Changes in Regional Gray and White Matter Volume in Patients with Myofascial-type Temporomandibular Disorders: A Voxel-based Morphometry Study

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Aims: *To use magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) to search for evidence of altered brain morphology in patients with temporomandibular disorders (TMD).* ***Methods:*** *Using VBM, regional gray and white matter volume was investigated in nine TMD patients and nine carefully matched healthy controls.* ***Results:*** *A decrease in gray matter volume occurred in the left anterior cingulate gyrus, in the right posterior cingulate gyrus, the right anterior insular cortex, left inferior frontal gyrus, as well as the superior temporal gyrus bilaterally in the TMD patients. Also, white matter analyses revealed decreases in regional white matter volume in the medial prefrontal cortex bilaterally in TMD patients.* ***Conclusion:*** *These data support previous findings by showing that TMD, like other chronic pain states, is associated with changes in brain morphology in brain regions known to be part of the central pain system.* J OROFAC PAIN 2011;25:99–106

Key words: anterior cingulate gyrus, central sensitization, chronic pain, neuroimaging, voxel-based morphometry

Temporomandibular disorders (TMD) are defined on the basis of clinical signs and symptoms, including temporomandibular joint (TMJ) sounds, impaired mandibular movement or limitation of mouth opening, and pain located in preauricular, facial, and masticatory muscle regions. Patients with TMD often describe symptoms of pain and dysfunction that also affect the ears, eyes, or throat, and headaches that involve virtually any cranial region and often cervical regions as well.[1] Most recently, there has been growing international agreement to classify TMD into three categories: *(1)* myofascial pain, manifesting as pain primarily in masticatory muscles, *(2)* TMJ disc-condyle discoordination, involving irregularities of joint mechanics, and *(3)* arthritides of the TMJ, eg, rheumatoid or osteoarthritis.[2–4]

According to US National Institutes of Health statistics, TMD represent the most common chronic orofacial pain, and they are the second-most common chronic pain condition behind lower back pain.[5] Historically, TMD pain was believed to be caused by peripheral mechanisms such as acute or chronic inflammation of the joint, tenderness of the masticatory musculature due to microtrauma, oromotor dysfunction, or "imbalance" of the dentoskeletal and neuromuscular systems. However, recent attention has been turned toward genetic predispositions[6] and the concept of central sensitization.[7] From a neurobiological perspective, the mechanisms contributing to pain amplification and chronicity are heterogeneous and are thought to occur at various levels of the peripheral and central nervous system (CNS). 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. In such cases, studies of brain anatomy, function, and physiology are critical to understanding the root etiologies and pathophysiologies of chronic pain conditions such as TMD.

To date, numerous human neuroimaging studies have provided insights into brain activation associated with pain perception.[8,9] Recent findings provide promising results regarding aberrant activation patterns in response to painful stimuli in chronic pain states, such as fibromyalgia (FM),[10–12] a chronic pain condition often associated with TMD.[13] Furthermore, changes in brain morphology have been described in various chronic pain conditions affecting the head and face, including chronic tension-type headache,[14] migraine,[15,16] chronic trigeminal neuropathic pain,[17] persistent idiopathic facial pain,[18] and, very recently, also TMD.[19] The most reproducible finding across pain syndromes is a decrease in gray matter (GM) density/volume in the anterior cingulate gyrus (ACC) and insular cortex (IC).[20] It has been suggested that changes in regional brain morphology not only contribute to the evolution of chronic pain but might also contribute to other clinical traits frequently found in chronic pain patients, such as increased levels of anxiety and depression, as well as cognitive impairment.[21] However, little research has been done in this regard on TMD patients.

Therefore, the aim of this study was to use magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) to search for evidence of altered brain morphology in patients with TMD.

Materials and Methods

Subjects

Nine female patients with myofascial-type TMD and nine age-, gender-, ethnicity-, weight-, and height-matched healthy controls were recruited for the study. All subjects with TMD were carefully examined and screened by an experienced orofacial pain investigator who applied the Research Diagnostic Criteria (RDC) for the diagnosis of myofascial-type TMD (Group Ia,b).[4] Only those subjects who fulfilled the Group I myofascial pain criteria were included. All subjects were right-handed. Because pain symptoms can be coupled to menstrual cycle phase in premenopausal women and women on oral contraceptives,[22] all subjects participated in pain and imaging studies within 3 days of menstrual onset.

Inclusion and exclusion criteria consisted of the following. Inclusion criteria included: *(1)* presence of ongoing pain in the face, jaws, or temples > 1 time per week, *(2)* presence of pain symptoms for > 3 months, and *(3)* meeting the RDC/TMD criteria for myofascial pain Group Ia,b. The main inclusion criterion for healthy controls was absence of TMD pain, or facial pain < 1 time per week. Exclusion criteria for all subjects included physical impairment, any outstanding history of systemic or medical conditions, psychiatric illnesses, substance abuse within 2 years, and presence of head or neck pain other than masticatory myalgia. Nonsteroidal anti-inflammatory drugs were allowed until 3 days before the pain and scanning trials. All participants signed an informed consent that detailed the procedures of the study. The study had been approved by the Institutional Review Board at the University of Michigan.

Clinical Pain

The clinical pain experience of patients with TMD and healthy controls was assessed using the visual analog scale (VAS) and the pain rating index (PRI) from the Short Form McGill Pain Questionnaire (SF-MPQ).[23] The VAS consisted of a 10-cm line anchored on the left with "no pain" and on the right with "worst possible pain." Participants in the study were asked to rate their present orofacial pain by placing a tick along this line. The PRI component of the SF-MPQ consisted of 15 word descriptors (11 sensory and 4 affective). Participants rated these descriptors as either "none," "mild," "moderate," or "severe," giving a score of 0, 1, 2, or 3, respectively, for each descriptor. The measures were added to yield sensory, affective, and total scores. Another questionnaire used to evaluate clinical pain was the Brief Pain Inventory (BPI).[24] Information from this measure was used to determine both severity of pain and the degree of pain interference. Questions for these measures were answered using a 0 to 10 numeric rating scale for each item.

Depression and Anxiety

The State-Trait Personality Inventory (STPI) is a self-report tool designed to measure anxiety and depression. The STPI consists of eight 10-item subscales. The trait depression and anxiety scales were used to assess each subject's emotional disposition, and both scales were rated on a four-point intensity scale.[25]

Due to the relatively small sample size, the Mann-Whitney *U* test was applied to assess significant differences in age, height, and behavioral scores (pain, depression, and anxiety) between groups. Differences were deemed significant at $P < .05$ (corrected for multiple comparisons). Table 1 provides detailed information on patients and healthy controls. The Spearman

Table 1 Behavioral Data of Individual Subjects

	Age (y)	Gender	Pain duration (y)	BPI SEV	BPI INT	MPQ Tot	MPQ Sens	MPQ Aff	MPQ-VAS	STPIDA Ax	STPIDA D
TMD patients											
t01	23	F	1.5	0.25	0.43	3	2	1	0.6	16	13
t02	26	F	1.75	2.75	0	6	6	0	1.9	12	13
t03	23	F	3	2	0.14	5	5	0	1.7	12	11
t04	27	F	0.5	3.75	8.29	3	3	0	1.5	25	25
t05	25	F	4	2.5	6.71	16	14	2	5	22	18
t06	24	F	1	3	0.71	14	12	2	3.8	12	10
t07	24	F	0.75	3	1.43	3	3	0	2.6	19	18
t08	31	F	7	0.75	0	3	3	0	2	11	10
t09	26	F	3	0	0	2	2	0	1	26	27
Controls											
c01	25	F	0	2	0	0	0	0	0.1	17	15
c02	25	F	0	NA	NA	0	0	0	0	17	11
c03	22	F	0	0	0	0	0	0	0	10	10
c04	24	F	0	0	0	0	0	0	0	10	10
c05	25	F	0	0.75	0	4	4	0	1.7	14	10
c06	26	F	0	0	0	0	0	0	0	12	10
c07	24	F	0	0.75	0	0	0	0	0	11	10
c08	25	F	0	0.25	0	0	0	0	0.2	13	10
c09	27	F	0	0.75	0.71	0	0	0	0	12	14
Mann-Whitney	0.796			0.136	0.190	0.001*	0.001*	0.258	< 0.001*	0.136	0.050

BPI INT = Brief Pain Inventory pain interference; BPI SEV = Brief Pain Inventory pain severity; MPQ Tot = Short Form McGill Pain Questionnaire Pain Rating Index – Total Score; MPQ Sens = Short Form McGill Pain Questionnaire Pain Rating Index – Sensory Score; MPQ Aff = Short Form McGill Pain Questionnaire Pain Rating Index – Affective Score; MPQ-VAS = Short Form McGill Pain Questionnaire Visual Analog Scale; NA = not available, missing data; STPIDA Ax = State-Trait Personality Inventory trait anxiety; STPIDA D = State-Trait Personality Inventory trait depression. Mann-Whitney *U* test was used for group comparison. *P* values were deemed significant at $P < .05$ after correction for multiple comparisons (*significant differences).

rank correlation analysis was also used to test for significant correlations between pain measures (pain duration, BPI scores, MPQ scores), depression, and anxiety measures. Correlations were deemed significant at $P < .05$ (corrected for multiple comparisons).

Scanning Protocol

Magnetic resonance imaging (MRI) was performed on a 3.0 Tesla GE Signa scanner (LX [VH3] release, neuro-optimized gradients). For each subject, a T-1 weighted gradient echo data set (TR 1400 ms, TE 5.5 ms, flip angle 20 degrees, FOV 256 x 256, yielding 124 sagittal slices with a defined voxel size of 1 × 1 × 1.2 mm) was acquired. Inspection of individual T1 MRI scans revealed no gross morphological abnormalities for any patient or subject.

Preprocessing and Statistical Analysis

The SPM5 software package (Functional Imaging Laboratories) running under Matlab 7b was used to preprocess and analyze structural data.[26] Estimation of total gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid (CSF) was performed by segmenting the original image, using the Ibaspm toolbox (toolbox for automatic parcellation of brain structures), provided by the Cuban Neuroscience Center.[27] Groups were then compared using a Mann-Whitney *U* test.

Preprocessing 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 for

Table 2 Behavioral Data of the Two Groups			
	TMD	Controls	*P*
Age	25.4 ± 2.5	24.8 ± 1.4	.796
Pain duration	2.5 ± 2.1	0 ± 0	
BPI SEV	2.0 ± 1.3	0.6 ± 0.7	.136
BPI INT	2.0 ± 3.2	0.1 ± 0.3	.190
MPQ Tot	6.1 ± 5.2	0.4 ± 1.3	.001*
MPQ Sens	5.6 ± 4.4	0.4 ± 1.3	.001*
MPQ Aff	0.6 ± 0.9	0 ± 0	.258
MPQ VAS	2.2 ± 1.4	0.2 ± 0.6	< .001*
STPIDA Ax	17.2 ± 6.0	12.9 ± 2.7	.136
STPIDA D	16.1 ± 6.4	11.1 ± 2.0	.050

Mann-Whitney *U* test was used for group comparison. *P* values were deemed significant at $P < .05$ after correction for multiple comparisons (*significant differences).

GM images). Normalized white matter (WM) images were smoothed with a kernel of 12 mm. Modulated images were used for statistical analyses; correspondingly, GM and WM values are referred to as regional GM or WM volume. Significant regional differences in GM and WM values between groups were identified by applying voxel-wise statistics using the SnPM (Statistical nonParametric Mapping) toolbox, which uses the general linear model to construct pseudo t-statistic images, and then assesses the data for significance by using a nonparametric multiple comparison procedure based on permutation testing. Permutation tests are recommended for designs with low degrees of freedom.[28] The following design module was applied: two groups; two sample *t* test; one scan per subject; with age as nuisance variable. To avoid possible edge effects around the border between gray and white matter and to include only relatively homogeneous voxels, all voxels were excluded with a matter value of < 0.1 (maximum value of 1). A total of 5,000 permutations were performed for GM and WM analyses. With respect to the brain regions shown to be activated by noxious stimuli, as well as the structural changes described in chronic pain patients,[20] which are most frequently found in the ACC and IC, the authors had a clearly defined a priori hypothesis. Therefore, a threshold of $P < .001$ (uncorrected for multiple comparisons, with a cluster extent of 200 contiguous voxels) was applied. For correlation analyses, the eigenvariate was extracted from a sphere of 4 mm around the peak coordinates of the GM clusters, yielding an average GM value for that region in each person; values were then transferred to SPSS version 17 (IBM) where correlation analyses (Spearman rank correlation) were performed, correlating extracted GM values with pain duration, pain intensity (VAS), STPI Trait-anxiety, and STPI Trait-Depression scores in the TMD group. Anatomical labeling of brain regions was performed using the SPM5 extension xjView.

Results

Subjects

Both groups did not differ significantly in age ($P = .48$), height ($P = .91$), or weight ($P = .76$). Furthermore, there were no significant differences in ethnicity (both groups consisted of one African American, three Asian, and five Caucasian participants).

Clinical Pain, Depressive, and Anxious Symptoms

After correcting for multiple comparisons, patients with TMD displayed significantly higher VAS scores ($P < .001$) than healthy controls (Table 2). TMD patients also showed higher scores than healthy controls for the measures of MPQ Tot ($P = .001$) and the MPQ Sens ($P = .001$), as shown in Table 2.

Within the TMD group, the STPI Trait-anxiety scores were significantly correlated with STPI Trait-depression scores ($\rho = 0.95$, $P < .001$). However, they were not significantly correlated with BPI pain scores or MPQ scores. Pain duration correlated with BPI severity ($r = –0.69$, $P = .04$), but this correlation did not survive correction for multiple comparisons.

Global GM and WM Volumes

There were no significant differences in GM or WM volumes between TMD patients (GM: 705.780 mm^3, SD = 60.174; WM: 419.005 mm^3, SD = 24.194) and healthy controls (GM: 699.154 mm^3, SD = 72.558; WM: 410.976 mm^3, SD = 37.692 mm^3; $P_{GM} = .83$, $P_{WM} = .60$).

VBM

A decrease occurred in regional GM volume among TMD patients compared with healthy controls at the following locations: the left ACC, the right posterior cingulate gyrus (PCC), the right IC, the left inferior frontal gyrus (IFG), as well as the superior temporal gyrus (STG) bilaterally, extending into the middle temporal gyrus (MTG) on the right-hand side. A decrease in regional WM volume was observed in the medial frontal (MFG) and superior frontal gyrus (SFG) bilaterally, left precuneus and left middle/inferior frontal gyrus. An increase in regional WM

Table 3 Results of Group Analyses–VBM

	Side	BA	Cluster size (no. of voxels)	Pseudo *t* values (peak voxel)	Coordinates X	Y	Z
GM group analysis*							
Decrease in regional GM in the TMD group							
IFG	L	45/46	676	4.86	–47	25	19
ACC/medial frontal gyrus	L	8/9/6/32	794	4.71	–7	21	45
PCC/Precuneus	R	31	339	4.21	11	–42	41
STG	L	22	322	4.03	–49	5	–3
Parahippocampal gyrus	R	36	394	3.88	32	–18	–25
STG/MTG	R	21	268	3.75	51	–7	–12
Anterior IC	R	47/13	320	3.47	29	23	–8
WM group analysis*							
Decrease in regional WM in the TMD group							
MFG/SFG/ACC	L		4133	4.79	–16	25	40
Precuneus	L		526	4.56	–17	–82	36
Inferior frontal/precentral gyrus	R		575	4.37	59	3	22
MFG/SFG/ACC	R		2007	4.26	18	25	43
Middle frontal gyrus	L		622	4.26	-35	26	29
Increase in regional WM in the TMD group							
STG/supramarginal gyrus	R		2887	5.07	43	–52	20
STG/MTG	L		1090	4.96	–35	–56	19

BA = Brodmann area; * = two sample *t* test with age as nuisance variable.

volume was found in the posterior parts of the STG bilaterally, reaching into the supramarginal gyrus on the right side. For details, see Table 3 and Fig 1. GM volume in the right STG/MTG correlated negatively with pain duration ($\rho = -0.78$, $P < .05$). The other clusters identified by the cohort analysis were not correlated with any pain, anxiety, and/or depression measures.

Discussion

A main finding in TMD patients was a decrease in GM volume in various parts of the central pain system, such as the left ACC, the right PCC, the right anterior IC, the left IFG, and STG bilaterally. WM analysis, on the other hand, revealed a decrease in WM volume in the medial prefrontal cortex, predominantly in the MFG and SFG bilaterally in TMD subjects. An increase in regional WM volume in TMD patients was found in the posterior STG bilaterally, reaching into the supramarginal gyrus on the right side. No differences in global GMV or WMV were detected.

The most reproducible finding across morphometric studies investigating chronic pain syndromes is a decrease in GM density/volume in the ACC and IC.[20] Interestingly, a regional atrophy in the ACC and IC has also been found in other headache[14,15,29] and facial pain syndromes.[18] Both structures are known to play a critical role in various aspects of pain experience and assessment, including anticipation of pain and antinociception. As such, the present findings could reflect either a local atrophy associated with hyperactivity in pain-perceptive brain structures, eg, a loss of inhibitory interneurons, or an impairment of antinociceptive structures, such as a loss of neurons contributing to descending inhibitory pathways.

On the other hand, it is conceivable that GM changes as delineated by VBM do not reflect neuronal damage, but rather changes in synaptic density or even altered regional blood flow, eg, microvascular volume changes.[30] However, in this study, GM atrophy in the ACC was accompanied by a neighboring atrophy of WM in the MFG and SFG (see below), and it has been suggested that shrinkage of local GM volume with evidence of concomitant loss of WM

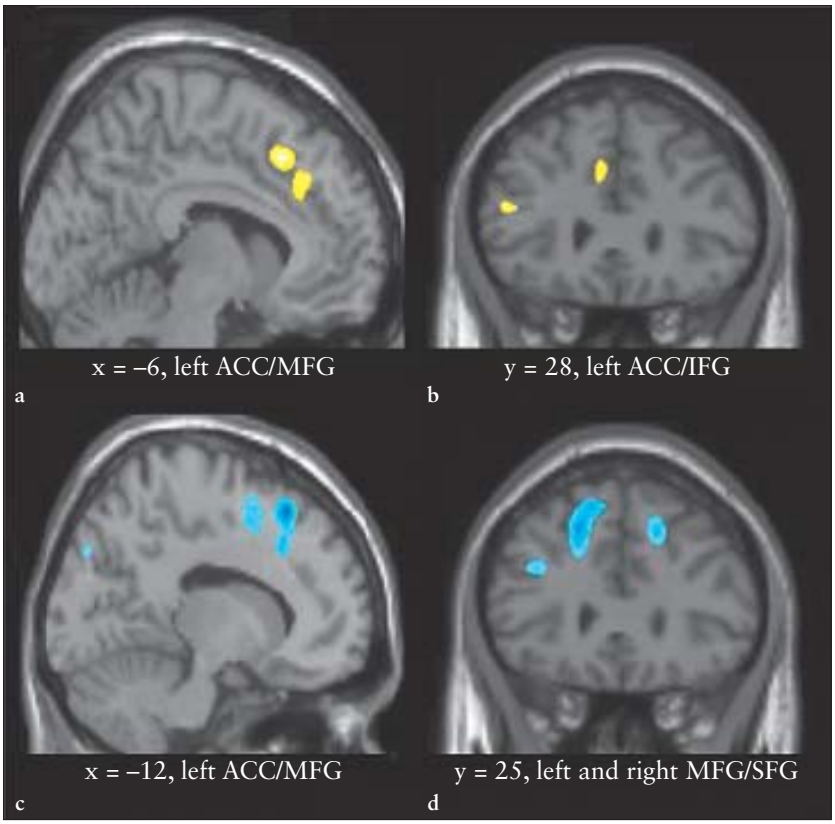

Fig 1 Regional changes in gray and white matter volume. *(a)* and *(b)* show statistical non-parametric maps (SnPM) demonstrating differences (decrease) in regional GM volume between TMD patients and healthy controls (significant findings are superimposed in yellow). *(c)* and *(d)* SnPM demonstrate differences (decrease) in regional WM volume between TMD patients and healthy controls (significant findings are superimposed in blue). *(a)* and *(c)* show left medial frontal cortex (sagittal view). *(b)* and *(d)* show coronal view. SnPMs were superimposed on a normalized high resolution image. The left sides of the pictures *(b)* and *(d)* are the left side of the brain. Significance threshold: $P < .001$ (uncorrected).

connectivity supports the neurodegeneration hypothesis.[31] It is tempting to hypothesize that these changes reflect a disconnection between the ACC and the superior/medial frontal gyrus. Interestingly, Geha et al reported a decrease in fractional anisotropy in the left cingulum-callosal bundle in patients with chronic regional pain syndrome (projecting close to the region where decreases in WM volume in TMD patients were found in this study), which they interpreted as an indication of a decreased structural connectivity between the ACC and supplementary motor cortex.[31] It has been demonstrated that the MFG and SFG play an important role in higher cognitive functions, such as working memory and decision making,[32] but also in cognitive evaluation of pain. Perhaps such a disconnection could either cause cognitive deficits, as they have been frequently described in chronic pain patients[33–35] (but not specifically investigated in this study), or aggravate the pain situation by further disabling cognitive modulation of pain.

Although not part of the classical pain system, the MTG and STG appear to be involved in the processing of trigeminal sensory input,[36] experimental dental pain,[37] and even virtual dental treatment,[38] suggesting that these regions may be noteworthy in chronic trigeminal pain conditions such as TMD. Interestingly, within the TMD group, GM volume in the right MTG/STG in this study was negatively correlated with pain duration. Other VBM studies investigating chronic pain states have also found an atrophy in the STG in FM patients[39] and chronic migraine patients.[16] Again, the present findings corroborate results from previous studies in these terms and suggest that the role of the MTG and STG in chronic pain may need to be more carefully studied.

Finally, an increase in WM volume was found in the posterior part of the STG and supramarginal gyrus. There had been no strong a priori hypothesis for this region, and to the authors' knowledge, such changes have not previously been reported in chronic pain syndromes. However, changes were rather pronounced, thus compelling an explanation. VBM does not allow an assessment of fiber orientation, enabling the allocation of the cluster to a specific fiber tract. However, the changes most likely map to the posterior thalamic radiation and/or the superior longitudinal fasciculus, which, in this location, connects the temporal lobe to the insular and frontal cortex. From this perspective, it is intriguing to hypothesize that the WM increase reflects a structural hyperconnectivity between the STG/MTG and the insular cortex and/or frontal lobe. However, at this

stage, findings should be viewed with caution, and assumptions are rather speculative.

In a recently published VBM study, Younger et al investigated 14 TMD patients and 14 healthy controls and reported decreased GM volume in the right somatosensory cortex, as well as increased GM volume in several brain areas, including the right IFG, right anterior IC, the right lentiform nucleus, and the thalamus bilaterally.[19] In addition, brainstem structures, including the trigeminal nucleus bilaterally and the middle cerebellar peduncle bilaterally, were shown to have an increase in GM volume. Both the study by Younger et al and the present study did not find any differences in global GMV between groups. Also, both studies identified the left ACC as an area that showed pain-related structural changes. On the other hand, both studies report opposite findings between the TMD and healthy control groups in the right anterior IC.

There are several reasons that could possibly account for the apparent differences in results between the two studies, both of which used the same methodological approach in the same pain condition. First, the study cohort investigated by Younger et al showed more diversity in age, and study participants were an average of 15-years older than those investigated in the present study. Secondly, the cohort investigated by Younger et al showed higher pain ratings as a group than those participating in the present study. Finally, nine out of 14 patients in the Younger et al study took centrally active drugs, mostly cyclobenzaprine, whereas, in the present study, all patients were drug naïve.

In most studies, chronic pain is associated with a decrease in regional GM volume, especially in the IC; however, there are several brain regions where an increase in GM volume and/or density has been described, eg, the thalamus [29,40] and the lentiform nucleus.[39,41] It is likely that the direction of change, whether it be an increase or a decrease, depends on the anatomical structures involved, the location of the nociceptive source, duration or chronicity of pain, and pain intensity. It is also important to acknowledge that centrally active drugs can have neuroplastic effects, eg, serotonin reuptake inhibitors,[42] neuroleptic drugs,[43] and opioids.[44] It will be critical for future studies to control for possible medication effects, by either including drug-naïve patients only or by applying a wash-out period prior to scanning.

Finally, several limitations inherent in the present study should be noted. Firstly, this study included a relatively small number of patients, and, as such, the study needs to be viewed as a pilot study. Secondly, 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. Thirdly, it is unclear whether GM volumetric reductions in the left ACC predispose someone to developing chronic TMD pain, or whether chronic TMD pain leads to GM volumetric reductions in the ACC. Future cross-sectional studies with larger sample sizes and longitudinal studies, including cross-correlation with functional imaging data, are required to confirm the present findings and to disclose the interaction between atrophy, pain, and brain plasticity. Finally, it needs to be pointed out that three out of nine TMD patients, although fulfilling the diagnostic criteria of TMD, had BPI severity scores and BPI interference scores < 1 at the time of the investigation. This might be a potential weakness in the sense that the TMD group investigated in the present study manifested relatively mild symptoms. On the other hand, the present results possibly reflect a snapshot of chronic pain in patients who are young and at the beginning of the chronification process. Such study samples might be interesting for future (longitudinal) studies that intend to unravel causes and consequences of chronic pain and to account for symptom heterogeneity among patients.

In conclusion, these data further support the idea that chronic pain is associated with structural changes of the CNS that are likely to contribute to pain chronification and the development of other core symptoms, such as anxiety and depression. Neuroimaging in TMD is just at its beginning, and further research is needed to uncover TMD-related changes in CNS function and structure.

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