Patients With Pain Disorder Show Gray-Matter Loss in Pain-Processing Structures: A Voxel-Based Morphometric Study

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Objective: To investigate whether the functional changes in pain disorder might be reflected by structural brain changes. Pain disorder assessed with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria is characterized by persistent and distressing chronic pain at one or more body sites which cannot be fully explained by a physiological process or somatic disorder. Psychological factors are thought to play a major role. Recent neuroimaging studies evidenced altered pain processing in patients suffering from this disorder. **Methods:** Fourteen right-handed women fulfilling the DSM-IV criteria for pain disorder and 25 healthy age-matched women were investigated with magnetic resonance imaging. In the voxel-based morphometry analysis, we compared both groups for changes of gray-matter density. We included age and Beck Depression Inventory scores as nuisance variables to minimize possible confounding effects of age or depressive comorbidity. **Results:** In the patient group, we found significant gray-matter decreases in the prefrontal, cingulate, and insular cortex. These regions are known to be critically involved in the modulation of subjective pain experiences. **Conclusions:** In the context of similar results in patients with other functional pain syndromes, such as fibromyalgia and chronic back pain, we suggest that structural changes in fronto-limbic brain circuits represent not only an objective marker of these pain syndromes but also constitute a critical pathophysiological element. These findings represent a further proof of the important role of central changes in pain disorder. **Key words:** pain disorder, idiopathic chronic pain, voxel-based morphometry, orbitofrontal cortex, ventromedial prefrontal cortex, classification.

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **ICD-10** = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; **VBM** = voxel-based morphometry; **fMRI** = functional magnetic resonance imaging; **GM** = gray matter; **WM** = white matter; **CSF** = cerebrospinal fluid; **BDI** = Beck Depression Inventory; **MNI** = standardized reference space defined by the Montreal Neurological Institute; **SOMS** = screening for somatoform symptoms; **PPS** = Pain Perception Scale; **SCID** = Structured Clinical Interview for DSM-IV disorders.

INTRODUCTION

According to the diagnostic criteria of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), pain disorder is defined as persistent and chronic pain at one or more sites that cannot be fully explained by a physiological process or physical disorder. This disorder seems to be regularly linked to emotional dysregulation, which is associated with a high affective description of individual pain (1). An overlap with anxiety and/or depressive disorders has been described in 25% to 60% of cases (1). It has a lifetime prevalence of 12.2%, accounting for the vast majority of the total 12.9% somatoform disorder prevalence rates in the German general population (2).

Patients suffering from functional somatic syndromes, such as pain disorder (3,4), fibromyalgia (5–7), idiopathic chronic low back pain (8), or irritable bowel syndrome (9–11) seem to have an altered cerebral pain processing as evidenced with functional magnetic resonance imaging (fMRI). Recent voxel-based morphometry (VBM) studies point to structural brain changes associated with these syndromes, which have been already observed in patients with fibromyalgia (12,13) or chronic back pain (14,15).

VBM is a novel method that has been proven to be a powerful method for the in vivo study of human brain structure in healthy subjects and patients (16). However, the physiological basis of structural changes in VBM is not well understood. It is widely assumed that gray matter (GM) loss in VBM corresponds to neural degeneration (17,18). This assumption has been proven for neurodegenerative diseases, such as Huntington disease, Parkinson disease, Alzheimer disease, mild cognitive impairment, and multiple system atrophy (19–22). Furthermore, several studies have demonstrated that changes of regional GM density are directly related to alterations of functional abilities (23–25). Moreover, increases of GM density seem to be related with increases of task-specific neuronal activation (26).

Encouraged by the VBM results in certain chronic pain syndromes and our previous findings of functional alterations of cerebral pain processing in pain disorder (3), we investigated patients suffering from pain disorder using VBM and hypothesized that GM changes would occur in pain-processing brain structures.

Furthermore, the classification of pain disorder as a mental disorder (Axis I) within the framework of DSM-IV has been hardly criticized. Therefore, it has been suggested to move pain disorder like other functional somatic syndromes to Axis III (general medical disorders) (27). Up to now, there is no clear evidence for structural central damage in pain disorder, which may be suggestive of explanatory pathology (28). If, beyond functional central nervous system changes, structural brain changes could be demonstrated in pain disorder, assigning the diagnosis of pain disorder to Axis III (general medical disorders) would no longer seem appropriate. Instead, such a

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finding would favor a new category of so-called general medical mental interface disorders (29,30).

METHODS

Patients and Volunteers

The study was approved by the local Ethics Committee of the Technische Universität München and written informed consent was obtained from all participants. The patient and healthy volunteer investigations took place between 2004 and 2006.

Fourteen right-handed female patients (medium age = 51.1 years; range = 28–68 years) fulfilling the DSM-IV criteria (American Psychiatric Association, 1994) (31) for pain disorder were selected from a consecutive sample of patients scheduled for a visit in the psychosomatic outpatient department of the Klinikum rechts der Isar, Technische Universität München, Germany. The predominant, although in most cases diffuse, clinical pain in the patient group was located in the head, neck, and shoulder region (diffuse headache, n = 4), in the lower back region (low back pain, $n = 7$), temporomandibular (facial pain, $n = 1$), in the pelvic region (lower abdomen, $n = 1$), or in the lower limbs ($n = 1$). Three subjects reported more than one predominant pain location (two subjects with headache as well as back pain, one subject with pain of the sacrococcygeal region and thigh with the pain radiating to the heel). From a clinical point of view, we considered these patients as severely affected for the diagnostic group of pain disorder. Physical and technical examinations of the patients were performed by a neurologist and orthopedic surgeon to exclude any somatic cause of the pain syndrome. Most of the patients also participated in a recently published fMRI study (3).

Twenty-five healthy controls (medium age = 51.7 years; range = 32–60 years) were recruited and matched for age, gender, and handedness. These participants were healthy, had no chronic/ongoing pain, and did not fulfill criteria for any psychiatric diagnosis according to the DSM-IV criteria.

Inclusion Criteria for Pain Disorder

Inclusion criteria were female gender, right-hand preference according to the Edinburgh Handedness Inventory (32), ages between 20 and 68 years, duration of clinical pain of at least 2 years, and diagnosis of pain disorder according to the DSM-IV.

The screening for somatoform symptoms (SOMS) was completed with the SOMS-2 questionnaire (33). It asks for the presence of 53 physical complaints lacking an organic disease during the previous 2 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 International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) somatization disorder, and the ICD-10 somatoform autonomic dysfunction symptom list. The DSM-IV somatization index is a central outcome sum score recruited by the single 33 DSM-IV items of the SOMS-2.

A further inclusion criterion was the report of a high affective dimension of the clinical pain syndrome as measured by the Pain Perception Scale (PPS) (34). This 24-item questionnaire describes the sensory and the affective qualities of pain in a "global affective score" and a "global sensory score." It had proven to be a reliable and valid tool to measure the affective and sensory component of pain in various studies and is an essential part of the pain questionnaire of the German IASP chapter (DGSS). The cut-off value for the inclusion of patients into the study was set to a minimum of 40 points (maximum value = 56).

The patients were asked for the average clinical pain intensity of the last 4 weeks, using an 11-point numerical rating scale (NRS) (0–10, where 0 = no pain and 10 = worst pain imaginable).

Exclusion Criteria

We excluded patients with the diagnosis of fibromyalgia as characterized by chronic widespread pain (involving all four quadrants of the body as well as the axial skeleton) and diffuse tenderness for two reasons (35). First, there is an ongoing debate whether patients with fibromyalgia can also be diagnosed as pain disorder or whether fibromyalgia has to be regarded as a separate disease entity (30). Second, recent VBM findings in patients suffering from fibromyalgia already exist (12,13) and we wanted to cover a broader spectrum of pain disorder. Patients who were not able to stop their pain medication for at least 1 week were also excluded. We also excluded controls or patients with magnetic resonance imaging (MRI) signs of cerebral atrophy diagnosed by a neuroradiologist, who visually analyzed the MRI images.

Structured Clinical (Psychiatric) Interview for DSM-IV(SCID)

The occurrence of psychiatric disorders was assessed during a structured clinical (psychiatric) interview (SCID-I, German version) (31) by a consultant psychiatrist according to the DSM-IV criteria (American Psychiatric Association, 1994). The SCID assesses current (last 4 weeks before interview) and lifetime psychiatric status for major Axis I psychiatric disorders, using the criteria which are in accordance with the DSM-IV.

Beck Depression Inventory (BDI)

The BDI is a 21-item self-report instrument that measures cognitive and endogenous aspects of depression on a 4-point scale (range = 0–3). This questionnaire has undergone extensive reliability and validation studies (36).

MRI Acquisition Parameters

MRI sequences were acquired from every participant, using a 1.5-Tesla scanner (Siemens Magnetom Symphony, Erlangen, Germany). For VBM, a T1-weighted MPRAGE sequence with sagittal slices was used (160 slices; slice thickness = 1 mm; voxel size = $1 \times 1 \times 1$ mm^3; flip angle = 15 degrees; field of view = 256×256 mm; TR = 8.9 ms; TE = 3.93 ms; TI = 800 ms). To exclude structural lesions, a FLAIR sequence with axial 6-mm slicing was used. No abnormal findings were detected in our investigated collective.

VBM—Preprocessing and Statistical Analysis

For preprocessing and statistical analysis, an extension toolbox named VBM2 (http://dbm.neuro.uni-jena.de/vbm) for the functional neuroimaging software SPM2 (http://www.fil.ion.ucl.ac.uk/spm) was used. VBM2 applies an "optimized" protocol for preprocessing high-resolution anatomical images (37) and for statistical analysis using a hidden Markov random field model (38). We used study-specific prior probability maps for segmentation and stereotactic normalization to the MNI standardized reference space defined by the Montreal Neurological Institute (Montreal, Quebec, Canada), and applied a Gaussian kernel of 8 mm for smoothing.

Analyses of Global GM Volumes

Global volumes of GM, white matter (WM), and cerebrospinal fluid (CSF) were derived from the nonnormalized segmented images as provided by SPM2 after the 1st segmentation process. A two-sided independent t test was performed with Prism 4 for Windows (GraphPad Software Inc., San Diego, California) to detect differences of GM volumes between the patient and control groups. Furthermore, we performed correlation analyses of GM volumes with subjects' age, BDI score, intensity and duration of pain, using Prism 4.

Voxel-Based Analyses of GM Changes

We included only voxels with a GM value >0.2 (maximum value = 1) and greater than the WM and CSF values to analyze only voxels with sufficient GM and to avoid possible edge effects around the border between GM, WM, and CSF.

In a cross-sectional design, regional GM changes between patient and control groups were investigated using the voxel-by-voxel analysis of covariance (ANCOVA). Age and BDI scores were included as nuisance variables to remove GM variance explained by age and depression. The problem of multiple comparisons on a voxel-wise whole brain level was handled by using the False-Discovery-Rate procedure (FDR) (39), which is a widely accepted approach for the analysis of neuroimaging data. Instead of controlling the chance of any false positives (as in Bonferroni or random field methods), FDR

TABLE 1. Demographic and Psychometric Variables and SCID Diagnosis (Pain Disorder and Comorbidity)

Demographic and Psychometric Variables	Patient Group	Control Group	*p*
Age	51.1 ± 11.1[a]	51.7 ± 7.2	>.05*
Pain duration (years)	9.8 ± 7.2	—	—
Rating of clinical pain (NRS 0–10)	8.8 ± 0.9	—	—
PPS, global affective score (0–54)	44.1 ± 7.8	12.3 ± 2.7	<.001
SOMS-2, DSM-IV somatization index	6.4 ± 3.7	1.7 ± 1.3	<.001
BDI, depression score (0–44)	21.6 ± 8.4	3.9 ± 3.5	<.001
SCID			
Pain disorder	14/14	0/25	<.001
Somatization disorder	3/14	0/25	<.002
Unspecific somatization disorder	0/14	0/25	>.05*
Current major depressive episode	7/14	0/25	<.001
Major depression in history	4/14	1/25	<.004
Other psychiatric disorders	4/14	0/25	<.004

SCID = Structured Clinical (Psychiatric) Interview for the DSM-IV; NRS = numerical rating scale; PPS = Pain Perception Scale; SOMS = screening for somatoform symptoms; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; BDI = Beck Depression Inventory.

[a] Mean ± standard deviation.

* NS.

controls the expected proportion of false positives among suprathreshold voxels. The statistical significance threshold for the categorical comparisons of GM densities between patient and control collective was set to $p < .05$ corrected with FDR.

Within the patient group, regional GM density was analyzed for correlations with the SOMS score, the global affective score (PPS), as well as duration and intensity of pain. Again, we applied ANCOVA with age and BDI scores as nuisance variables. Additionally, we performed a correlation analysis of the BDI scores only with GM density to detect depression-related effects on GM alterations (hereby only age was used as nuisance variable). For all correlation analyses, the statistical significance threshold was set to $p < .001$ uncorrected.

RESULTS

Psychometric Variables

Demographic and psychometric variables of the study sample are shown in Table 1. The mean duration of clinical pain was 9.7 ± 8.2 (standard deviation) years. The mean intensity of clinical pain during the last 4 weeks was 8.8 ± 0.9 out of 10 on an NRS. The amount of depressive symptoms (BDI of patients: 21.6 ± 8.4 versus controls: 3.9 ± 3.5; $p < .001$) and the DSM-IV somatization index score (SOMS of patients: 6.4 ± 3.7 versus controls: 1.7 ± 1.3; $p < .001$) were significantly higher in patients than in controls. Accordingly, SCID-I interviews revealed comorbidity with current major depressive episodes in 7 of 14 patients.

Global Volumes

We found neither significant differences in global GM volumes between both groups nor significant correlations of clinical parameters with global GM volumes.

Regional GM Changes

Comparing patients against controls, VBM (depression and age included as nuisance variables) revealed decreases of GM density in the patient group in the prefrontal cortex, including the ventromedial prefrontal (VMPFC)/orbitofrontal cortex (OFC) as well as in the middle frontal and superior medial frontal cortex ($p < .05$ FDR corr.) (Figure 1, Table 2). Decreases were also observed in the anterior (ACC) and posterior (PCC) cingulate cortex, insular cortex, parahippocampal and inferior temporal cortex as well as in the cerebellum ($p < .05$ FDR corr.) (Figure 1, Table 2). Vice versa, no significant increase of GM density could be detected ($p < .05$ FDR corr. as well as $p < .001$ uncorr.).

Correlations With Regional GM Changes

No correlations of the somatisation (SOMS), global affective (PPS) or clinical pain intensity scores with an increase or decrease of GM density on a voxel-wise whole-brain level were found. For regions of interest, such as VMPFC/OFC and ACC, no correlations of GM density alterations with the depression scores (BDI) were found.

The voxel-wise correlation analysis of GM density with the duration of clinical pain revealed a negative correlation in the left parahippocampal cortex (MNI coord. = −32 −17 −24; Z value = 3.82; $p < .001$ uncorr.) (Figure 2A), and a positive correlation in the right thalamus (MNI coord. = 19 −20 −2; Z value = 4.24; $p < .001$ uncorr.) (Figure 2B).

DISCUSSION

The combined results of DSM-IV diagnosis and specific questionnaires to further assess somatization (SOMS-2 and the pain perception scale) show that we included patients suffering from pain in more than one location and with a high affective pain quality. In these patients, our VBM study revealed significant GM decreases. The affected brain structures, such as the prefrontal cortex including the VMPFC/OFC, anterior, PCC and insular cortex, are known to be critically involved in pain processing (40) and play an important role in the amplification and exacerbation of the pain experience by mood and emotional state (41). The matrix of structural changes shows striking similarities with results of other VBM studies on patients with distinct types of chronic pain disorders, such as fibromyalgia (12,13), chronic tension type headache (42), and chronic back pain (14,15).

Although we found region-specific abnormalities similar to previous studies, there are also remarkable differences. Whereas Kuchinad et al. and Apkarian et al. observed age-related global GM decreases (13,14), we did not find such a decrease in our patient group. Most likely, this discrepancy may be attributed to our exclusion criteria, excluding any controls or patients with MRI signs of cerebral atrophy. Another difference to the other VBM studies is that half of our patient group fulfilled the DSM-IV criteria for an acute episode of major depression according to the SCID and showed elevated scores in the BDI. As there is evidence from the literature that depression is associated with GM decrease,

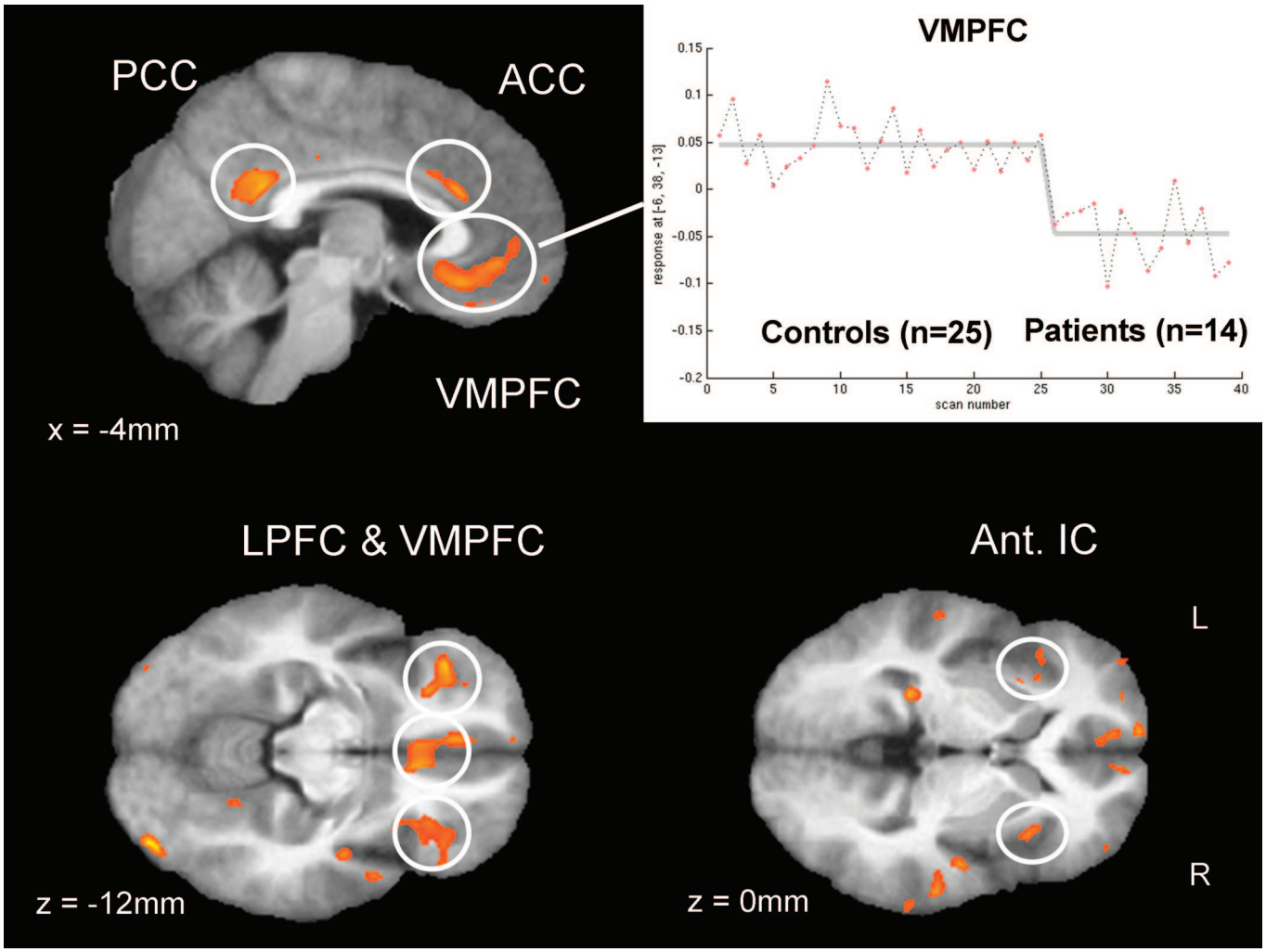

Figure 1. Decreases of gray matter (GM) density in female patients (n = 14) with pain disorder compared with a healthy age-matched female control population (n = 25). GM decrease is observed in the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), lateral prefrontal cortex (LPFC), ventromedial prefrontal cortex (VMPFC), and anterior insular cortex (IC). An exemplary plot of GM densities for the VMPFC is demonstrated, showing on the left the GM densities for controls and on the right side the GM densities for the patients. Right side of the image corresponds to the right side of the brain. The x, y, and z values indicate the slice position according to the standardized reference space defined by the Montreal Neurological Institute.

preferentially in prefrontal areas (43–45), we included the BDI scores as nuisance variable in our analysis to exclude any GM changes related to depression. In a further step, we performed correlation analyses of BDI scores with global GM volumes as well as with region-specific GM densities of the VMPFC/OFC and ACC, to examine the influence of depression on GM changes. No correlation was revealed. Therefore, we conclude that the GM decrease observed in pain-processing structures of our study group represent a pathophysiological marker of pain disorder.

VMPFC/OFC

In a recent fMRI study, we evidenced an altered cerebral pain processing in patients with pain disorder and suggested a dysfunction in pain-processing structures (3). One of the main findings was a decreased pain-related activation of the VMPFC/OFC. It is very interesting that the observed functional changes overlap with GM decreases in almost identical parts of the VMPFC/OFC in this study. Other disorders, such as fibromyalgia or chronic tension-type headache, also exhibit structural changes in prefrontal regions (13,42). These findings underline the relevance of the VMPFC / OFC in the pathophysiology of pain disorder and more generally in functional somatic syndromes.

There is accumulating evidence from animal and functional neuroimaging studies that the cingulo-frontal area, including the rostral ACC and VMPFC/OFC, is involved in the processing and modulation of pain (46–51). These studies support the view of a top-down inhibitory or facilitatory capacity of the cingulo-frontal area which is involved in hypnosis, cognitive and emotional modulation of pain, placebo and opioid analgesia. Therefore, we speculate that the GM decrease in the cingulo-frontal area points to a defective pain regulation.

In addition, the VMPFC/OFC turned out to be the exclusive area in which hypoactivity remained even after withdrawal from long-term analgesics in patients with chronic analgesic-overuse headache evolving from episodic migraine, indicating a role in the maintenance of chronic pain (52).

TABLE 2. Decreases of Gray Matter Density in Patients With Pain Disorder Compared to Age-Matched Healthy Volunteers

Region	Decreases of Gray Matter Density			
	Side	x/y/z	Z Value	Cluster Size (mm^3)
Mid orbitofrontal cortex/ VMPFC	L	−10 66 −5	4.91	189
		−6 38 −13	5.14	809
Inf. orbitofrontal cortex/ LPFC	L	−37 43 −13	5.72	507
	R	31 23 −15	5.16	218
Middle frontal cortex	L	−42 54 −7	5.12	200
Sup. medial frontal cortex	L	−7 53 22	5.09	125
ACC (BA24′)	R	7 40 14	5.57	252
PCC	L	−3 −45 25	5.53	340
Ant./mid insula	R	35 19 1	5.46	170
Post. insula	R	43 −11 −8	5.21	210
Transition zone Parahippocampal cortex/post. thalamus	L	−23 −36 3	5.53	472
Inf. temporal cortex	L	−43 −27 −26	5.66	492
Cerebellum	R	8 −46 −23	4.45	252

VMPFC = ventromedial prefrontal cortex; LPFC = lateral prefrontal cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex.
Brain regions stated in MNI (standardized reference space defined by the Montreal Neurological Institute) coordinates with maxima of gray matter decrease, threshold at $p < .05$ False-Discovery-Rate procedure corrected for multiple comparisons. Minimum cluster size is 125 voxel (5 mm × 5 mm × 5 mm = 125 mm^3).

An explanation for the GM decrease and the decreased functional activation of the VMPFC/OFC might be an abnormal brain chemistry as evidenced with MR spectroscopy in patients suffering from chronic back pain (53). However, further studies are needed, such as animal studies, to get a better understanding of what is behind GM-density decreases in VBM studies. The possibility should be considered that reduced GM volume/density may precede rather than follow the chronic pain.

Cingulate and Insular Cortex

Clusters of GM decrease were observed in the cingulate cortex and in the insular cortex. GM decreases with similar locations have been found in patients with fibromyalgia (13), chronic tension-type headache (42), and migraine (54). The ACC has neuroanatomical connections with the OFC, amygdala and periaquaeductal gray, structures known to be involved in the modulation of pain (inhibition/facilitation) (40,55). Regarding the anterior insular cortex, neuroanatomical connections to the limbic system (amygdala), prefrontal cortex (OFC/VMPFC), and temporal lobe have been described (56). In general, the ACC plays an important role in the evaluation, processing, and integration of sensory, motor, cognitive, and emotional aspects of pain (57–60). In our study, the GM decrease of this region might be related to the constantly increased pain experience in patients suffering from pain disorder.

The anterior insular cortex is important for linking emotions to cognitive processes and behavioral responses (61). It is also involved in aversive interoceptive processing, e.g., coding of pain intensity (62) and the processing of emotional- and memory-related aspects of pain (40,63). An extensive GM decrease of the insular cortex has been found in patients with posttraumatic stress disorder (64). The authors assumed that this region is involved in the pathology of posttraumatic stress disorder and might relate to the cognitive deficits often found in these patients. Although we did not systematically evaluate cognitive functioning in our patients, cognitive deficits are not a typical hallmark of pain disorder and none of the patients had a previous diagnosis of mild cognitive impairment or dementia. We therefore suggest that the GM decrease in the cingulate and insular cortex is the consequence of a reorganization induced by the heightened activation level (3) of these areas in patients suffering from pain disorder.

Negative Correlation of Pain Duration With GM Density of the Parahippocampal Cortex

In the correlation analysis, we found that the GM density in the parahippocampal cortex is decreasing, the longer the pain syndrome continues. GM decreases of this region have been found mainly in stress-related disorders, such as posttraumatic stress disorder (64–67) or chronic fatigue syndrome (68,69). The involvement of the amygdala and the parahippocampal cortex in the processing of anxiety, fear, and aversive contents of pain has been demonstrated in several functional neuroimaging studies (70,71). Activation changes, especially of the hippocampal formation, were observed in healthy subjects when the pain sensation is accompanied by anxiety (72). Whether the permanent recall of memory contents related to anxiety or the disease progression itself may cause the GM decrease in this brain region remains an open question.

Positive Correlation of Pain Duration With GM Density of the Thalamus

Although there was no significant GM increase in the thalamus in the categorical analysis, we found a positive correlation of GM density with the duration of pain. Similar results were obtained in a VBM study investigating patients with chronic back pain, where structural changes with an increase in GM density were found in the thalamus (15). Moreover, in patients with esophageal dysfunction (73) and patients with chronic low back pain (74), increased pain-related thalamic responses were found. It was suggested that these responses are a sign of generalized hypervigilance to noxious stimuli. Thus, it may be speculated that long lasting hypervigilance to body signals may be the cause of the increasing GM density in the thalamus in our patient cohort.

General Considerations Regarding the Interpretation of the Study Results

A potential limitation of this study is related to the fact that, in 50% of our patient collective, a current major depressive episode was diagnosed. This is due to the fact that depression

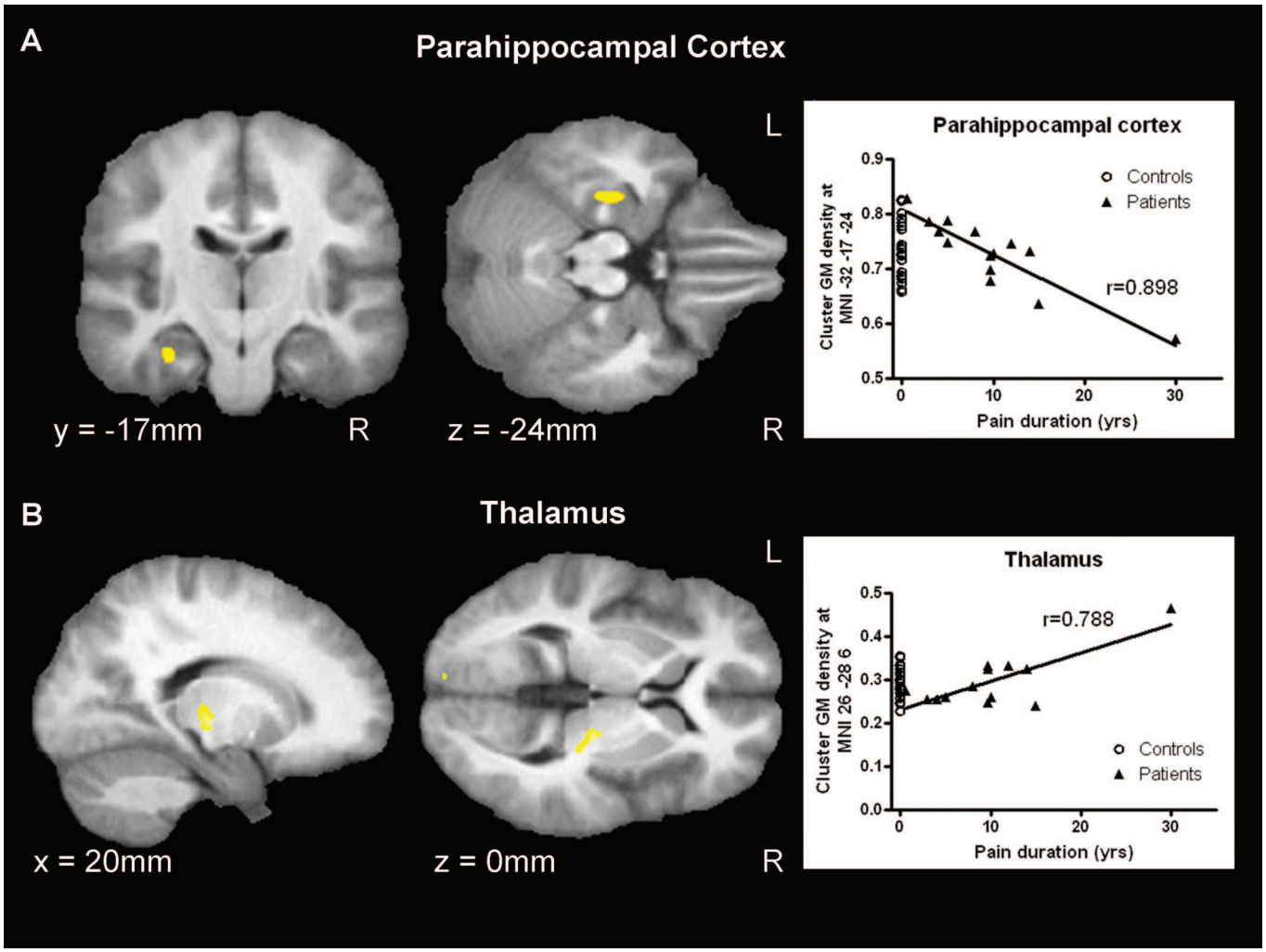

Figure 2. **A** Negative correlation of clinical pain duration with gray matter (GM) density in the left parahippocampal cortex ($p < .001$). **B** Positive correlation of clinical pain duration with GM density in the right thalamus ($p < .001$). Right side of the image corresponds to the right side of the brain. The x, y, and z values indicate the slice position according to the standardized reference space defined by the Montreal Neurological Institute.

is an often observed psychiatric comorbidity in pain disorder (75). Although we controlled this effect using the BDI scores as nuisance variable, an alternative and probably more optimal approach would have been to investigate an additional control collective of patients suffering from major depressive disorder without pain disorder.

We discussed most of the GM changes in the patient cohort as being related to their clinical pain. However, it must be acknowledged that patients with a long history of pain and very high pain scores often reduce their exercise levels and therefore reduce their cognitive load, which is related to disability and underemployment. One might therefore argue that these factors could contribute to the brain differences observed.

However, the results of our study raise further important questions: Do the brain differences precede the onset of the chronic pain and are they hence a possible cause of pain disorder? There also remains the question of plasticity and reversibility of the observed changes. Future longitudinal studies will have to clarify whether the reduction in GM density recovers when the pain is reduced. First, VBM studies on the question of plasticity by Draganski et al. suggested that changes in GM density as measured by VBM might be (partly) reversible, as shown in training-induced VBM changes (76) and in experiments with repetitive pain stimulation (77). These points should set the stage for subsequent research into this important area.

CONCLUSION

As far as the DSM-IV classification of pain disorder is concerned, experts have seen no adequate reason for classifying this disorder as a mental one (27,28). Obviously, a further proof of the important role of central changes in pain disorder is still needed. In some organ- or system-based functional somatic syndromes like fibromyalgia (12,13), chronic back pain (14,15), and chronic tension-type headache (42), recent VBM studies have already discovered structural central nervous changes. Pain disorder, in extension to these functional somatic syndromes, is a more generic diagnostic category not restricted to a specific organ- or system-based dysfunction.

VBM OF PATIENTS WITH PAIN DISORDER

Our results show that patients with pain disorder may also suffer from structural brain damage, which indeed is a core element of mental disorders. Thus, our study results argue in favor of a new category of general medical-mental interface disorders (29,30), comprising the whole group of functional somatic syndromes. This diagnostic approach would cover pathophysiological changes in the whole variety of functional somatic syndromes, which are to be found in the peripheral as well as in the central nervous system.

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