, both supplementary motor areas, and both postcentral gyri (data not shown). No significant group differences were detected (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level and $p < .05$ corrected for multiple comparisons at the cluster level; extent threshold $k > 10$ voxels).

controlled for, introduction of the BDI-I, TAS-20, and IRI scores as confounding variables did not change the comparison results (Table 4).

- Group comparison: "Pain > No Pain." In the post hoc *t* test, the control group exhibited a higher activation of the left pACC compared with the patients when comparing "Pain > No Pain" (Table 5, Fig. 2).

Controlling for the influence of the BDI-I, TAS-20, and IRI scores as confounding variables did not change the results (Table 5, Fig. 2).

Additional Findings and Methodological Remarks

This study used thresholds of $p < .001$ uncorrected at the voxel level and $p < .05$ corrected for multiple comparisons at the cluster level (extent threshold of 10 voxels). Interestingly, a statistically "stronger" correction at the voxel level ($p < .05$ corrected for false discovery rate) led to an "additional" significant activation found in the left dorsal ACC in the control group. Controlling for the influence of the BDI-I, TAS-20, and IRI scores as confounding variables did not change the results. This finding clearly provides further evidence for the risk of false-positive results with the use of the false discovery rate correction in fMRI imaging analysis, as recently stated by Chumbley and Friston (73), and will not be further discussed.

Negative Results

No significant group differences in the activation of the anterior insular cortex could be found in any of the analyses mentioned herein. Even at a more lenient threshold ($p < .01$ uncorrected at the voxel and cluster levels), no significant differences were detected in the insula. None of our behavioral measures, especially TAS-20, correlated with insular activation, even when the participants of both groups were pooled. No sex differences in pain perception (74) could be determined in our sample.

DISCUSSION

In this study, we aimed to show that the ability to imagine how one would feel in a particular painful situation is disturbed in patients with chronic pain disorder. Our results demonstrate that, compared with healthy controls, the patients exhibited a significantly lower activation of the left pACC, indicating an altered neuroprocessing of both inner-oriented and outer-oriented emotional awareness in patients with chronic pain disorder (75). Self-rating measures of depression, alexithymia, and general cognitive and emotional empathy did not influence the neuroimaging results.

Accordingly, our study expands the findings of Valeriani et al. (76), who showed that explicitly healthy individuals who received painful laser stimulations map the observed pain of others

TABLE 4. BOLD Signal Differences Between Patients and Controls in the "No Pain > Baseline" Contrast

Region of Interest	No Pain > Baseline			
	Montreal Neurological Institute Coordinates (*x y z*)	*k*	*T*	*p*
Controls				
Left insula	−36 22 −2	156	6.27	<.001
Left supplemental motor area	−4 16 50	421	5.66	<.001
Right supplemental motor area	4 18 66	209	5.09	<.001
Left postcentral gyrus	−40 −36 42	33	4.95	.04
	−60 −22 30	*23*	*4.68*	*.06*
Patients				
Left anterior cingulate cortex	−2 4 30	25	5.11	.03
Left middle cingulate cortex	*−2 2 32*	*12*	*4.25*	*.06*
Left insula	−30 22 4	133	5.14	<.001
Right insula	34 22 −2	124	5.42	<.001
Left supplemental motor area	0 12 54	327	5.84	<.001
Right supplemental motor area	4 16 52	292	6.04	<.001
Left postcentral gyrus	−42 −34 44	74	6.12	.009
	−46 −8 50	46	5.20	.02
	−42 −42 58	40	4.44	.03
Right postcentral gyrus	48 −28 40	100	5.28	.004
Controls > Patients				
No suprathreshold voxels				
Patients > Controls				
No suprathreshold voxels				

BOLD = blood oxygenation level–dependent.
The table presents Montreal Neurological Institute coordinates, *T*-scores, and cluster sizes in voxels for pain-related brain areas that were activated in response to nonpainful picture stimuli (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level; $p < .05$ corrected for multiple comparisons at the cluster level [the actual value of the latter is given in the table]; extent threshold $k > 10$ voxels; nonsignificant activations are presented in italics).

according to their own feelings rather than the feelings attributed to a stranger. These results suggest that the subjective experience of pain influences social interactions by inducing the sufferer to evaluate others according to an egocentric stance. Thus, the regulation of one's egocentric perspective is important for understanding others (77). In our study, we report on the psychometric and neural BOLD characteristics of patients with chronic pain disorder mapping the introjective (78–80) pain of others, a topic previously unaddressed in the literature. Individuals with this disorder are often psychologically characterized as having difficulty realizing and interpreting emotional signals within themselves, thus perceiving the signals as mere sensory sensations (8). We found functional neural disturbances that seem to correspond to some of the clinically relevant emotional challenges faced by patients and their social networks, such as their family and physicians.

Activation of Pain Matrix in Patients With Chronic Pain Disorder Compared With Healthy Participants

In the control group, "Pain" pictures elicited activation of the core regions of the pain matrix (81,82), such as the left somatosensory cortex, both insulae, and left dorsal ACC, compared with the "No Pain" condition (Table 5, Fig. 2). In contrast to the control group, the patients showed no significant activation of these regions when comparing "Pain > No Pain" (Table 5, Fig. 2).

In general, the pain matrix is best evaluated by activating acute pain experience (83), and one may speculate whether the differences in neural activations found in this study are another example of the different activation patterns attributable to the long-lasting experience of nonacute chronic pain. Thus, the pain matrix may not be viewed as a stand-alone entity but rather as a substrate modulated by a variety of brain regions, and this interaction largely determines the pain experience (84). Thus, the cerebral signature for the pain perception of subjective spontaneous pain versus acute experimentally induced pain in chronic pain conditions may not necessarily be represented by the conventional pain matrix concept (84–86).

Mental Comorbidity Pattern in Patients With Chronic Pain Disorder

Chronic pain disorder is a somatoform disorder that has a high comorbidity with major depression and anxiety disorders (87,88). This comorbidity pattern (89–91) is also present in our patients with respect to ratings for depression (92), anxiety (93), and alexithymia (94). However, because most psychotherapy studies for somatic conditions improved patients' physical symptom severity but not their psychological distress (e.g., for depression) (95,96), there seems to be an independent relationship between medically unexplained somatic complaints and depression (97). In this study, the self-report measures for

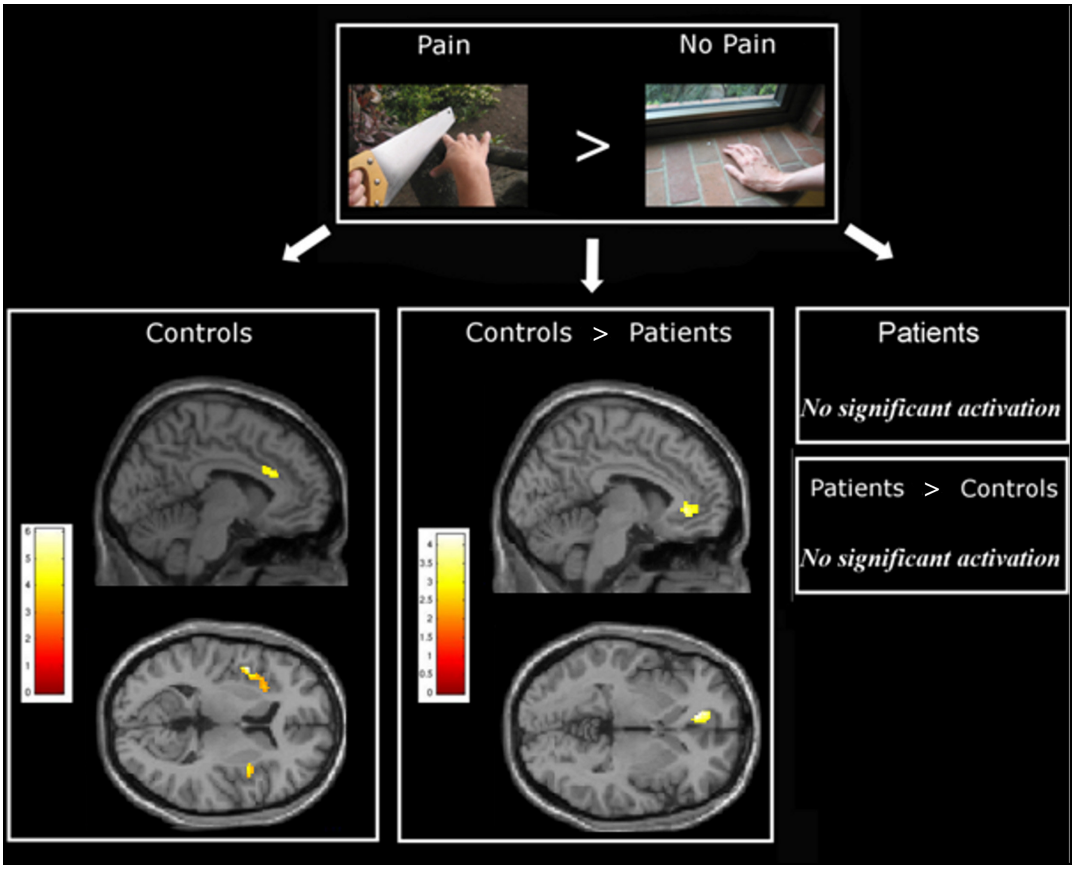

Figure 2. (Montreal Neurological Institute coordinates ($x\ y\ z$) = −8 38 0; cluster extent k = 54 voxels; T = 4.28; p = .006) (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level and $p < .05$ corrected for multiple comparisons at the cluster level; extent threshold $k > 10$ voxels; for illustration purposes, a more lenient height threshold of $p < .005$, uncorrected, was used).

TABLE 5. BOLD Signal Differences Between Patients and Controls in the "Pain > No Pain" Contrast

Region of Interest	Pain > No Pain			
	Montreal Neurological Institute Coordinates ($x\ y\ z$)	k	T	p
Controls				
Left anterior cingulate cortex	−4 24 24	90	4.92	.002
Left middle cingulate cortex	*−2 22 32*	*16*	*4.44*	*.05*
Left insula	−44 6 8	39	6.11	.02
Right insula	38 6 6	19	4.18	.02
Left postcentral gyrus	−58 −22 26	144	6.00	<.001
Patients				
No suprathreshold voxels				
Controls > Patients				
Left anterior cingulate cortex	−8 38 0	54	4.28	.006
Left supplemental motor area	*−10 8 58*	*16*	*3.82*	*.05*
Patients > Controls				
No suprathreshold voxels				

BOLD = blood oxygenation level–dependent.
The table presents Montreal Neurological Institute coordinates, T-scores, and cluster sizes in voxels for pain-related brain areas that were activated in response to painful picture stimuli (region of interest–based analysis; height threshold $p < .001$ uncorrected at the voxel level; $p < .05$ corrected for multiple comparisons at the cluster level [the actual value of the latter is given in the table]; extent threshold $k > 10$ voxels; nonsignificant activations are presented in italics).

depression, alexithymia, and interpersonal reactivity did not explain our neuroimaging results upon the introduction of the appropriate behavioral measures (BDI-I, TAS-20, and IRI) as confounding variables. As a first approximation, this incongruity between behavioral and biological measures is consistent with the general fallibility of self-assessments (97). Furthermore, it is noteworthy that brain activity during experimental pressure pain in patients with fibromyalgia (chronic widespread pain) was recently shown to not be modulated by depressive symptoms and anxiety, using the BDI-I and STAI-T, respectively (98). Furthermore, a similar discrepancy between BOLD activations and behavioral measurements was described in a study investigating altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder (5), among other studies. Thus, the differences between our two groups may be more easily detected via neuroimaging methods than via self-assessed behavioral ratings (33,99–102).

pACC and the Affective Dimension of Chronic Pain Disorders

Compared with patients with chronic pain disorder, the control group demonstrated a higher activation of the left pACC when comparing "Pain > No Pain." This activation was not attributable to greater activity in this region during the "No Pain" condition, relative to the baseline condition in patients compared with that in the control participants. In general, pACC plays a role in processing affective information (which includes assigning emotional valence to internal and external stimuli and conditioned emotional learning), regulating autonomic and endocrine functions, and assessing motivation (103–105), empathy for pain (106), and, eventually, generation of affective meaning (21). Furthermore, pACC was found to be involved in the processing of both somatic (107–109) and visceral (110,111) pain. Vogt et al. (112) suggested that activation of pACC may be involved in affective responses to noxious stimuli, such as the suffering associated with pain, and Frewen et al. (113) observed a correlation between activation of pACC and emotional awareness in healthy participants as they recalled traumatic experiences. Interestingly, pACC is also functionally related to the onset of the uncertainty of impending, externally applied thermal stimuli at noxious and non-noxious temperatures (114). In contrast to the control participants, our patients with chronic pain were subjectively accustomed to the sensory experience of lasting pain (i.e., they are certain that they will feel persistent pain). Thus, we suggest that, in our healthy controls, the experience of pain induced by the visual pain paradigm may be more surprising and thus more intensive and differentiable, resulting in higher pACC activation and a trend corresponding with a higher pain intensity rating. One may speculate about a type of "habituation" among patients with chronic pain in the affective dimension of the painful experience that was isolated in this study using the visual pain paradigm. Against this background, prolonged activation of pain processing areas could potentially diminish stimulus-evoked BOLD responses in those areas and thus explain the finding that patients with chronic pain exhibited lower pACC activation than pain-free controls (115).

In a study of patients who never felt nociceptive pain due to CIP, conducted by Danziger et al. (116), the functional activity of pACC in the healthy control group was positively correlated with emotional empathy, especially the "empathic concern" score of IRI (31). Our results might reflect an antipodal minus activation of the same region in patients who always feel non-nociceptive somatoform pain. Hence, one could speculate that pACC plays a pivotal role in the processing of pain as an affective regulator (i.e., pACC could be an affective-motivational pain core region or hub) (21,117). Thus, pACC could be a brain area with a high degree of connectivity, equalizing both self-centered and other-centered emotional awareness (in a broader sense, the bidirectional empathetic feelings) of pain. Current social psychology interpretations of the different subscales of IRI posit that the "empathic concern" subscale refers to the affective component of empathy (76). This idea is consistent with patients with chronic pain disorder showing a positive correlation between the pain ratings after scanning and the "empathic concern" subscore of IRI. Thus, the idea that this part of the ventromedial prefrontal cortex for self-evaluation and other evaluations of emotion (118) "is integral in shaping subcortical responses and may participate in the construction and deployment of (affective) "meaning" is particularly tempting (21) as it could, for example, provide a neural basis for the characteristic problems of pain reappraisal and distraction found in patients with chronic pain disorder (119).

Leftward Appearance of the Neural and the Nonvariation of Insular Activations

The leftward location of our BOLD signaling in the insula may be attributable to several factors in our right-handed participants. There is evidence of left hemisphere dominance for local, narrowly focused attention, and right hemisphere dominance for broad, sustained, global, and flexible attention (120–123). Altogether, the self-centered mental simulation of the sensory qualities of others' pain may be lateralized to the left hemisphere (124). Another factor to consider is that the right anterior insula is more typically associated with remapping to the conscious experience of bodily sensations (125,126). Thus, the left insula may reflect registration of pain that is accessible to consciousness but may not necessarily be conscious (127).

As the insula is associated with the subjective evaluation of bodily states and is involved in human feelings, this study has shown that the individual affective-cognitive style is associated with insular activity in pain empathy processing (128). The potential contribution of insular dysfunction to the development of hyperalgesia has been demonstrated in rat models via local manipulations of dopaminergic, GABAergic, and opioidergic neurotransmissions within this region, and insular hypometabolism in a patient with fibromyalgia was recently demonstrated (55). In contrast, similar to Abbass et al. (100), who could not find initial differences in the insula between patients with autism spectrum conditions and controls, we did not find differences between patients with chronic pain disorder and our healthy participants. However, we could not confirm one of the subsequent results of both Abbass et al. (100) and

Bird et al. (101)—that differences in insular activity were especially correlated with the level of alexithymia reported by all participants (i.e., healthy controls and patients with autism spectrum conditions) and that the strength of empathic brain responses to the suffering of others is predictive of the degree of alexithymia in our pooled participants, respectively, because the response did not vary as a function of the group. Thus, upon combination of the knowledge that, first, there is a core network consisting of the bilateral anterior insular cortex and the ACC that is associated with emotional awareness for pain in the healthy population (38) and, second, we could show clear insular activation in each of our participant groups, it seems obvious that it is not so much the participation of insular circuits that plays a dominant role in perturbed emotional awareness processing in somatoform pain disorder but rather the ACC. This functional distinction between the insula and the ACC underscores the fact that the ACC (and its subregions) adds something more to emotional responses than the somatic component provided by the insula (and its subregions) and that the relative noninvolvement of pACC in patients with chronic pain disorder in the current context corresponds to their tendency to experience emotions as pronounced physical sensations. Finally, considering the importance of emotions for personal judgments in mind, the necessary introspection function needed to make subjective preference judgments is provided by the insular and cingulate cortices, whereas the medial orbitofrontal cortex and posterior ventrolateral prefrontal cortex/insula cortex contribute to stimulus evaluation and motivational aspects of response selection, respectively (129). In the context of our current results involving pACC, these distinctions shed light on the difficulty of patients with somatoform disorders in distinguishing bodily needs from psychological needs.

Limitations

A limitation of our study is that we did not measure pain unpleasantness directly; instead, only pain intensity was measured. We did not ask for a third-person perspective of pain empathy ("How much pain is the subject of this picture in?") because it may have confused our distressed patients, particularly about the actual objectives of our experiment. Future studies, including electrodermal activity, electroencephalogram, and eye-tracking measures, could help to further elucidate the mechanisms underlying deficits in pain-related affective meaning construction from both the first-person perspective and the third-person perspective in people with chronic pain disorders.

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Study II

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Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder

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Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder

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Abstract

Background: Recent functional imaging studies on chronic pain of various organic etiologies have shown significant alterations in both the spatial and the temporal dimensions of the functional connectivity of the human brain in its resting state. However, it remains unclear whether similar changes in intrinsic connectivity networks (ICNs) also occur in patients with chronic pain disorder, defined as persistent, medically unexplained pain.

Methods: We compared 21 patients who suffered from chronic pain disorder with 19 age- and gender-matched controls using 3T-fMRI. All neuroimaging data were analyzed using both independent component analysis (ICA) and power spectra analysis.

Results: In patients suffering from chronic pain disorder, the fronto-insular 'salience' network (FIN) and the anterior default mode network (aDMN) predominantly oscillated at higher frequencies (0.20 - 0.24 Hz), whereas no significant differences were observed in the posterior DMN (pDMN) and the sensorimotor network (SMN).

Conclusions: Our results indicate that chronic pain disorder may be a self-sustaining and endogenous mental process that affects temporal organization in terms of a frequency shift in the rhythmical dynamics of cortical networks associated with emotional homeostasis and introspection.

Keywords: Chronic pain disorder, Somatoform pain disorder, Resting state networks, Intrinsic connectivity networks, Functional brain imaging, fMRI

Background

Chronic pain disorder, as defined in the DSM-IV [1], is a somatoform disorder lasting longer than 6 months in which the predominant symptoms are bodily complaints of pain. Psychological factors are thought to be central to the onset, severity, exacerbation and maintenance of the complaint. Characteristically, patients with this clinically prevalent disorder have difficulties recognizing and interpreting emotional signals within themselves; they perceive these signals as physical symptoms [2]. Moreover, the disorder itself leads to significant neural alterations in regions associated with emotional awareness [3], affective meaning construction [4], and bodily state monitoring [5], such as the medial prefrontal cortex, the anterior cingulate cortex, and the insula [6].

In addition to studies concerning morphology and paradigm-based activations, the temporal dimension of neural processing has recently gained attention [7-9]. This dynamic view of brain functioning emphasizes the importance of the functional interplay between different brain regions, with a particular focus placed on altered resting state connectivity in mental disorders [10]. One of the strongest disruptors of this complex equilibrium seems to be pain [11-14]. In a recent study of 10 patients suffering from nociceptive chronic pain, the spatial coherence of the fronto-insular 'salience' network (FIN) was altered in the resting state [15]. Chronic pain influenced the temporal aspects of functional connectivity by changing the frequency of the rhythmic oscillations in the BOLD-signal within the FIN from lower levels (below 0.12 Hz) to a higher range (between 0.12

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and 0.24 Hz) [15]. Moreover, chronic back pain seems to disrupt the integrity of the so-called default mode network (DMN) [11], whereas diabetic neuropathic pain changes the temporal coherence of the DMN [16].

Interestingly, chronic pain not only influences neural circuits but also tends to operate in a domain-general manner. Neuropathic diabetic pain, for example, also changes the spatial functional anatomy of the sensorimotor network (SMN) [16]. However, the aforementioned studies [15,16] have focused on chronic pain conditions without distinguishing between pain that can be clearly associated with a convincing organic correlate and somatoform pain (e.g., in chronic lower back pain [17]) or generalized pain.

Thus, the present study aims to fill this gap, examining whether chronic pain disorder patients show similar alterations in frequency and functional connectivity within the brain's functional architecture. We define chronic pain disorder as pain that is not the result of a clear organic etiology or that is out of proportion to the intensity of physical findings and that is caused by a well-classified mental disorder (ICD-10: F45.4x, DSM-IVR: 307.80), characterized predominantly by chronic ongoing pain [1,18]. Given that there is an endogenous central process that is observed in chronic pain disorder, we hypothesize that pain-related resting state networks such as the DMN, FIN, and SMN will fluctuate at even higher frequencies in patients than in healthy controls. We also hypothesize that these networks will show evidence of disturbed spatial functional connectivity.

Methods

This study was approved by an institutional ethics committee (Klinikum rechts der Isar, Medical Faculty of Technische Universitaet Muenchen, Germany) and was performed in accordance with the Declaration of Helsinki.

Nineteen healthy controls (mean age: 48.79 years, SD 12.25, 12 females) and 21 German-speaking patients (mean age: 46.62 years, SD 12.49, 17 females) with chronic pain disorder, defined as a pain-predominant multisomatoform disorder diagnosed by an experienced physician using a modified SCID-I interview, provided informed written consent and participated in the experiment. The main feature of somatoform disorders is "the repeated presentation of physical symptoms together with persistent requests for medical investigations, despite repeated negative findings and reassurances by physicians that the symptoms have no physical basis. If any physical disorders are present, they do not explain the nature and extent of the symptoms or the distress and preoccupation that the patient has with them" [18]. Multisomatoform disorder, a medium-to-severe somatoform disorder, is defined as three or more medically unexplained, currently bothersome, physical symptoms in addition to a long (≥ 2 years) history of somatization [19]. Because of the striking comorbidity of multisomatoform disorder with major depression and anxiety disorders, it has been suggested that overlapping psychobiological mechanisms mediate depression, anxiety, and somatization symptoms [20]. Compared with mood and anxiety disorders alone, multisomatoform disorder is associated with comparable impairments in health-related quality of life, a greater number of self-reported disability days and clinic visits, and the highest levels of provider frustration [21,22].

The Physical Component Summary (PCS) measure [23] in our patient group had to be 1 standard deviation or more below the population norm (≤ 40), as measured with the SF-36 (see below). A score less than 40 also meets the DSM-IV criterion B for "significant distress or psychosocial impairment due to the somatoform pain" in patients with pain disorder [1]. As a second precondition, sum scores on the 15-item Patient Health-Questionnaire (PHQ-15) had to be above 10, representing at least medium somatic symptom severity (see below). The German version of the Brief Pain Inventory (BPI) [24] was used to estimate the intensity of each participant's pain. We reviewed patients' medical charts and contacted the treating physicians to rule out possible or unclear organic explanations for the symptoms of our chronic pain patients. Patients with insufficient cognitive abilities, severe and chronic somatic or nervous diseases, unambiguous nociceptive pain, hypochondriasis, a severe comorbid mental disorder causing major impairment in social functioning (e.g., schizophrenia or severe substance abuse) or insufficient German language skills were excluded. All participants were white, of Caucasian origin, and right handed, as assessed by the Edinburgh handedness inventory [25]. Additional file 1: Table S6 lists all medications that patients were currently taking.

Psychometric measurement

Somatoform disorders were diagnosed using a modified semi-structured psychiatric interview, the German version of the SCID-I (Structured Clinical Interview for DSM Disorders) [26]. The SCID-I is the diagnostic criterion standard and evaluates current (i.e., the 4 weeks preceding the interview) and lifetime psychiatric status for major Axis I mental disorders using criteria that correspond to the DSM-IV [1].

The SF-36 is a multipurpose, short form health survey consisting of 36 questions [27]. It yields an 8-scale profile of functional health and well-being scores, psychometrically based physical and mental health summary measures, and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proved useful in surveys of both general

and specific population groups. It compares the relative burden of disease and differentiates the health benefits generated by a wide range of different treatments [28]. Its German translation has been validated in a variety of German health care settings [29,30].

The PHQ-15 is a brief, self-administered questionnaire that has proved useful in screening for somatization and in monitoring somatic symptom severity in clinical practice and in research. Scores of 5, 10, and 15 represent the cutoff points for low, medium, and high somatic symptom severity, respectively [31,32].

The BPI, based on the Wisconsin Brief Pain Questionnaire, was developed by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care to provide information on the intensity of pain (the sensory dimension) and the degree to which pain interferes with function (the reactive dimension) [33]. The validity of the German version [24] and the ability of the BPI to measure pain in patients without cancer [34] have been demonstrated.

The applied Beck Depression Inventory I (BDI-I) is a 21-item self-reported instrument that measures cognitive and endogenous aspects of depression on a four-point scale ranging from 0 to 3. The standard cut-offs are as follows: 0–9 indicates no depression, 10–18 indicates mild depression, 19–29 indicates moderate depression, and >30 indicates severe depression. This questionnaire has undergone extensive reliability and validation studies [35,36].

The German version of the Trait Anxiety Inventory (STAI-T) is a valid and reliable 20-item questionnaire that measures the general level of anxiety on four-point scales ranging from 1 to 4 [37].

Functional MRI resting state paradigm

Participants were asked to close their eyes and relax but to remain awake. This portion of the experiment lasted 370 seconds. Following the scanning session, participants were asked whether they had fallen asleep during the scan; those who provided a positive or ambiguous answer were excluded from the study.

Data acquisition and fMRI procedures

Images were acquired with a 3T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands) using a standard 8-channel SENSE head coil. Thirty-two contiguous slices (no gap), with a steep angulation to exclude the eyes, were acquired using a gradient echo-planar (EPI) sequence with the following parameters: 2000 ms repetition time (TR); 35 ms echo time (TE); 82 degree flip angle; 220 mm FOV; 4 mm slice thickness; 80_80 matrix; voxel size 2.75_2.75 mm; SENSE factor 2. Anatomical images were obtained using a T1-weighted turbo gradient echo sequence with the following parameters: 9 ms TR; 4 ms TE; 8 degree flip angle; 240 mm field of view (FOV); 240_240 matrix; voxel size 1 mm isotrop; 170 slices; no gap.

Data analysis and image processing

Data analysis was performed using SPM5 (Statistical Parametric Mapping software, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The first three images for each run were discarded to allow for equilibration of longitudinal magnetization. The preprocessing steps included (1) realignment and unwarping of the images to correct for movement artifacts and related susceptibility artifacts, (2) coregistration of the anatomical images to the functional images, (3) segmentation and normalization of the anatomical images to a standard stereotactic space (Montreal Neurological Institute, MNI; Quebec, Canada), (4) application of a normalization transformation to the functional images, and (5) smoothing with a Gaussian kernel of 8 mm for group analysis.

Connectivity analysis

We performed an independent component analysis (ICA) by using the "group ICA" function included in the fMRI toolbox (*GIFT version 1.3h*; http://icatb.sourceforge.net) developed for the analysis of fMRI data [38-40]. First, the individual data were concatenated across time, followed by the computation of subject-specific components and time courses. The analysis proceeded in three stages: (1) data reduction, (2) application of the ICA algorithm, and (3) back reconstruction for each individual subject [38]. In the first step (1), data from each subject underwent principal component analysis to reduce the computational complexity of the analysis. In so doing, most of the content of the data was preserved. After concatenating the resulting volumes, the number of independent sources was estimated using the GIFT dimensionality estimation tool based on the aggregated data and using the minimum-description-length criteria [41]. The final reduction step, according to the selected number of components, was achieved again using principal component analysis. In the second stage of the analysis (2), we used the *Infomax* algorithm to run the appropriate ICA and a mask based on all subjects. In the final stage of back reconstruction (3), time courses and spatial maps were computed for each subject. The resulting mean spatial maps of each group were transformed to z scores for display [38].

Individual subject maps of the ICNs were entered into random effects analyses in SPM5. The results were thresholded at $p = 0.05$ and corrected for family wise error (FWE) with a cluster extent threshold of 50 voxels.

To enhance both the reliability and validity of this study, the ICNs were compared with networks that were calculated from a sample of approximately 600 healthy people in a study previously published by Allen et al.

[42] that used spatial correlation (multiple regression) in the GIFT program [38] (see below for details).

For comparison between groups, we used two-sample t-tests with the available psychometric depression and anxiety scores as covariates of no interest. To detect even weak effects, a more lenient threshold was used for the group comparison ($p = 0.005$, uncorrected on the voxel level ($z > 2.58$), and $p = 0.05$, corrected for multiple comparisons on the cluster level, extent threshold $k > 10$ voxels). Correlation analysis was performed at the same threshold. The connectivity maps from GIFT were entered into SPM5. We performed a partial correlation analysis (Pearson correlation) between functional connectivity and the level of depression on the BDI-I, controlling for the level of anxiety on the STAI-T. We also performed a partial correlation analysis between functional connectivity and the level of anxiety on the STAI-T, controlling for the level of depression on the BDI-I. Finally, we correlated the average subjective pain during the last week (item 5 on the BPI) with the functional connectivity using a bivariate correlation.

Power spectra analysis

The GIFT toolbox "spectral group compare" function was used to calculate power density frequency spectra for each subject at six equally spaced frequency bins between 0 and 0.24 Hz at 0.04 Hz intervals (2-sample t-test, $p < 0.0083 \cong 0.05/6$; Bonferroni-correction for 6 frequency bins). Several previous studies have also used power-spectra analysis (see [15,16,43,44]; please note that the number of bins and the intervals are different in each study). The level of depression (BDI-I) and the level of anxiety (STAI-T) were introduced as nuisance covariates. Correlation analyses with all psychometric data were performed at the same threshold.

Results

Pain ratings

Prior to scanning, the German version of the Brief Pain Inventory (BPI) was used to estimate the intensity of the patients' chronic pain during the previous week. On average, subjects rated their pain as a 7 (SD 2.24) using a Numerical Rating Scale (NRS), which ranged from 0 (*"no pain"*) to 10 (*"pain as bad as you can imagine"*) on item 5 of the BPI. For comparison, in cancer-induced bone pain, the most common cause of pain in patients with cancer, the median average pain using the BPI was found to be 4 [45]. All patients suffering from chronic pain disorder experienced pain throughout the fMRI scan.

Psychometric measurement

Patients with chronic pain disorder showed significantly higher BDI-I levels in the form of mild depression, higher trait-anxiety (STAI-T) scores and higher pain levels on the BPI (item 5) compared with the control group (Table 1). The level of depression was significantly correlated with the level of anxiety ($R = 0.593$, $p = 0.005$). No relevant correlation was observed between the level of clinical pain (BPI, item 5) and the level of depression ($R = -0.01$, $p = 0.996$) or the level of anxiety ($R = 0.083$, $p = 0.736$).

Functional MRI data – spatial connectivity analysis (Figures 1 and 2)

The ICA estimation resulted in 29 independent components. In accord with published data from other groups, we identified the following pain-related networks (Figures 1 and 2, Additional file 2: Table S1, Additional file 3: Table S2):

1. The anterior default mode network (aDMN), which comprises cortical midline structures such as the medial prefrontal cortex and the precuneus [11,12,16,46]. The aDMN showed the strongest overlap with component 25 from Allen et al. [42], which represents the anterior part of the default mode network (multiple regression value: 0.22).
2. The posterior default mode network (pDMN) of the precuneus [11,12,16,46]. The pDMN showed the strongest overlap with component 50 from Allen et al. [42], which represents the posterior part of the default mode network (multiple regression value: 0.14).
3. The fronto-insular network (FIN), which comprises both the insula and the cingulate cortex [15,47]. Component 55 from Allen et al. [42], which represents the fronto-insular salience network, showed the strongest overlap with this network (multiple regression value: 0.22).
4. The sensorimotor network (SMN), which comprises the pre- and post-central gyrus [48]. The SMN showed the strongest overlap with component 29 from Allen et al. [42], which represents a sensorimotor network (multiple regression value: 0.14).

No significant differences in spatial functional connectivity between the patient and control groups were detected (Additional file 4: Table S3). Moreover, no significant correlation was observed between the psychometrically measured level of pain (BPI), anxiety (STAI-T), depression (BDI-I) and spatial functional connectivity [42] in the patient group (Additional file 5: Table S4).

Functional MRI data – power spectra analysis (Table 2, Figure 3)

Compared to the control group, patients showed higher power spectra in the aDMN and the FIN, ranging between 0.20 and 0.24 Hz. No significant correlation was observed among the level of pain, depression, trait-

Table 1 Averages and comparisons of group scores

	Patients				Controls				t-Test -p-value;
	Mean	Median	SD	Range	Mean	SD	Median	Range	
BPI (Item 5)	7	6	2.24	2 - 9	0	0	0	-	0.000
BDI-I:	17.84	20	9.03	3 - 37	4.43	4.70	2	0 -16	0.000
STAI-T	47.10	49	12.4	20 -70	35.94	8.56	34	23 - 50	0.002

Two-sample t-tests of average pain intensity (BPI), depression (BDI-I) and trait-anxiety (STAI-T) in patients with chronic pain disorder and healthy controls. The threshold of significance is $p < 0.05$.

anxiety and spectral power (Additional file 6: Table S5). These group differences were not influenced by levels of depression and trait-anxiety as measured by the BDI-I and STAI-T, respectively.

Discussion

This study reveals that neural activity within the FIN and the aDMN in patients with chronic pain disorder shows significantly shifted frequencies in comparison with healthy controls. Moreover, a general trend toward higher power in the 0.20 - 0.24 Hz frequency bin was evident in patients compared with control subjects. However, significant changes in the spatial dimensions of functional connectivity were not detected.

Our results support the study hypothesis that there is a shift of the endogenous oscillations of the brain's resting state to higher frequencies in patients suffering from chronic ongoing pain, even when a physical examination cannot (fully) explain the subjective symptoms and the patients fulfill the official criteria for chronic pain disorder.

Furthermore, by demonstrating higher BOLD fluctuations in the FIN and DMN in chronic pain disorder, our findings expand the results of both Malinen et al. [15] and Cauda et al. [16]. Other authors have discovered similar alterations in temporal coherence among patients suffering from chronic neuropathic pain associated with obvious organic diseases [49,50]. Compared to previous studies on the brain's temporal dynamics in chronic

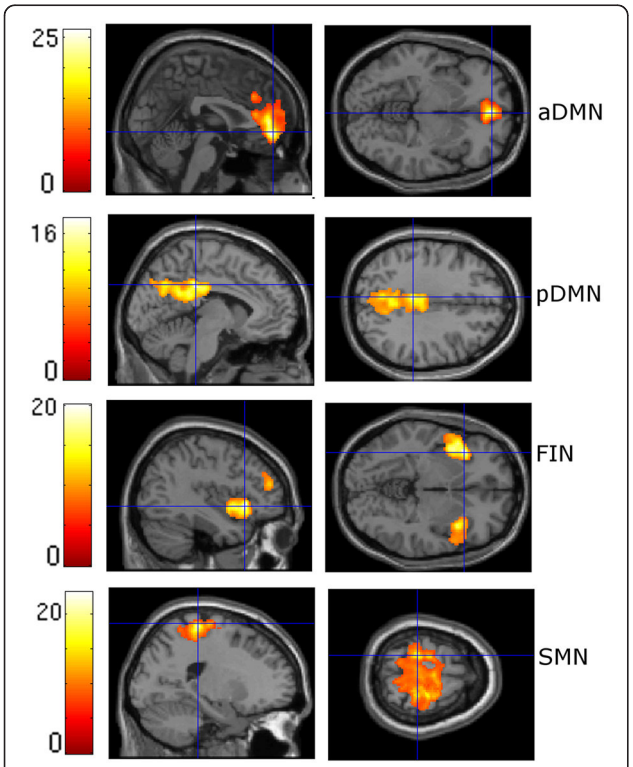

Figure 1 ICNs of the control group. For illustration purposes, spatial maps were thresholded at P = 0.05, corrected for family wise error (FWE) with a cluster extent threshold of 50 voxels; aDMN = anterior default mode network, pDMN = posterior default mode network, FIN = fronto-insular network, SMN = sensorimotor network.

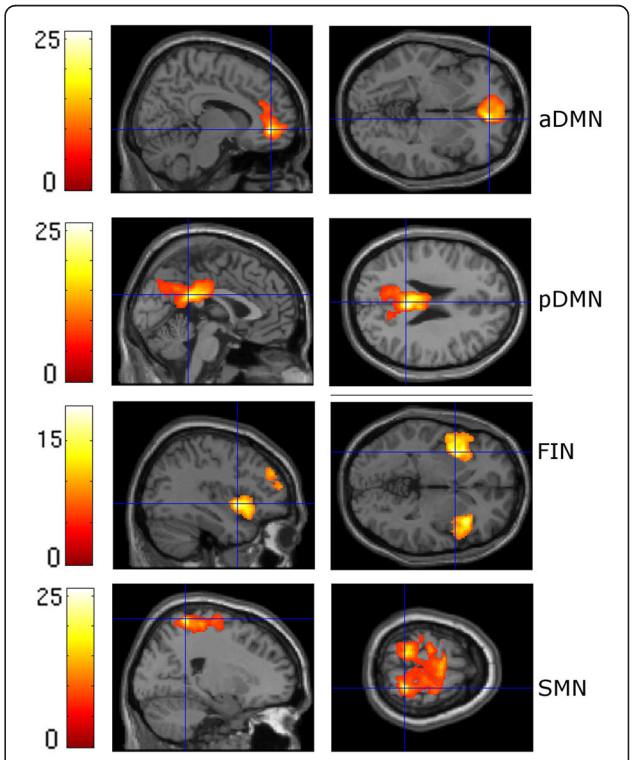

Figure 2 ICNs of the patient group. For illustration purposes, spatial maps were thresholded at P = 0.05, corrected for family wise error (FWE) with a cluster extent threshold of 50 voxels; aDMN = anterior default mode network, pDMN = posterior default mode network, FIN = fronto-insular network, SMN = sensorimotor network.

Table 2 Comparison of power spectra for all ICNs between patients and healthy controls

ICN	Group	Spectral power at different frequency-bins in percent of the whole power					
		0.0 – 0.04 Hz	0.04 – 0.08 Hz	0.08 – 0.12 Hz	0.12 – 0.16 Hz	0.16 – 0.20 Hz	0.20 – 0.24 Hz
aDMN	Controls	31.732	20.831	12.677	15.703	12.415	**9.881**
	Patients	29.507	19.989	12.833	12.960	11.932	**15.351**
	p-value (t-test)	0.338	0.510	0.856	0.015	0.693	**0.001**
pDMN	Controls	29.651	22.137	13.550	16.374	12.520	9.312
	Patients	29.637	21.374	14.290	14.306	11.008	12.377
	p-value (t-test)	0.993	0.580	0.373	0.118	0.175	0.019
FIN	Controls	33.751	22.393	12.880	14.318	10.797	**9.067**
	Patients	31.438	22.477	13.702	12.661	9.854	**12.728**
	p-value (t-test)	0.262	0.933	0.260	0.179	0.378	**0.005**
SMN	Controls	36.671	19.570	14.069	13.729	10.771	7.827
	Patients	31.919	21.600	14.297	14.030	9.650	11.512
	p-value (t-test)	0.117	0.153	0.852	0.839	0.343	0.016

Two-tailed t-test, $p < 0.05/6$, significant differences are included in bold.

pain, we used a different binning strategy for spectral analyses. Malinen et al. [15] calculated spectral power at three frequency bins (0–0.05 Hz; 0.05 - 0.12 Hz; 0.12 - 0.25 Hz), whereas Cauda et al. [16] defined four intervals of interest (0.008 - 0.02 Hz; 0.02 - 0.05 Hz; 0.05 - 0.1 Hz; 0.1 - 0.25 Hz). In our study, six equally spaced frequency bins were used (0–0.04 Hz; 0.04 - 0.08 Hz; 0.08 - 0.12 Hz; 0.12 - 0.16 Hz; 0.16 - 0.20 Hz; 0.20 - 0.24 Hz). The main advantage of using 6 bins compared to a greater number of bins is that it reduces the number of multiple comparisons (level of significance $p < 0.0083 \cong 0.05/6$; Bonferroni-correction for 6 frequency bins). A lower number of bins, however, might have led to false-negative results because the spectral changes are rapid, increasing as a function of frequency. Furthermore, whereas Malinen et al. [15] used a relatively broad interval for the higher frequencies (0.12 – 0.25 Hz), we were able to show that the upper end of the high-frequency interval (between 0.20 and 0.24 Hz), in particular, might be relevant in chronic pain disorder.

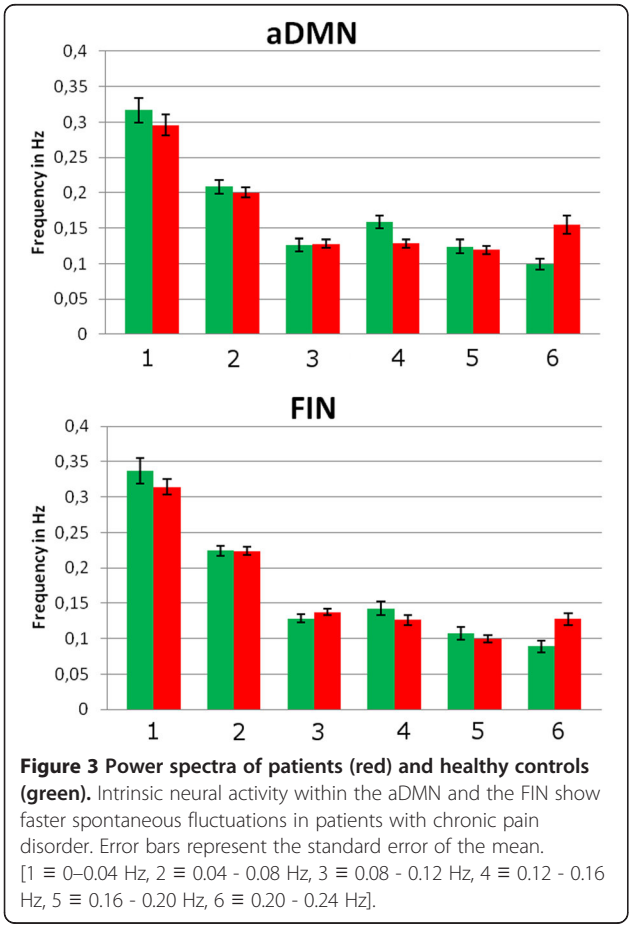

Figure 3 Power spectra of patients (red) and healthy controls (green). Intrinsic neural activity within the aDMN and the FIN show faster spontaneous fluctuations in patients with chronic pain disorder. Error bars represent the standard error of the mean. [1 ≡ 0–0.04 Hz, 2 ≡ 0.04 - 0.08 Hz, 3 ≡ 0.08 - 0.12 Hz, 4 ≡ 0.12 - 0.16 Hz, 5 ≡ 0.16 - 0.20 Hz, 6 ≡ 0.20 - 0.24 Hz].

There was no significant correlation between shifts in frequency of the BOLD-signal and the psychometric level of anxiety [51], depression [20,52,53] or pain intensity in the patient group of our study. Nevertheless, we cannot definitely exclude the possibility that changes were not due to persistent somatoform pain but were due to other unknown variables. Furthermore, there was no significant correlation between spectral power and anxiety [51] or depression [20,52,53] Importantly, a similar discrepancy between BOLD activations and behavioral measurements was also described in a study investigating an altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder [6]. Thus, differences between our two groups may be more easily detected via neuroimaging methods than through subjective behavioral ratings, in accord with several other studies [54-57].

Although our study does not demonstrate causal relationships, several findings suggest a strong relationship between pain-condition and altered spectral power.

Somatoform pain is associated with higher autonomic arousal [58,59], which, in turn, has been associated with increased activation in the fronto-insular regions [16,60]. Although autonomic activation was not measured directly in our study, an altered psycho-vegetative state [57] might be the behavioral equivalent of increased FIN oscillations in chronic pain disorder, as proposed by Malinen et al. [15]. Remarkably, the FIN and DMN networks seem to be involved in affective neuroprocessing: Whereas the DMN subserves introspection, autobiographic memory, self-referential processing, and social understanding [61-64], the FIN has been linked with personal salience, emotional awareness, and bodily state monitoring [5,47,65]. Moreover, the various bodily complaints in patients with somatoform pain have consistently been associated with a high affective component of individual pain, which indicates impaired emotional regulation [66-69]. Given these data, one might synoptically speculate that our findings reflect one neurobiological facet of the strong clinical impression that patients who suffer from chronic pain disorder often show impaired subjective emotional awareness, affective meaning construction [4] and social understanding [3].

No significant group differences were detected in the SMN, although previous studies have shown that chronic pain leads to functional reorganization, decreased gray matter density, and increased metabolism within the somatosensory cortex [70-74]. One might speculate that chronic pain disorder relies more on disturbed affective and introspective processing than on the disturbed somatosensory circuits that occur in patients who suffer from pain dependent on nociceptive input, for example, in a patient with posttraumatic osteoarthritis in the sample in Malinen et al. [15].

We did not find changes in spatial functional connectivity, in contrast to Malinen et al. [15], who reported weaker functional connectivity between the insula and anterior cingulate cortex in predominantly nociceptive chronic pain, and Baliki et al. [11], who found diminished DMN-connectivity in chronic back pain patients. In contrast to pain caused by diverse peripheral causes, we presume that chronic somatoform pain, which at least cannot be fully explained by possible nociceptive input, is not associated with alterations in the spatial and functional architecture of the brain's resting state.

Altogether, chronic pain disorder seems to be associated with a frequency shift in the anterior default mode network and the salience network to higher (eigen)frequencies. The resting state of the human brain is thought to serve as a ´memory of the future´ [63,75], which stores behavioral algorithms to allow a person to adequately cope with upcoming environmental events. Therefore, our research on resting state connectivity as a special form of neuronal oscillations in cortical networks [76] might provide a useful neurobiological framework that underlies one facet of the behavioral changes that impair the daily lives of patients with chronic pain disorder.

Conclusions

Though our study does not ascribe causation, our results indicate that patients suffering from chronic pain disorder show distinct alterations in the temporal organization of their brains. A persistent peripheral algetic input does not seem to be pivotal for changes in the functional architecture of the human brain associated with persistent somatoform pain in patients with chronic pain disorder.

Limitations

The present study is limited because of the lack of measurements of possible sources of physiological artifacts (e.g., respiration, cardiac function and blood pressure). However, high agreement with previous findings of alterations in temporal activity in the FIN and the DMN suggests that our results were most likely not confounded by these factors [15,16]. The analgesic and antidepressant medication administered to most of our outpatients (Additional file 1: Table S6) could have influenced the reported frequency shift [77,78]; the enduring influence of such drugs on BOLD oscillations is currently still unknown. It is noteworthy that, despite ethical reasons, it was nearly impossible to convince our patients with chronic pain disorder to interrupt their psychotropic medication in this intentionally naturalistic study.

Additional files

Additional file 1: Table S6. Medication of all 21 patients with chronic pain disorder.

Additional file 2: Table S1. MNI-coordinates of the ICNs in the control group. Results were thresholded at p = 0.05 and corrected for family wise error (FWE) on the voxel level with a cluster extent threshold of k = 50 voxels.

Additional file 3: Table S2. MNI-coordinates of the ICNs in the patient group. Results were thresholded at p = 0.05 and corrected for family wise error (FWE) on the voxel level with a cluster extent threshold of k= 50 voxels.

Additional file 4: Table S3. MNI-coordinates of the group comparisons. Results were thresholded at p = 0.005, uncorrected at the voxel-level, and p < 0.05, corrected for multiple comparisons on the cluster level, with a cluster extent threshold of k = 50 voxels; p represents p on the voxel-level.

Additional file 5: Table S4. Correlation between functional connectivity and psychometric measurement. Results were thresholded at p < 0.005, uncorrected on the voxel-level, and p < 0.05, corrected on the cluster level, with a cluster extent threshold of k > 10 voxels; p represents p on the cluster level; R represents Pearson's correlation-coefficient. No significant correlation was detected.

Additional file 6: Table S5. Pearson's correlation between spectral power and psychometric measurements *The correlation with depression (BDI-I) is controlled for anxiety (STAI-T) and vice versa; the level of significance is p < 0.05; R represents the correlation-coefficient. No significant correlation was detected.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MN-H designed and conducted the research, analyzed the data, and contributed to the writing of the paper. AO conducted the research, analyzed the data, and contributed to the writing of the paper. AMW designed and performed the research. CZ and HG designed the research. All authors discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Table S6 Medication of all 21 patients with chronic pain disorder

Patient	*Drug(s)*
p01	Oxycodone, Citalopram, Valsartan/Hydrochlorothiazide
p02	Amitriptyline, Paroxetine
p03	Ibuprofen, Hypericin
p04	Oxycodone/Naloxone, Pregabalin, Amitriptyline, Tramadol, Tetrazepam, Omeprazole, Lynestrenol
p05	
p06	
p07	Oxcarbazepine
p08	Hypericin; Cimicifuga racemosa
p09	Tramadol, Amitriptyline
p10	
p11	Pregabalin, Citalopram, L-Thyroxine
p12	
p13	Metformin, Simvastatin, Pioglitazone
p14	Diclofenac, Mirtazapine
p15	
p16	Irbesartan
p17	Tilidine/Naloxone, Pregabalin, Doxepin, Esomeprazole
p18	Oxazepam
p19	Pregabalin, Hypericin
p20	Amitriptyline, Atenolol, Chlorthalidone
p21	Amitriptylin, Novaminsulfone, Hydromorphone, L-Thyroxine, Lercanidipine, Atenolol, Rampril/Hydrochlorothiazide, Acetylsalicylic acid, Allopurinol, Simvastatin

Table S1 MNI-coordinates of the ICNs in the control group Results were thresholded at p = 0.05 and corrected for family wise error (FWE) on the voxel level with a cluster extent threshold of k = 50 voxels.

Network	Region	MNI	k	T	p
aDMN	R gyrus frontalis medius, pars orbitalis	2 50 -6	2650	26,12	0.000.
pDMN	L middle cingulate cortex	-6 -34 34	2805	17.64	0.000.
FIN	L insula	-38 20 -4	1455	20.06	0.000.
	R insula	38 22 -16	1112	18,73	0.000.
	L supplementary motor area	0 10 64	878	15.14	0.000.
	L gyrus frontalis medius	-40 46 20	339	12.94	0.000.
	L middle cingulate gyrus	0 -16 42	62	9.94	0.000.
	R supramarginal gyrus	56 -42 30	52	9,38	0.000.
SMN	L postcentral gyrus	-20 -32 70	6896	23.17	0.000.
	R precentral	52 -12 48	55	8.86	0.000.

Table S2 MNI-coordinates of the ICNs in the patient group Results were thresholded at p = 0.05 and corrected for family wise error (FWE) on the voxel level with a cluster extent threshold of k= 50 voxels.

Network	Region	MNI	k	T	p
aDMN	R gyrus frontalis medius, pars orbitalis	10 46 -4	3425	26.55	0.000
	L precuneus	-6 -56 22	277	10.29	0.000
pDMN	R posterior cingulate cortex	4 -42 24	3692	26.71	0.000
FIN	L insula	-36 8 -2	1966	19.11	0.000
	L supplementary motor area	0 8 44	1730	17.27	0.000
	R insula	38 20 0	1064	16.64	0.000
	L gyrus frontalis medius	-34 44 30	435	11.54	0.000
	L supramarginal gyrus	-62 -44 28	125	10.59	0.000
	R gyrus frontalis medius	36 48 30	123	8.76	0.000
SMN	R gyrus parietalis superior	22 -48 70	7101	26.42	0.000

Table S3 MNI-coordinates of the group comparisons Results were thresholded at p = 0.005, uncorrected at the voxel-level, and p < 0.05, corrected for multiple comparisons on the cluster level, with a cluster extent threshold of k = 50 voxels; p represents p on the voxel-level.

Network	Region	MNI	k	T	p
aDMN: controls > patients	L gyrus frontalis superior	-24 38 36	24	3.40	0.538
aDMN: patients > controls	-	-	-	-	-
pDMN: controls > patients	-	-	-	-	-
pDMN: patients > controls	L cuneus	-10 -76 38	10	2.95	0.734
SMN: controls > patients	R gyrus praecentralis	52 -14 46	212	4.11	0.103
	L paracentral lobule	-14 -32 54	73	3.81	0.285
	R gyrus postcentralis	18 -38 60	44	3.74	0.527
	L supplemental motor area	-10 2 70	10	3.21	0.928
SMN: patients > controls	-	-	-	-	-
FIN: controls > patients	R gyrus frontalis inferior, pars opercularis	58 16 20	13	4.03	0.900
FIN: patients > controls	L gyrus frontalis inferior, pars opercularis	-44 10 10	69	3.82	0.308
	L middle cingulated cortex	-6 -22 42	11	3.47	0.921

Table S4 Correlation between functional connectivity and psychometric measurement Results were thresholded at p < 0.005, uncorrected on the voxel-level, and p < 0.05, corrected on the cluster level, with a cluster extent threshold of k > 10 voxels; p represents p on the cluster level; R represents Pearson's correlation-coefficient. No significant correlation was detected.

BDI positive						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	L gyrus frontalis, pars orbitalis	-2 58 -6	15	3.26	0,396	0.5993
	L anterior cingulate cortex	-2 40 4	10	3.18	0.585	0.5894
pDMN	-	-	-	-	-	-
SMN	R gyrus praecentralis	24 -26 70	31	4.31	0.400	0.5737
	R middle cingulate cortex	2 -16 50	50	3.82	0.6384	0.412
	L gyrus postcentralis	-22 -30 60	22	3.40	0.526	0.5035
	L paracentrale lobule	-6 -34 72	12	3.16	0.704	0.4809
FIN	L gyrus frontalis medius	-26 48 26	21	3.79	0.455	0.5364
	R gyrus frontalis medius	30 48 26	10	3.58	0.665	0.5151
BDI negative						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	L gyrus frontalis medialis	0 54 16	93	3.86	0.32	-0.7432
pDMN	-	-	-	-	-	-
SMN	-	-	-	-	-	-
FIN	-	-	-	-	-	-
STAI-T positive						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	-	-	-	-	-	-
pDMN	-	-	-	-	-	-
SMN	L precuneus	-14 -42 70	12	3.56	0.704	0.390
FIN	-	-	-	-	-	-
STAI-T negative						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	-	-	-	-	-	-
pDMN	-	-	-	-	-	-
SMN	-	-	-	-	-	-
FIN	L gyrus frontalis medialis	-6 16 42	22	3.85	0.439	-0.5413
	L insula	-36 8 -6	22	3.70	0.439	-0.5357
	L middle cingulate cortex	0 8 40	13	3.45	0.600	-0.5083
BPI – item5 positive						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	-	-	-	-	-	-
pDMN	-	-	-	-	-	-
SMN	-	-	-	-	-	-
CIN	L gyrus frontalis medius	-34 44 22	41	3.95	0.221	0.6916
BPI – item5 negative						
Network	**Region**	**MNI**	**k**	**T**	**p**	**R**
aDMN	R gyrus rectus	4 52 -16	26	3.84	0.256	-0.6812
pDMN	L precuneus	-6 -64 36	16	3.59	0.376	-0.6567
SMN	-	-	-	-	-	-
CIN	-	-	-	-	-	-

Table S5 Pearson's correlation between spectral power and psychometric measurements *The correlation with depression (BDI-I) is controlled for anxiety (STAI-T) and vice versa; the level of significance is $p < 0.05$; R represents the correlation-coefficient. No significant correlation was detected.

ICN	Psychometrics		Spectral power at different frequency-bins in percent of the whole power					
			0.0 – 0.04 Hz	0.04 – 0.08 Hz	0.08 – 0.12 Hz	0.12 – 0.16 Hz	0.16 – 0.20 Hz	0.20 – 0.24 Hz
aDMN	BPI	R	0.077	-0.300	-0.400	-0.056	0.315	0.116
		p	0.755	0.212	0.090	0.820	0.188	0.636
	BDI-I*	R	0.188	0.040	-0.232	-0.268	-0.436	0.186
		p	0.427	0.866	0.325	0.252	0.055	0.433
	STAI-T*	R	0.168	0.000	0.224	0.016	0.136	-0.342
		p	0.479	0.998	0.342	0.945	0.569	0.140
pDMN	BPI	R	-0.445	-0.150	0.284	0.415	0.381	-0.044
		p	0.056	0.540	0.238	0.077	0.108	0.859
	BDI-I*	R	-0.041	0.269	-0.201	-0.140	-0.167	0.106
		p	0.865	0.252	0.397	0.555	0.481	0.655
	STAI-T*	R	0.105	-0.258	-0.004	-0.90	0.087	0.090
		p	0.661	0.272	0.987	0.706	0.717	0.706
FIN	BPI	R	-0.105	-0.090	-0.293	0.188	0.227	0.103
		p	0.669	0.714	0.224	0.441	0.350	0.674
	BDI-I*	R	0.424	-0.426	-0.137	-0.157	-0.379	0.145
		p	0.063	0.061	0.564	0.508	0.099	0.542
	STAI-T*	R	-0.020	0.208	0.078	0.014	0.338	0.325
		p	0.932	0.379	0.745	0.954	0.145	0.162
SMN	BPI	R	-0.301	0.272	0.267	0.445	0.044	-0.197
		p	0.210	0.261	0.269	0.056	0.858	0.419
	BDI-I*	R	0.366	0.297	-0.437	-0.290	-0.378	-0.136
		p	0.112	0.203	0.054	0.215	0.100	0.567
	STAI-T*	R	0.031	0.007	0.076	0.002	0.075	-0.134
		p	0.898	0.976	0.749	0.992	0.753	0.572

Study III

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Functional network connectivity of pain-related resting state networks in somatoform pain disorder: an exploratory fMRI study

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Research Paper

Functional network connectivity of pain-related resting state networks in somatoform pain disorder: an exploratory fMRI study

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Background: Without stimulation, the human brain spontaneously produces highly organized, low-frequency fluctuations of neural activity in intrinsic connectivity networks (ICNs). Furthermore, without adequate explanatory nociceptive input, patients with somatoform pain disorder experience pain symptoms, thus implicating a central dysregulation of pain homeostasis. The present study aimed to test whether interactions among pain-related ICNs, such as the default mode network (DMN), cingular–insular network (CIN) and sensorimotor network (SMN), are altered in somatoform pain during resting conditions. **Methods:** Patients with somatoform pain disorder and healthy controls underwent resting functional magnetic resonance imaging that lasted 370 seconds. Using a data-driven approach, the ICNs were isolated, and the functional network connectivity (FNC) was computed. **Results:** Twenty-one patients and 19 controls enrolled in the study. Significant FNC ($p < 0.05$, corrected for false discovery rate) was detected between the CIN and SMN/anterior DMN, the anterior DMN and posterior DMN/SMN, and the posterior DMN and SMN. Interestingly, no group differences in FNC were detected. **Limitations:** The most important limitation of this study was the relatively short resting state paradigm. **Conclusion:** To our knowledge, our results demonstrated for the first time the resting FNC among pain-related ICNs. However, our results suggest that FNC signatures alone are not able to characterize the putative central dysfunction underpinning somatoform pain disorder.

Introduction

Somatoform pain disorder is a mental disorder characterized by chronic bodily complaints without sufficient explanatory peripheral pathology.[1] Although the causes and mechanisms behind this mental disorder remain unclear, both functional and structural alterations in the limbic structures seem to correlate with this non-nociceptive chronic pain condition.[2–4] Moreover, human brain imaging studies have revealed new roles that cortical neuronal networks play in chronic pain,[5] including the unpleasant quality of pain.[6] The current study expanded upon a new approach for testing one important facet of the network model to examine the intrinsic functional connectivity between networks active during resting state: the functional network connectivity (FNC).[7]

The human brain's resting state is characterized by low-frequency fluctuations of spontaneous neural activity.[8] Without stimulation, this activity is highly organized in several intrinsic connectivity networks (ICNs).[9] Some of the ICNs appear to be pain-related, such as the default mode network (DMN), which comprises cortical midline structures and lateral parietal regions,[10–12] the cingular-insular network (CIN), and the sensorimotor network (SMN).[8,13–19] There is interplay among the regions within an ICN and among the ICNs themselves. As shown recently in individuals with schizophrenia, differences in internetwork communication regarding FNC could be a valid measure that reflects the deficiencies in cortical processing in patients with chronic psychiatric symptoms.[20] Therefore, we aimed to test the practical relevance of FNC for chronic, medically unexplained pain. Specifically, given a central

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disconnection of pain-related neural systems, we hypothesized that alterations exist in the FNC between the DMN, CIN and SMN in patients with somatoform pain disorder.

Methods

This study was approved by the local ethics committee (*Ethikkommission der Fakultaet fuer Medizin der Technischen Universitaet Muenchen*) and conducted in accordance with the Declaration of Helsinki. We obtained written informed consent from all participants. Healthy controls were recruited from the general community. All patients had pain-predominant multisomatoform disorder[12,21] and were recruited from outpatient departments of neurology, internal medicine and pain treatment centres. Pain-predominant multisomatoform disorder, a medium–severe somatoform disorder, was primarily diagnosed by an experienced physician (M.N.-H.), who performed a modified Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), verifying the official criteria for somatoform and chronic pain disorder. We modified the interview to check for the presence of multisomatoform disorder according to the published criteria.[22] The main feature of somatoform disorders is the repeated presentation of physical symptoms with persistent requests for medical examinations, despite repeated negative findings and reassurances by doctors that the symptoms have no physical basis. If any physical disorders are present, the disorders do not explain the nature and extent of the symptoms or the distress and preoccupation of the patient.[23] Multisomatoform disorder is defined as "3 or more medically unexplained, currently bothersome physical symptoms plus a long (≥ 2 years) history of somatization."[22] It has been shown that, compared with mood and anxiety disorders, multisomatoform disorder is associated with comparable impairments in health-related quality of life, more self-reported disability days and clinic visits, and the highest level of provider frustration.[22,24]

In this context, as a precondition, the physical component summary (PCS) measure[25] in our patient group was required to be 1 standard deviation [SD] or more below the population norm (i.e., ≤ 40, as measured by the SF-36), thus meeting the DSM-IV criterion B for significant distress or psychosocial impairment due to the somatoform pain in patients with pain disorder.[1] The second precondition was that the score on the 15-item Patient Health Questionnaire (PHQ-15) had to be greater than 10, which represents medium somatic symptom severity. We used the German version of the Brief Pain Inventory[26] to estimate the intensity of the participant's pain. We excluded patients with insufficient cognitive abilities, severe chronic somatic diseases, unambiguous nociceptive pain (postsurgical or phantom limb pain), hypochondria, posttraumatic stress disorder (PTSD), a severe comorbid mental disorder that caused major social functioning impairment (e.g., schizophrenia or severe substance abuse), or insufficient German language skills. We assessed handedness using the Edinburgh Handedness Inventory.[27]

Psychometric measurement

The occurrence of somatoform disorder was assessed according to a modified structured psychiatric interview based on the German version of the SCID-I.[28] The SCID-I evaluates the present (i.e., the 4 weeks preceding the interview) and lifetime psychiatric status for major Axis I psychiatric disorders using criteria that correspond with the DSM-IV.[1]

The SF-36 is a multipurpose, short-form health survey comprising 36 questions.[29] It yields an 8-scale profile of functional health and well-being scores, psychometrically based physical and mental health summary measures, and a preference-based health utility index. This questionnaire is a generic measure instead of one that targets a specific age, disease or treatment group. Accordingly, the SF-36 has been proven useful in surveys of general and specific population groups because it compares the relative burden of disease and differentiates the health benefits of a wide range of treatments.[30] Its German translation has been validated in a variety of German health care settings.[31,32] The PCS subscore of the SF-36 has been shown to be a valid and change-sensitive indicator of bodily function and quality of life;[33] moreover, it addresses the major concerns of our patients more directly than the mental component summary.[34]

The PHQ-15[35,36] is a brief, self-administered questionnaire that is useful in screening for somatization and monitoring the severity of somatic symptoms in clinical practice and research. Scores of 5, 10 and 15 represent the cutoff values for low, medium and high somatic symptom severity, respectively.

The Brief Pain Inventory (BPI)[37] was developed by the Pain Research Group of the World Health Organization Collaborating Centre for Symptom Evaluation in Cancer Care to provide information on the intensity of pain (the sensory dimension) and degree to which pain interferes with function (the reactive dimension). The validity of the BPI has been demonstrated in both the German version[26] and for measuring pain in patients without cancer.[38] The BPI item scores for each patient are provided in Appendix, Table S1, available at cma.ca/jpn.

The Beck Depression Inventory (BDI-I)[39,40] is a 21-item self-report instrument that measures cognitive and endogenous aspects of depression on a 4-point scale ranging from 0 to 3. The standard cutoffs are as follows: a total score of 0–9 indicates no depression, 10–18 indicates mild depression, 19–29 indicates moderate depression and a score of 30 or greater indicates severe depression. This questionnaire has undergone extensive reliability and validation studies.

According to the homepage of the publishing house Pearson Assessments,[41] "the Symptom Checklist-90-R (SCL-90-R) instrument helps evaluate a broad range of psychological problems and symptoms of psychopathology. The instrument is also useful in measuring patient progress or treatment outcomes." The 90 items of the German version of this checklist are scaled from 0 to 4 and are associated with problems that the patient has been experiencing during the last 7 days.[42] The summarizing global severity index is a de facto standard for psychotherapy clinical practice and research, and it serves as a "symptom severity thermometer." The 9 specific subscales of the SCL-90 (e.g., SOM: somatization) provide an overview of the spectrum of patient complaints.[43]

Functional MRI resting state paradigm

Participants were asked to stay awake but close their eyes and relax for 370 seconds. After the scanning session, participants were asked whether they had fallen asleep during the scan. Patients who responded positively or ambiguously were excluded from the study.

Data acquisition and fMRI procedures

Images were acquired using a 3 T Philips Achieva scanner with a standard 8-channel SENSE head coil. Thirty-two contiguous slices (no gap) were acquired with a steep angulation, such that the eyes were excluded, using a gradient echo-planar sequence with the following parameters: repetition time (TR) 2000 ms, echo time (TE) 35 ms, 82° flip angle, field of view (FOV) 220 mm, slice thickness 4 mm, 80 × 80 matrix, 2.75 × 2.75 mm voxel size, and SENSE factor 2. Anatomic images were obtained using a T_1-weighted turbo gradient echo sequence with the following parameters: TR 9 ms, TE 4 ms, 8° flip angle, FOV 240 mm, 240 × 240 matrix, 1 mm isotropic voxel size, 170 slices and no gap.

Image processing and data analysis: preprocessing

The data analysis was performed using the SPM5 (Statistical Parametric Mapping software, Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk). We discarded the first 3 images of each run to allow for equilibration of the longitudinal magnetization. The preprocessing steps included

1. the realignment and unwarping of the images to correct for movement artifacts and related susceptibility artifacts,
2. a coregistration of the anatomic to the functional images,
3. the segmentation and normalization of the anatomic image to the standard stereotactic space (Montreal Neurological Institute [MNI]),[4]
4. the application of a normalization transformation to the functional images, and
5. the smoothing with a 8 mm Gaussian kernel for the group analysis.

Connectivity analysis

We performed an independent component analysis (ICA) on all participants (patients and controls) using the group ICA from the fMRI toolbox (GIFT version 1.3h; http://icatb.sourceforge.net) developed for fMRI data analysis.[44] Following the method of Jafri and colleagues,[20] we additionally performed 2 separate group ICAs on patients and controls "to ensure that the resulting components had similar resting state fluctuations in the 2 groups, as in the resulting components attained from all [...] participants combined."[20] For group comparisons, however, a separate group ICA may not be optimal because it biases toward false-positive results of group differences.[45] Therefore, we reported and used the data of the combined ICA for group comparisons.

First, the individual data sets were concatenated across time. This was followed by computing the subject-specific components and time courses. The toolbox performed the analysis in 3 stages: data reduction, application of the ICA algorithm and back reconstruction for each participant.[44] In the initial step, the data from each participant underwent principal component analysis to reduce the computational complexity. Thus, most of the informational data content was preserved. After concatenating the resulting volumes, 29 independent sources were estimated using the GIFT dimensionality estimation tool based on the aggregated data. The final reduction was again achieved using principal component analysis according to the selected number of components. In the second stage of the analysis, we used the Infomax algorithm to run the ICA and a mask based on all participants. In the final stage of back reconstruction, the time courses and spatial maps were computed for each participant. The resulting mean spatial maps for each participant were transformed to z scores for display.[44]

Individual participant maps of the ICNs were entered into 1-sample t tests for 1-group analyses and 2-sample t tests for group comparison in SPM5. Results were thresholded at $p = 0.05$ and corrected for family-wise error with a cluster extent threshold of 50 voxels.

Functional network connectivity

The functional networks isolated by ICA are both spatially and temporally independent.[44] However, temporal correlations can exist between the networks. To measure this functional network connectivity (FNC), we computed a constrained maximal lagged correlation using the FNC toolbox (http://mialab.mrn.org/software/#fnc).[20] Next, the maximal lagged correlation was assessed between all pair-wise combinations of the 4 ICNs selected for the analysis, which led to 6 possible combinations.

We calculated the correlation between the 2 time courses using the following formula, where ρ is the correlation between 2 time courses, X is time course 1 (dimension T × 1 unit), Y is time course 2 (dimension T × 1 unit), T is the number of time points in the time course, i_o is the starting reference of the 2 original time courses, Δi is the noninteger change in time in seconds, X_{io} is X at the initial reference point i_o, $Y_{io+\Delta i}$ is Y shifted from the reference point i_o, $\rho_{\Delta i}$ is the maximal lagged correlation and Δi is the lag between the time courses in seconds:[20]

$$\rho_{i0+\Delta i} = \frac{(X_{i0}^{T})(Y_{i0+\Delta i})}{\sqrt{(Y_{i0+\Delta i}^{T}Y_{i0+\Delta i})}\sqrt{(X_{i0}^{T}X_{i0})}}$$

The correlation and lag values were computed for all participants and then averaged for the controls and patients. The correlation value reflects the dependency between 2 resting state networks. Significant correlation combinations from the 6 possible combinations were separately extracted for both groups, which led to FNC maps for each group (t test, $p < 0.05$). In addition, corresponding to the significant correlation combinations, the averaged lag values, which represent

the amount of delay between 2 correlated component time courses, were calculated for each group.[20]

Group difference

Significant differences in the FNC between patients and controls were calculated using a 2-sample t test ($p < 0.05$, corrected for false discovery rate).[46] The lag values were compared between both groups (2-sample t test, $p < 0.05$, corrected for false discovery rate).

Correlation analysis

The FNC was correlated with the BDI and BPI scores ($p < 0.05$, corrected for multiple comparisons).

Results

In all, 19 healthy controls (mean age 48.79 [SD 12.25] yr; 12 women) and 21 outpatients (mean age 46.62 [SD 12.49] yr; 17 women) were involved in this study. All participants were native speakers of German and were of Caucasian origin. All participants were right-handed. Participant demographic and clinical characteristics are summarized in Table 1.

Before the fMRI scan, the mean value of pain intensity among participants with somatoform pain disorder (item 5) using the BPI was 7 of 10 (SD 2.24). All of the patients with chronic pain but none of the controls experienced persistent somatoform pain throughout the scan (Table 1 and Appendix 1, Table S1).

In accordance with published results, we identified the following pain-related networks by visual inspection (Fig. 1 and Table 2):

- the anterior default mode network (aDMN), which consists of the cortical midline structures, such as the medial prefrontal cortex and precuneus;[15–17,47]
- the posterior default mode network (pDMN), which consists of the lateral parietal regions and precuneus;[15–17,47]
- the CIN, which consists of both the insular and cingular cortex;[13,19] and
- the SMN, which consists of the pre- and postcentral gyrus.[14]

The FNCs of the patients with chronic pain and the control group are shown in Figure 2. Both groups showed a significant FNC between the CIN and SMN, the aDMN and pDMN/SMN, and the pDMN and SMN. No significant differences in FNCs were found between groups (Fig. 3). No significant correlation was found between the FNC and BDI or BPI scores ($p < 0.05$, corrected for multiple comparisons).

Table 1: Demographic and clinical characteristics of healthy controls and patients with somatoform pain

	Group; mean (SD) [range]*	
Characteristic	Controls	Patients
Age, yr	48.79 (12.25) [24–64]	46.62 (12.49) [22–68]
Sex, no. male:female	7:12	4:17
Medication, no.		
Antidepressants	—	10
Analgesics/relaxants/NSAIDs	—	10
Anxiolytics	—	1
BDI score	4.43 (4.70)† [0–16]	17.84 (9.03)† [3–37]
BPI item (scale)		
1: Pain within the last week (yes/no)	19 no†	21 yes†
2: Pain today (yes/no)	19 no†	21 yes†
3: Pain at its worst during the last week (0–10)	—	7 (2.25)†
4: Pain at its least during the last week (0–10)	—	4.21 (2.5)†
5: Pain on the average (0–10)	—	5.63 (2.1)†
6: Pain right now (0–10)	—	5.53 (2.9)†
8: Pain relief by therapy (0–10)	—	5.50 (2.8)†
9: Impairment (0–10)	—	
9A: General activity	—	5.74 (2.6)†
9B: Mood	—	4.84 (2.9)†
9C: Walking ability	—	4.32 (3.1)†
9D: Normal work	—	5.37 (2.5)†
9E: Relation with other people	—	4 (2.6)†
9F: Sleep	—	4.89 (3.0)†
9G: Enjoyment of life	—	4.86 (2.8)†
SCL-90-R		
Global severity index	0.28 (0.28)†	0.96 (0.56)†
Somatization	0.34 (0.31)†	1.4 (0.64)†

BDI = Beck Depression Inventory;[39] BPI = Brief Pain Inventory;[26] NSAID = nonsteroidal anti-inflammatory drug; SCL-90-R = Symptom Checklist 90 R;[42] SD = standard deviation.
*Unless otherwise indicated.
†Significant group differences, $p < 0.05$.

Discussion

The present study shows how pain-related ICNs are interconnected during the resting state using a reasonably sized group of clinically well-classified participants. Using a data-driven approach, we isolated the CIN, SMN and DMN. According to previous studies, an anterior and posterior subsystem of the DMN could be identified.[47,48] The aDMN is associated with cognitive control of emotions and self-referential processing, whereas the pDMN is related to mnestic functions.[49–53] The CIN subserves affective reactions, and the SMN underpins sensory-discriminative processing.[18,19] The SMN strongly interacts with the CIN, aDMN and pDMN. These interactions suggest that sensory-discriminative processing is highly related to affective processing, self-referential thoughts and memory functions. Furthermore, the SMN lags the time course of the other ICNs by seconds. Emotional and cognitive processing appear to precede the activity of the sensorimotor system during the resting state. This may explain the influence of the inner world, with its various subjective states, such as anxiety, sadness and individual predictions about the future on the perception of the outer world via sensory systems.[54–56] Because our analysis does not provide insight into causality, our results encourage further research on the putative effects of DMN and CIN activity on the SMN.

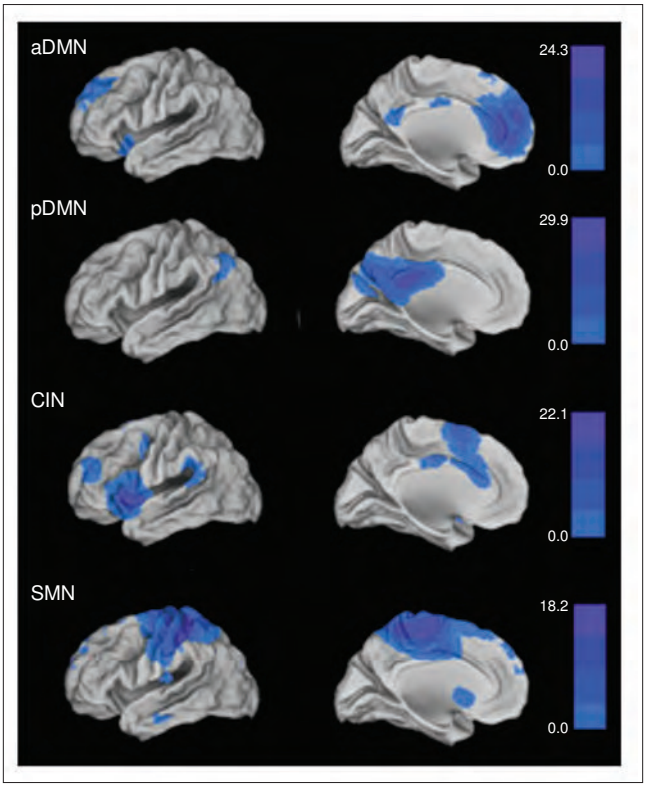

Fig. 1: Intrinsic connectivity networks (ICNs) of the entire participant group (19 healthy controls and 21 patients with somatoform pain): anterior default mode network (aDMN), posterior default mode network (pDMN), cingular-insular network (CIN) and sensorimotor network (SMN). For illustration purposes, the spatial maps of the patients and controls were concatenated into SPM5 and thresholded at $p < 0.05$, corrected for family-wise error; the colour bars represent t values.

Contrary to our hypothesis, the present study shows that somatoform pain does not lead to significantly disturbed FNC among pain-associated networks during the resting state. This finding is remarkable because chronic pain has been shown to be a strong disruptor of intranetwork functional connectivity within the somatosensory, affective and cognitive neural systems.[13–15,17] Notably, our patients subjectively experienced severe ongoing pain, as their pain intensity rating using the BPI was 7 of 10. In comparison, in cancer-induced bone pain, for example, which is the most common cause of pain in cancer patients, the median average pain rating based on the BPI has been reported to be 4 of 10.[57] One may speculate several explanations for this finding. Evidence for an important role of resting FNC in central nervous system disorders stems from research on schizophrenia, which is widely known to be characterized by bizarre inner processes, such as hallucinations, delusions and disorganized thoughts.[20] One important characteristic of schizophrenia is the patient's disability to distinguish between inner experiences caused by psychotic states and outer reality. Somatoform pain, however, is not associated with a disturbed sense of reality or personality. Thus, disturbed FNC may reflect highly disorganized states of consciousness rather than symptoms, such as ongoing non-nociceptive pain.

Furthermore, as external triggers, such as aversive emotional experiences, are considered to be relevant in the etiology of somatoform pain disorder, one may speculate that significant differences in FNC are not elicited during rest but in response to stimulation. For example, noxious heat led to higher blood oxygen–level dependent signalling in the insula and parahippocampal gyrus, while medial prefrontal cortex activity was reduced.[58] Reduced insula and amygdala activity was observed during emotional empathy, indicating disturbed emotional processing.[59]

However, fibromyalgia, which most closely resembles somatoform pain disorders in many aspects, displays a characteristic connectivity pattern during rest, as recently shown by Cifre and colleagues.[60] They found that functional connectivity of the anterior cingulate, insula and somatosensory regions with amygdala and basal ganglia was enhanced, whereas the interplay between somatosensory and default mode regions was reduced. In our study, however, a nonsignificantly higher FNC between the CIN and SMN was observed in controls, whereas the FNC of the aDMN/pDMN, aDMN/SMN, and pDMN/SMN was nonsignificantly higher in patients with somatoform pain. For this reason, the lack of differences between controls and patients in terms of FNC may mirror methodological issues rather than etiological characteristics of different psychiatric and psychosomatic entities.

Limitations

An important limitation of the current study was medication. Antidepressants and analgesics were being taken by more

Table 2: Intrinsic connectivity networks*

Network	Region	MNI coordinate†			Cluster size, voxels	*t* value
		x	*y*	*z*		
Anterior default mode network	Left anterior cingular cortex	–2	46	6	7559	24.33
	Left gyrus frontalis inferior, pars orbitalis	–34	18	–20	328	10.34
	Left precuneus	–6	–54	24	180	10.26
	Right gyrus frontalis inferior, pars orbitalis	38	24	–16	379	10.20
	Left middle cingular cortex	0	–14	36	115	9.89
	Right precuneus	6	–52	24	30	7.52
	Right thalamus	4	–16	6	49	7.03
	Left gyrus parahippocampalis	–22	–28	–14	8	6.38
Posterior default mode network	Right posterior cingular cortex	6	–42	26	7846	29.88
	Left gyrus angularis	–42	–62	40	686	10.17
	Right gyrus angularis	38	–58	38	423	7.69
	Left gyrus temporalis medius	–54	–10	–18	3	6.20
Cingular–insular network	Left insula	–40	16	–6	2940	22.08
	Right supplementary motor area	2	12	64	2642	17.01
	Right gyrus frontalis inferior, pars orbitalis	40	24	–12	2046	16.39
	Left gyrus frontalis medius	–36	52	18	765	10.63
	—	–2	–16	–44	211	10.56
	Left gyrus supramarginalis	–60	–42	24	295	8.97
	Left precentral gyrus	–40	–2	54	242	8.93
	Right gyrus supramarginalis	62	–40	26	150	8.06
	Left gyrus frontals inferior, pars opercularis	–52	14	32	41	7.37
	Right gyrus frontalis medius	30	50	22	72	7.03
	Right precentral gyrus	46	6	48	19	6.89
	Right gyrus temporalis medius	52	–22	–12	12	6.21
Sensorimotor network	Right precentral gyrus	24	–16	70	16580	18.19
	Right insula	34	–24	14	48	8.19
	—	–2	10	–4	16	6.82
	Right gyrus temporalis inferior	52	–66	–6	3	5.96

MNI = Montreal Neurological Institute.
*$p < 0.05$, corrected for family wise error.
†Determined using the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/software/PickAtlas).

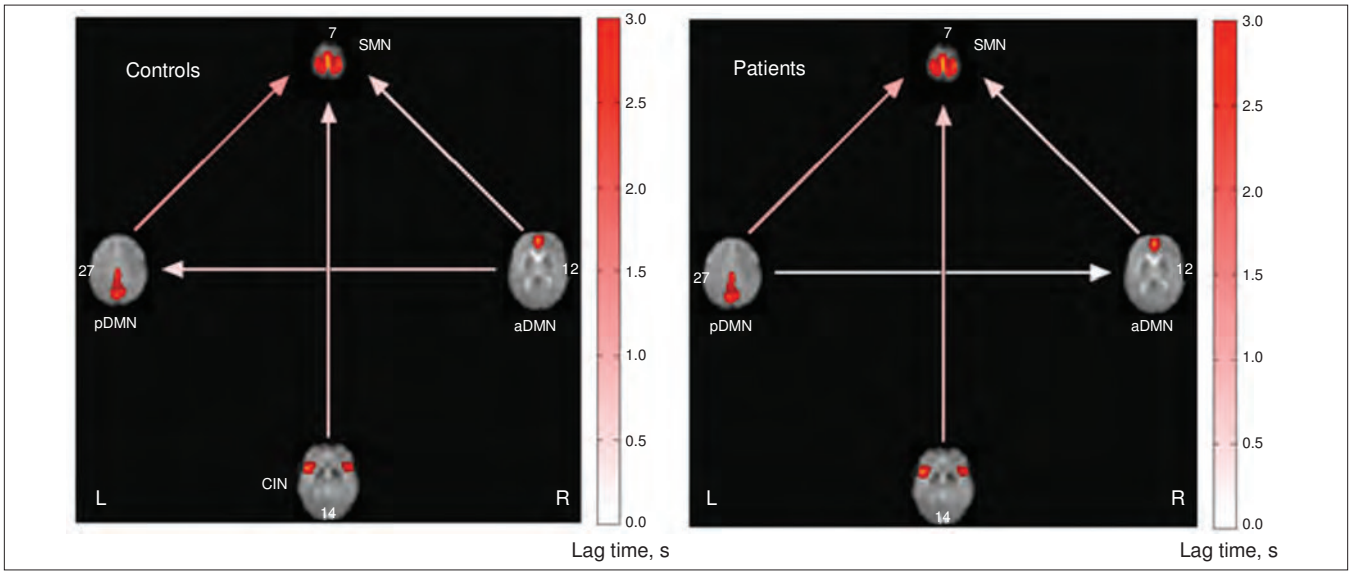

Fig. 2: Functional network connectivity (FNC) between the anterior default mode network (aDMN), posterior default mode network (pDMN), sensorimotor network (SMN) and cingular–insular network (CIN) in the control group (left) and patient group (right). Arrows represent a significant correlation between components ($p < 0.05$, corrected for false discovery rate). The lag time between the connected networks is shown by the direction of each arrow. An arrow that connects the CIN and SMN (pointing toward the latter) signifies that the time course of the SMN is delayed with respect to the CIN. However, no significant group differences were detected ($p < 0.05$, corrected for false discovery rate).

than half of our patients. It is of note that despite ethical reasons, it was nearly impossible to convince patients with somatoform pain to interrupt their (psychotropic) medication in this intentionally naturalistic study. As the patients of Cifre and colleagues[60] did not undergo a drug washout, we cannot exclude the possibility that medication influenced our results. Moreover, regarding the poor health status of our patients, our resting paradigm lasting 370 seconds was relatively short. Other studies used rest sessions of about 10 minutes.[13,60] However, given that patients with somatoform pain normally complain about long recumbency in the scanner, one may argue that a longer paradigm may have enhanced patient pain and led to false-positive results.

Given the high comorbidity of somatoform pain with affective disorders[61] and their influence on brain function,[58,62] depressive symptoms may have influenced our results. Several studies have indicated an important role of functional connectivity in depressive symptoms. For example, functional connectivity within the DMN was enhanced in our study, which has been correlated with stronger self-referential processes in depressed patients.[63–65] Northoff and colleagues[66] found meta-analytic evidence that not only intranetwork connectivity, but also disturbed interplay between several brain systems, may be the neural underpinning of this disease. In our study, however, no significant effect of depression on FNC was observed.

Conclusion

To our knowledge, our results demonstrate for the first time resting FNC between pain-related ICNs and its association with somatoform pain disorder. In contrast to our hypothesis, the resting FNC approach may not sufficiently explain the putative central dysfunction of pain homeostasis in chronic non-nociceptive pain. Our negative results encourage further research on the effect of chronic pain and affective disorders on the FNC of the human brain.

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Contributors: A. Otti conducted the research, analyzed data, and

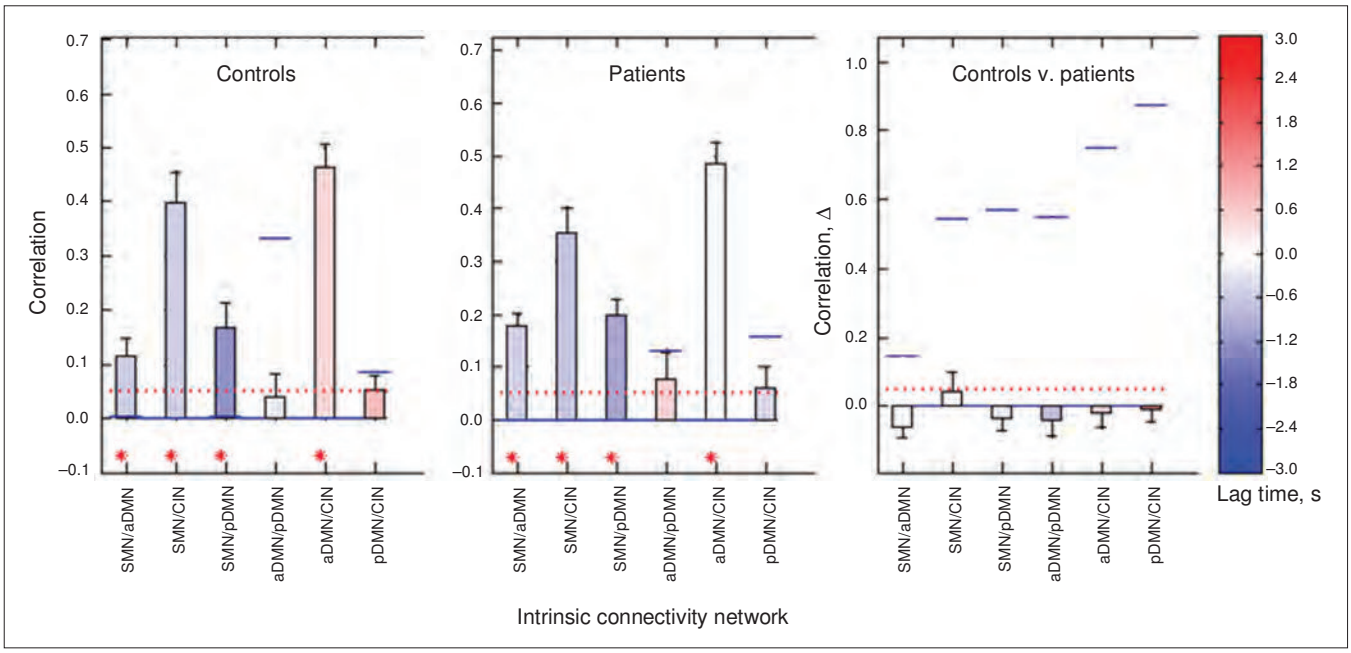

Fig. 3: Correlation and lag values between intrinsic connectivity networks (ICNs) of the controls (left) and patients (middle) and a group comparison (right). The numbers on the abscissa represent the 6 possible combinations between the ICNs. The ordinates show the correlation coefficient describing the functional network connectivity (FNC) of each combination for the controls and patients and the difference in the correlation coefficient (correlation Δ) between the controls and patients. The red-dotted horizontal line shows the user p value threshold ($p < 0.05$, corrected for false discovery rate). Blue horizontal lines show correlation p values of each test. The colour of the bars represents the lag time in seconds. In controls and patients, significant FNC was detected between the SMN/aDMN, SMN/CIN, SMN/pDMN and aDMN/pDMN but not the aDMN/CIN or pDMN/CIN. Compared with the control group, the FNC of patients was nonsignificantly lower between the SMN/CIN and nonsignificantly higher between all the other ICNs. aDMN = anterior default mode network; CIN = cingular–insular network; pDMN = posterior default mode network; SMN = sensorimotor network.

wrote the paper. H. Guendel designed the research and wrote the paper. P. Henningsen and C. Zimmer designed the research. A.M. Wohlschlaeger designed and performed the research. M. Noll-Hussong designed and conducted the research, analyzed the data, and wrote the paper. All authors have approved the final article.

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Appendix 1 to Otti A, Guendel H, Henningsen P, et al. Functional network connectivity of pain-related resting state networks in somatoform pain disorder: an exploratory fMRI study. *J Psychiatry Neurosci* 2012.

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Table S1: Brief Pain Inventory item scores for each patient*

	BPI item													
Patient	1	2	3	4	5	6	8	9A	9B	9C	9D	9E	9F	9G
1	Yes	Yes	5	5	5	2	3	4	5	4	3	7	6	8
2	Yes	Yes	8	3	6	5	8	8	7	7	7	4	4	7
3	Yes	Yes	8	7	7	8	7	8	9	6	7	7	10	9
4	Yes	Yes	10	9	9	10	9	10	4	9	10	9	9	3
5	Yes	Yes	9	4	5	6	5	7	7	0	7	3	1	4
6	Yes	Yes	2	1	2	1	—	2	1	3	3	1	0	1
7	Yes	Yes	4	0	2	1	—	3	1	2	3	1	2	1
8	Yes	Yes	—	—	—	—	—	—	—	—	—	—	—	—
9	Yes	Yes	6	3	5	4	3	5	6	1	8	5	5	7
10	Yes	Yes	10	7	9	9	0	9	9	10	1	5	9	7
11	Yes	Yes	10	7	8	10	0	9	0	4	2	0	2	0
12	Yes	Yes	7	5	6	8	5	4	2	1	4	0	6	1
13	Yes	Yes	5	4	4	5	5	4	3	5	7	4	5	3
14	Yes	Yes	8	6	8	8	7	8	9	8	8	6	8	8
15	Yes	Yes	—	—	—	—	—	—	—	—	—	—	—	—
16	Yes	Yes	8	6	7	7	—	4	2	3	4	2	5	3
17	Yes	Yes	5	1	3	3	9	3	5	3	6	5	5	6
18	Yes	Yes	7	4	6	5	3	6	5	7	3	4	7	5
19	Yes	Yes	5	0	4	3	5	2	3	2	4	1	0	3
20	Yes	Yes	7	3	4	3	5	5	7	0	7	5	3	6
21	Yes	Yes	9	5	7	7	2	8	7	7	8	7	6	7

BPI = Brief Pain Inventory (Radbruch L, Loick G, Kiencke P, et al. Validation of the German version of the Brief Pain Inventory. *J Pain Symptom Manage* 1999;18:180-7.)

*Missing data are indicated with an em-dash. BPI items are as follows: 1 = pain within the last week, 2 = pain today, 3 = pain at its worst during the last week, 4 = pain at its least during the last week, 5 = pain on the average, 6 = pain right now, 8 = pain relief by therapy, 9A = impairment of general activity, 9B = impairment of mood, 9C = impairment of walking ability, 9D = impairment of normal work, 9E = impairment of relations with other people, 9F = impairment of sleep, 9G = impairment of enjoyment of life.