TECHNISCHE UNIVERSITÄT MÜNCHEN

Klinik und Poliklinik für Psychosomatische Medizin und Psychotherapie

Klinikum rechts der Isar

(Direktor: Univ.-Prof. Dr. P. Henningsen)

Altered Brain Activation in Response on Induced Pain in Pain Disorder

Christian F. Sorg

Dissertation

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Content

Abstract

Objective: Pain disorder (PD) is a frequent chronic pain syndrome characterized by the dominating role of emotional aspects of pain in the mental life of patients. In patients with idiopathic chronic pain such as fibromyalgia syndrome (FMS) or idiopathic low back pain acute pain is associated with changed brain responses in several cortical and subcortical regions, most consistently in the medial prefrontal cortex (mPFC). The mPFC is involved in pain regulation, which is impaired in PD.

We hypothesized that patients with PD show altered medial prefrontal activation compared to control subjects during experimentally induced noxious heat stimulation.

Methods: 13 right handed women (mean age 47.4 yrs) fulfilling DSM-IV criteria of somatoform pain disorder were recruited from an interdisciplinary pain clinic as well as 13 age-matched healthy control subjects (mean age 47.3 yrs). Functional magnetic resonance imaging (fMRI) was performed using a 1.5 Tesla MRI scanner. Noxious heat stimulation was administered to the subjects left forearm.

Results: The mean pain ratings between patients and controls on a numerical rating scale (NRS) were not significantly different for pain intensity (6.8 vs 7.3) and pain unpleasantness (7.0 vs. 7.6). The group analysis of fMRI data revealed one region significantly hypoactivated in subjects with PD compared to healthy controls: the right ventromedial and orbitofrontal cortex (BA 10/11). In contrast, noxious heat stimulation resulted in significant stronger activation in PD in the left parahippocampal gyrus, secondary somatosensory, amygdala and left anterior insular cortex.

Conclusions: In PD reduced activation of the mPFC during acute pain indicates the involvement of the mPFC in impaired pain regulation in PD.

Zusammenfassung

Ziel: Die somatoforme Schmerzstörung (SFS) ist ein häufig auftretendes chronisches Schmerzsyndrom, das durch die beherrschende Rolle von Schmerzen im Leben der betroffenen Patienten charakterisiert ist. Bei Patienten mit idiopatischem Rückenschmerz oder Fibromyalgie ist die Verarbeitung von akutem Schmerz verbunden mit veränderter Hirnaktivierung in mehreren kortikalen und sub-kortikalen Regionen, am konsistentesten im medialen präfrontalem Kortex (mPFC). Der mPFC ist beteiligt an Prozessen der Schmerzregulation. Schmerzregulation ist bei Patienten mit SFS beeinträchtigt.

Wir vermuteten, dass Patienten mit SFS bei der Antwort auf experimentell induziertem Hitzeschmerz eine veränderte mPFC Aktivität zeigen.

Methoden: Wir rekrutierten 13 rechtshändige Patientinnen mit SFS sowie 13 gesunde, alters- und geschlechtsgleiche Kontrollpersonen. Wir untersuchten diese Personen mittels 1.5Tesla fMRT und gleichzeitiger Hitzeschmerzstimulation.

Ergebnisse: In der Einschätzung der Schmerzintensität und der Schmerzunangenehmheit unterschieden sich die beiden Gruppen nicht. Bei den Patientinnen zeigte sich eine verstärkte Schmerzantwort im linken parahippocampalen Gyrus, im somatosensorischem Kortex, der Amygdala und der vorderen Insel. Reduzierte Schmerz-bezogene Aktivität zeigte der mPFC in SFS.

Schluß: Die reduzierte Schmerzantwort des mPFC bei Patienten mit SFS weist daraufhin, dass der mPFC bei der gestörten Schmerzregulation in SFS beteiligt sein könnte.

Introduction

Objective: Pain disorder (PD) is a frequent chronic pain syndrome with a lifetime prevalence of about 12% (Meyer et al., 2000). PD is characterized by a mismatch between somatic changes and reported symptoms (Henningsen and Lowe, 2006; Rief et al., 2008). In patients with PD pain - especially in its emotional aspects - dominates the mental life of patients. PD-patients excessively ruminate about pain-associated factors, they strongly attend on pain perception, and they catastrophize pain i.e. they characterize pain as awful, horrible and unbearable. Additionally these patients have a highly increased risk – 40-60% - for affective syndromes such as major depression (MD) and anxiety disorder (Frohlich et al., 2006; Lieb et al., 2000).

The aim of our study was to explore the neural correlates of acute pain in PD by the use of functional magnetic resonance imaging (fMRI) during experimentally induced pain. We suggested changed pain responses of brain regions especially involved emotional aspects of pain.

In order to motivate our study and to specify the hypothesis regionally I will next shortly refer to the following topics: acute pain and its neuronal correlates, chronic pain and its neuronal correlates, specifying the hypothesis for PD.

Acute pain, pain regulation and their neuronal correlates: Pain is a highly subjective experience, illustrated by the definition of the International Association for the Study of Pain: "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merksey H., 1994).

Regarding neural correlates of pain, pain has been traditionally conceptualized as a sub-modality of cutaneous sensation, or exteroception (for example (Willis and Westlund, 1997)). In this view – the so-called gate control theory of pain - pain is represented centrally by convergent somatosensory activity transferred by wide-dynamic-range cells in the deep dorsal horn of the spinal cord to a modifiable pattern detector in the somatosensory thalamus and cortices. However this model has been challenged by observations that neither damage nor stimulation of the somatosensory cortices or thalamus affects pain (for

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review (Craig, 2003a)). Recently, several findings have been reported that suggest pain as homeostatic emotion akin to temperature, itch, hunger or thirst (Craig, 2002; Craig, 2003b). In this model, pain emerges in primates as a feeling from the body, which is generated by specific sensory pathways, within a direct thalamocortical projection that extends the afferent limb of the hierarchical homeostatic system to the cortical level. This means that pain integrates two aspects: an aspect of interoception – sensing the physiological condition of the body - and an aspect of a specific behavioral motivation – resulting in an urge to act.

Accordingly, anatomical sites involved in pain overlap with the Lamina 1 spinothalamocortical pathway associated with homeostatic regulatory processes: lamina 1 of the dorsal horn, lateral spinothalamic tract, centers in the brainstem such as parabrachial nucleus and periaqueductal grey (PAG), hypothalamus and posterior thalamus, insula, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC) (Craig, 2003a). Especially the cortical areas together with brainstem areas are strongly involved in pain regulatory processes (for review (Bingel and Tracey, 2008; Tracey and Mantyh, 2007)). For example, opioid and placebo analgesia are associated with increased activity in the pre-genual ACC but also with co-variation between the activity of the pre-genual ACC and the brainstem; notably, this co-variation was not present for pain alone (Petrovic et al., 2002). Valet and colleagues used connectivity analysis on fMRI data collected from controls receiving painful stimulation while performing an attentional distraction task (Valet et al., 2004). They showed that the mPFC exerts top-down influences on the PAG and posterior thalamus to modulate pain during distraction.

Chronic pain and its neuronal correlates: The standard definition of chronic pain stated by the International Association for the Study of Pain refers to chronic pain as pain that persists past the healing phase following an injury (Merksey H., 1994). Several points of this definition ask for critical discussion. First, defining the end of an healing phase after injury is difficult: for chronic back pain this time is relatively arbitrary defined as 6 months, for post-herpetic neuralgia 3 months (Apkarian et al., 2009). Second, focused on peripheral injury,

basic research has subdivided chronic pain conditions into inflammatory and neuropathic categories. However, in clinical settings these subdivisions are rarely observed independently. The type of injury most likely also has unique underlying physiology and thus specific pain perception and underlying circuitry (Apkarian et al., 2009). In patients with affective-somatic syndromes associated with chronic or recurrent pain peripheral changes are mostly not sufficient causes for pain-related symptoms. Third, chronic pain, defined as pain persisting past the healing process is characterized by spontaneous pain, i.e. perception of pain in the absence of physical stimuli, as well as increased responses to physical stimuli, i.e. hyperalgesia and allodynia. These pain-related changes are essentially associated with brain changes, however these brain changes are not addressed – even indirectly – by the given definition. For example, in patients with chronic back spontaneous pain is related with increased activity in the mPFC (Baliki et al., 2006). In patients with fibromyalgia hyperalgesia and pain-catastrophizing is associated with augmented activations in several areas usually involved in acute pain and emotion processing (Giesecke et al., 2004; Gracely et al., 2004). In chronic back pain atrophy has been reported for the frontal cortex and the thalamus (Apkarian et al., 2004). Changed structural connectivity mainly centered on the mPFC has been recently reported for patients with chronic complex regional pain syndrome (Geha et al., 2008). These imaging findings point at a substantial reorganization of central pain mediating circuits, which are very likely associated with the chronic manifestation of pain.

Bearing in mind these three points it has been suggested to recast the standard definition of chronic pain in terms of memory and learning (Apkarian et al., 2009): "Chronic pain is a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury." From this viewpoint the peripheral afferent barrage can be modeled as part of the inciting event and the central reorganization as the memory trace, which predictively predispose future pain-related events (Bar, 2009); relative contributions of each would then delineate types of pain conditions within the framework of mechanisms of memory of pain. In the following we will use this framework to analyze chronic pain in PD particularly its neuronal correlates during induced

acute pain.

Implicitly involved in the definition of chronic pain as persistent learning, is the fact that aversive emotional associations are continuously made with incident events due to the persistent presence of spontaneous pain. This point is supported by the evidence that several regions – most consistently the mPFC -, which are changed in chronic pain by atrophy or altered activity responses on pain or pain regulation, are also associated with emotion and emotion regulation (for review see (Phillips et al., 2008; Tracey and Mantyh, 2007)). For example, Etkin et al. revealed an explicit modulatory influence of the mPFC on activity within the amygdala during emotional conflict (Etkin et al., 2006). During the cognitive reappraisal of negative stimuli increased activity was found in the amygadala, OFC and ACC (Ochsner et al., 2002). Equipped with this background-knowledge we can specify our hypothesis on altered brain responses on induced pain in patients with PD, who are particularly characterized by the impaired regulation of emotional pain aspects.

Hypothesis: We suggested for patients with PD altered pain responses on induced heat pain in areas involved in emotion and pain: mPFC, ACC, insula, amygdala.

Methods

Subjects: 13 right-handed female patients fulfilling DSM-IV criteria (Association, 2000) for somatoform pain disorder (medium age 47.4 years, range 28-59) were selected from a consecutive sample of patients scheduled for a visit in the psychosomatic out-patient department of the Klinikum rechts der Isar, Technische Universität München. Neurological history-taking and physical examinations were performed by a neurologist to screen for concurrent illnesses. Inclusion criteria were female gender, right-handedness, age 20 – 65, and diagnosis of somatoform pain disorder according to DSM-IV - criteria. According to the Edinburgh Handedness Inventory all subjects had a right-hand preference. Excluded were patients with the diagnosis of fibromyalgia characterized by chronic widespread pain (involving all 4 quadrants of the body as well as the axial skeleton) and diffuse tenderness.

In addition, 13 healthy normal controls (MA: 47.3, range 28-59) were matched for age, gender and handedness and did not fulfil criteria for any psychiatric diagnosis according to DSM-IV criteria.

Participants refrained from smoking, drinking caffeine or alcoholic beverages, and taking analgesic medication for 3 days prior to the fMRI session. Patients receiving long-term opioid medication were excluded. 3 of our 13 patients with somatoform pain disorder were on an antidepressant medication (Fluoxetine 20mg; Amitriptyline 25mg; Citalopram 20mg) in the days before the fMRI experiment. Patients were instructed to stop antidepressant intake at least three days prior to the scanning.

The study was approved by the ethics committee of the Technische Universität München, and written informed consent was obtained from all participants.

The completion of self-report questionnaires and participation in the fMRI procedure were performed on the same day.

Clinical and Psychometric Characterization of Subjects:

Psychiatric evaluation (SCID): The occurrence of psychiatric disorders was assessed during a structured psychiatric interview (SCID-I) by a consultant psychiatrist according to DSM-IV – criteria (Association, 2000). The SCID assesses current (last 4 weeks before interview) and lifetime psychiatric status

for major Axis I psychiatric disorders using criteria in accordance with the DSM-IV.

Global assessment of functioning (GAF): The Global Assessment of Functioning scale (GAF) was completed by all study participants. The GAF scale is a numeric scale (0 through 100) used by mental health clinicians to rate the individual's overall (social, occupational and psychological) level of functioning in adults (Association, 2000).

Beck Depression Inventory (BDI): The BDI is a 21-item self-report instrument measuring cognitive and endogenous aspects of depression on a four-point scale that ranges from 0 to 3. This questionnaire has undergone extensive reliability and validation studies (Beck et al., 1961).

Pain Perception Scale (PPS): This 24-item questionnaire describes the sensory and the affective qualities of pain in a "global affective score" and a "global sensory score". It has been proved to be a reliable and valid measure of the affective and sensory component of pain in various studies and is essential part of the pain questionnaire of the German society for the study of pain (DGSS) (Geissner, 1995). In this study we measured the global affective score of the clinical pain description related to the leading chronic pain symptom. Cut-Off value for the inclusion of patients into the study was a minimum of 40 points out of 56 on this score.

Screening for Somatoform Symptoms (SOMS): The SOMS-2 (Rief, 1997) asks for the presence of 53 physical complaints lacking an organic disease during the previous two years and verifies further classification criteria with another 15 questions to be answered by the patient. The questionnaire includes all 33 physical complaints of the DSM-IV somatization disorder symptom list, the symptoms of ICD-10 somatization disorder, and the ICD-10 somatoform autonomic dysfunction symptom list. Therefore the SOMS-2 is suitable to screen for the presence of somatoform disorders. This scale shows high internal consistency (alpha = 0.92) and is a reliable and valid instrument. The DSM-IV – somatization index is a central outcome sum score recruited by the single 33 DSM-IV items of the SOMS-2. In our study, only female patients with a baseline

DSM IV somatization index score ≥ 6 were included. This criterion was introduced by Escobar et al. to identify somatization syndromes of clinical relevance beyond DSM diagnosis (Escobar et al., 1989).

Clinical pain rating: Clinical pain was assessed using an 11 point numerical rating scale (NRS 0-10). The two endpoints for this were 0 = no pain and 10 = worst pain imaginable. Patients gave their responses verbally during the clinical interview prior to the scanning.

Experimentally induced Heat Pain

Assessment of individual pain threshold: The individual pain threshold was assessed using a steps protocol, with increase of the temperature from baseline (35°C) at a rate of 4°C per second to the target temperature which was maintained for 40 seconds. Individually, the steps protocol was applied and repeated with 0.5 °C increments in the target temperature until the temperature giving rise to a moderate pain sensation (numerical rating between 5-7/10) was reached. Subjects were blind to the applied temperature of the thermode; the temperature reaching moderate pain sensations was then used during all fMRI scans.

Experimental pain protocol during fMRI: Subjects of both groups received a series of 8 noxious and 8 innocuous stimuli, 1°C above and 3°C below individual pain threshold each with a length of 40 seconds during the fMRI scanning (figure 1). Between the stimuli a 20 second neutral stimulus of 35 °C was used to determine basal neuronal activity for the fMRI analysis. Stimuli were applied to the inner side of the left forearm with a 30 x 30 mm sized thermode using the MEDOC TSA-2001 (Israel) thermal stimulator. To avoid any skin damage during the 40 second painful heat stimulus, the temperature undulated with a frequency of 0.5 Hz and amplitude of 1°C starting from the individual pain threshold.
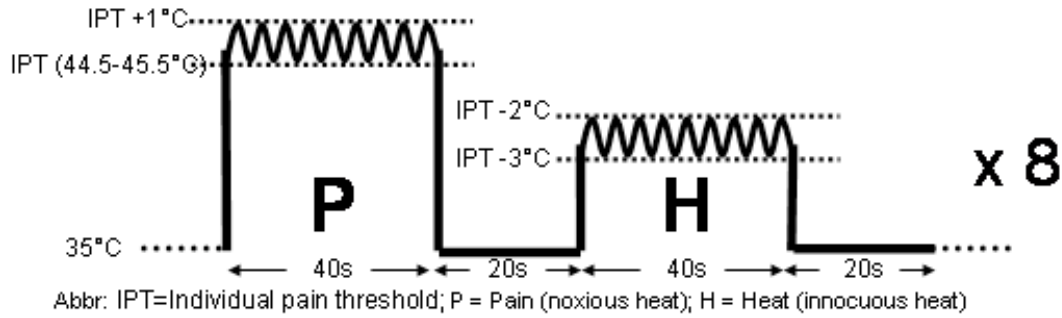
Figure1: Pain stimulation paradigm with the application of 8 noxious (undulating 1°C above individual pain threshold) and 8 innocuous heat stimuli (undulating 3°C below individual pain threshold) to the left volar forearm using a 30 mm x 30 mm sized thermode. The temperature undulated during each condition with a frequency of 0.5 Hz and amplitude of 1°C. Each stimulus condition was presented for 40 seconds followed by 20 second baseline (35°C).

After fMRI scanning the subjects were asked to rate acute perception of pain intensity and unpleasantness using an 11-point numerical rating scale (0-10). Statistics of the psychophysiological parameters between both groups were assessed with a two-sided student's t-test.

fMRI: imaging and data analysis

Imaging parameters: Functional neuroimaging was performed on a Siemens Symphony 1.5 Tesla MR scanner with EPI sequence technique (330 images, first 5 images discarded because of T1 equilibration effects, matrix: 64x64; TE: 50ms; TR: 2.51s; alpha: 90°; FOV: 192mm, 28 axial slices; resulting voxel size: 3x3x5mm). This sequence allows indirectly to measure neuronal activity by determining the blood oxygenation level dependent contrast.

Preprocessing and statistical analysis: Preprocessing and statistical analysis were conducted with the software SPM2, available from the Wellcome Department of Imaging Neuroscience, London, UK (Friston et al., 1999). The fMRI data were realigned to correct for motion artifacts, normalized to standard reference space according to the EPI template of SPM (mean brain of 305 healthy subjects

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determined at the Montreal Neurological Institute) and resampled with a 3 x 3 x 3 mm voxel size. Finally, data were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half maximum to account for anatomical individual variances and to improve the signal-to-noise ratio.

For the statistical analysis subject-specific t-contrast images for pain effects were calculated using the general linear model approach (block design, conditions convolved with hemodynamic response function) and applied for second level analysis (random effects-analysis). Statistical parametric maps of pain effects were calculated separately for each group (single sided t-test) and further compared against each other (two sided paired t -test) to check for differences in pain processing between patients and healthy volunteers. Maps were thresholded at $P < 0.001$ with a minimum cluster size of 5 voxel uncorrected for multiple comparisons, as we expected activation in the well defined pain processing network (brainstem, thalamus, S1, S2, insular, parietal and prefrontal cortex). Statistical parametric maps were also calculated for innocuous stimuli to differentiate pain specific effects from temperature related activation.

Results

Psychometric variables: Demographic and psychometric variables of the study sample are shown in Table 1. Regional locations of pain were head and neck (n=3), lower back (n=6), temporomandibular (n=1), pelvis (n=2), lower limbs (n=1). None of the patients fulfilled the 1990 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia. The amount of depressive symptoms (BDI: 21.9 ± 9.4 vs. 1.8 ± 2.3; p<.001) and the DSM IV somatization index score (SOMS: 7.9 +/- 1.9 vs. 2.0 +/- 2.0; p<.001) was significantly higher in patients than controls, and the level of global functioning (GAF: 58.8 ± 6.3 vs. 93.3 ± 3.9; p<.001) was significantly reduced in patients vs. controls. Accordingly, SCID-I interviews revealed a comorbidity with current major depressive episodes in 6 of 13 patients, but not at all in controls. No patient had a current or lifetime anxiety disorder (Table 1).

Table 1. Demographic and psychometric variables and SCID-diagnosis (pain disorder and comorbidity)

Demographic and psychometric variables	Patient group	Control group	p-value
Age	47.4 ± 9.8	47.3 ± 9.3	n.s.*
PPS, global affective score	44.0 ± 9.1	16.5 ± 3.3	p<0.001
BDI, depression score	21.9 ± 9.4	1.8 ± 2.3	p<0.001
GAF, global functioning	58.8 ± 6.3	93.3 ± 3.9	p<0.001
SOMS, DSM IV somatization index	7.9 +/- 1.9	2.0 +/- 2.0	p< 0.001
Pain duration (years)	9.0 ± 7.7	-	-
Rating of clinical pain (NRS)	8.9 ± 1.0 / 10	-	-
Intensity of experimental pain (NRS)	6.8 ± 1.5 /10	7.3 ± 1.1 / 10	n.s.*
Unpleasantness of experimental pain (NRS)	7.0 ± 1.8 / 10	7.6 ± 1.6 / 10	n.s.*
Pain disorder	13/13	0/13	n.s.*
Somatization disorder	3/13	0/13	n.s.*
Unspecific somatization disorder	1/13	0/13	n.s.*
Current major depressive episode	6/13	0/13	n.s.*
Major depression in history	3/13	0/13	n.s.*
Other psychiatric disorders	3/13	0/13	n.s.*

* p> 0.05 not significant

Pain ratings for the fMRI experiment: The individual mean pain threshold for the patient group was 44.8°C ± 0.3°C SD, and for the control group 44.8°C ± 0.3°C SD (Table 1). Subjective pain perception of the heat stimuli ranged for patient and control group on a moderate to strong level. On the 11 point NRS (0-10) the

mean pain unpleasantness rating obtained immediately after each scanning session of the patient group was 7.0 ± 1.8 SD and for intensity 6.8 ± 1.5 SD. Pain ratings of the control group were for unpleasantness 7.6 ± 1.6 SD and for intensity 7.3 ± 1.1. SD. Since no significant differences in individual pain threshold (two sided student's t-test for pain temperature p=0.99 n.s.) and subjective pain perception between both groups were observed (unpleasantness: p=0.40 n.s., intensity: p=0.39 n.s.), it may be assumed that physical (pain temperature) and psychophysical parameters (pain ratings) in this study are well controlled and differences in cerebral pain processing may not be attributed to these factors.

Cerebral pain processing network in patient and control group: The fMRI analyses of the activation responses under the condition pain (compared vs. baseline 35°C) revealed both in the patient and the control group significant activation of the bilateral medial thalamus, bilateral anterior-/mid and posterior insular cortex, bilateral (patients) vs. right (controls) secondary somatosensory cortex, contralateral anterior cingulated cortex, contralateral (patients) vs. bilateral (controls) posterior cingulate cortex and bilateral inferior parietal cortex (SPM2, RFX-analysis, one sample t-test, p<0.001; table 2, figure 2a and figure 2b). Additional activation of the contralateral medial prefrontal cortex and bilateral lateral prefrontal cortex was only observed in the control group (table 2, figure 2b).
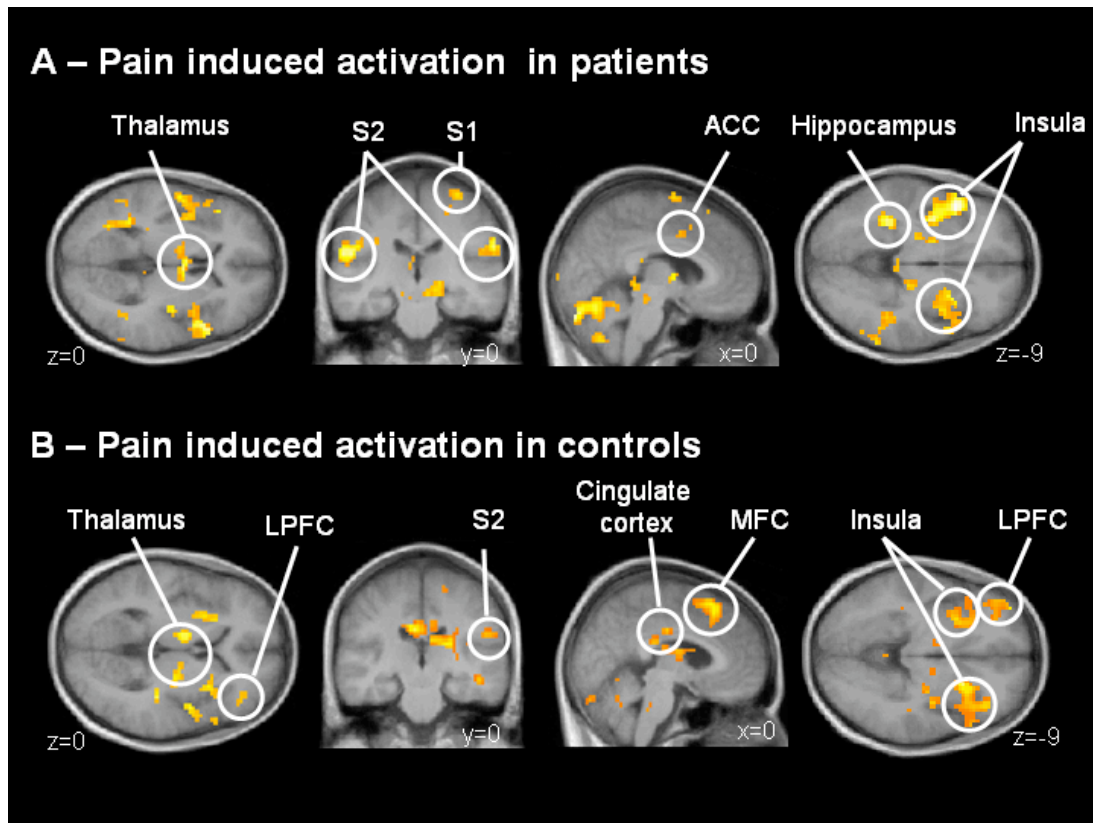
Figure 2: Cerebral pain processing of painful heat stimuli **(A)** in patients with somatoform disorder and **(B)** in controls. Noxious heat stimulation evokes activation of the sensory-discriminative pain coding system (e.g.: S2, thalamus, posterior insular cortex) and affective-motivational system (medial thalamus, ACC, anterior insular cortex). The LPFC is significantly activated only in the control group. Activation maps (threshold at $p<0.001$) are superimposed on the mean normalized anatomical T1 image of the subjects. Neurological convention: Right side of the image corresponds to right side of the brain. Abbr.: LPFC=lateral prefrontal cortex, MFC=medial frontal cortex, ACC=anterior cingulated cortex, S1=primary somatosensory cortex, S2=secondary somatosensory cortex.

Table 2. fMRI results of noxious heat stimulation in chronic pain patients with somatoform pain disorder and age-matched healthy volunteers

Region	Patients			Controls			Patients > Controls			Controls > Patients		
	Side	x / y / z	T-Value	Side	x / y / z	T-Value	Side	x / y / z	T-Value	Side	x / y / z	T-Value
Med. Thalamus	R L	12 -3 6 -12 -3 6	5.82 5.13	R L	21 -21 15 -12 -9 6	6.06 5.86						
Ant./Mid. Insula	R L	39 6 9 -42 3 -3	5.46 7.07	R L	27 15 -3 -27 18 9	5.14 6.17	R	36 6 -15	4.16			
dorsal ACC				R L	9 -18 33 -6 -21 30	5.88 7.64						
ACC (BA24')	R	9 3 39	4.3									
post. Insula	R L	39 -12 6 -36 -18 12	6.68 4.49	R	39 -18 15	4.24						
S2	R L	51 -36 18 -42 -39 21	5.07 4.56	R	57 -36 24	5.76	L	-39 -39 15	4.28			
S1	R	36 -30 66	6.96				R	33 -27 66	4.13			
MFC (BA8)				R	3 24 51	6.22						
PCC	R	15 -33 30	6.46									
LPFC (BA11,10)				R L	39 39 0 -45 45 -9	4.51 4.02						
IPC (BA40)	R L	51 -45 45 -48 -45 42	6.83 5.72	R L	45 -48 51 -57 -48 30	5.61 4.87	L	-27 -48 57	4.09			
Amygdala							R	21 0 -15	4.49			
Parahippocampal gyrus							L	-36 -45 -6	4.16			
Orbitofrontal cortex / MFC (BA11)										R	9 51 -15	3.73

Shown is the pain related activity maximum of each region in MNI coordinates, thresholded at p<0.001 uncorrected for multiple comparisons. Minimum activity size is 5 voxel (1 voxel = 3x3x3mm).
Abbr.: ACC=anterior cingulate cortex, S2=secondary somatosensory cortex, MFC= medial frontal cortex, PCC=posterior cingulate cortex, LPFC=Lateral prefrontal cortex, IPC=Inferior parietal cortex.

The application of non-painful heat stimuli (innocuous heat condition compared vs. baseline 35°C) revealed no significant activation of the brain neither in the patient nor in the control group (SPM2, p<0.001, data not shown).

Differences in the cerebral pain processing network between patient and control group: Direct statistical comparison of the cerebral activation pattern of the patient versus healthy volunteer group showed *increased activation* of the contralateral amygdala, ipsilateral parahippocampal gyrus, ipsilateral S2, contralateral insular cortex, ipsilateral inferior parietal cortex and contralateral S1 in patients (two sample t-test, p<0.001, table 2, figure 3b).

Decreased activation during pain was found in the contralateral orbitofrontal
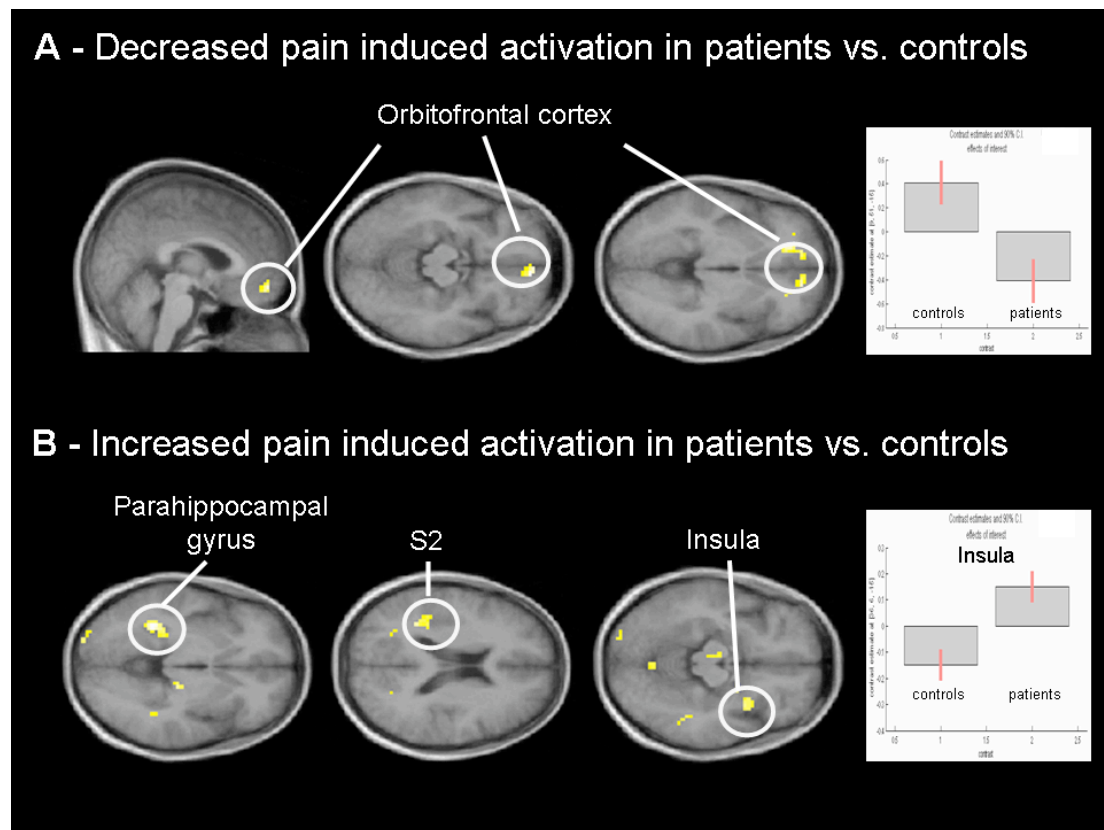
cortex (BA 11) (p<0.001, table 2, figure 3a).

Figure 3: (A) Decreased cerebral pain processing and **(B)** increased pain processing in patients with somatoform disorder compared to controls. Decreased activation was observed in the orbitofrontal cortex **(A)**. Increased activation was found in the parahippocampal gyrus, posterior and anterior insular cortex. Activation maps (threshold p<0.01 for illustrative purposes) are superimposed on the mean normalized anatomical T1 image of the subjects. Neurological convention: Right side of the image corresponds to right side of the brain. A bar plot of the 'contrast estimates' is also shown for the peak voxel in the orbitofrontal and insular cortex. The contrast estimates correspond to the average fit of the effects of interest and is a measure of how much BOLD signal the contrast explains after the variance explained by the rest of the general linear model has been accounted for.

Additionally we performed an ANCOVA analysis (p<0.001) using the BDI score as covariate of no interest to exclude possible depression related variances.

Decreased activation in the patient group compared to the control group was still found in the orbitofrontal cortex (MNI 33 27 -15, t = 4.47, BA11). Increased activation was found in similar brain structures as reported above for the categorical comparison of patients versus healthy volunteers without inclusion of a covariate of no interest (not further listed). A correlation analysis between BDI scores and brain activity during noxious stimuli revealed no significant positive or negative correlation with the orbitofrontal cortex (threshold at $p<0.01$).

Discussion

In our study we demonstrated altered brain activation in patients with PD in response on painful heat stimulation. For the contralateral amygdala, the ipsilateral parahippocampal gyrus, the anterior and middle insula, the primary and secondary somatosensory cortex and the inferior parietal cortex pain response was increased. Amygdala, insula and somatosensory cortex are routinely involved in acute pain and show increased pain response in other chronic pain syndromes (Baliki et al., 2006; Gracely et al., 2004; Kwan et al., 2005). For the mPFC/OFC pain response was decreased in PD. The mPFC is involved in spontaneous pain and pain regulation (Baliki et al., 2006; Petrovic et al., 2002; Valet et al., 2004). We suggest that in PD impaired pain regulation is associated with altered mPFC processes.

In the following we will discuss the most important findings separated for each region that shows altered pain response. We start this section with discussing behavioral pain ratings.

Pain ratings: Across groups of patients and controls we found no differences in both the individual pain thresholds and the subjective pain ratings for intensity and unpleasantness. Two points of these results are of interest. First, due to the missing group differences in behavior we could compare brain activations between groups without controlling for behavioral results. Second, due to characteristic symptoms in PD one might expect at least changes in pain unpleasantness ratings in PD. However, a similar discrepancy between detectable differences in brain activation and no differences in self-report scales of aversive psychological state (e.g. fear, anger, pain) has been observed in several studies (Baliki et al., 2006; Kirsch et al., 2005; Sheline et al., 2009; Strigo et al., 2008). For example, in accordance with our results, Baliki et al. found no differences between CLBP patients and healthy subjects regarding the intensity and temporal profile of pain ratings to thermal stimuli (Baliki et al., 2006). These somewhat surprising results might be partly explained by the observation that study participants often respond in a way that they knew expected of them (Baliki et al., 2006; Sheline et al., 2009; Strigo et al., 2008). Otherwise imaging

methods might be more sensitive to detect differences between subjects than behavioral scores.

Amygdala and parahippocampal cortex: The exact role of the amygdala in pain processing in general and especially in the processing of aversive responses to pain and pain memory is still emerging. As basic emotional processing functions critically depend on the in- and output of the amygdala, it might also be involved in the processing of affective components of pain (Geuze et al., 2007; Kulkarni et al., 2007; LeDoux, 2000). It has been recently suggested that the amygdala integrates nociceptive information and plays a facilitatory and inhibitory role in the modulation of emotional pain behavior (Bingel and Tracey, 2008). The heightened amygdalar activation in our study might point to an increased emotional load in the processing of painful stimuli.

The amygdala is supposed to modulate hippocampal activity in relation to memory encoding, storage and retrieval of pleasant or aversive stimuli (Hamann et al., 1999). A recent neuroimaging study investigating sensitization phenomenon of pain in human beings by application of daily series of noxious heat stimulation over 12 days demonstrated increased affective pain ratings and an increase of hippocampal and amygdalar activation (Valet, 2006). Another fMRI study in healthy subjects showed that pain modulation by anxiety is associated with activation changes especially of the hippocampal formation (Ploghaus et al., 2001). Patients with posttraumatic stress disorder showed also an altered activation pattern in the amygdala and parahippocampal cortex in comparison to healthy controls when subjected to painful heat stimuli (Geuze et al., 2007). We therefore assume that the increased activation of the amygdala and parahippocampal cortex in our study might point to memory-related processes that are relevant for affective pain processing and perception.

Insular Cortex: Within the context of pain and emotion, several studies suggest that the anterior insula is associated with the affective dimension of pain (Craig, 2002; Craig, 2009; Rainville et al., 1997; Singer et al., 2004; Strigo et al., 2008). These results are in line with the data of Ploghaus et al. showing that the anticipation of pain activates preferably the anterior insular, whereas the actual

experience of pain activates rather the posterior insula (Ploghaus et al., 2001). Another study in major depression observed increased pain responses of the anterior insula as well as increased anterior insula activity during the anticipation of pain in depressive patients (Strigo et al., 2008). Especially the anterior insula (AI) is critically involved in interoceptive and emotional awareness (Craig, 2009). Critchley and colleagues demonstrated that the neural activity in the right AI predicts subjects' accuracy in heartbeat detection that correlates with emotional awareness (Critchley et al., 2004). Phillips et al. observed activation in the bilateral AI (right > left) during nonpainful oesophageal distention or viewing of fearful faces; such activation displayed synergistic enhancement when these stimuli were processed simultaneously, suggesting that emotional states are integrated with interoceptive states in the representation of the subjective feelings (Phillips et al., 2003). On the background of slightly increased ratings of pain unpleasantness in our patient group, increased activation in anterior/mid-insula in somatoform pain disorder patients may contribute to both the affective response to and awareness of painful stimuli. Similar findings have been previously described in fibromyalgia (Gracely et al., 2004) and in pain catastrophizing during mild pain (Seminowicz and Davis, 2006).

Medial prefrontal cortex: The result of reduced activation of the ventromedial prefrontal/orbitofrontal cortex supports previous findings of a neuroimaging study on fibromyalgia patients in which the medial frontal cortex is activated to a lesser degree (Gracely et al., 2002). There is accumulating evidence that the cingulo-frontal area, including the perigenual ACC (BA 32), and orbitofrontal cortex (BA 10/11), is generally involved in the processing of pain regulation (for review (Tracey and Mantyh, 2007)). Recently mPFC-activity has been demonstrated as selectively related to the intensity of spontaneous pain, which is critical for chronic pain (Baliki et al., 2006). Relating spontaneous pain with mPFC-activity suggests a substantial reorganization of the mPFC. This suggestion has been supported by the observation that in chronic complex regional pain the atrophy of the mPFC is associated with changed structural connectivity between the vmPFC and right limbic-visceromotor areas (Geha et al., 2008).

Pain catastrophizing is another aspect, which is associated with hypoactivation of the prefrontal cortex and hyperactivation of the insular cortex in healthy subjects (Seminowicz and Davis, 2006). This activation pattern is intriguingly similar to the pattern that we now observed in patients with somatoform pain disorder. Although we did not measure pain catastrophizing directly in this study, we exclusively included patients with a high affective dimension of pain (global affective score of the PPS with at least 40 out of 56). A high affective dimension in pain experience and description clearly correlates with pain catastrophizing. Thus, the similarities in BOLD activation patterns in the study from Seminowicz et al., and in our study underscore the validity of this finding.

The levels of depressive symptoms as well as the extent of psychiatric comorbidity differentiate patients from controls (Table 1). Thus, especially the depressive symptomatology might interfere with the neural correlates of somatoform pain disorder. However, the performed covariation analysis approach, i.e. the correlation of BDI scores with brain activity during noxious stimulation, did not support an influence of depressive symptoms on pain processing in the orbitofrontal cortex. Moreover, the ANCOVA using the BDI score as nuisance variable still found orbitofrontal hypoactivation and unchanged activation in multiple brain areas in our group of somatoform pain disorder patients compared to healthy controls. Orbitofrontal/ventromedial hypoactivation seems to be an essential finding in somatoform pain disorder, which is not depending on the extent of depression.

Conclusion: Our study provides evidence for an altered central pain processing in somatoform pain disorder as opposed to healthy controls. In addition to augmented activation within the brain areas encoding the affective (insula, parahippocampal gyrus) and sensory (S2) dimension of pain, our finding of a hypoactivation of the right ventromedial prefrontal cortex may indicate a contribution of impaired mPFC processes in diminished pain regulation in patients with somatoform pain disorder.

Literature

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders - DSM IV - TR (Washington, DC: American Psychiatric Association).

Apkarian, A. V., Baliki, M. N., and Geha, P. Y. (2009). Towards a theory of chronic pain. Prog Neurobiol *87*, 81-97.

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., and Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci *24*, 10410-10415.

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., and Apkarian, A. V. (2006). Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci *26*, 12165-12173.

Bar, M. (2009). Predictions: a universal principle in the operation of the human brain. Introduction. Philos Trans R Soc Lond B Biol Sci *364*, 1181-1182.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., and ERBAUGH, J. (1961). An inventory for measuring depression. Arch Gen Psychiatry *4*, 561-571.

Bingel, U., and Tracey, I. (2008). Imaging CNS modulation of pain in humans. Physiology (Bethesda) *23*, 371-380.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci *3*, 655-666.

Craig, A. D. (2003a). Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci *26*, 1-30.

Craig, A. D. (2003b). A new view of pain as a homeostatic emotion. Trends Neurosci *26*, 303-307.

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci *10*, 59-70.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., and Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. Nat Neurosci *7*, 189-195.

Escobar, J. I., Rubio-Stipec, M., Canino, G., and Karno, M. (1989). Somatic symptom index (SSI): a new and abridged somatization construct. Prevalence and epidemiological correlates in two large community samples. J Nerv Ment Dis *177*, 140-146.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron *51*, 871-882.

Friston, K. J., Holmes, A. P., Price, C. J., Buchel, C., and Worsley, K. J. (1999). Multisubject fMRI studies and conjunction analyses. Neuroimage *10*, 385-396.

Frohlich, C., Jacobi, F., and Wittchen, H. U. (2006). DSM-IV pain disorder in the general population. An exploration of the structure and threshold of medically unexplained pain symptoms. Eur Arch Psychiatry Clin Neurosci *256*, 187-196.

Geha, P. Y., Baliki, M. N., Harden, R. N., Bauer, W. R., Parrish, T. B., and Apkarian, A. V. (2008). The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron *60*, 570-581.

Geissner, E. (1995). [The Pain Perception Scale--a differentiated and change-sensitive scale for assessing chronic and acute pain]. Rehabilitation (Stuttg) *34*, XXXV-XLIII.

Geuze, E., Westenberg, H. G., Jochims, A., de Kloet, C. S., Bohus, M., Vermetten, E., and Schmahl, C. (2007). Altered pain processing in veterans with posttraumatic stress disorder. Arch Gen Psychiatry *64*, 76-85.

Giesecke, T., Gracely, R. H., Grant, M. A., Nachemson, A., Petzke, F., Williams, D. A., and Clauw, D. J. (2004). Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum *50*, 613-623.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., and Clauw, D. J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain *127*, 835-843.

Gracely, R. H., Petzke, F., Wolf, J. M., and Clauw, D. J. (2002). Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum *46*, 1333-1343.

Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci *2*, 289-293.

Henningsen, P., and Lowe, B. (2006). Depression, pain, and somatoform disorders. Curr Opin Psychiatry *19*, 19-24.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V. S., Gallhofer, B., and Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci *25*, 11489-11493.

Kulkarni, B., Bentley, D. E., Elliott, R., Julyan, P. J., Boger, E., Watson, A., Boyle, Y., El-Deredy, W., and Jones, A. K. (2007). Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum *56*, 1345-1354.

Kwan, C. L., Diamant, N. E., Pope, G., Mikula, K., Mikulis, D. J., and Davis, K. D. (2005). Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology *65*, 1268-1277.

LeDoux, J. E. (2000). Emotion circuits in the brain. Annu Rev Neurosci *23*, 155-184.

Lieb, R., Pfister, H., Mastaler, M., and Wittchen, H. U. (2000). Somatoform syndromes and disorders in a representative population sample of adolescents

and young adults: prevalence, comorbidity and impairments. Acta Psychiatr Scand *101*, 194-208.

Merksey, H., Bogduk, N. (1994). Classification of Chronic Pain (Seattle: IASP Press).

Meyer, C., Rumpf, H. J., Hapke, U., Dilling, H., and John, U. (2000). [Lifetime prevalence of mental disorders in general adult population. Results of TACOS study]. Nervenarzt *71*, 535-542.

Ochsner, K. N., Bunge, S. A., Gross, J. J., and Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci *14*, 1215-1229.

Petrovic, P., Kalso, E., Petersson, K. M., and Ingvar, M. (2002). Placebo and opioid analgesia-- imaging a shared neuronal network. Science *295*, 1737-1740.

Phillips, M. L., Gregory, L. J., Cullen, S., Coen, S., Ng, V., Andrew, C., Giampietro, V., Bullmore, E., Zelaya, F., Amaro, E., Thompson, D. G., Hobson, A. R., Williams, S. C., Brammer, M., and Aziz, Q. (2003). The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. Brain *126*, 669-684.

Phillips, M. L., Ladouceur, C. D., and Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry *13*, 829, 833-57.

Ploghaus, A., Narain, C., Beckmann, C. F., Clare, S., Bantick, S., Wise, R., Matthews, P. M., Rawlins, J. N., and Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci *21*, 9896-9903.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., and Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science *277*, 968-971.

Rief, W., Zenz, M., Schweiger, U., Ruddel, H., Henningsen, P., and Nilges, P. (2008). Redefining (somatoform) pain disorder in ICD-10: a compromise of different interest groups in Germany. Curr Opin Psychiatry *21*, 178-181.

Rief, W., Hiller, w., Heuser, J. (1997). Das Screening für Somatoforme Störungen (SOMS - Screening for Somatoform Disorders) (Bern: Verlag Hans Huber).

Seminowicz, D. A., and Davis, K. D. (2006). Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain *120*, 297-306.

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., Mintun, M. A., Wang, S., Coalson, R. S., and Raichle, M. E. (2009). The default mode network and self-referential processes in depression. Proc Natl Acad Sci U S A *106*, 1942-1947.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., and Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. Science *303*, 1157-1162.

Strigo, I. A., Simmons, A. N., Matthews, S. C., Craig, A. D., and Paulus, M. P. (2008). Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. Arch Gen Psychiatry *65*, 1275-1284.

Tracey, I., and Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. Neuron *55*, 377-391.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., and Tolle, T. R. (2004). Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain *109*, 399-408.

Valet, M., Sprenger T., Boecker, H., Rummeny, E., Tolle TR. (2006). Repetitive pain exposure: neural correlates in the brain. In Proceedings of the 11th world congress on pain, Flohr, H., Kalso, E., ed. (Seattle: IASP Press), pp. 431-437.

Willis, W. D., and Westlund, K. N. (1997). Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol *14*, 2-31.

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Sorg C, Riedl V, Perneczky R, Kurz A, Wohlschläger AM. Impact of Alzheimer's disease on the functional connectivity of spontaneous brain activity. Cur Alzheimer Research (in press)

Gündel H, Valet M, Sorg C, Huber D, Zimmer C, Sprenger T, Tölle TR. Altered cerebral response to noxious heat stimulation in patients with somatoform pain disorder. Pain. 2007 Nov 15

Valet M, Gündel H, Sprenger T, Sorg C, Mühlau M, Zimmer C, Henningsen P, Tölle TR. Patients with pain disorder show grey matter loss in processing structures: a VBM study. Psychosomatic Medicine 71: 49-56 (2009)

Perneczky R, Pohl C, Sorg C, Hartmann J, Komossa K, Alexopoulos P, Wagenpfeil S, Kurz A. Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. Age Ageing. 2006 May;35(3):240-5

Perneczky R, Pohl C, Sorg C, Hartmann J, Tosic N, Grimmer T, Heitele S, Kurz A. Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. Int J Geriatr Psychiatry. 2006 Feb;21(2):158-62

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