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Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients

T. Schmidt-Wilcke [a], E. Leinisch [a], S. Gänßbauer [a], B. Draganski [a], U. Bogdahn [a], J. Altmeppen [b], A. May [a,c,*]

[a] *Department of Neurology, University of Regensburg, Germany*
[b] *Department of Anaesthesiology, University of Regensburg, Germany*
[c] *Department of Systems Neuroscience, University of Hamburg Eppendorf (UKE), Martinistr. 52, D-20246 Hambug, Germany*

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Abstract

Although chronic back pain is one of the most frequent reasons for permanent impairment in people under 65, the neurobiological mechanisms of chronification remain vague. Evidence suggests that cortical reorganisation, so-called functional plasticity, may play a role in chronic back pain patients. In the search for the structural counterpart of such functional changes in the CNS, we examined 18 patients suffering from chronic back pain with voxel-based morphometry and compared them to 18 sex and age matched healthy controls. We found a significant decrease of gray matter in the brainstem and the somatosensory cortex. Correlation analysis of pain unpleasantness and the intensity of pain on the day of scanning revealed a strong negative correlation (i.e. a decrease in gray matter with increasing unpleasantness/increasing intensity of pain) in these areas. Additionally, we found a significant increase in gray matter bilaterally in the basal ganglia and the left thalamus. These data support the hypothesis that ongoing nociception is associated with cortical and subcortical reorganisation on a structural level, which may play an important role in the process of the chronification of pain.
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1. Introduction

In many countries, chronic back pain is one of the most frequent pain disorders among humans. 70–85% of all people have experienced back pain at some point in their lifetime (Andersson, 1998). Nevertheless, the mechanisms of chronification are the subject of intense research and debate. Chronic pain states are currently attributed to abnormal nociceptive/antinociceptive function on different levels (Wall and Melzack, 1999), yet with a normal brain structure. Recent neurobiological research, however, suggests cortical reorganisation on a functional level (Grusser et al., 2004). This "functional reorganisation" was not only detected in patients suffering from phantom limb pain (Flor et al., 1995), but also in chronic back pain patients (Flor et al., 1997). Regarding chronic back pain, increased cortical responsitivity and a shift of the cortical representation of the back, which was interpreted as an expansion of the back's representation into the neighbouring foot and leg area (Flor et al., 1997), were found. In patients suffering from chronic regional pain syndrome (CRPS Typ I), magnetic and electric source imaging revealed a shrinkage of the representational field of the affected

* Corresponding author. Tel.: +49 040 42803 9189; fax: +49 040 42803 9955.
E-mail address: a.may@uke.uni-hamburg.de (A. May).

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arm. The extent of shrinkage correlated highly with the intensity of pain and the magnitude of mechanical hyperalgesia (Maihofner et al., 2003; Pleger et al., 2004).

Apart from functional plasticity in chronic pain states, few studies have addressed the issue of structural reorganisation. In primates, a transneuronal atrophy has been demonstrated in the cuneate and thalamic nuclei, following long-term denervation of an upper limb (Jones and Pons, 1998). Very recently in humans, it was demonstrated that chronic back pain is accompanied by brain atrophy and it was suggested that the pathophysiology of chronic pain includes thalamo-cortical processes (Apkarian et al., 2004). Specifically, this study found a decrease in gray matter in the dorsolateral prefrontal cortices bilaterally and a decrease in gray matter in the right thalamus. Given that the physiology of nociception involves a complex interaction of the peripheral and central nervous system (Woolf and Salter, 2000), one would expect that in the process of the chronification of pain, functional and structural changes would probably occur in modulatory mechanisms of nociception, namely, the antinociceptive system.

Two fundamental questions arise:

- Is there any evidence that adult humans suffering from chronic pain show an alteration in brain morphology in structures specific to the perception and behavioral response to pain, such as the thalamus, insulae, sensorimotor and cingulate cortex and the antinociceptive descending pathways?
- Is this alteration the cause or the consequence of chronification?

To investigate the first issue, we applied voxel-based morphometry (VBM) on structural MRI scans. We compared a group of 18 chronic back pain patients with 18 sex and aged matched healthy volunteers. All chronic back pain patients had a pain history longer than six months. At the time of scanning, no acute neurological symptoms were identifiable. We also searched for correlations between changes in gray matter volume and pain duration, pain intensity and pain unpleasantness.

2. Methods

2.1. Study population and clinical assessment

Eighteen patients (9 male, 9 female; aged 34–59 years; mean age 50.4 years $\pm$ 6.8 years) suffering from chronic back pain and 18 healthy volunteers (9 male, 9 female, aged 32–60; mean age 49.9 $\pm$ 8.7 years) participated in the study (see Table 1). Gender was exactly matched, the age was not significantly different between the groups ($p = 0.84$). The healthy controls did not differ from the patients except for the presence of chronic low back pain and consequent medication. The diagnosis of *chronic* back pain was based on the definition of the Quebec Task Force (Spitzer, 1987) (7 weeks from onset), as well as on the definition given by Bonica (Bonica, 1990) (pain that persists a month beyond the usual course of an acute disease or a reasonable time for an injury to heal). The duration of chronic back pain ranged from 6 months to 28 years (mean duration 176 $\pm$ 87.60 months). Chronification is a multimodal concept, regarded as the result of multiple interrelating physical, psychological,and social/occupational factors (Turk and Rudy, 1987; Waddell, 1996; Nagel et al., 2002). We therefore assessed anxiety, depression and affect in all patients. Nearly all of the patients took analgesic medication on a regular basis (for demographic details, analgesic and concomitant medication see Tables 1 and 2). All patients had become pre-occupied with pain, limiting daily activities (fulfillment of the second part of the Quebec Task Force). None of the participants had a history of head injury or other psychiatric/neurological disorders, apart from herniated discs, which had in some cases been operated (a minimum two years prior to the VBM-study). 15 out of 18 patients had received a CT or MRI scan of the lumbar spine and/or sacroiliac joints within the past three years with no evidence of acute abnormalities. All patients underwent a thorough neurological examination. Patients with a higher degree of sensorimotor deficits (pareses $>$ 4/5 and/or sensory deficits involving more than 1 dermatom) were excluded from the study. All patients and healthy volunteers received a high-resolution T_1-weighted cerebral MRI. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients and healthy volunteers prior to the examination.

2.2. Perceptual measures of pain and depression

All chronic back pain patients underwent an examination by a psychiatrist (LE) to rule out a depressive disorder. Perceptual measures of pain and depression were carried out on the day of imaging (details listed in Table 1). The tests included the following assessments of pain and depression: the pain experience scale (SES) (Geissner, 1995), present pain intensity using a Numerical Rating Scale (NRS) (De Conno et al., 1994), the Hamilton Depression Scale (HAMD) (Hamilton, 1960) and the Montgomery-Asperg Depression Scale (MADRS) (Montgomery and Asberg, 1979) as external assessment scales, and a self-assessment depression scale (ADS) (Hautzinger, 1993).

The pain experience scale consists of 24 descriptors: 14 affective and 10 sensory. These are rated on a scale from 1 to 4 in ascending intensity of the item. The pain experience scale is a continuation of the McGill Pain Questionnaire (MPQ) (Melzack, 1975). The present pain intensity on the day of imaging was indicated on a Numerical Rating Scale (NRS) from 0 to 10, 0 representing no pain and 10 the worst possible pain imaginable.

The Hamilton Depression Scale is an assessment scale with 21 descriptors for symptoms of major depression, which are rated on an intensity scale from 0 (none) to 4. Based on an interview, the Montgomery Asberg Depression Scale includes 10 items scaled from 0 to 6. The investigator evaluates the severity of the symptom from 0 (none or normal occurrence) to 6. The common depression scale (self-assessment scale) is the German version of the Center for Epidemiological Studies-Depression scale (CES-D; R) (Radloff, 1977). The questions refer to the previous week and are answered on a four-scale rating: 0, rare to 3, mostly.

Table 1
Demographic data, pain and depression scores

Patient No.	Sex/age (years)	Pain medication (dosage per day, if known)	Medical history	Neurological deficits	Duration of pain (months)	NRS	SES	HAMD	MADRS	ADS
1	F/59	Flupirtine, 6 tab	Laminectomy L3/4/5 several years ago	4/5 paresis of left iliopsoas m. and left extensor hallucis longus m. since years	240	10	41	12	13	29
2	F/57	Miscellaneous analgesics when needed	2 disc operations in 1985	Patellar tendon reflex: re < li, 4/5 paresis of right tibialis anterior m.	276	5	36	8	9	24
3	F/55	NSAID when needed	Lumbar stenosis	hypesthesia left thigh, since years	120	2	51	16	19	28
4	M/58	Morphine 150–350 mg	Cervical disc prolaps C5/6 several years ago	–	120	5	32	7	7	5
5	M/48	Tramadol 400 mg	–	Achilles tendon reflex: lft < r	336	6	40	17	20	43
6	M/52	Miscellaneous analgesics when needed	Syringomyelia Th6–10	Patellar tendon reflex: lft < r, 4+/5 paresis of iliopsoas m. & Quadriceps m.	60	6	45	8	8	6
7	F/43	Diclofenac 50–150 mg	Hysterectomy, strumectomy	Pallhypesthesia: feet bilaterally	108	9	37	9	8	13
8	F/46	Metamicol, Diclofenac, Amitryptiline	Hysterectomy	–	312	6	39	6	6	18
9	M/34	Indometacin 75 mg Tetrazepam	Morbus Bechterew (suspected)	–	132	2	27	8	10	12
10	F/47	Diclofenac when needed	Operation of herniated disc L5/S1 several years ago, arthrosis of sacroiliac joints	–	240	8	25	5	5	6
11	M/53	Morphine 60 mg, Amitryptiline 150 mg	Herniated disc L5/S1, nucleotomy, C4/5 (1995), C5/6 (1997), C6/7 and L5/S1 (2000)	–	96	9	46	9	15	46
12	F/57	Tramadol 600 mg		–	276	9	55	15	13	31
13	M/53	Diclofenac when needed	Lumbar stenosis, herniated disc L5/S1 right (1990)	hypesthesia: exterior of right lower leg and right foot since years	216	6	48	18	18	37
14	M/39	Miscellaneous analgesics, when needed	Multiple degenerative alterations in the lumbar spine, coxarthrosis	–	132	5	32	7	9	23
15	M/53	Flupirtine, Tramadol when needed	Herniated disc L5/S1 several years ago	Achilles tendon reflex r < lft	180	8	40	10	18	24
16	M/50	Morphine 4 tab	Coxarthrosis	–	132	7	53	13	16	22
17	F/49	Carbamazepin 900 mg, Gabapentin 1200 mg, Metamizol 32 mg	Herniated discs, operation L4/5 (1993 and 2001), L3/4 (2001)	Hypesthesia dorsum of right foot	156	7	42	7	3	11
18	F/55	Diclofenac 150 mg, Morphine 50 mg,	Herniated disc L5/S1 several years ago	–	36	3	28	5	4	11

Demographic data including medication, medical history and neurological deficits of patients suffering from chronic back pain and clinical characteristics and perceptual measures for depression and pain of 18 patients with chronic back pain.
NRS, Numerical Rating Scale, indicating intensity of pain on day of imaging on a scale from 0 to 10 the: 0, no pain; 10, worst possible pain.
HAMD, Hamilton Depression Scale (foreign assessment).
MADRS, Montgomery Asberg Depression Rating Scale (foreign assessment).
ADS, Common Depressive Scale (self-assessment).
SES, pain experience scale, affective items.
M, male, F, female.

2.3. Data acquisition

Magnetic resonance imaging was performed on a Siemens Symphony scanner (Erlangen, Germany) operating at 1.5 Tesla. A 3D structural MRI was acquired on each subject using a T_1 weighted prepared rapid gradient echo (MP-RAGE) sequence (TR 11.08 ms, TE 4 ms, TI 300 ms, flip angle 15°, matrix size 256×192, FOV 256×192) yielding 150 sagittal slices with a defined voxel size of $0.97 \times 0.97 \times 1.08$ mm. The latter sequence was chosen in order to provide a high-resolution anatomical image and a good gray/white matter contrast for subsequent segmentation.

2.4. Pre-processing of structural data and analysis

VBM is based on high-resolution structural 3D-MR-images, registered in common stereotactic space, and designed to seek significant regional differences by applying voxel-wise statistics in the context of Gaussian random fields (Friston et al., 1999; Ashburner and Friston, 2000). VBM has been cross-validated with region-of-interest measurements and functional data in a number of studies (May et al., 1999; Woermann et al., 1999). The data pre-processing and analysis was performed using SPM99 (Welcome Department of Cognitive Neurology, London, UK) running under Matlab (Mathworks, Sherborn, MA, USA). Preprocessing of the data involved spatial normalization (Ashburner and Friston, 1997, 1999), gray matter segmentation (Ashburner and Friston, 1997) and spatial smoothing with a Gaussian kernel (Ashburner and Friston, 2000). For the pre-processing steps, we used a previously described optimized protocol (Good et al., 2001). This protocol creates an additional step for optimized normalization parameters, involving a fully automated extraction of non-brain voxels (skull, sinus, etc.) in order to facilitate segmentation. The optimized parameters, estimated while normalizing extracted gray matter images to the gray matter template, are reapplied to the original whole brain images.

To reduce the potential scanner dependent bias of the normalization step, we created a scanner- and study-specific gray matter template, generated from 21 healthy controls, which were not included in this study. We applied the estimated optimized parameters in an additional step to the non-normalized, non-segmented original images. The spatially normalized whole brain images were then segmented. Subsequently, all images were smoothed by convolving them with an isotropic Gaussian kernel of 10 mm full-width at half maximum (FWHM).

2.5. Statistical analysis

The SPM analysis is an implementation of the general linear model (GLM) using the theory of Gaussian random fields. Using the GLM, a voxel-wise statistical parametric map is created, which identifies brain regions containing significant differences of gray matter in both groups. We used *t*-tests in order to detect these regional differences. To avoid possible edge effects around the border between gray and white matter and to include only relatively homogeneous voxels, we excluded all voxels with a matter value of <0.2 (of a maximum value of 1). We hypothesised, based on findings from electrophysiological (Flor et al., 1997; Bentley et al., 2003; Frot and Mauguiere, 2003) and functional imaging (Derbyshire et al., 2002; Peyron et al., 2000) studies, the involvement of the pain transmitting CNS network, which permitted an uncorrected threshold of $p < 0.001$ throughout the whole brain.

In order to further evaluate the relationship between the morphological alterations and to differentiate between the relevance of pain duration, pain intensity, and pain unpleasentness, we performed a correlation analysis using different indices to delineate which of these factors may best describe the findings of the group analysis. The indices were defined as

1. Pain duration in months.
2. Pain intensity on the day of examination and
3. The affective component of pain experience, obtained by the SES score, and referred to as "pain unpleasantness".

3. Results

3.1. Global differences in brain morphometry

Conventional MR-imaging was normal in all chronic back pain patients and controls. No significant between-group differences were observed in the comparison of chronic back pain patients and controls in global brain volume (gray matter patients: 682 ± 11.0 ml and gray matter controls 690 ± 56.3 ml).

3.2. Group analysis

Compared to healthy controls, chronic back pain patients showed a significant reduction in gray matter in the right somatosensory cortex and in the brainstem ($p < 0.001$, uncorrected). Lowering the significance threshold resulted in a bilateral decrease of gray matter in the somatosensory cortex. Additionally, we found decreases in gray matter in the right dorsolateral prefrontal cortex (DLPFC) and the right temporal lobe (Table 2).

A significant increase in gray matter was found in the putamen bilaterally ($p < 0.001$, uncorrected) and the left posterior thalamus. No small volume correction was carried out, as we had not defined a strong a priori hypothesis for these regions. There were no significant alterations in any other brain areas. For details (i.e. peak coordinates and *z*-values) see Table 2.

3.3. Correlation analysis

To further specify the intrinsic relevance of pain duration, pain intensity on the day of scanning, and pain unpleasantness to the structural alterations found in the group analysis, we performed a correlation analysis using a linear regression ($p < 0.001$, uncorrected). This tests the null hypothesis that the slope of a least square fit (regression) describing the relationship between a predictor and an outcome variable is zero. We found the following:

Table 2
Areas of significant change in gray matter

Region	Brodmann area	Talairach coordinates in mm			Z score of peak change $p < 0.001$	T	Gray matter change
		x	y	z			
R putamen		28	−17	2	$Z = 3.91$	4.44	Increase
L putamen		−24	−14	5	$Z = 3.76$	4.22	Increase
L thalamus		−22	−25	3	$Z = 3.18$	3.46	Increase
Dorsal rostral pons		2	−25	−18	$Z = 3.51$	3.88	Decrease
R somatosensory cortex	BA 1/2	12	−38	80	$Z = 3.79$	4.26	Decrease
R prefrontal lobe (DLPFC)	BA 8/9	38	32	39	$Z = 3.70$	4.15	Decrease
R temporal lobe	BA 37	47	−25	−24	$Z = 4.39$	5.14	Decrease
L lateral occipitotemporal gyrus	BA 19/37	−34	−61	−10	$Z = 3.81$	4.31	Decrease

Significant changes (increase and decrease of cerebral gray matter) in chronic back pain patients when compared to healthy controls. The changes are tabulated in terms of the brain region and the corresponding Brodmann's area (BA). The x, y, z co-ordinates are according to the atlas of Tailarach and Tournoux. Each location is the peak within a cluster (defined as the voxel with the highest Z-score).

(1) There was no significant correlation between possible structural changes and pain duration.
(2) There was a strong negative correlation (i.e. decrease in gray matter with increasing pain intensity) between the brainstem and the left somatosensory cortex and pain intensity on the day of scanning and a positive correlation (i.e. increase in gray matter with increasing pain intensity) in the left thalamus and left putamen.
(3) Analysis of pain unpleasantness on the day of scanning revealed a strong negative correlation (i.e. a decrease in gray matter with increasing unpleasantness) in the brainstem and in the somatosensory cortex bilaterally (Table 3).

Pain intensity and SES scores correlated strongly in our population ($r = 0.79$). Performing a multiple regression and using both parameters together, only the cluster in the brainstem ($r = 0.65$) showed a strong negative correlation with these components of pain.

4. Discussion

Using VBM we found significant differences in CNS gray matter between chronic back pain patients and healthy controls (Fig. 1), which fall into two broad groups:

- areas showing a *decrease* in gray matter mainly involving the brainstem and the somatosensory cortex and
- areas showing an *increase* in gray matter, such as the thalamus and basal ganglia.

These data suggest that prolonged nociceptive input leads to an alteration in morphology and/or cytoarchitecture of anterograde projection areas, which in turn may have contributed to chronification, i.e. pain experience lasting longer than the initial pain trigger.

4.1. Decrease in gray matter: Brainstem

In humans, stimulation of the brainstem is suggested to be effective in intractable pain states (Gybels and Kupers, 1990; Duncan et al., 1991). Interestingly, in patients suffering from both back pain and dysesthetic leg pain, the back pain component seemed to respond better to PAG stimulation, whereas dysesthetic leg pain was controlled more effectively by somatosensory region stimulation (Hosobuchi, 1986). In functional imaging studies, an activation in the mesenscephalon following the application of pain stimuli has been frequently described (Derbyshire, 1999; Peyron et al., 2000). Recently, evidence has been provided that iron levels in the PAG might be abnormally high in migraine

Table 3
Correlation analyses with NRS and SES scales as regressors

Region	Talairach coordinates in mm			NRS r values	Talairach coordinates in mm			SES r values	Correlation
	x	y	z		x	y	z		
L putamen	−22	−13	8	0.54					Positive
L thalamus	−22	−31	11	0.55					Positive
Dorsal rostral pons	1	−24	−18	−0.69	0	−20	−16	−0.52	Negative
R somatosensory cortex	7	−43	−77	−0.53	12	−39	78	−0.56	Negative
L somatosensory cortex	−30	43	72	−0.63					Negative

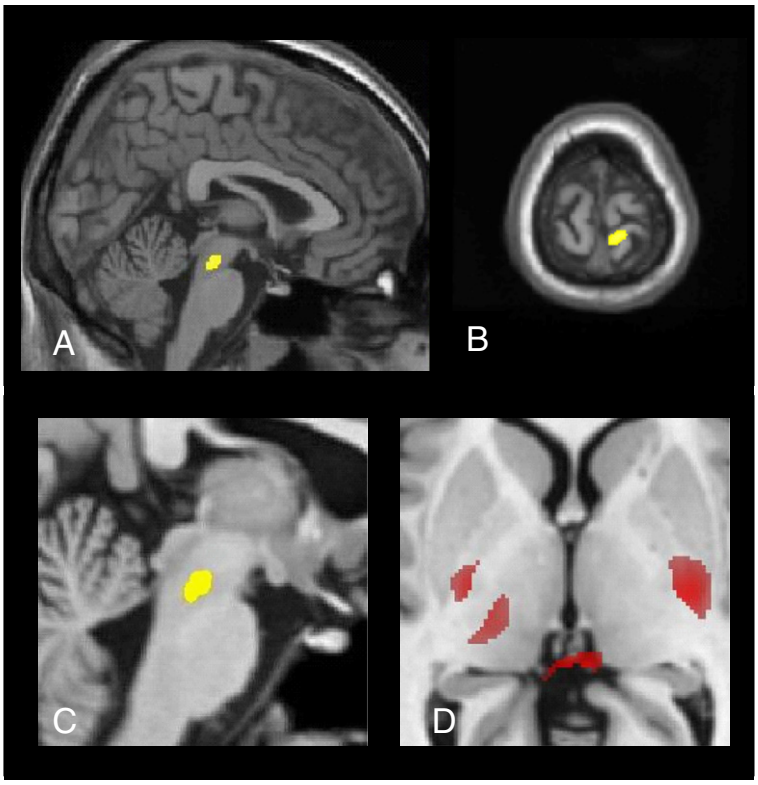

Fig. 1. Statistical parametric maps demonstrating the structural difference in gray matter between chronic back pain patients and unaffected control subjects. Significant gray matter changes are shown superimposed in yellow (decrease of gray matter) and red color (increase of gray matter), respectively, on a normalized image of a healthy control subject. The left side of the picture is the left side of the brain. (A and C) Significant decrease of gray matter in the brainstem. (B) Significant gray matter decrease in the somatosensory cortex on the right side. Lowering the significance threshold resulted in a bilateral decrease of gray matter in the somatosensory cortex. (D) Significant gray matter increase in the basal ganglia bilaterally and left thalamus.

patients (Welch et al., 2001). It is not clear whether VBM could detect high iron levels in specific regions; however, using VBM in migraine with and without aura, no structural changes have been identified (Matharu et al., 2003; Schmidt-Wilcke et al., 2005).

The decrease of gray matter in a brain region that is highly associated with pain suppression could certainly lead to a loss of effective antinociception. We suggest that our findings of a gray matter decrease in the brainstem may promote the chronification of back pain. Abnormal modulation of brain nociceptive systems, at first transient, but becoming permanent with continuing illness, can in part explain the shift from acute to chronic pain. Our results regarding the correlation analyses suggest that the gray matter decrease in the brainstem does not correlate with pain duration, but rather with pain intensity and pain unpleasantness experienced at the time of scanning, thus possibly accounting for the degree of impaired antinociception at that time. However, examining the time course is crucial in understanding the complex mechanisms in nociception and antinociception. The question whether alterations in the brainstem precede or succeed the clinical process of chronification needs to be thoroughly addressed in future studies, focussing on longitudinal data investigating patients over time.

4.2. Decrease in gray matter: Somatosensory cortex and DLPFC

The lateral thalamus and SI cortex belong to the so-called "lateral" pain system (Derbyshire, 1999; Schnitzler and Ploner, 2000), which projects predominantly to the somatosensory cortex with a high degree of somatotopic organisation on each level of subcortical and cortical structures. On a functional level, both shrinkage (Soros et al., 2001; Maihofner et al., 2003; Pleger et al., 2004) and extension (Braun et al., 2001; Karl et al., 2001) of the representational fields have been described for various painful and non-painful conditions.

At first glance, our finding seems to contrast with previous electrophysiological data in 10 chronic back pain patients, showing an expansion of functional brain maps (Flor et al., 1997). On the other hand, in CRPS patients, a shrinkage of the representational field of the affected arm, which was highly correlated with the intensity of pain and hyperalgesia, has been repeatedly demonstrated (Maihofner et al., 2003; Pleger et al., 2004). However,

these electrophysiological studies investigated (using evoked magnetic fields) the phenomenon of functional reorganisation, i.e. the recruitment and/or coordination of neural activity, whereas our results show a *structural* reorganisation. The discordance of an expansion of the functional representation of the back, on one hand, and the relative loss of gray matter in the somatosensory cortex, on the other hand, mirror at the least a pain-correlated alteration in this region, which presumably sustains the experience of pain.

We also found a decrease in gray matter in the right DLPFC, which is in part in accordance with the literature (Apkarian et al., 2004). The authors found a bilateral decrease in gray matter of chronic back pain patients and suggested that neurodegeneration, rather than tissue shrinkage without a substantial impact on neuronal properties, may be the cause of this finding. Future studies involving longitudinal designs and treatment protocols are needed to answer the question of whether treatment could reverse the decrease in brain gray matter.

4.3. Increase in gray matter: Thalamus

Functional reorganisation in the thalamus, which acts as a relay station between spinal and cortical structures, has been demonstrated in rats, monkeys, and humans (Wall and Egger, 1971; Jones and Pons, 1998). Our finding of structural reorganisation may reflect the consequence of constant input of afferent nociceptive information, i.e. a ''projected pathology'', from the actual lesion site. The notion, that a change in afferent input may be followed by specific structural changes in the central nervous system, has been recently demonstrated using VBM in patients suffering from cervical (Draganski et al., 2003) and hand (Garraux et al., 2004) dystonia, Huntington's disease (Kassubek et al., 2004), restless legs syndrome (Etgen et al., 2005) and following amputations (Draganski et al., 2006). In this regard, however, it is noteworthy that we have found no gray matter changes in other structures known to be involved in sensory transmission, such as the cingulate cortex or anterior insulae. It is also important to mention a recent VBM study by Apkarian et al., who found a decrease in gray matter in the dorsolateral prefrontal cortex bilaterally and a decrease in gray matter in the right thalamus in patients suffering from chronic back pain (Apkarian et al., 2004). The differences regarding the study by Apkarian et al., and our study are not easy to interpret, as both groups compared the same number of patients. However, we only included patients without radiating pain, including radiculopathy, whereas Apkarian studied a mixture of patients with and without neurological manifestations as well as patients indicating presence of pain outside this region (for example, in the upper back). In our group of patients, we cannot confirm that chronic back pain is accompanied by brain atrophy (Apkarian et al., 2004), but rather suggest specific alterations, which correlate to the intensity and unpleasantness of pain, in structures known to play a crucial role in antinociception.

4.4. Increase in gray matter: Basal Ganglia

The importance of the basal ganglia in the motor response is well established (Alexander et al., 1990; Bingel et al., 2004). Non-nociceptive aspects of persistent musculoskeletal pain involve altered musculoskeletal activity, altered posture, and even immobility, which may in turn also influence our findings of structural alterations in the basal ganglia. Unlike the somatosensory cortex and the brainstem, we had no strong *a priori* hypothesis for the basal ganglia. We therefore did not use small volume correction in this region and only report uncorrected results, which consequently have to be viewed with caution.

4.5. Relationship to current theories of chronic pain

A lot of thought about chronic pain has been devoted to considering changes in primary afferents, dorsal root ganglia, and spinal cord dorsal horn (Woolf and Salter, 2000). Recent evidence has revealed that the adult brain is capable of substantial plastic changes on a functional level (Merzenich et al., 1984; Flor et al., 1995) and these findings have implications for our understanding of chronic pain. As the adult human brain may even change its structure in response to environmental demands (Draganski et al., 2004; May et al., 2006), the central question arises of whether our findings of cortical morphological alterations may arise as a consequence of chronic pain, or contribute to the neurobiological basis of the chronification of pain or both. Considering that we found no correlation between duration of pain and structural changes, but a strong correlation between the intensity and unpleasantness of pain, we conclude that our findings are a cause rather than a consequence of the chronification of back pain.

We suggest that the reorganisation processes of the cortical and subcortical areas in chronic back pain patients probably reflect two, not mutually exclusive, mechanisms: (1) persistent nociceptive input might interfere with subcortical relays of sensory perception in the thalamus and basal ganglia, and (2) a presumable ''degeneration'' of antinociceptive brainstem areas might, among other mechanisms, contribute to a disproportionate amount of nociceptive signals to neocortical brain structures. As both pain and the degree of functional reorganisation could be reduced by a sensory discrimination training programme (Flor et al., 2001), the crucial question needs to be addressed in future studies

of whether the morphological changes can be reversed as well.

In summary, we suggest that a morphometric alteration in cortical and subcortical areas, e.g. some kind of "stuctural plasticity", contributes, together with other peripheral, spinal and central mechanisms, to the development of chronic pain. Although all of our patients took analgesics, it is unlikely that the differences between chronic pain patients and controls are due to NSAID alone, as chronic headache patients show similar changes, yet did not take NSAID on a regular basis (Schmidt-Wilcke et al., 2005). Further studies are needed to explore the development of such alterations, which may reveal structural reorganisation to be a process, thereby endorsing and extending the concept of functional reorganisation.

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References

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia–thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990;85:119–46.

Andersson GB. Epidemiology of low back pain. Acta Orthop Scand Suppl 1998;281:28–31.

Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 2004;24:10410–5.

Ashburner J, Friston K. Multimodal image coregistration and partitioning – a unified framework. Neuroimage 1997;6:209–17.

Ashburner J, Friston KJ. Nonlinear spatial normalization using basis functions. Hum Brain Mapp 1999;7:254–66.

Ashburner J, Friston KJ. Voxel-based morphometry – the methods. Neuroimage 2000;11:805–21.

Bentley DE, Derbyshire SW, Youell PD, Jones AK. Caudal cingulate cortex involvement in pain processing: an inter-individual laser evoked potential source localisation study using realistic head models. Pain 2003;102:265–71.

Bingel U, Glascher J, Weiller C, Buchel C. Somatotopic representation of nociceptive information in the Putamen: an event-related fMRI study. Cereb Cortex 2004.

Bonica J., 1990. Definitions and taxonomy of pain. p. 18–27.

Braun C, Heinz U, Schweizer R, Wiech K, Birbaumer N, Topka H. Dynamic organization of the somatosensory cortex induced by motor activity. Brain 2001;124:2259–67.

De Conno F, Caraceni A, Gamba A, Mariani L, Abbattista A, Brunelli C, et al. Pain measurement in cancer patients: a comparison of six methods. Pain 1994;57:161–6.

Derbyshire SW. Meta-analysis of thirty-four independent samples studied using pet reveals a significantly attenuated central response to noxious stimulation in clinical pain patients. Curr Rev Pain 1999;3:265–80.

Derbyshire SW, Jones AK, Creed F, Starz T, Meltzer CC, Townsend DW, et al. Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. Neuroimage 2002;16:158–68.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, et al. Neuroplasticity: changes in grey matter induced by training. Nature 2004;427:311–2.

Draganski B., Moser T., Lummel N., Gaenssbauer S., Bogdahn U., Haas F. et al. Decrease of thalamic gray matter following limb amputation., Neuroimage, 2006. in press.

Draganski B, Thun-Hohenstein C, Bogdahn U, Winkler J, May A. "Motor circuit" gray matter changes in idiopathic cervical dystonia. Neurology 2003;61:1228–12231.

Duncan GH, Bushnell MC, Marchand S. Deep brain stimulation: a review of basic research and clinical studies. Pain 1991;45:49–59.

Etgen T, Draganski B, Ilg C, Schroder M, Geisler P, Hajak G, et al. Bilateral thalamic gray matter changes in patients with restless legs syndrome. Neuroimage 2005;24:1242–7.

Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neurosci Lett 1997;224:5–8.

Flor H, Denke C, Schaefer M, Grusser S. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet 2001;357:1763–4.

Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al. Phantom–limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995;375:482–4.

Friston, K.J., Holmes, A.P., Ashburner, J. Poline, J.-B., SPM99, 1999. World Wide Web, <http://www.fil.ion.ucl.ac.uk/spm>.

Frot M, Mauguiere F. Dual representation of pain in the operculoinsular cortex in humans. Brain 2003;126:438–50.

Garraux G, Bauer A, Hanakawa T, Wu T, Kansaku K, Hallett M. Changes in brain anatomy in focal hand dystonia. Ann Neurol 2004;55:736–9.

Geissner E. The Pain Perception Scale – a differentiated and change-sensitive scale for assessing chronic and acute pain. Rehabilitation (Stuttg) 1995;34:XXXV–XLIII.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36.

Grusser SM, Muhlnickel W, Schaefer M, Villringer K, Christmann C, Koeppe C, et al. Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. Exp Brain Res 2004;154:97–102.

Gybels J, Kupers R. Deep brain stimulation in the treatment of chronic pain in man: where and why? Neurophysiol Clin 1990;20:389–98.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

Hautzinger M. Allgemeine depressionsscala. Beltz: Weinheim; 1993.

Hosobuchi Y. Subcortical electrical stimulation for control of intractable pain in humans. Report of 122 cases (1970–1984). J Neurosurg 1986;64:543–53.

Jones EG, Pons TP. Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. Science 1998;282:1121–5.

Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci 2001;21:3609–18.

Kassubek J, Juengling FD, Kioschies T, Henkel K, Karitzky J, Kramer B, et al. Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study. J Neurol Neurosurg Psychiatry 2004;75:213–20.

Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology 2003;61:1707–15.

Matharu MS, Good CD, May A, Bahra A, Goadsby PJ. No change in the structure of the brain in migraine: a voxel-based morphometric study. Eur J Neurol 2003;10:53–7.

May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 1999;5:836–8.

May A, Hajak G, Ganssbauer S, Steffens T, Langguth B, Kleinjung T, et al. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. Cereb Cortex 2006.

Melzack R. The McGill Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.

Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 1984;224:591–605.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.

Nagel B, Gerbershagen HU, Lindena G, Pfingsten M. Development and evaluation of the multidimensional German pain questionnaire. Schmerz 2002;16:263–70.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000;30:263–88.

Pleger B, Tegenthoff M, Schwenkreis P, Janssen F, Ragert P, Dinse HR, et al. Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. Exp Brain Res. 2004.

Radloff L. The CES-D Scale. A self-report depression scale for research in general populations 1977:385–401.

Schmidt-Wilcke T, Leinisch E, Straube A, Kampfe N, Draganski B, Diener HC, et al. Gray matter decrease in patients with chronic tension type headache. Neurology 2005;65:1483–6.

Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. J Clin Neurophysiol 2000;17:592–603.

Soros P, Knecht S, Bantel C, Imai T, Wusten R, Pantev C, et al. Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. Neurosci Lett 2001;298:195–8.

Spitzer WO. State of science 1986: quality of life and functional status as target variables for research. J Chronic Dis 1987; 40:465–71.

Turk DC, Rudy TE. Towards a comprehensive assessment of chronic pain patients. Behav Res Ther 1987;25:237–49.

Waddell G. Low back pain: a twentieth century health care enigma. Spine 1996;21:2820–5.

Wall P, Melzack R. Textbook of pain Churchill Livingstone. Edingburgh, Londan: Madrid; 1999.

Wall PD, Egger MD. Formation of new connexions in adult rat brains after partial deafferentation. Nature 1971;232:542–5.

Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 2001;41:629–37.

Woermann FG, Free SL, Koepp MJ, Ashburner J, Duncan JS. Voxel-by-voxel comparison of automatically segmented cerebral gray matter – A rater-independent comparison of structural MRI in patients with epilepsy. Neuroimage 1999;10:373–84.

Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765–9.