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Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder

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ABSTRACT

Cortical plasticity is thought to occur following continuous barrage of nociceptive afferent signals to the brain. Hence, chronic pain is presumed to induce anatomical and physiological changes in the brain over time. Inherent factors, some pre-dating the onset of chronic pain, may also contribute to brain abnormalities present in patients. In this study we used structural MRI to examine whether patients with chronic temporomandibular (TMD) pain have abnormalities in gray matter (GM) within brain areas implicated in pain, modulation and sensorimotor function. We found that patients with TMD have cortical thickening in the primary somatosensory cortex (S1), frontal polar and the ventrolateral prefrontal cortex (PFC). These findings provide a structural basis for previous findings of TMD pain and cognitive sluggishness in TMD. We then examined the contribution of TMD characteristics to GM abnormalities. We found that 1) GM in the sensory thalamus positively correlated to TMD duration, 2) cortical thickness in the primary motor (M1) and the anterior mid-cingulate cortices (aMCC) were negatively correlated to pain intensity, and 3) pain unpleasantness was negatively correlated to cortical thickness in the orbitofrontal cortex (OFC). These findings suggest that an individual's TMD pain history contributes to GM in the brain. Lastly, we examined the contribution of a potential pre-existing vulnerability due to neuroticism. In the TMD patients, we found that there was an abnormal positive correlation between neuroticism and OFC thickness, in contrast to the negative correlation found in the healthy controls. Therefore, neuroticism may contribute to TMD pathophysiology. In sum, our data suggest that GM in the brain of patients with chronic TMD pain can be shaped by both personality and pain characteristics.

Introduction

Temporomandibular disorder (TMD) is a common chronic orofacial pain that is more prevalent in women than in men (Ramírez et al., 2005). TMD can be idiopathic in that there may not be any clear peripheral etiological factors identifiable (Dworkin, 1994; Dworkin and Massoth, 1994; Dworkin et al., 1994; Ohrbach and Dworkin, 1998). In this scenario, it is thought that the CNS may initiate and/or maintain the pain (Sarlani and Greenspan, 2005).

Although a clear pattern of change has yet to be determined, previous structural MRI studies of chronic pain populations have found both increases and decreases in gray matter (GM). For instance, some studies of headache and chronic facial pain populations have found that patients with chronic pain had GM increases in regions likely associated with pain perception (DaSilva et al., 2007; May, 2008; Obermann et al., 2009; Younger et al., 2010). Additionally, most studies of chronic pain patients have found reduced GM in cortical regions likely associated with pain modulation and limbic function (Blankstein et al., 2010; Geha et al., 2008; May, 2008). Interestingly, some studies have also reported GM loss in cortical and subcortical motor areas (Apkarian et al., 2009; May, 2008; Schmidt-Wilcke et al., 2010). However, the increases are not

Abbreviations: TMD, temporomandibular disorder; CTA, cortical thickness analysis; VBM, voxel-based morphometry; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; M1, primary motor cortex; ACC, anterior cingulate cortex; MCC, mid-cingulate cortex; aMCC, anterior mid-cingulate cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; VPM, ventroposterior medial nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; Po, posterior nucleus of the thalamus.

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limited to regions thought by some to be associated with pain perception, and the decreases are not limited to regions typically associated with pain modulation. Although the role of motor regions in pain is not fully established, there is evidence suggesting these areas play a role in pain modulation (Adachi et al., 2008; Brown and Barbaro, 2003; Craig and Dostrovsky, 1997; Garcia-Larrea et al., 2009, 1999; Lima and Fregni, 2008). In support of this concept are the motor abnormalities that can accompany chronic pain (Chen et al., 2009; Juottonen et al., 2002; Kirveskari et al., 2010; Svensson and Graven-Nielsen, 2001; Weissman-Fogel et al., 2011), possibly related to nocifensive behaviour (Murray and Peck, 2007).

There are two main routes by which the CNS may contribute to the development and/or maintenance of chronic pains such as TMD. One possibility is that long-term nociceptive input into the brain induces maladaptive brain plasticity, which may play a role in maintaining pain (Albanese et al., 2007; Woolf and Salter, 2000). For example, a recent study demonstrated that experimental pain that increased GM in nociceptive regions (Teutsch et al., 2008), induced pain habituation over time that was accompanied by decreased activity within nociceptive areas and increased activity within the antinociceptive system (Bingel et al., 2007). Chronic pain patients, however, may not be able to adapt in this way to nociceptive activity. For example, neuroimaging studies of chronic pain have shown hyperactivity in nociceptive regions, and hypoactivity in antinociceptive regions (Apkarian et al., 2005; Lev et al., 2010). Chronic pain patients' inability to habituate to increased nociceptive activity may be related to a reduced capacity of the brain to dampen pain by descending (top–down) controls (Bingel and Tracey, 2008). Indeed, many structural MRI studies have found GM differences in chronic pain populations associated with pain-related characteristics (intensity, unpleasantness, or duration) (Apkarian et al., 2004; Blankstein et al., 2010; May, 2008; Rodriguez-Raecke et al., 2009; Younger et al., 2010).

The second route by which the CNS may contribute to the development and/or maintenance of chronic pain relates to inherent personality-related factors that reduce the brain's capacity to modulate nociceptive input. This poor pain control represents a vulnerability to develop chronic pain. For example, there is evidence that neuroticism may be associated with pain-related suffering (Harkins et al., 1989), pain sensitivity (Costa, 1987; Goubert et al., 2004; Wade et al., 1992), nerve injury outcomes and neuropathic pain (Taylor et al., 2010) and inhibition of negative thoughts (Costa and McCrae, 1992). However, not all chronic pain patients have high neuroticism scores, and not all persons with neuroticism have chronic pain (Costa et al., 1986). Therefore, neuroticism alone is not sufficient to develop chronic pain. Rather, the normal relationship between neuroticism and brain structure and function may be disrupted within regions involved in pain modulation, such as the orbitofrontal cortex (OFC) (Wright et al., 2006) or the medial prefrontal cortex (mPFC) (DeYoung et al., 2010; Haas et al., 2008) and this could facilitate or maintain chronic pain.

Thus, in the current study we examined GM abnormalities in patients with idiopathic TMD and focused our investigation on the contribution of pain-related characteristics and neuroticism. Towards this goal, we measured GM in patients who had suffered from TMD over a range of pain intensities, unpleasantness and for varying durations, and neuroticism scores. Based on the aforementioned behavioural and neuroimaging studies, we specifically tested the hypotheses that TMD patients will have: 1) increased GM in areas associated with pain perception; 2) reduced GM in areas associated with pain modulation and motor function; 3) GM positively correlates with pain intensity, unpleasantness and TMD duration within areas associated with pain perception areas and negatively correlates with GM in areas associated with antinociception; 4) negative correlation between neuroticism and GM in regions implicated in pain modulation, and positive correlation in regions implicated in the affective dimension of pain, because of the interaction between affective processing and pain modulation in TMD (Turner et al., 2001).

Materials and methods

Subjects

A group of 17 females with idiopathic TMD (mean age ± SD: 33.1 ± 11.9 years) and 17 healthy females (mean age ± SD: 32.2 ± 10.1 years) provided informed written consent to procedures approved by the University Health Network and Mount Sinai Hospital Research Ethics Boards. All subjects were right-handed. Patients with TMD were screened using TMD research diagnostic criteria (TMD-RDC) (Dworkin and Leresche, 1992) by dentists at the Mount Sinai Hospital Dental Clinic. Inclusion criteria included: 1) TMD pain masticatory muscle region greater or equal to 4/10 for at least 3 months or pain that is aggravated by mandibular function; and 2) moderate pain to palpation and/or persisting pain after examination in at least 3 muscle sites and/or moderate pain to palpation of the temporomandibular joint (TMJ) region and/or limitation in the mandibular movement (opening less than 40 mm). Patients were asked to remain analgesic-free for 24 h prior to scanning, as functional data was also being collected during the scanning session. For both patients and control subjects, exclusion criteria included: 1) serious metabolic, rheumatoid or vascular disorders and other diseases; 2) other craniofacial pain disorders, previously diagnosed psychiatric disorders (e.g., depression, schizophrenia and ADHD) or self-reported history of an abnormal neurological examination; 3) any contraindication to MRI scanning (e.g., claustrophobia and metal); and 4) use of psychotropic drugs. In addition, healthy controls were not eligible for the study if they had a history of chronic pain.

Questionnaires

Each participant completed the NEO-Five Factor Inventory (NEO-FFI) (Costa and McCrae, 1992). The NEO-FFI is a self-report questionnaire comprising of 60 statements. Participants were asked to indicate the degree to which they agree with a statement on a five-point scale (strongly disagree, disagree, neutral, agree and strongly agree), each of which is coded to a number (0–4). A total of 15 of 60 questions probe for aspects of neuroticism in this questionnaire.

Prior to scanning, patients were interviewed. They were asked to verbally provide a numerical pain score for their current pain intensity and pain unpleasantness and their average pain intensity and unpleasantness over the last month before scanning. They were specifically asked the following questions: “Please rate your current/average pain/unpleasantness rating over the last month on a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable)”. The duration of the patients' TMD was also recorded for each patient.

Imaging parameters

Brain imaging data were acquired using a 3T GE MRI system fitted with an eight-channel phased array head coil. Subjects were placed supine on the MRI table and each subject's head was padded to reduce movement. A whole brain three dimensional (3D) high-resolution anatomical scan was acquired with a T_1-weighted 3D IR-FSPGR sequence: 128 axial slices, $0.94 \times 0.94 \times 1.5$ mm^3 voxels, 256×256 matrix size, field of view = 24×24 cm, one signal average, flip angle = 20°, TE = 5 ms, TR = 12000ms, TI = 300 ms.

Structural brain imaging analysis

We used the analysis approaches best suited to measure GM cortically and subcortically from high-resolution MRI images. At the cortical level, we evaluated differences in cortical thickness (measured in mm) with cortical thickness analysis (CTA) (Fischl and Dale, 2000; Lerch and Evans, 2005; MacDonald et al., 2000), and subcortically we used voxel-based morphometry (VBM) (Ashburner and Friston, 2000) to measure subcortical GM volume. To verify the

validity of measuring GM differences between groups, we correlated whole-brain GM to age for each group, and performed a group comparison with Fisher's r-to-z transformation. We then used masks of specific brain regions (i.e., region of interest (ROI) analysis) to test our specific *a priori* hypotheses; this focus also reduced multiple comparisons to regions of no interest (see below).

Cortical thickness analysis

CTA was carried out using the Freesurfer software (http://surfer.nmr.mgh.harvard.edu); methods are described in full detail elsewhere (see: Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2001, 1999a, 1999b). Briefly, pre-processing included intensity normalization, skull stripping, separation of the hemispheres, and GM segmentation. The white matter/GM border (i.e., white surface) and GM/CSF border (i.e., pial surface) were identified and modeled as surfaces. The software then calculated the distance between the two borders at every point on the cortex, for each hemisphere. The GM surface was then warped such that homologous gyri and sulci were aligned across all subjects. Each individual subject's cortex underwent automatic anatomical parcellation, and each sulcus and gyrus was labeled during pre-processing (Fischl et al., 2004). To restrict our search to regions hypothesized to be involved in TMD chronic pain, we used the cortical parcellations map implemented into FreeSurfer (aparcs2005) on a standard subject (fsaverage). Two masks were created: (1) a sensorimotor/pain mask which included primary and secondary somatosensory cortices (S1 and S2) the primary motor cortex (M1), and the mid-cingulate cortex (MCC) (see Fig. 1 a); and (2) a cognitive/modulatory mask of the frontal lobe that included the OFC, prefrontal cortex (PFC), insula and the anterior cingulate cortex (ACC) and MCC (see Fig. 1 b). The MCC has been implicated in both nociception and pain modulation (Apkarian et al., 2005) and so this region was included in both masks. To compensate for topographical heterogeneity amongst the different subjects, a 6 mm full-width half-maximum (FWHM) Gaussian spatial smoothing kernel was applied to the data prior to statistical analysis. A vertex represents a point on a two-dimensional sheet, and, in this study, the distance between two vertices is 0.71 mm.

Subcortical analysis with voxel-based morphometry

Image processing and statistical analyses were performed in the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) running under Matlab (Mathworks). The VBM analysis used Gaser's VBM 5.1 toolbox (http://dbm.neuro.uni-jena.de/vbm) within SPM 5; detailed methodology is described elsewhere (Ashburner and Friston, 2000). Briefly, the preprocessing included setting the origin of the image at the anterior commissure of each subject, spatial normalization to the International Consortium for Brain Mapping (ICBM-152) template, GM segmentation, Jacobian modulation to adjust for the effects of spatial normalization, and spatial smoothing with a 10 mm FWHM Gaussian kernel. Total intracranial volume (TIV) was calculated for each subject from the volume estimates output during segmentation. An absolute threshold mask of 0.10 was applied to restrict the results to GM only. We constructed a single mask for our subcortical VBM analysis (See Fig. 1 c). We used prefabricated anatomical masks in WFU Pickatlas (http://www.nitrc.org/projects/wfu_pickatlas). The subcortical mask was used to investigate regions that cannot be investigated using CTA, and comprised the basal ganglia, amygdala, brainstem and thalamus.

Statistical analyses

Demographics

Group differences between characteristics of the patients and controls were evaluated using a multivariate analysis of variance in SPSS 18.0 (http://www.spss.com/). Age and neuroticism scores were compared between the groups. The significance threshold was set at $p<0.05$.

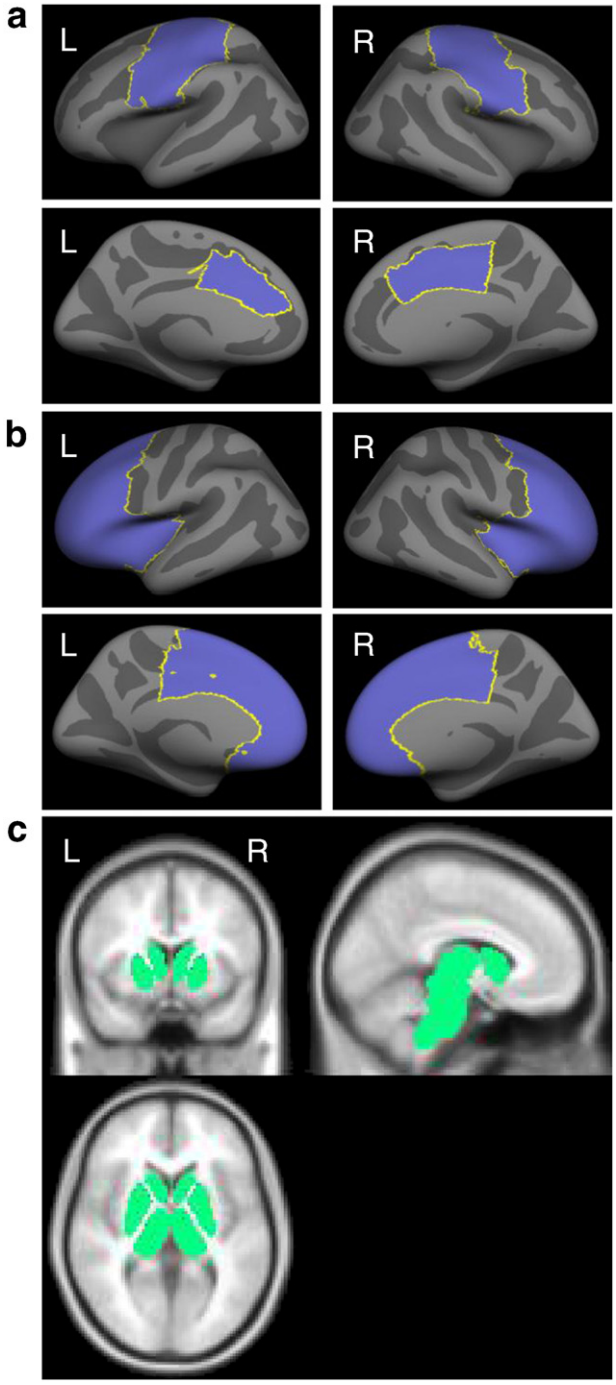

Fig. 1. Masks used to restrict analyses. Our three masks, used to restrict our analyses to regions of interest: a) the sensorimotor/pain mask included cortical sensorimotor regions (primary and secondary somatosensory cortices (S1 and S2), the primary motor cortex (M1), and the mid-cingulate cortex (MCC), b) the cognitive/modulatory mask which included the insula, the prefrontal cortex (PFC), the orbitofrontal cortex (OFC), and the cingulate cortex (ACC/MCC), and c) a subcortical mask used for voxel-based morphometry, including the basal ganglia, thalamus, amygdala and the brainstem. CTA results are overlaid onto the fsaverage standard brain in FreeSurfer.

GM group differences

CTA

To test our first hypothesis that patients have thicker cortex in perception areas, we ran a general linear model (GLM) testing for

group differences in cortical thickness at every vertex within the sensorimotor/pain mask. Age was included as a regressor of no interest. To test our second hypothesis that patients have thinner cortex in modulatory/cognitive areas, we ran a second GLM testing for group differences at every vertex within the cognitive/modulatory mask. Percent change was calculated using the following formula: ((Mean of patients' thickness−mean of controls' thickness)/mean of controls' thickness)×100.

All data were thresholded at an experiment-wide Bonferroni corrected $p<0.05$. To do so, we calculated the corresponding cluster-wide p-value to reach significance and so the experiment-wide correction was based on conducting 6 tests: (1) thicker cortex in pain perception regions, (2) thinner cortex in cognitive/modulatory regions, (3) the contribution of pain intensity, (4) the contribution of pain unpleasantness, (5) the contribution of TMD duration to cortical abnormalities, and (6) group by neuroticism interactions in cortex. Thus the correction for the threshold was $0.05/6=0.008$. Therefore, to achieve a Bonferroni-corrected threshold of $p<0.05$, CTA data were thresholded at image-wide threshold of $p<0.008$. Our two masks were of different sizes; thus, we used Monte Carlo permutation to calculate an image-wide threshold for each. For the sensorimotor/pain mask, this was derived from an uncorrected voxelwise $p<0.01$ and 190 contiguous vertices (379 voxels), and for the cognitive/modulatory mask, this was derived from an uncorrected voxelwise $p<0.01$ and 220 contiguous vertices (436 voxels). Monte Carlo simulations were run with 1000 iterations using AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim), as we have used previously (Taylor et al., 2009).

VBM

To test both our first and second hypotheses, we used student's *t*-test to test for group differences in each voxel within the subcortical mask, as previously described. The GLM included age and TIV as covariates of no interest. All data were thresholded at a voxelwise corrected $p<0.05$ using false discovery rate (FDR), as implemented in SPM 5.

Clinical correlates

To assess pain-related plasticity, we correlated pain intensity, pain unpleasantness and TMD duration to GM. For all the correlations, age was included as a regressor of no interest. However, for the correlation of GM to TMD duration we could not include age as a covariate, as these two explanatory variables (age and TMD duration) are correlated ($r=0.536$, $p=0.027$). For the CTA analysis, pain intensity, pain unpleasantness and TMD duration correlations were performed within the sensorimotor/pain mask and the cognitive/modulatory mask. For the VBM analysis, we ran correlations in each voxel within our subcortical mask, as previously described. TIV was included as a covariate of no interest in every model.

Neuroticism effects

To determine whether chronic pain may be affected by neuroticism in TMD, we performed a Pearson correlation between TMD duration and neuroticism scores in the patient group.

To investigate whether neuroticism has an abnormal relationship to GM, and thus contribute to TMD onset, we performed an interaction analysis. Specifically, in CTA, we performed a group by neuroticism interaction using the FreeSurfer software on a vertex-wise basis within the cognitive/modulatory mask. In the VBM analysis, to test this hypothesis, we performed a group by neuroticism interaction in each voxel within our subcortical mask.

Results

Patient demographics

The characteristics of individual patients are shown in Table 1. Patients and controls did not differ in age (patients: mean age ± SD: 33.1 ± 11.9 years; controls: 32.2 ± 10.1 years; $p=0.94$) or in neuroticism scores (patients: mean age ± SD: 19.35 ± 6.84; controls: 18.35 ± 7.95; $p=0.70$). Interestingly, TMD pain intensity and pain unpleasantness scores were not significantly correlated ($r=0.40$, $p=0.12$), unlike the tight correlation of these dimension in healthy subject in acute pain paradigms (Rainville et al., 1992). Patient neuroticism scores showed no significant relationship to TMD duration ($r=0.33$, $p=0.21$).

Group differences: S1 and frontal thickening in TMD

There were prominent group differences ($p<0.05$, corrected) in GM thickness in the TMD patients compared to controls (see Table 2, Fig. 2). In line with our first hypothesis, the ventrolateral S1 was 22% thicker in the TMD group compared to controls. This region of thickening was located in a region consistent with the somatosensory representation of the face (DaSilva et al., 2002; Moulton et al., 2009). However, contrary to our second hypothesis, we did not identify statistically significant cortical thinning in any pain modulation or motor region. Unexpectedly though, we identified regions in the left frontal pole and ventrolateral PFC cortex (vlPFC) that were thicker in the patient group compared to controls by 17% and 15% respectively (see Table 2 and Fig. 2). The VBM analysis did not reveal any significant subcortical differences between patients and controls.

Effect of chronic pain intensity and unpleasantness

We also examined the relation between pain intensity and pain unpleasantness in GM within our cortical masks. Cortical thinning that correlated with the degree of TMD pain intensity or unpleasantness was found within three brain regions (see Fig. 3 and Table 3). A significant negative correlation was found between pain intensity and GM thickness in the anterior MCC (aMCC; BA32; $r=-0.83$), and in the ventrolateral aspect of M1 in a region consistent with the representation of the face (Woolsey, 1958) ($r=-0.83$). Our test of the impact of pain unpleasantness on cortical thickness within our two masks revealed a significant effect only in left OFC. This region showed a negative correlation between GM thickness and unpleasantness (BA 47; $r=-0.74$). Interestingly, in these three brain areas, the patients reporting intense pain had GM that was thinner than the healthy controls, but the individuals with only mild pain had GM either slightly thicker than the controls or within the normal range. Of note is that we did not identify any significant GM subcortical correlations with pain intensity or unpleasantness.

Effect of TMD chronicity

The subcortical VBM analysis revealed that GM in the sensory thalamus was positively correlated to the length of time that patients had been suffering with TMD ($r=0.91$; see Table 4 and Fig. 4 for details). This region of GM increase included the left posterior nucleus (Po), the left ventrolateral nucleus (VL), and bilateral ventroposterior medial nucleus (VPM) of the thalamus. Interestingly, the patients who had TMD for only a few years showed GM within the normal range (see Fig. 4) but patients who had TMD for 7 or more years showed a progressive increase in thalamic GM. We did not find any significant correlations between TMD duration and GM thickness in the *a priori* hypothesized cortical ROIs.

Table 1
Patient demographics.

#	Age	TMD dur (yrs)	Pain intensity	Pain unpl	Pain sites	TMD laterality	Other pains	Medication	Oral contraceptive
1	22	2	4	5	J	Bilateral	Knee pain	NSAID	Yes
2	20	3	3	3	M, J	Bilateral		A*, cyc*	No
3	24	7	4	8	J	Right	Headache	N, P	Yes
4	38	20	7	6	J	Bilateral		NSAID	No
5	42	0.75	2	3	M	Bilateral		F*	No
6	33	4	5	6	M, J	Bilateral	Shoulder, neck	A*, F*	No
7	28	17	3	5	M, J	Left			No
8	34	14	2	8	J	Bilateral		A*, F*, Hy*	No
9	50	10	7	6	M	Bilateral		A, Ch, Di	No
10	59	13	7	7	M, J	Bilateral	Whiplash (neck and shoulder), gastric distress		No
11	18	3	6	8	M, J	Bilateral			Yes
12	34	15	2	3	M	Right	Neck, sciatica		No
13	52	30	4	5	M, J	Bilateral		A	No
14	31	2	6	5	M, J	Right	Ovarian cyst	N	No
15	33	17	5	8	M, J	Bilateral		A, F, NSAID	No
16	22	1	4	1	J	Bilateral			Yes
17	23	8	2	5	J	Bilateral			Yes

Abbreviations: M = masticatory muscles; J = TMJ; NSAID: Non-steroidal anti-inflammatory, over the counter, as needed; A: arthrotec; cyc: cyclobenzapine; Ch: champix; Di: dixarit (clonidine); F: flexoril; Hy: hydromorphone; N: naproxen; P: prevacid; TMD Dur: TMD duration; Unp: unpleasantness; yrs: years. The asterisk (*) denotes that subjects discontinued the use of the drug prior to our study. A and N are also NSAIDs, but were patients were prescribed to take these medications daily- rather than when needed. Gastric distress was described as "burning in the stomach" by the patient.

Effect of neuroticism

Because of the expectation that neuroticism manifests differently in patients than healthy controls, we tested whether there was neuroticism by group interaction in the cognitive/modulation mask. The controls showed a negative correlation ($r = -0.32$) between GM thickness in the left OFC (BA11; Talairach coordinates −18, 22, −18) and neuroticism scores, whereas patients show a positive relationship ($r = 0.61$) in this region. The area of the interaction in this ROI was 517 mm^2 (peak vertex *t*-score = −2.87; $p<0.05$, experiment-wide Bonferroni corrected; see Fig. 5). We did not identify any significant neuroticism by group interactions in the subcortical VBM analysis.

Discussion

This structural imaging study identified striking abnormalities in patients with chronic idiopathic TMD pain and highlights the contribution of both TMD-related and neuroticism-related factors. Our key findings were that, compared to controls, patients with TMD had 1) cortical thickening of the S1, frontal pole and vlPFC, 2) pain intensity-dependent cortical thinning in the aMCC and M1 and pain unpleasantness-dependent cortical thinning in the OFC, 3) TMD duration-dependent GM increase in the sensory thalamus, and 4) a positive correlation between cortical thickness in the OFC and neuroticism, in contrast to a normally negative correlation.

S1 and thalamic GM increases in TMD

Our finding of S1 thickening in TMD is consistent with other GM studies of chronic pain in the trigeminal system (DaSilva et al., 2007; Younger et al., 2010). However, trigeminal chronic pains are heterogeneous, and so may produce different patterns of GM changes specific to the particular symptomology or pathology. Nonetheless, the convergence of increased S1 thickness suggests that there may be prolonged or repeated barrage of nociceptive input to the cortex from the thalamus. Evidence for this hypothesis comes from a study by Teutsch and colleagues (2008) that showed persistent noxious stimulation in healthy subjects can induce increased GM in S1. Since we also found that in TMD patients there was a positive correlation between thalamic GM and TMD duration, it is possible that sustained trigeminothalamic nociceptive activity over time leads to increased GM in sensory thalamus. The patients included in our study have a larger range of TMD durations (0.75–30 years) compared to Younger et al.'s (0–11 years). Thalamic changes were more apparent in patients with longer reports of TMD duration, which may explain why our findings are different than those reported by Younger and colleagues (2010). Increased firing to the thalamus may lead to increased thalamocortical activity to S1 and plasticity (Woolf and Salter, 2000). The cellular basis of cortical thickening (plasticity) is not yet established but is thought to include increases in synaptic boutons, dendritic branching, glial cells, and/or neurons (May, 2008; Metz et al., 2009).

Table 2
Group differences in cortical thickness.

Contrast	Region	BA	TAL of Peak			Area (mm^2)	Peak *T*-score
			X	Y	Z		
Patients>controls	R S1	2	50	−18	37	1132	5.18
	L FP	10	−30	45	6	569	4.87
	L vlPFC	9/10	−38	35	4	531	3.41

Peak vertex Talairach coordinates are reported. All results are significant at $p<0.05$, corrected for multiple comparisons. Abbreviations: R: right; L: left; BA: Brodmann's area; FP: frontal polar cortex; S1: primary somatosensory cortex; vlPFC: ventrolateral prefrontal cortex.

Cortical thickening in cognitive and modulatory regions in TMD

We found that patients with TMD had cortical thickening in the frontal pole. These findings diverge from those of Younger et al.'s (2010) study. A factor that may have contributed to the different findings is that their study examined patients with myofascial TMD, whereas our TMD group consisted of a somewhat more clinically representative group of mixed muscular and/or joint TMD.

Activation of the frontal pole has been reported during spontaneous pain in patients with chronic pain (Baliki et al., 2006). The frontal pole has also been implicated in a number of complex executive cognitive functions such as learning behavioural routines (Jenkins et al., 1994; Koechlin et al., 2000; Strange et al., 2001), cognitive branching (the ability to put a pending task on hold to execute an ongoing one) (Koechlin and Hyafil, 2007), behavioural flexibility/adaptability (Boorman et al., 2009) and post-hoc monitoring or evaluating decisions based on feedback (Tsujimoto et al., 2010). Therefore, the frontal pole may process the cognitive dimension of pain, which suggests that pain has a cognitive load. We propose that

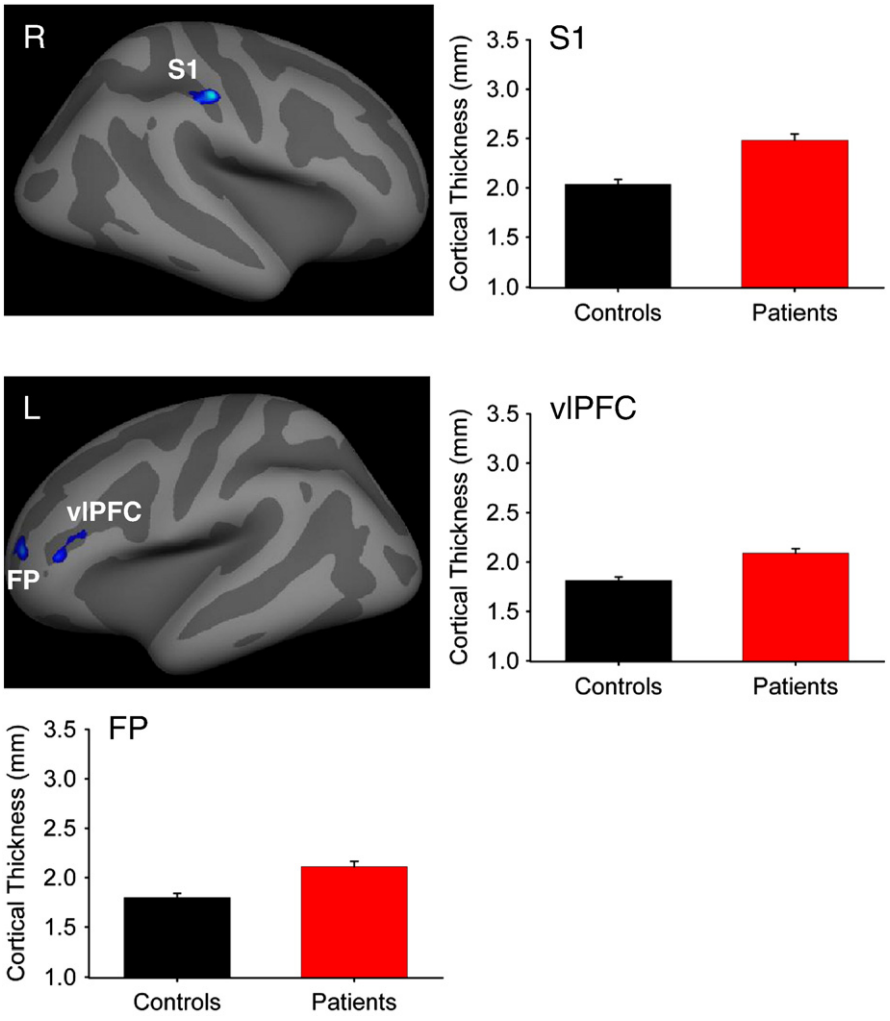

Fig. 2. Cortical thickening in TMD. The CTA GLM group analyses within the cortical masks identified three cortical regions (shown in blue on the brain images) that showed significant group differences at a corrected $p<0.05$. The top panel shows that the TMD patient group had thicker right primary somatosensory cortex (S1) (peak *T*-score = 5.18) compared to controls, with the effect of age regressed out. The bottom panel shows that the TMD patient group has thicker ventrolateral prefrontal cortex (vlPFC) (peak *T*-score = 3.41) and frontal polar (FP) cortices (peak *T*-score = 4.87). All labeled regions are significant at a corrected $p<0.05$. The graphs indicate the mean cortical thickness ± SE (age not regressed out). CTA results are overlaid onto the fsaverage standard brain in FreeSurfer.

the cognitive load of pain may require constant engagement of the frontal polar cortex for cognitive branching. That is, chronic pain may need to be put "on hold" in order for a patient to engage in another competing cognitive load. However, if the cognitive branching system is limited, a chronic pain load may impact the ability to properly complete tasks (Legrain et al., 2009). In support of this, we have recently shown that patients with TMD have sluggish reaction times to low and high conflict cognitive interference tasks, but not to a simple sensorimotor task (Weissman-Fogel et al., 2011). Further evidence for cognitive branching of pain comes from studies showing that an increase in cognitive load modulates acute pain perception in healthy controls (Wiech et al., 2005). Therefore, one possibility for the thickening of the frontal polar cortex is that chronic TMD pain bears a cognitive load that the brain needs to 'put on hold' in order to address more immediate environmental demands.

The other frontal area we found to be thicker in TMD than controls was the vlPFC. This region has been implicated in pain anticipation (Salomons et al., 2007), pain modulation (Wager et al., 2007), and behavioural inhibition (Aron et al., 2003). There is evidence that patients with TMD are hypervigilant (Hollins et al., 2009; Slade et al., 2007), which is related to increased pain anticipation. Therefore, vlPFC thickening may be related to patients' hypervigilance and increased anticipation to pain.

Relationship between chronic pain intensity and cortical thickness in M1 and aMCC

We found that GM in the orofacial region of M1 showed a negative correlation to pain intensity. Several studies have reported abnormal stimulus-evoked fMRI activity in motor regions of chronic pain patients, although the implication of these abnormalities is not often discussed (see: Apkarian et al., 2005). One interpretation of our finding is that there is an adaptive mechanism that responds to sustained, intense nociceptive activity by dampening motor output to prevent further damage to the affected region. Evidence for this concept comes from studies of both acute and chronic orofacial pains. For instance, TMD pain inhibits craniofacial motor function (Svensson and Graven-Nielsen, 2001), and dampens motor neuron output (Lund et al., 1991). Similarly, acute pain stimuli applied to the orofacial region can decrease M1 excitability (Adachi et al., 2008). Interestingly, Kirveskari et al. (2010) reported that patients with CRPS had weaker M1 reactivity with increased spontaneous pain ratings, that is to say that there is a negative correlation between pain intensity and M1 activation. Another possibility is that TMD patients make fewer jaw movements to avoid eliciting pain. This reduced jaw activity may lead to atrophy of the orofacial region of the motor cortex. Conversely, there is evidence to suggest

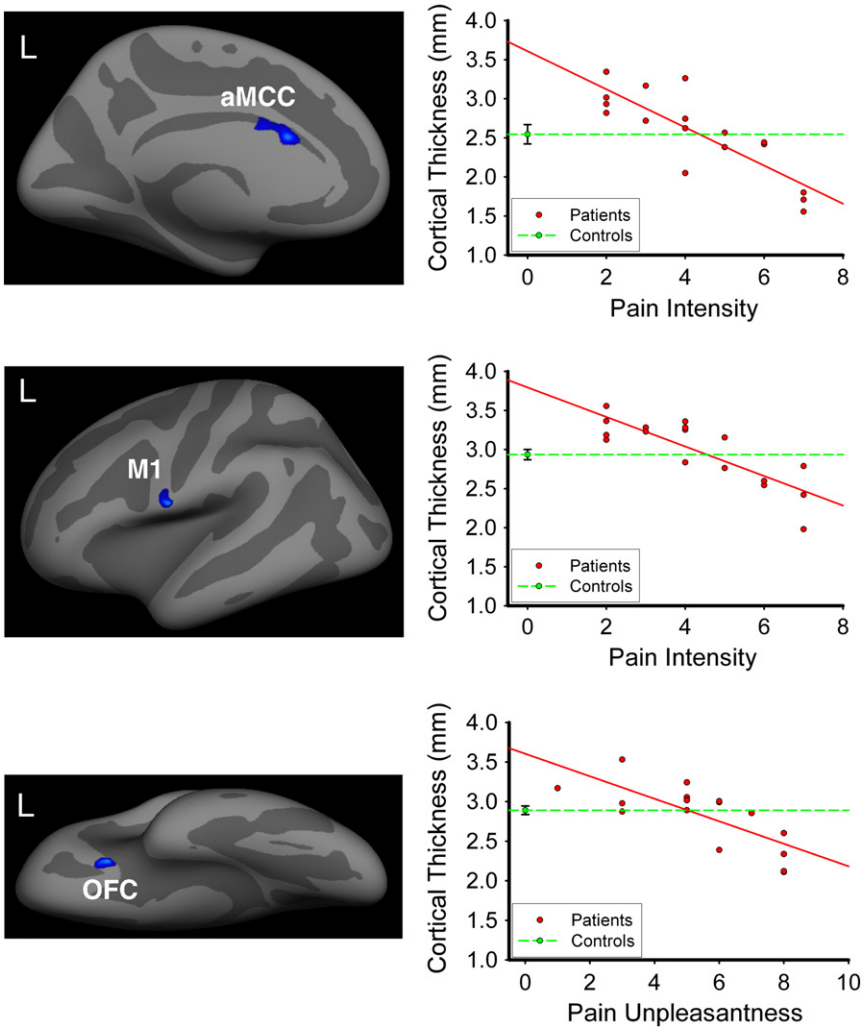

Fig. 3. TMD pain intensity and unpleasantness are negatively correlated to modulatory regions. The CTA regressions within the cortical masks in the TMD group identified three cortical regions (shown in blue on the brain images) that were significantly correlated with individual pain scores at a corrected $p<0.05$. The top panel shows that pain intensity has a negative correlation to anterior mid-cingulate cortex (aMCC) ($r=-0.83$, peak T-score $=-3.94$). The middle panel shows that pain intensity is negatively correlated to cortical thickness in the left primary motor cortex (M1) ($r=-0.83$, peak T-score $=-4.15$). The bottom panel shows that pain unpleasantness negatively correlated to cortical thickness in the left orbitofrontal cortex (OFC; $r=-0.75$, peak T-score $=-4.22$), with the effect of age regressed out. All labeled regions are significant at a corrected $p<0.05$. The graphs indicate the mean cortical thickness $\pm$ SE for each subject versus pain intensity (age not regressed out). CTA results are overlaid onto the fsaverage standard brain in FreeSurfer.

that M1 may play a role in central processing of pain (Al-Chaer et al., 1998; Dettmers et al., 2001; Kanda et al., 2003; Sessle, 2006) and pain modulation (Craig and Dostrovsky, 1997). For instance, motor cortex stimulation has been shown to have some, albeit limited, analgesic effect in chronic pain (Garcia-Larrea et al., 2009; Peyron et al., 1995). Therefore, another interpretation of our finding is that M1 maybe, in part, involved in descending modulation of pain.

The other GM region we identified that was negatively correlated to pain intensity is the aMCC. This finding had also been identified in a previous study of GM in TMD (Younger et al., 2010). Experimental acute pain in healthy subjects is associated with activity in the MCC (caudal BA24) (Peyron et al., 2000) and nociceptive-specific neurons have been identified in caudal BA24 (Hutchison et al., 1999). The top–down descending antinociceptive system is thought to arise from the

Table 3
Cortical thickness negatively correlates with TMD pain intensity or unpleasantness.

TMD attribute	Region	BA	TAL of peak			Area (mm^2)	Peak T-score
			X	Y	Z		
Pain intensity	L aMCC	32	−4	18	19	718	−3.94
	L M1	4	−57	−3	13	674	−4.15
Unpleasantness	L OFC	11/47	−27	16	−19	472	−4.22

Peak vertex Talairach coordinates (TAL) are reported. All results are significant at $p<0.05$, corrected for multiple comparisons. Abbreviations: L: left; aMCC: anterior mid-cingulate cortex; M1: primary motor cortex; OFC: orbitofrontal cortex.

Table 4
TMD duration is positively correlated to gray matter in sensory thalamus.

Region	TAL of peak			Cluster size (mm^3)	Peak T-score
	X	Y	Z		
L Thalamus				2312	
Po	−14	−26	12		7.84
VL	−14	−14	17		5.70
VPM	−12	−16	9		5.12
R VPM	15	−19	14	14	4.21

Peak voxel Talairach coordinates (TAL) are reported. All results are significant at a FDR-corrected $p<0.05$. Abbreviations: L: left; R: right; Po: posterior nucleus; VL: ventrolateral nucleus; VPM: ventroposterior medial nucleus.

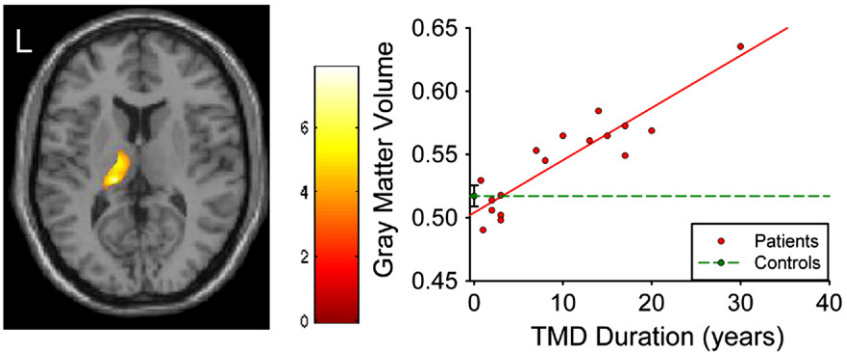

Fig. 4. TMD duration is related to plasticity in the thalamus. The TMD patient group showed a positive correlation between TMD duration (measured in years) and GM in a cluster in the sensory nuclei in the left thalamus (posterior (PO), ventral lateral (VL), ventral posterior medial (VPM)) (2312 voxels, peak *T*-score = 7.84, r = 0.91). The finding is significant at a false-discovery rate corrected $p < 0.05$. The graph indicates each TMD patient's gray matter volume (GM) versus her individual TMD duration (in years). The dashed lines represent the mean GM volume of controls ± SE. VBM results are displayed on the single subject standard brain in SPM.

aMCC (possibly triggered by activity in cingulate nociceptive neurons) (Bingel and Tracey, 2008). The aMCC also shows increased rCBF during analgesic thalamic stimulation (Davis et al., 2000). Furthermore, this region shows opioid-related pain modulation (Garcia-Larrea et al., 2009).

Therefore, both the M1 and the aMCC have been implicated in descending modulation of pain (Peyron et al., 1995). We identified that TMD patients with thicker cortex in both the aMCC and M1 report lower TMD pain intensity, whereas patients with thinner cortex in these regions report higher pain intensity. Therefore, thicker cortex in these regions may provide a greater capacity to modulate TMD pain, whereas thinner cortex maybe related to an impairment of this descending modulation system.

Interaction between neuroticism and prefrontal GM

We investigated two factors that have not been previously examined in imaging studies of TMD: neuroticism and TMD pain unpleasantness. Neuroticism is described as a personality trait associated with heightened sensitivity and/or processing of negative affective stimuli (Costa and McCrae, 1992; Costa et al., 1986; Wade et al., 1992). We found that in patients with TMD there is a positive correlation between neuroticism and cortical thickness in the left ventromedial prefrontal cortex (vmPFC, part of the OFC); an area that normally shows a negative correlation between GM and neuroticism (Wright et al., 2006). Neuroticism is considered to be a stable trait across the lifespan (Costa and McCrae, 1992). Therefore, our observation highlights the contribution of neuroticism to abnormal GM in the OFC of patients with TMD and, perhaps, to the development of TMD. An alternative interpretation is that chronic pain may have modified the relationship between neuroticism and OFC thickness. However, the lack of correlation of TMD duration and neuroticism scores in our TMD patients does not support this hypothesis.

We also found that unpleasantness is negatively correlated to GM in an adjacent region of the OFC. The OFC has been implicated in cognitive reappraisal and emotional regulation (Ray et al., 2005) related to interoception and somatoviscero stimuli, for directing our behaviour appropriately (Barrett et al., 2007; Wiech et al., 2005). The OFC is also thought to play a role in mental flexibility and adaptability (for a critical review, see: Schoenbaum et al., 2009). Therefore, our finding suggests that patients with TMD may have abnormal emotional regulation and reappraisal, which may lead to pain behaviours and exaggerated affective responses to pain.

Caveats

A few limitations in study design and results should be considered in the interpretation of our data. First, it is not known whether medications used by some of the patients have an effect on GM. Second, some of our patients had co-morbid chronic pains (see Table 1), and these pains (mostly related to TMD) may have contributed to our findings. Third, we cannot disassociate an age effect from a pure TMD duration effect because of the strong correlation between age and TMD duration. Furthermore, duration (and intensity) may not fully describe the effect of pain on GM structure. Due to the nature of TMD pain, other factors that we did not collect, such as the number of days of pain in a month may have more explanatory variance. Finally, we cannot totally rule out a contribution of ventricular volume to the VBM analysis of subcortical structures. Despite these limitations, our study does provide considerable evidence in line with previous findings in the literature about GM abnormalities in chronic pain.

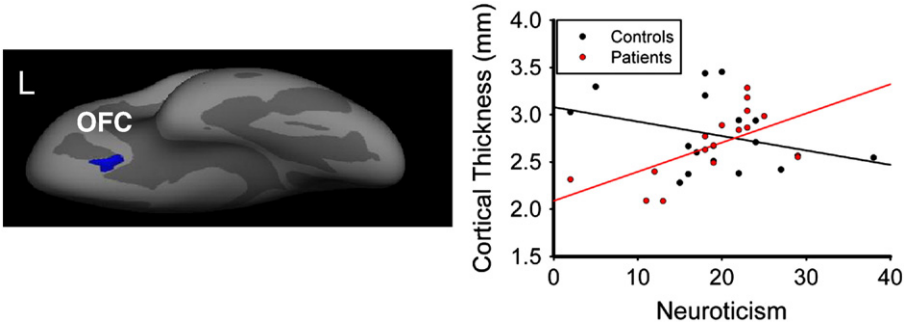

Fig. 5. Patients show an abnormal positive relationship between OFC thickness and neuroticism. Neuroticism showed an interaction in the left orbitofrontal cortex (OFC; peak *T*-score = 3.97), with the effect of age regressed out. For all correlations, mean cortical thickness ± SE (age not regressed out) versus raw neuroticism score is graphed. CTA results are overlaid onto the fsaverage standard brain in FreeSurfer.

Conclusions

This study provides evidence for GM abnormalities in both the ascending pain and descending antinociceptive systems as well as motor and cognitive areas in TMD. Further, we have shown that the personality trait neuroticism and TMD characteristics can affect GM, suggesting the presence of both personality-based and chronic pain-related abnormalities.

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