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White matter brain and trigeminal nerve abnormalities in temporomandibular disorder

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ABSTRACT

Temporomandibular disorder (TMD) is a prevalent chronic pain disorder that remains poorly understood. Recent imaging studies reported functional and gray matter abnormalities in brain areas implicated in sensorimotor, modulatory, and cognitive function in TMD, but it is not known whether there are white matter (WM) abnormalities along the trigeminal nerve (CNV) or in the brain. Here, we used diffusion tensor imaging, and found that, compared to healthy controls, TMD patients had 1) lower fractional anisotropy (FA) in both CNVs; 2) a negative correlation between FA of the right CNV and pain duration; and 3) diffuse abnormalities in the microstructure of WM tracts related to sensory, motor, cognitive, and pain functions, with a highly significant focal abnormality in the corpus callosum. Using probabilistic tractography, we found that the corpus callosum in patients had a higher connection probability to the frontal pole, and a lower connection probability to the dorsolateral prefrontal cortex, compared to controls. Finally, we found that 1) FA in tracts adjacent to the ventrolateral prefrontal cortex and tracts coursing through the thalamus negatively correlated with pain intensity; 2) FA in the internal capsule negatively correlated with pain intensity and unpleasantness; and 3) decreases in brain FA were associated with increases in mean diffusivity and radial diffusivity, markers of inflammation and oedema. These data provide novel evidence for CNV microstructural abnormalities that may be caused by increased nociceptive activity, accompanied by abnormalities along central WM pathways in TMD.

1. Introduction

Temporomandibular disorder (TMD) is a chronic pain disorder characterized by pain in the masticatory muscles and/or temporomandibular joint, and can be exacerbated by mandibular function. TMD is prevalent in ~10%–20% of the population, mostly in women [27,33,57,70]. In idiopathic TMD there is no clear aetiology [26,28,29,67]. Abnormal central nervous system (CNS) function is thought to initiate or maintain TMD pain [74] based on TMD symptomatology such as persistent pain, allodynia, and hyperalgesia, sometimes extending to regions distant from the face [32,35,42,62,73,94]; enhanced temporal summation of pain to repetitive noxious heat stimuli [60]; and dysfunctional diffuse noxious inhibitory controls [49]. Abnormalities of these centrally mediated processes suggest that ascending nociceptive pathways and/or descending pain modulatory pathways [54] are affected. Additionally, TMD patients can exhibit cognitive [37–39] and motor dysfunction [86] possibly related to abnormalities in brain regions associated with these functions [77,78,87,100].

Structural brain imaging provides an opportunity to delineate anatomical substrates of CNS abnormalities in TMD. We reported that patients with TMD have increased cortical thickness in the orofacial region of the primary somatosensory cortex (S1), the ventrolateral prefrontal cortex (vlPFC), and the frontal pole [63].

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Similarly, Younger and colleagues [101] reported increased gray matter volume in motor, limbic, and sensory regions, including trigeminal brainstem nuclei, in myofascial TMD. These studies indicate that TMD patients have gray matter abnormalities in sensory, motor, and cognitive/limbic regions. Our finding of a correlation of thalamic gray matter with TMD duration [63] supports the concept of long-term peripherally-induced central plasticity. Therefore, although clinical observations have not clearly identified gross peripheral abnormalities in TMD, the trigeminal nerve may indeed undergo microstructural changes due to abnormal persistent activity.

Previous studies examining white matter (WM) in other clinical conditions with sensory abnormalities and/or chronic pain [18,36,59,89] found abnormalities in brain areas involved in sensory, modulatory, and cognitive functions, and some of these WM abnormalities correlated with clinical findings. Therefore, studying the correlation between TMD characteristics and measures of WM integrity can provide insight into whether chronic pain drives changes in WM microstructure.

The main aim of this study was to evaluate the WM abnormalities in TMD. Specifically, we determined whether there are abnormalities along the trigeminal nerves or in WM tracts in the brain associated with sensory, cognitive, or motor functions, compared to healthy controls. Towards this goal, we used diffusion tensor imaging (DTI), a brain imaging technique sensitive to the inherent diffusion of water molecules that allows us to assess WM microstructure. Fractional anisotropy (FA) is a DTI metric that reflects WM tract integrity or structure [4,5,7,66]. We tested for abnormalities in FA along the trigeminal nerve of patients with TMD. Further, we used 2 approaches to assess WM in the CNS: first, we quantified brain FA abnormalities in TMD with tract-based spatial statistics (TBSS) [81], and second we used probabilistic tractography [9] to determine the connectivity of main regions of WM disruption. Finally, we determined whether there is a link between WM microstructure and clinical characteristics of TMD.

2. Methods

2.1. Subjects

The study consisted of a cohort of 17 right-handed females with idiopathic TMD (mean age ± SD: 33.1 ± 11.9 years) and 17 healthy right-handed females (mean age ± SD: 32.8 ± 9.8 years). Informed written consent was obtained from all study participants for procedures approved by the University Health Network and Mount Sinai Hospital Research Ethics Boards. All patients were examined and diagnosed as having TMD by dentists who are TMD specialists in the Pain Unit of the Mount Sinai Hospital Dental Clinic, using the standard clinical diagnostic criteria from this institution. These criteria included the involvement of myofascial and/or temporomandibular joint, based on clinical examination. Inclusion criteria included: 1) nontraumatic TMD (idiopathic TMD [90]); 2) musculoligamentous pain in the temporomandibular area; 3) pain in the muscles of mastication rated verbally as at least 4/10 for at least 3 months at the time of evaluation, or pain that is aggravated by mandibular function; and 4) moderate [on a scale of no (0), low (1), moderate (2), or severe (3)] pain to palpation and/or pain persisting postexamination in at least 3 muscle sites and/or moderate pain to palpation of the temporomandibular joint and/or limited mandibular movement (opening < 40 mm) (see Appendix A, Supplemental Methods for further details).

Exclusion criteria for all subjects included: 1) left-handedness; 2) self-report of metabolic, rheumatoid, or vascular diseases or disorders, or any other serious diseases; 3) self-report of commonly comorbid functional chronic pain disorders (irritable bowel syndrome and fibromyalgia); 4) self-report of psychiatric disorders (eg, depression, schizophrenia, attention deficit hyperactivity disorder); and 5) self-report history of an abnormal neurological examination; 6) contraindication to magnetic resonance imaging (MRI) scanning; 7) self-report of substance abuse. Additionally, healthy controls were excluded if they had a history of chronic pain and patients were excluded if they had a pain disorder other than TMD. Data collected for this study were part of a larger project that included assessment of gray matter [63] and cognitive task-evoked functional MRI responses [100].

2.2. Questionnaires

Patients provided verbal ratings of their current pain and unpleasantness, as well as their average pain intensity and unpleasantness ratings over the last month before scanning on a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable). Specifically, patients provided a numerical pain score for pain intensity and pain unpleasantness by answering the following questions: 1) "Please rate the intensity of your average pain over the last month, 0 being no pain and 10 being the worst pain imaginable." and 2) "Please rate the unpleasantness of your average pain over the last month, 0 being not unpleasant and 10 being the most unpleasant pain imaginable." The patients also reported the duration of their TMD symptoms.

2.3. Imaging parameters

All subjects underwent scanning in a 3-Tesla GE MRI system (GE Healthcare, Waukesha, WI, USA) fitted with an 8-channel phased-array head coil. Each subject's head was padded to reduce movement. The DTI acquisition consisted of 2 runs of diffusion-weighted scans (repetition time = 14,500 ms, field of view: 24 cm × 24 cm, 128 × 128 matrix, 1.875 mm × 1.875 mm in-plane resolution, 3-mm thick axial slices, with Array Spatial Sensitivity Encoding Technique with a factor of 2, maximum gradient strength = 40 mT/m, maximum slew rate = 150 T/m/s) acquired along 23 non-collinear, isotropic directions (b = 1,000 s/mm^2). Additionally, 2 non-diffusion-weighted scans (b = 0 s/mm^2; B0) were acquired at the beginning of each run. Between 49 and 55 axial slices were acquired to ensure coverage from the top of the head to the second cervical spinal process. Recent studies have reported that cardiac pulsatility can corrupt DTI data [48]. Although we did not perform cardiac gating during the DTI acquisition, we visually checked our dataset and verified that it did not contain corrupt images.

2.4. DTI preprocessing

The diffusion-weighted images were imported into the Oxford Centre for Functional MRI of the Brain's (FMRIB) software library (FSL v. 4.1.8) (http://www.fmrib.ox.ac.uk/fsl) for quality control [82]. Preprocessing included eddy current and motion artefact correction using the FSL diffusion toolbox (FDT) [47]. Each subject's 2 DTI runs were averaged to a single volume to achieve a greater signal-to-noise ratio. Then, individual brain masks were created using the Brain Extraction Tool [80]. These images were then processed through 2 different pipelines for 1) voxel-wise analysis and 2) tractography (see Supplemental Methods for tractography).

The preprocessed images were fit with a diffusion tensor model using DTIFIT in the FMRIB Diffusion Toolbox v. 2.0 (FDT). We then calculated voxel-wise values of FA and other DTI metrics (see Supplemental Methods).

2.4.1. Assessment of trigeminal nerve

The DTI metrics of FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (λ_1) values (see below and Fig. 1) were

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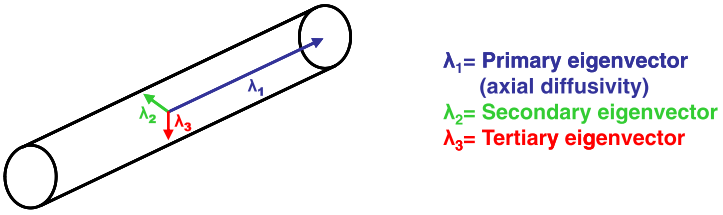

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/3$$

$$FA = (3/2)^{1/2} \times \{[(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2]^{1/2}/(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)^{1/2}\}$$

$$RD = (\lambda_2 + \lambda_3)/2$$

Fig. 1. Schematic of diffusion tensor imaging, and summary of eigenvectors and metrics. Lambda (λ) represents each of the eigenvectors that make up the tensor model. The equations to calculate mean diffusivity (MD), fractional anisotropy (FA), and radial diffusivity (RD) from these eigenvectors are also provided.

calculated for each of the DTI volumes. To assess the trigeminal nerves, we manually drew a region of interest (ROI) (3.75 mm × 3.75 mm × 3 mm) in the axial plane on each subject's trigeminal nerve root in the cisternal space in native space (see Supplemental Fig. 1). The nerves were identified on color orientation maps of the primary eigenvector (λ_1) image overlaid onto the FA map (Fig. 2A). DTI metrics (MD, RD, λ_1, and FA) were extracted from the ROIs. Independent samples *t*-tests were used to assess group differences in FA for each trigeminal nerve. Furthermore, a paired *t*-test was utilized to compare left and right trigeminal nerve FA values within the patient group. Lastly, FA values derived from each of the patient's nerves were correlated with TMD characteristics (pain

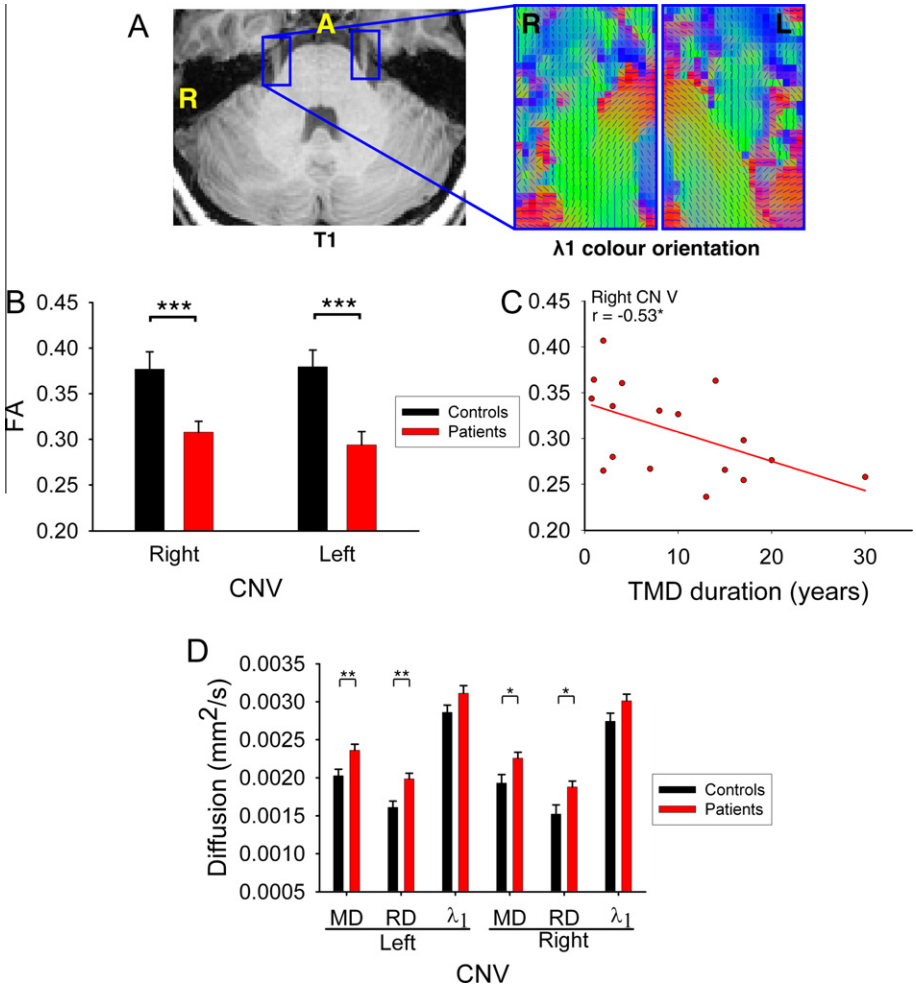

Fig. 2. Trigeminal nerve fractional anisotropy (FA) abnormalities in temporomandibular disorder (TMD). (A) The trigeminal nerve roots (within the blue boxes) at the pontine level are shown on an axial slice from a high-resolution T1-weighted magnetic resonance imaging scan. The magnified view of the right nerve is from a diffusion-weighted scan. The direction of the primary vector of the tensor model (λ_1) within each voxel is color-coded (green = anterior-posterior, red = left-right, blue = in the inferior-superior plane) and the primary vector shown within each voxel. (B) TMD patients have lower FA in bilateral trigeminal nerves, compared to controls. (C) FA is negatively correlated with TMD duration. (D) Group differences in trigeminal nerve mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (λ_1). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$. CNV, trigeminal nerve.

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intensity, unpleasantness, and duration). Statistical significance was set at $P < 0.05$. All statistical tests were performed in SPSS v. 19.0 (http://www.spss.com/).

2.4.2. Tract-based spatial statistics

TBSS v.1.2 [81,83] was used to compare FA between the TMD and healthy control cohorts. Briefly, FA maps underwent nonlinear registration to a $1 \times 1 \times 1$-mm FA map in standard space (FMRIB58_FA, available in FSL), a mean image derived from all the subjects was created and thinned to represent the center of major WM tracts common to all subjects, forming a WM skeleton. Each subject's peak FA value perpendicular to the thinned track was then projected onto the skeleton. One skeleton was created for analysis of group differences that included all study participants, and a second patient-only skeleton was created for correlation analyses of TMD pain characteristics (see below). The mean skeleton images were set at a threshold of 0.2 to include FA values that are related to WM [81]. Additionally, we performed a separate patient group analysis to assess which areas of the skeleton correlate with TMD characteristics (pain intensity, unpleasantness, or duration).

2.4.3. TBSS with other DTI metrics

To gain more insight into FA findings, we also assessed other DTI metrics in the clusters with significant group difference. Axial (longitudinal) diffusivity (λ_1) is thought to reflect diffusion along a tract, and reductions in this value suggest disruptions along the tract diffusivity. Radial (or perpendicular) diffusivity (RD) is believed to reflect changes in membrane permeability and, to some extent, myelination [1,2]. RD is calculated by averaging the 2 radial vectors of the tensor model (λ_2 and λ_3). Finally, MD was measured because it is associated with oedema and inflammation. Fig. 1 provides a schematic of these DTI metrics. DTI metrics (FA, MD, λ_1, λ_2 and λ_3) are calculated using DTIFIT in the FDT toolbox. The TBSS skeleton is created based on FA, and peak FA values are projected onto the skeleton. For statistical analysis of the other DTI metrics, MD, RD, and λ_1 values from the same voxels are projected onto the skeleton. To test for group differences, we performed a multivariate analysis of variance with each of the DTI metrics as dependent variables, and group as an independent variable.

2.4.4. Probabilistic tractography

Probabilistic tractography was used to assess the connectivity of findings from the TBSS analysis (http://www.fmrib.ox.ac.uk.fsl/fdt/index.html [9,10]). First, we downsampled the preprocessed diffusion-weighted images to create isotropic voxels ($3 \times 3 \times 3$ mm). The images were then processed in FDT. Probability density functions on up to 2 principal fibre directions were estimated at each voxel in the brain. We then used multi-fibre tractography and drew 5000 samples from each seed voxel along the probability density functions. The seed voxels were binarised images of the significant clusters. Together, each seed voxel's streamlines provide an estimate of its connectivity. When a streamline reaches a voxel with more than one fibre direction, the streamline follows the direction closest to the direction at which it arrives at the voxel. The pathways generated by the algorithm represent the number of samples that have passed through a voxel. To eliminate spurious connections, each computed pathway in each subject was thresholded at 10 samples (of the 5000 generated from each seed voxel) that passed through the voxels. These thresholded tracts were consistent between subjects. To visualize the findings, each of the subject's tracts were binarised and overlaid on a standard brain to produce a probabilistic map of the pathways for controls and patients. The values in these maps reflect the number of subjects who share a pathway. Further details on the tractography methodology and seed thresholds are found in the Supplemental Methods.

2.5. Statistical analyses

2.5.1. Whole brain white matter

We assessed group differences in global (whole brain) FA and the WM skeleton FA. To do so, we extracted mean FA values across every voxel in the brain and every voxel in the skeleton for each subject and performed a 2-tailed *t*-test.

2.5.2. Mask analysis

A mask was created to restrict the analysis to a priori WM ROIs, including the WM regions containing the pathways subserving nociceptive, antinociceptive, motor, and cognitive functions. Thus, the mask included the brainstem WM (including the WM that contains the trigeminothalamic tract and the corticospinal tract [CST]), thalamocortical tract (including tracts to S1 and the anterior corona radiata), the internal capsule containing the CST, the cingulum, the rostrum, genu, and the body of the corpus callosum, the uncinate fasciculus, and the external/extreme capsules. The mask also included the thalamus, as WM courses through this region. The ROIs were identified with the Johns Hopkins University WM Tractography Atlas, ICBM-DTI-81 WM Atlas [65,97], the Harvard-Oxford Cortical Atlas, and the Harvard-Oxford Subcortical Atlas, available within FSL (http://www.cma.mgh.harvard.edu/fsl_atlas.html). The final mask corresponded to voxels within the FA skeleton.

A between-group voxel-wise *t*-test within the skeleton mask was performed to identify regions with significant group differences in FA, with age included as a covariate of no interest. We used 2 complementary statistical thresholding methods with 5000 permutations testing in FSL's randomise toolbox: 1) threshold-free cluster enhancement (corrected cluster $P < 0.01$) [84], which is sensitive to spatially extensive areas of significant difference; and 2) cluster-mass correction ($P < 0.05$), which requires clusters to meet a specific height threshold and, therefore, is sensitive only to *t*-values above the threshold, which we set at $t > 2.3$.

An additional set of post-hoc analyses was run to characterize regions with significant group differences in FA. First, we determined whether the findings were related to specific characteristics of TMD. To do so, we extracted each subject's mean FA values from significant group difference clusters. The patients' FA values from each of these clusters then were correlated with the TMD pain intensity, unpleasantness, and duration in SPSS v. 19.0 (http://www.spss.com/). Statistical significance was set at $P < 0.05$. Second, we extracted the mean values of MD, RD, and λ_1 for each of the clusters and assessed whether there were significant group differences between TMD patients and controls using a multivariate analysis of variance with each of the DTI metrics as dependent variables and group as an independent variable. Statistical significance was set at $P < 0.05$.

All significant TBSS results are thickened with the "tbss_fill" tool implemented in FSL for ease of visualization. This tool uses a 3-mm Gaussian smoothing kernel to thicken significant results to the WM tract (as defined by FA > 0.2).

3. Results

3.1. Patient characteristics

The ages of the patient and control groups were not significantly different (mean age ± SD: patients = 33.1 ± 11.9 years; controls = 32.8 ± 9.8 years; $P = 0.94$). Details of the individual patient demographics have been tabulated in our previous publication of this cohort [63]. Of importance for this study is that there was variability in the durations of TMD, intensity, and unpleasantness of pain that facilitated assessment of these factors in correlation

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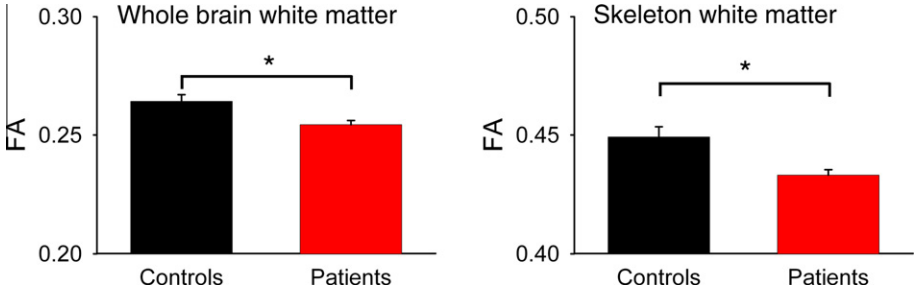

Fig. 3. Group differences in mean fractional anisotropy (FA) between temporomandibular disorder patients and controls. Patients had significantly lower whole brain FA (left panel) and skeleton FA (right panel). Asterisks (*) indicate $P < 0.05$.

analyses. The duration of TMD ranged from 0.75 to 30 years (mean ± SD: 9.8 ± 8.2 years), while pain intensity ranged from 2 to 7 (mean ± SD: 4.3 ± 1.8), and unpleasantness ranged from 1 to 8 (mean ± SD: 5.4 ± 2.1). Patients reported that their TMD pain was confined to the temporomandibular joint (n = 6), the muscles of mastication (n = 3), or both the joint and muscles (n = 8). Most patients reported bilateral pain (n = 13), but some reported unilateral pain (3 right-sided, 1 left-sided). The duration of TMD significantly correlated with the patients' age ($r = 0.536$, $P = 0.027$).

3.2. Trigeminal nerve FA

We tested the trigeminal nerve roots, in the cisternal space (see Supplementary Fig. 1), for group differences in FA, MD, RD, and λ_1. We found that TMD patients had significantly lower FA in both trigeminal nerves (right and left: $P < 0.001$) (Fig. 2B). FA in the right trigeminal nerve was also negatively correlated with TMD duration ($r = -0.53$, $P = 0.028$) (Fig. 2C). The left trigeminal nerve was not significantly correlated with TMD characteristics. MD and RD were significantly higher in both trigeminal nerves (right: $P < 0.01$; left: $P < 0.05$), compared to controls (Fig. 2D), but there were no significant group differences in λ_1.

Table 1
Group differences in whole brain skeletonised white matter.

	Controls		Patients		*P* value
	Mean ($\times 10^{-4}$ mm^2/s)	SD	Mean ($\times 10^{-4}$ mm^2/s)	SD	
MD	7.3	0.16	7.6	0.12	<0.05
RD	5.4	0.19	5.6	0.10	<0.05
λ_1	11.2	0.22	11.4	0.23	<0.05

MD, mean diffusivity; RD, radial diffusivity; λ_1, axial diffusivity.
Group means ± SD are presented for each group. Bonferroni post-hoc *P*-values are calculated based on independent-samples *t*-tests.

3.3. Patients have lower white matter FA

To investigate global differences in WM microstructure, we tested for group differences in FA across the whole brain and within the WM skeleton. Compared to controls, the TMD patient group showed a 3.8% reduction in whole brain FA (mean ± SD: controls = 0.264 ± 0.012; patients = 0.254 ± 0.008; $P = 0.003$) and 3.6% reduction in whole brain skeletonised FA (controls = 0.449 ± 0.018; patients = 0.433 ± 0.001; $P = 0.006$) (Fig. 3). We also evaluated MD, RD, and λ_1 across the WM skeleton and found that there was a significant group difference [Pillai's trace = 0.416; $F(3,30) = 7.117$; $P < 0.001$], and Bonferroni post-hoc tests revealed that all 3 DTI metrics were significantly higher in the patient group compared to the control group (all post-hoc tests: $P < 0.05$; see Table 1 for details).

The mask-wide TBSS analysis ($P < 0.01$; threshold-free cluster enhancement corrected) identified WM clusters that had 6.6%-16.8% lower FA in the patient cohort compared to controls (Table 2, Fig. 4A). Two of these clusters were localized to the right internal capsule, and 2 were in the right external/extreme capsule adjacent to the insula. Other significant clusters were at the junction of the right internal and external/extreme capsules, adjacent to the vlPFC, and in the WM adjacent to right S1 and primary motor cortex (M1). The largest cluster included the bilateral anterior body of the corpus callosum, and extended to the left cingulum, the bilateral anterior corona radiata, the bilateral internal capsules, the left external/

Table 2
White matter regions in TMD patients with significantly lower fractional anisotropy compared to controls.

Regions	FA				# Voxels	T	% Decrease	MNI		
	Controls		TMD					x	y	z
	Mean	SD	Mean	SD						
Thalamus	0.371	0.0326	0.32	0.0002	305	4.08	13.8	17	−15	12
WM adjacent to S1/M1	0.428	0.0476	0.356	0.0012	129	3.51	16.8	32	−22	38
IC_{AL}	0.564	0.0613	0.526	0.0046	3	3.06	−11.1	14	12	−2
EC/ExC	0.373	0.0335	0.339	0.0059	4	2.90	9.1	33	6	3
EC/ExC	0.399	0.0283	0.366	0.0073	3	2.82	8.3	32	9	1
Internal capsule	0.599	0.0454	0.558	0.0132	581	2.60	6.8	11	1	3
IC_{AL} and EC/ExC	0.513	0.0501	0.456	0.0332	55	2.27	6.6	26	24	11
Diffuse*	0.853	0.0521	0.786	0.0018	10,283	3.46	7.8	−5	26	10

TMD, temporomandibular disorder; FA, fractional anisotropy; IC, internal capsule; WM, white matter; S1, primary somatosensory cortex; M1, primary motor cortex; IC_{AL}, anterior limb of the internal capsule; EC/ExC, external/extreme capsules.
Mean and SDs of FA values, *T*-scores, percent decrease, and MNI coordinates are reported for the peak voxel.
All clusters are significant at $P < 0.01$, voxel-wise, mask-wide, corrected with threshold-free cluster enhancement. Voxels are 1 mm^3.
* Diffuse cluster includes white matter in the corpus callosum, corticospinal tracts, internal capsule, external/extreme capsules, fornix, cingulum, anterior corona radiata, cerebellar peduncle, and pontine tracts.

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extreme capsules, the fornix, the left and right thalamus, and the brainstem. Although the thalamus is mostly a gray matter structure, WM does course through it, and we identified a cluster within the right thalamus with significantly lower FA in patients with TMD, compared to controls. Individual clusters are shown in Supplementary Fig. 2.

Because one of our findings encompassed a large, diffuse region, we performed a secondary analysis to test for more focal, highly significant group differences in FA. To do so, we used a cluster-mass correction that requires significant clusters to reach a specified threshold, in this case $t(32) = 2.30$. This analysis revealed a single focal cluster in the corpus callosum (peak voxel MNI coordinates: −4, 26, 9, $t(32) = 2.31$, cluster size 353 voxels) (Fig. 5A).

We also determined whether the WM tracts with lower FA in patients with TMD also showed changes in MD, RD, and λ_1, indicative changes in axonal diffusion, permeability, and myelination. We found that there was a significant between-group difference in these microstructural variables [Pillai's trace = 0.958; $F(7,26) = 6.182$; $P = 0.009$]. Bonferroni post-hoc tests revealed that all of the clusters with lower FA showed significantly increased MD and RD ($P < 0.05$), but there were no significant differences in λ_1 (Table 3).

3.4. Probabilistic tractography

Because the corpus callosum is a large structure that contains interhemispheric fibres, we used tractography to elucidate the connectivity of our finding of lower FA in the corpus callosum. We evaluated the relationship between FA and connectivity by determining the connectivity of a region with lower FA in patients. To do so, we used multifibre probabilistic tractography to determine pathways passing through the corpus callosum finding from the cluster-mass correction analysis (Fig. 5A). We first performed a qualitative analysis to determine the connectivity of the corpus callosum finding within each group. As shown in Fig. 5A, there were denser connections between the corpus callosum and the bilateral dorsolateral prefrontal cortex (dlPFC) in controls, compared to patients. Conversely, connections between the corpus callosum and the bilateral frontal pole were quite dense in patients, but sparse in controls. Quantification of these connection probabilities (see Supplemental Methods) verified that significantly fewer voxels from the corpus callosum connect with the left and right frontal poles in controls, compared to patients with TMD (Fig. 5B, C). We also found that TMD patients have significantly higher numbers of samples (ie, connection probability) between the corpus callosum and the left frontal pole ($P < 0.05$). There were no significant group differences in the connection probabilities of the corpus callosum and the right frontal pole. Additionally, we found that patients had significantly lower connection probability between the corpus callosum and the right dlPFC ($P < 0.05$), but not the left dlPFC ($P > 0.05$) (Fig. 5C).

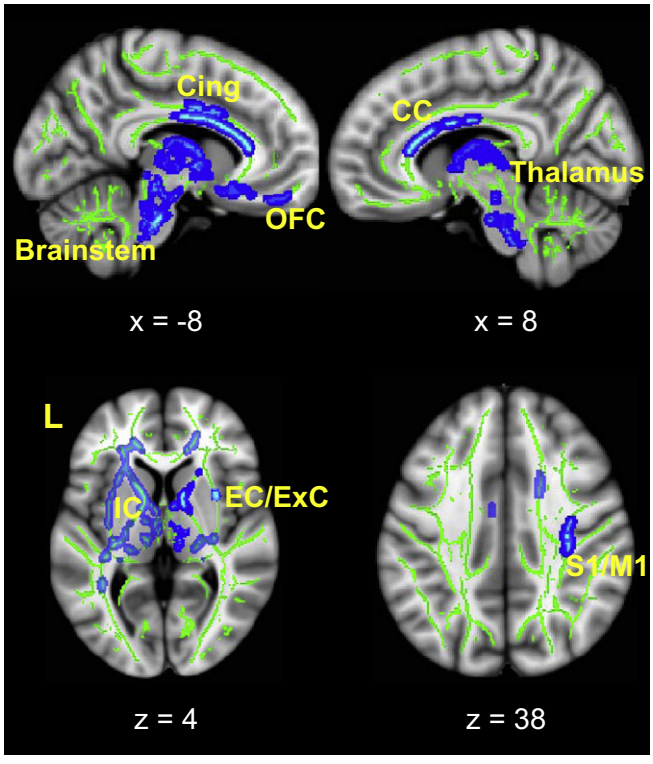

Fig. 4. Group differences in fractional anisotropy (FA) between temporomandibular disorder (TMD) patients and controls. Blue regions indicate areas showing significant reduction in fractional anisotropy in TMD compared to controls using threshold-free cluster enhancement (corrected $P < 0.01$) and overlaid on the white matter skeleton (shown in green) (significant clusters have been thickened for enhanced visualization). Widespread abnormalities are observed in bilateral internal (IC) and external/extreme capsules (EC/ExC), corpus callosum (CC), cingulum (Cing), thalamic, and brainstem white matter. S1, primary somatosensory cortex; M1, primary motor cortex; OFC, orbitofrontal cortex.

3.5. White matter FA related to TMD pain characteristics

We tested whether each of the clusters with significant group differences in FA was correlated with TMD characteristics (TMD pain intensity, unpleasantness, and duration). We found that 3 of these clusters showed significant FA-TMD correlations. Specifically, the FA within the cluster at the junction of the internal and external/extreme capsules (adjacent to the vlPFC) was significantly negatively correlated with TMD pain intensity ($r = -0.49$, $P = 0.046$) (Fig. 6A). We also identified a significant negative correlation between FA in the thalamic cluster and TMD pain intensity ($r = -0.59$, $P = 0.013$) (Fig. 6B). Finally, we identified a significant negative correlation between a cluster in the right internal capsule and both pain intensity ($r = -0.72$, $P = 0.001$) and pain unpleasantness ($r = -0.63$, $P = 0.007$) (Fig. 6C).

4. Discussion

This study is the first report to show that both peripheral nerve and CNS WM abnormalities contribute to TMD pain. In support of a peripheral contribution, we found that TMD patients had lower FA in both trigeminal nerves, and FA in the right trigeminal nerve was negatively correlated with TMD duration. In support of a central component to TMD, we found that TMD patients had 1) widespread abnormalities in the microstructure of WM tracts related to sensory, motor, cognitive, and pain functions, including a focal area of the corpus callosum; 2) stronger connectivity between the corpus callosum and the frontal pole, but sparser connectivity with the dlPFC, compared to controls; 3) FA abnormalities that correlated with TMD characteristics; and 4) reduced brain FA that was associated with greater MD and RD, markers of inflammation and oedema.

4.1. Trigeminal nerve abnormalities

This is the first study to assess the trigeminal nerve WM integrity in TMD. We found that TMD patients had significantly lower FA and higher MD and RD in both trigeminal nerves. We also found that the FA in the right trigeminal nerve was negatively correlated with TMD duration. Previously, TMD was considered idiopathic because there were no observable or major peripheral abnormalities in the TM joint or muscles [74]. However, the DTI-based imaging technology used here clearly shows microstructural abnormalities

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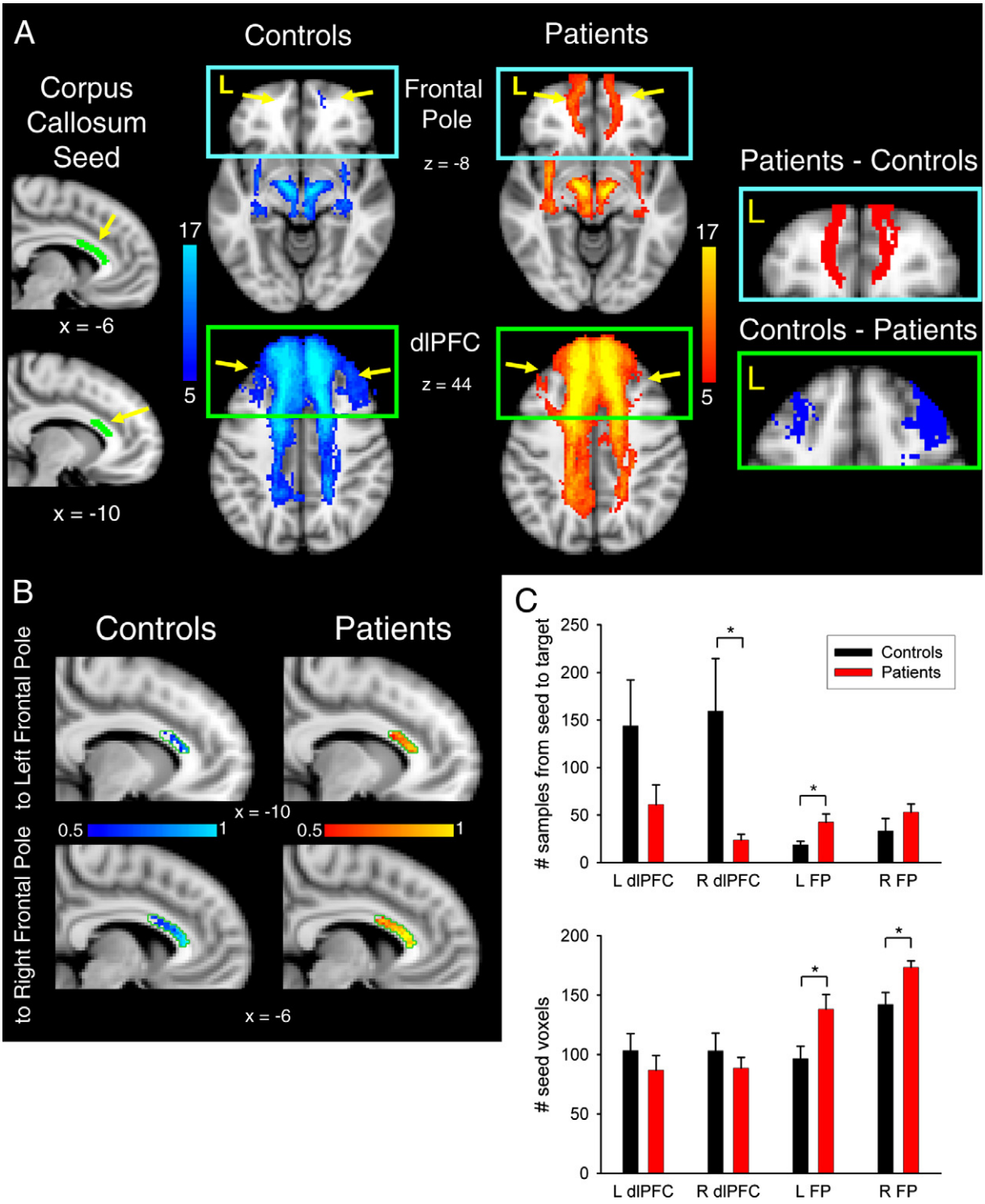

Fig. 5. Probabilistic tractography of the cluster-mass corrected ($t > 2.3$, $P < 0.05$) cluster in the left corpus callosum. (A) Qualitative tractographic analysis revealed that this abnormal white matter region has different connections (yellow arrowhead) in temporomandibular disorder and controls. The right panel shows a subtraction map that reveals that patients have sparser connections between the corpus callosum seed and the frontal pole (blue box), and denser connections to the dorsolateral prefrontal cortex (dlPFC; green box). The colour bar indicates the number of subjects contributing to the cluster at each voxel. To quantify the observed qualitative differences we performed a second tractographic analysis with specified targets based on the observed differences. Quantitative tractography (B, C) revealed that more voxels from the seed region (in green) in the corpus callosum project to the frontal pole in the patients, compared to controls. The colour bar in (B) represents the proportion of subjects with projections to the frontal pole in each voxel. (C) Also, controls have a higher connection probability between the corpus callosum and the right dlPFC, whereas patients have a higher probability of connection between the corpus callosum and the left frontal pole. Graphs show mean number of samples (± SE) that reach the target in each group (top panel), and the mean number of voxels (± SE) in the seed mask that have samples that project to the target masks. *$P < 0.05$.

in the trigeminal nerve. Therefore, increased nociceptive firing either from the periphery or from aberrant firing patterns (see below) over time could affect the microstructure of the trigeminal nerve and could also contribute to central abnormalities along the ascending nociceptive system. This concept is supported by findings of increased pain sensitivity within and outside the tri-

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Table 3
Group differences in mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (λ_1) in clusters with significant group differences in FA.

	MD ($\times 10^4$ mm^2/s)			RD ($\times 10^4$ mm^2/s)			λ_1 ($\times 10^3$ mm^2/s)		
	Controls	TMD	*P* value	Controls	TMD	*P* value	Controls	TMD	*P* value
IC_{AL}	8.0	8.5	<0.001	5.3	6.0	<0.001	1.3	1.3	n.s.
EC/ExC	7.5	7.9	<0.005	6.0	6.5	<0.001	1.0	1.1	n.s.
EC/ExC	7.6	8.0	<0.001	6.2	6.7	<0.001	1.0	1.1	n.s.
IC_{AL}/EC/ExC	7.2	7.6	<0.01	5.0	5.4	<0.001	1.2	1.2	n.s.
S1/M1	6.7	6.9	<0.05	4.8	5.1	<0.001	1.1	1.0	n.s.
Thalamus	7.5	7.8	<0.001	6.0	6.4	<0.001	1.0	1.0	n.s.
IC	7.0	7.2	<0.005	4.1	4.5	<0.001	1.3	1.3	n.s.
Diffuse[a]	7.6	7.9	<0.001	4.8	5.3	<0.001	1.3	1.3	n.s.
Corpus callosum[b]	8.2	8.8	<0.05	3.8	4.6	<0.005	1.7	1.7	n.s.

IC, internal capsule; IC_{AL}, anterior limb of the internal capsule; EC/ExC, external/extreme capsules; S1, primary somatosensory cortex; M1, primary motor cortex.
Mean DTI metric values and *P*-values are shown for 2-tailed *t*-tests for MD, RD, and λ_1 values in each cluster from Table 1 and the cluster-mass corrected cluster. n.s. indicates that the *t*-test did not reach significance ($P \geqslant 0.05$).
[a] See Table 1 for description of the diffuse cluster.
[b] Corpus callosum cluster is from the cluster-mass correction.

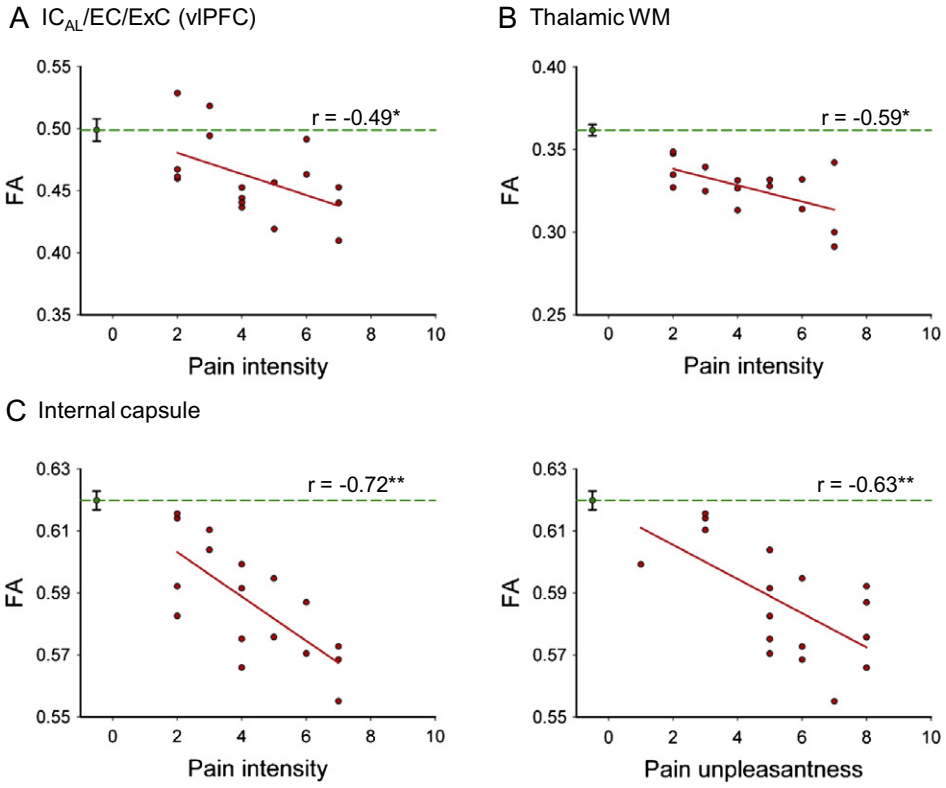

Fig. 6. Regions with group differences in fractional anisotropy (FA) are also correlated with temporomandibular disorder (TMD) characteristics: (A) the junction between the right internal and external/extreme capsules (IC_{AL}/EC/ExC) adjacent to the ventrolateral prefrontal cortex (vlPFC), (B) thalamic white matter (WM), and the (C) right internal capsule are negatively correlated with TMD pain intensity. The right internal capsule is also negatively correlated with TMD unpleasantness. Controls' mean ± SE FA for each region is shown in green. $^{*}P < 0.05$; $^{**}P < 0.01$.

geminal region [34,49,60–62,88]. The laterality of the trigeminal nerve FA and TMD duration finding is curious, given that 13 of 17 patients reported bilateral pain, and future studies should further investigate these findings.

4.2. Abnormal sensorimotor tracts in TMD

In addition to the peripheral nerve findings, we also found that patients have lower FA in the brainstem, WM coursing through the thalamus, the internal capsule, and tracts adjacent to S1/M1. Therefore, decreases in FA and increases in MD and RD along the ascending nociceptive pathways could be induced or maintained by aberrant peripheral input from the trigeminal nerve. In support of this concept is our previous report that in TMD patients there is a positive correlation between gray matter volume in the thalamus and TMD duration, and thicker cortex in the orofacial region of S1 [63], suggesting that increased activity may lead to structural brain changes over time.

Given that DTI cannot distinguish between ascending and descending tracts [6], it is possible that the abnormal WM tracts contain descending projection fibres (the corticofugal tracts) and corticothalamic tracts. The corticofugal tracts are comprised of the CST, corticobulbar, corticoreticular, and corticopontine tracts [65]. These tracts largely contain motor efferents, and so abnormalities in these tracts may underlie motor abnormalities in TMD, such as the masticatory muscle hyperactivity, and abnormal jaw

motor function under cortical control [86,87]. Furthermore, TMD patients have been shown to have increased cortical activity in motor regions and sluggish reaction times during a cognitive task [100].

4.3. Cognitive interference of pain and decreased modulation in TMD

We also identified lower FA in the cingulum bundle (adjacent to the mid-cingulate cortex), WM tracts coursing to the orbitofrontal cortex and the subgenual cingulate cortex, tracts adjacent to the vlPFC, the anterior corona radiata (in the anterior limb of the internal capsule, which projects to the prefrontal cortex), and the external/extreme capsule adjacent to the right mid-insula. The so-called medial pain system is comprised of ascending nociceptive fibres that project to the medial thalamus and further to the cingulate cortex, the insula, and the PFC [24,53,91]. It is believed that these regions contribute to the cognitive-affective dimension of pain. The insula, mid-cingulate cortex, and vlPFC have been implicated in pain perception, negative emotion, and cognitive function [2,11,15,16,21–23,31,45,72,76,95]. The orbitofrontal cortex and the subgenual cingulate cortex are thought to contribute to descending pain modulation [12]. TMD patients have widespread pain [32,60,62,94], abnormal diffuse noxious inhibitory controls [49]. Therefore, the observed microstructural abnormalities in both the ascending medial pain system and descending modulatory system provide a plausible neural substrate for abnormal cognitive and antinociceptive function in TMD.

4.4. Abnormal connectivity in TMD

Another main finding of this study is that we identified a significant decrease in FA in the corpus callosum (identified using cluster-mass correction). This is a region that connects interhemispheric prefrontal regions [102], and this portion of the corpus callosum is also connected to the cingulate cortex. Similarly, a study examining WM abnormalities in complex regional pain syndrome reported decreased FA in a similar region of the corpus callosum of patients, compared to controls [36].

In our study, probabilistic tractography revealed that patients had differential connectivity between the corpus callosum and 2 regions that have been implicated in executive control and pain perception and/or modulation: the frontal polar cortex and the dlPFC [1,3,14,17,20,43,44,46,50–52,58,64,85,92,93,96,99]. In line with these findings, we have previously identified structural abnormalities and functional abnormalities in these regions [63,100]. Further, studies have shown that pain interferes with cognitive processes [56]. Given the possibility that cognitive resources are limited, these competing demands can interfere with one another, and impede cognitive performance. Evidence for the cognitive interference of pain comes from studies that have shown that acute pain can modulate performance in a cognitive task [30,56,68,69]. Further evidence comes from studies that have reported that chronic pain patients have slower reaction times in cognitive tasks [37,38,55,90,100]. Within the context of these findings, our results may represent that FA differences in the corpus callosum are related to differential connectivity in the brain, and potentially related to interaction between executive cognitive function and pain in TMD.

4.5. Intense and prolonged TMD may drive plasticity in white matter

We have previously reported that both preexisting and chronic pain-driven factors contribute to gray and WM brain abnormalities in patients with irritable bowel syndrome (see [13,18]). In the current study, the intensity and unpleasantness of TMD pain also correlated with regions with lower FA in patients. It is conceivable that WM abnormalities are preexisting and therefore could influence the degree of TMD pain. Alternatively, more intense, unpleasant, or longer TMD pain may induce WM plasticity, reflected as changes in FA. Evidence that pain induces structural brain plasticity comes from recent studies that have reported that gray matter abnormalities in chronic pain are reversible, once the source of the pain has been resolved [41,71,75], which suggests that pain can potentially induce gray matter plasticity (see below). In this study, decreased FA in the right trigeminal nerve was related to the duration of TMD, which provides support for the latter possibility – that is, pain-induced plasticity. Similarly, the relationship between regions with abnormal FA in the brain (ie, tracts adjacent to the vlPFC, within the internal capsule, and coursing through the thalamus) and TMD pain intensity suggest that TMD pain may be driving the decrease in FA, and the observed group difference. However, it is possible that the observed CNS WM abnormalities occur independently of the peripheral input. As mentioned above, these findings suggest that increased peripheral firing or abnormal firing in the trigeminal nerve of TMD patients may alter its microstructure over time. This represents a particularly novel finding given the emphasis of a central aetiology for TMD [74].

4.6. Biological basis of changes in FA

It is likely that the pathophysiological process that results in TMD chronic pain and the accompanying cognitive and motor dysfunctions underlies the diffuse WM abnormalities observed in this study.

The factors that contribute to reduced FA may be macrostructural, such as increased branching, more crossing fibres, or larger tracts (more axons) and/or microstructural changes such as cell swelling (oedema), changes to protein filaments (neurofilament phosphorylation), disruptions to the cell membranes, and, to a certain extent, decreased myelin [7,8]. Prolonged nociceptive activity can engage biological processes such as central sensitization that contribute to pain chronification [19,54]. Recent studies have demonstrated that a feature of central sensitization is the activation of central neuroinflammatory processes [19,25,40,98], including activation of glia, oedema, and other inflammatory processes. Therefore, the observed changes in WM may be related to neuroinflammation rather than numbers/orientation of axons. Our study has examined other measures of WM microstructure (MD, RD, and λ_1) to better characterize group differences in FA. The neuroinflammation model is supported by our finding that regions with lower FA in TMD have higher MD and RD, which are markers of inflammation and/or oedema [6,7].

4.7. Study limitations

Our diagnostic criteria focused on idiopathic TMD patients, rather than the broader populations defined by the TMD-Research Diagnostic criteria [27]. Patients did not report previous diagnosis of depression or anxiety, although these can exist in TMD patients [26,79,90]. Thus we cannot exclude the contribution of these factors to our findings in general, and the degree to which our study cohort represents the broader classification of TMD. Since this was a cross-sectional study, we cannot determine whether the peripheral nerve abnormalities are driving the observed CNS abnormalities.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.04.003.

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