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Research Submission

Altered Regional Brain Morphology in Patients With Chronic Facial Pain

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Background.—Persistent idiopathic facial pain (PIFP) is defined as a persistent, unilateral facial pain, not associated with sensory loss or other physical signs and with no obvious structural abnormalities that would sufficiently explain pain experience.

Objective.—We were interested whether there is evidence of altered brain morphology in patients with PIFP as it has been described in other chronic pain conditions.

Methods.—Using voxel-based morphometry we investigated regional gray matter volume in 11 PIFP patients and 11 age- and sex-matched healthy controls. Furthermore we calculated lateralization indices (LI) to investigate differences in interhemispheric gray matter asymmetries.

Results.—We report a decrease in gray matter volume in the left anterior cingulate gyrus and left temporo-insular region, as well as in the left and right sensory-motor area, projecting to the representational area of the face. Analyses of LI values demonstrated an increased rightward asymmetry in the middle-anterior insular cortex in patients in comparison with healthy controls.

Conclusion.—Our data support previous findings showing that chronic pain states are display-altered brain morphology in brain regions know to be part of the pain system.

Key words: facial pain, chronic pain, brain morphology, brain imaging, lateralization index

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Persistent idiopathic facial pain (PIFP, previously used term: atypical facial pain) is defined as a persistent (chronic), unilateral facial pain, not associated with sensory loss or other physical signs and with no obvious structural abnormalities, that would sufficiently explain pain experience.[1] Pain may be initiated by surgery or injury to the face, teeth or gums, but persists without any demonstrable local cause.[1] Differential diagnoses include pain conditions such as temporomandibular disorders, chronic pulpitis, (atypical) trigeminal neuralgias and trigeminal neuropathic pain. In contrast to trigeminal neuropathic pain there is no obvious clinical evidence in PIFP for an affection of the somatosensory and/or nociceptive system in terms of a concomitant hypesthesia and/or allodynia. Patients lacking structural correlates for their pain, which implies that pain in such circumstances cannot accurately be described as being either nociceptive or neuropathic, pose a challenge to both physicians and pain researchers.

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From a neurobiological point of view, the mechanisms contributing to pain chronification are heterogeneous and are thought to occur at various levels of the peripheral[2] and central nervous system (CNS).[3,4] It is increasingly recognized that the role of the brain in chronic pain states is not purely receptive, but can be viewed as amplifying or possibly even constitutive. However, the underlying mechanisms remain to be fully elucidated. Functional brain imaging has shed light on central mechanisms of pain perception and unravelled differences in brain response to painful stimuli between healthy volunteers and pain patients.[5] In addition to altered brain function, variations in brain morphology are a matter of growing interest in the exploration of chronic pain as there is an expanding body of evidence that indicates that chronic pain patients display changes in global and regional brain morphology. Such differences have been described in various chronic pain conditions, such as chronic tension type headache,[6] chronic low backpain,[7,8] irritable bowl syndrome,[9] and chronic trigeminal, neuropathic pain.[10] The most reproducible finding across pain syndromes is a decrease in regional gray matter (GM) density or volume in the anterior cingulate gyrus (ACC) and insular cortex (IC).[11] The ACC and IC are part of the medial pain system[12] and are thought of as multisensory integration sites playing a role in various aspects of pain experience and assessment,[13] such as affective processing of pain, but also the anticipation of pain[14] and antinociception.[15-17] It has been suggested that changes in these brain regions can be looked at as a common "signature" of chronic pain.[11] Morphological changes in the lateral pain system (primary and secondary somatosensory cortex), thought to be critically involved in the processing of the sensory-discriminative aspect of pain, have also been described, but less frequently.[8,10]

Using voxel-based morphometry (VBM) we were interested whether patients with PIFP also display such differences, especially in regions known to be part of the medial or lateral pain system in comparison with a healthy control (HC) group. Second, as PIFP typically presents as a unilateral pain syndrome we were also interested, if we could detect differences in GM asymmetries between the two groups. In functional pain imaging studies (applying a one-sided pain stimulus) bihemispherical activation is often seen in various brain structures involved in pain perception, such as the IC and the secondary somatosensory cortex.[12,18] It has been suggested that there are hemispherical differences in perception and modulation of painful and non-painful stimuli[19,20] and it might well be possible that an interhemispherical imbalance in pain perceptive structures contributes to pain chronification. The assessment of GM asymmetries has been performed in various neuroscientific contexts, such as gender differences,[21] speech lateralization,[22] and brain asymmetry in musicians with and without absolute pitch.[23] One of the most commonly used approaches of assessing asymmetries is to calculate lateralization indices (LI). Only recently VBM using a voxel-wise approach has been shown to be a useful morphometric tool to investigate such differences.[23] However, to our knowledge this approach has not been applied to specifically investigate asymmetries in a chronic pain syndrome. In addition to VBM (cross-sectional analyses and LI analysis) we calculated global gray and white matter volumes in patients and HCs, as it has been suggested that chronic pain might be associated with an accelerated loss of global GM.[7,24]

PATIENTS AND METHODS

A total of 22 subjects were enrolled: 11 PIFP patients (2 men, 9 women; mean age: 52.2 years, SD 8.9) and 11 HCs (2 men, 9 women; mean age 51.3 years; SD: 8.6). Patients were recruited from the headache outpatient clinic in the Department of Neurology, University of Regensburg, fulfilling the International Headache Society (IHS) criteria for PIFP.[1] In addition to the IHS criteria only patients who had had pain for at least 3 months were included, to ensure that patients had chronic pain. Eight patients had left sided pain, while 3 patients (2, 4, and 11) had right-sided pain (for details see Table S in the Supporting Information section). Both groups were matched for age and gender. In addition to brain scanning patients were also assessed for depressive symptoms, pain intensity, and pain experience using the Beck Depression Inventory (BDI), the numerical rating scale (NRS, on the day of scanning), and the

Schmerzempfindungsskala (SES, adaptation of the McGill Pain Questionnaire[25] – Table S in the Supporting Information section, respectively). The study was approved of by the local ethics committee and all subjects gave written consent prior to enrolment.

Magnetic resonance imaging was performed on a Siemens Sonata system operating at 1.5 Tesla. For each subject, a T-1 weighted gradient echo MP-RAGE dataset (TR 1880 ms, TE 3.42 ms, flip angle 15°, FOV 256 × 192, yielding 176 sagittal slices with a defined voxel size of 1 × 1 × 1 mm) was acquired. Inspection of individual T1 MR-images revealed no gross morphological abnormalities for any patient.

The SPM5 software package (Institute of Neurology, London, UK) running under Matlab 7.1 was used to pre-process and analyze structural data.[26] Estimation of gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid (CSF) was performed by segmenting the original image, using the SPM_segment tool, provided by the UCL Institute of Neurology (http://www.nmrgroup.ion.ucl.ac.uk/atrophy/index.html). Prior to segmentation brains were scull-stripped using the imaging tool BET, implemented in MRicro to improve segmentation. Groups were then compared using a 2-sample *t*-test. Besides absolute volumes we calculated gray and white matter fractions (GMF, WMF), in order to correct for different brain sizes (total intracranial volume, TIV). This was done by dividing the GMV, respectively, WMV, by the TIV, where TIV is the sum of GMV, WMV, and CSF. Also GMF and WMF were compared between groups using a 2-sample *t*-test.

Pre-processing of structural images was performed using the VBM toolbox (VBM 5.1, provided by C. Gaser, default settings), which involved spatial normalization, segmentation, and spatial smoothing (Gaussian kernel of 8 mm full-width at half maximum). Modulated images were used for statistical analyses (only non-linear effects were modulated, thereby correcting for different brain sizes across subjects). Correspondingly GM values in each voxel are referred to as regional GM volume. Significant regional differences in gray and white matter values between groups were identified applying voxel-wise statistics within the general linear model (2-sample *t*-test with age as nuisance variable, also referred to as cohort analysis, Analysis A). To avoid possible edge effects around the border between gray and white matters and to include only relatively homogenous voxels, we excluded all voxels with a matter value of <0.1 (of a maximum value of 1). Since we had a clearly defined hypothesis, looking for differences in the medial and lateral pain system, a threshold of $P < .001$ (uncorrected for multiple comparisons, with a cluster extent of 200 contiguous voxels) was applied. A second analysis (2-sample *t*-test with age as nuisance variable) was performed after the images of the 3 patients with right-sided pain had been flipped, in order to describe differences in regional GM volume, specifically with respect to the affected side (Analysis B). In account of the relatively small number of participants we extracted the eigenvariate from the clusters, yielding an average GM value of the cluster in each person; values were then transferred to SPSS (Versions 17) and reanalyzed, using an non-parametric test (Mann–Whitney test for group comparison). Anatomical labeling of brain regions was performed using the SPM5 extension MSU.

To calculate LI, in order to enable a voxel-wise approach (a voxel-wise comparison between hemispheres) images were flipped. Specifically a new set of GM images were generated by flipping the normalized GM images (origGM) in the midsagittal plane (*x*-axis). LI images were then created by applying the formula: (origGM-flippedGM)/0.5 * (origGM + flippedGM).[23] This generated an LI value for every voxel. Each voxel had the same LI value as its corresponding contralateral voxel, but with the opposite algebraic sign. In the 3 subjects displaying pain on the right hand side LI images were flipped prior to statistical analysis, so that statistical analysis could be performed with respect to the affected side. For clarity we define the sides as ipsi- or contralateral to the pain side. Finally LI images were smoothed (8 mm FWHM) and groups were compared using a 2-sample *t*-test. Results were interpreted as follows: a group displaying lower LI values in a particular region (conversely higher LI values contralaterally) than the other group had a regionally increased asymmetry.

Table 1.—Differences in regional gray matter volume between patients with persistent idiopathic facial pain and healthy controls

A							
Cohort analysis (age as nuisance variable)	Brodmann area	*x*	*y*	*z*	Cluster size k	Z value	*U*-test
L STG /posterior IC		–43	0	–6	305	3.76	0.001
L medial frontal gyrus	BA10	–3	59	–5	243	3.67	0.001
L ACC	BA 32	–6	38	15	465	3.96	<0.001
L inferior frontal gyrus	BA 9	–49	6	35	400	4.53	<0.001
L postcentral gyrus	BA 3	–50	–14	49	448	3.87	0.001
R precentral gyrus	BA 4	37	–18	53	314	4.21	<0.001
B							
Cohort analysis (after images of patients 2,4 and 11 had been flipped)							
L STG /posterior IC		–45	7	–8	583	3,78	<0.001
L medial frontal gyrus	BA 10	–4	59	1	367	3,89	<0.001
L ACC	BA 24/32	–6	39	13	371	3,73	<0.001
R ACC	BA 32	8	27	32	268	3,55	<0.001
R superior/medial frontal gyrus	BA 6	8	12	52	226	4,10	<0.001
L inferior frontal gyrus	BA 9	–49	6	35	396	4,59	<0.001
L postcentral gyrus	BA 4	–50	–14	49	316	3,87	<0.001
L precentral gyrus	BA 3	–37	–13	58	409	3,85	<0.001
R postcentral/precentral gyrus	BA 4	37	–18	53	140†	3,42	<0.001
C							
Analysis of LI (*t*-test)							
L IC (PIFP-Pat. < HCs)		–33	18	–5	770	4.05*	<0.001

*Significant at $P < .05$, corrected for multiple comparison throughout the whole brain (cluster-level).
†Cluster did not survive cluster extent threshold of 200 voxels (see method and result section).
ACC = anterior cingulate gyrus; HCs = healthy controls; IC = insular cortex; LI = laterality index, PIFP = persistent idiopathic facial pain; STG = superior temporal gyrus; *U*-test = Mann–Whitney *U*-test (cluster-eigenvariate in SPSS, 16).

RESULTS

There were no significant differences neither in global volumes between patients (GMV: 706.098 mm^3, SD = 81.431, WMV: 292.765 mm^3, SD = 66.166) and HCs (GMV: 725.706 mm^3, SD = 63.813, WMV: 348.820 mm^3, SD = 107.550; $P_{GM} = .54$; $P_{WM} = .16$), nor in GMF, respectively WMF: $GMF_{Patients} = 0.59$; SD = 0.07; $GMF_{HC} = 0.56$, SD = 0.09, $P_{GMF} = .44$; $WMF_{Patients} = 0.24$, SD = 0.03, $WMF_{HC} = 0.26$, SD = 0.05, $P_{WMF} = .24$.

In the cohort analysis the group of PIPF patients displayed a decrease in regional GM volume in several brain regions such as the left ACC, the left medial prefrontal cortex, and the left temporo-insular region, as well as in the left postcentral gyrus and the right precentral region (Table 1A and Fig. 1A,B). There were no regions of increased GM volume in PIFP patients as compared with HCs. The same analysis, after flipping the images of the 3 patients with right-sided pain, revealed similar results with a decrease in GM volume in the left ACC (ipsilateral to the pain side), the left medial prefrontal cortex (ipsilateral to the pain side), and the left temporo-insular region (ipsilateral to the pain side), as well as in the left postcentral gyrus (ipsilateral to the pain side). In addition new clusters of regional atrophy were found in the left (ipsilateral to the pain side) motor cortex, as well as in the right medial frontal cortex (ACC and medial frontal gyrus, contalateral to the pain side) in the patients' group (Table 1B). The cluster of regional atrophy in the right precentral region (Analysis A) was still detectable, but did not survive the cluster extent threshold of 200 voxels (k = 140, for details see TableB). Again no regions of increased GM volume in PIFP patients could be detect.

While examining the LI, PIFP patients displayed significantly smaller LI values in the middle/anterior IC (ipsilateral to the pain side), indicating that in this region the difference between left and right hemi-

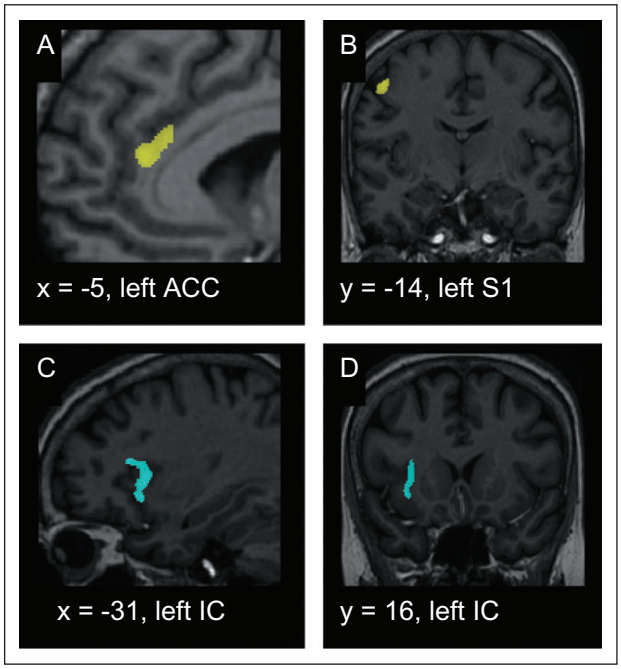

Fig 1.—A and B. Statistical parametric maps (SPM) demonstrating differences (decrease) in regional gray matter volume between the group of PIFP patients and the group of HCs (significant findings are superimposed in yellow). C and D. SPMs demonstrating a significant difference in LI (patients < HCs in the left insular cortex (IC), significant finding is superimposed in cyan). A. Left anterior cingulate gyrus (ACC, sagittal view); B. left somatosensory cortex (S1 cortex, coronal view); C. Left IC (sagittal view); D. Left IC (coronal view). SPMs were superimposed on a normalized high resolution image (3T) of one of the HCs. The left side of the picture is the left side of the brain (B and D). Significance threshold $P < .001$ (uncorrected).

sphere was more pronounced with higher GM values in the contralateral insula (in comparison with HCs, Table 1C, Fig. 1C,D).

DISCUSSION

As a main finding we report a decrease in GM volume in the left ACC and left temporo-insular region, as well as in the left and right sensory-motor area, projecting to (or close to) the representational area of the face.[27] Critically it must be noted that no fMRI was performed localizing the exact position of the representational field of the face in the somatosensory cortex. Flipping the images of the 3 patients with right-sided pain basically showed the same pattern of atrophy, revealing additional clusters of decreased GM volume in the left (ipsilateral to the pain side) motor cortex and right (contralateral to the pain side) medial frontal cortex. Analysis of LI values demonstrated an increased asymmetry in the middle-anterior IC in patients in comparison with HCs, with lower LI values in the hemisphere ipsilateral to the pain side. No significant differences in global GMV or WMV, respectively, GMF or WMF were seen.

The most reproducible finding across morphometric studies investigating chronic pain syndromes is a decrease in GM density/volume in the ACC and IC.[11] The ACC and IC are known to play a critical role in various aspects of pain experience and assessment, including anticipation of pain and antinociception. As such our findings could reflect both, a local atrophy associated with hyperactivity in pain-perceptive brain structures (eg, in terms of a loss of inhibitory interneurons) or an impairment of antinociceptive structures (eg, in terms of a loss of descending neurons). Interestingly neuropathic pain models in animals have begun to shed light on the mechanisms underlying cortical reorganization in the ACC and medial frontal cortex.[28,29] However, their relevance to human pain conditions is still unclear.

There are only a few studies that have investigated altered brain morphology in strictly unilateral pain syndromes.[10,30] Our data are in agreement with DaSilva et al, who reported a thinning in the ACC, as well as a bilateral thinning in the sensorimotor cortex, projecting to the representational area of the face (colocalized with functional activation during allodynic pain) in patients with trigeminal, neuropathic pain.[10] Interestingly thinning ipsilateral to the pain side was restricted to the somatosensory cortex, while on the contralateral side a thinning was found in both the somatosensory, and even more pronounced in the motor cortex, while in our study atrophy in the motor-sensory region tended to be more pronounced ipsilateral to the pain side (after flipping the images of the 3 patients with right-sided pain). Given that atrophy is the (morphological) hallmark in chronic pain (and not hypertrophy) the LI analysis also indicates a suspicious finding in the ipsilateral IC. Interestingly pronounced ipsilateral IC responses have frequently been described in deep muscle[31,32] and allodynic pain paradigms[33,34] and it has been proposed that

enhanced/additional responses to innocuous stimuli in the ipsilateral hemisphere may contribute to a shift in perception from innocuous to painful sensations. IC atrophy in PIFP patients might result from a prolonged sensory/nociceptive input inducing regional tissue shrinkage. However, it is still unclear whether PIFP really has a neuropathic and/or deep muscle component to it,[35] and our findings could also be indicative for a pre-existing condition, which makes individuals vulnerable for the development of a chronic pain state.

LIMITATIONS

There are several limitations to our study that need to be addressed. First of all our study includes a relatively small number of patients. This is partially due to the strict IHS criteria that postulate that pain needs to be present daily and persist for all or most of the day. From a methodological point of view VBM cannot disclose the neurobiological basis of morphological differences found and assumptions regarding the underlying cytoarchitecture, especially in a cross-sectional study, remain speculative for now. Future cross-sectional studies with larger sample sizes and longitudinal studies, including cross-correlation with functional imaging data, are required to confirm our findings and to disclose the interaction between atrophy, pain, and brain plasticity. The concept of lateralization has been used before in functional and morphometric brain imaging, but has, to our knowledge, not been applied to chronic (unilateral) pain syndromes. In this respect our data, as well as the methodology also await validation and further confirmation. In future studies using LI, handedness and speech lateralization should be evaluated systematically using validated questionnaires which had not been done in this study.

CONCLUSIONS

Overall our data support previous findings showing that chronic pain states are associated with differences in brain morphology in brain region known to be part of the pain system. In this study both the medial and lateral pain systems were affected. We assume that a regional atrophy in the medial pain system (ACC and IC) is a common feature shared by chronic pain syndromes, while the atrophy in the somatosensory and motor cortex (where it was found in this study) is probably specific to face pain. LI analyses could be of great interest in unilateral pain syndromes as they provide an intra-individual measure of regional GM density and/or volume and may thus help to identify conspicuous brain regions that escape conventional statistical analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Table S.—Epidemiological and behavioral data.

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