[Q4] White Matter Involvement in Chronic Musculoskeletal Pain

[Q7] Gregory Lieberman,^{*} Marina Shpaner,^{*} Richard Watts,[†] Trevor Andrews,^{†,‡}
Christopher G. Filippi,[§] Marcia Davis,^{*} and Magdalena R. Naylor^{*}

^{*}University of Vermont, MindBody Medicine Clinic and Fletcher Allen Healthcare Clinical Neuroscience Research Unit, Burlington, Vermont.

[†]University of Vermont, Department of Radiology and MRI Center for Biomedical Imaging, Burlington, Vermont.

[‡]Philips Healthcare, Best, the Netherlands.

[§]Columbia University, Department of Radiology, New York, New York.

Abstract: There is emerging evidence that chronic musculoskeletal pain is associated with anatomic and functional abnormalities in gray matter. However, little research has investigated the relationship between chronic musculoskeletal pain and white matter. In this study, we used whole-brain tract-based spatial statistics and region-of-interest analyses of diffusion tensor imaging data to demonstrate that patients with chronic musculoskeletal pain exhibit several abnormal white matter integrity compared with healthy controls. Chronic musculoskeletal pain was associated with lower fractional anisotropy in the splenium of the corpus callosum and the left cingulum adjacent to the hippocampus. Patients also had higher radial diffusivity in the splenium, right anterior and posterior limbs of the internal capsule, external capsule, superior longitudinal fasciculus, and cerebral peduncle. Patterns of axial diffusivity (AD) varied: Patients exhibited lower AD in the left cingulum adjacent to the hippocampus and higher AD in the anterior limbs of the internal capsule and in the right cerebral peduncle. Several correlations between diffusion metrics and clinical variables were also significant at a $P < .01$ level: Fractional anisotropy in the left uncinate fasciculus correlated positively with total pain experience and typical levels of pain severity. AD in the left anterior limb of the internal capsule and left uncinate fasciculus were correlated with total pain experience and typical pain level. Positive correlations were also found between AD in the right uncinate and both total pain experience and pain catastrophizing. These results demonstrate that white matter abnormalities play a role in chronic musculoskeletal pain: either as a cause, predisposing factor, consequence, or compensatory adaptation.

Perspective: Patients with chronic musculoskeletal pain exhibit altered metrics of diffusion in the brain's white matter compared with healthy volunteers, and some of these differences are directly related to symptom severity.

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Key words: DTI, white matter, chronic pain, neuroimaging.

Musculoskeletal pain syndromes such as chronic back pain and osteoarthritis are some of the most common forms of chronic pain.²² There is extensive evidence that abnormalities exist in the brains

of chronic musculoskeletal pain patients in gray matter (GM) volume/thickness,^{13,15,27,40,44,49,57,61} GM density,^{7,9,60,62,64,65} and both acute pain-related^{16,19} and resting state^{8,28,38,43} functional activity. Although some work has been published regarding the relationship between chronic pain disorders and neural white matter (WM),^{12,18,21,25,26,44,45,50,72,73} only 1 study⁵⁰ has used contemporary analysis approaches to compare measures of anisotropy and diffusion specifically between chronic musculoskeletal pain patients with temporomandibular disorder (TMD) and healthy volunteers. Moayed and colleagues showed that patients have highly significant clusters of lower fractional anisotropy (FA) and higher radial diffusivity (RD) in the trigeminal nerves, right internal capsule, and right external/extreme capsule, and diffusely throughout

Received December 10, 2013; Revised July 7, 2014; Accepted August 3, 2014.

Funded by National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) grant R01-AR059674 (to M.R.N.), the UVM MRI Center for Biomedical Imaging, and U.S. Department of Energy grant SC0001753.

The authors report no conflicts of interest.

Address reprint requests to Magdalena R. Naylor, MD, PhD, Clinical Neuroscience Research Unit, Department of Psychiatry, University of Vermont, 1 South Prospect Street, UHC/Arnold 6, Burlington, VT 05401. E-mail: Magdalena.Naylor@uvm.edu
1526-5900/\$36.00

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<http://dx.doi.org/10.1016/j.jpain.2014.08.002>

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other brain regions.⁵⁰ Buckalew and colleagues,¹¹ in another article, did not compare patients with healthy volunteers but did show that patients with disabling chronic back pain have lower FA in the splenium of the corpus callosum compared with patients with nondisabling chronic back pain, which correlated with pain duration. Overall, diffusion tensor imaging (DTI) findings have so far been inconsistent across studies of other types of chronic pain (eg, fibromyalgia,^{44,72} chronic complex regional pain syndrome,²⁶ migraine,⁷³ irritable bowel syndrome,^{18,21} and chronic pancreatitis²⁵), and WM integrity in chronic musculoskeletal pain remains a relatively poorly explored research topic. In addition, the generalizability of findings in TMD to other types of musculoskeletal pain is currently unknown.

The objectives of this study are to determine whether there are differences in pain-related WM pathways in the brains of a broad sample of chronic musculoskeletal pain patients (including diagnoses of osteoarthritis and back, limb, and abdominal muscle pain) compared with healthy volunteers. We hypothesized that chronic musculoskeletal pain patients would exhibit lower FA within specific fiber tracts shown to be involved in TMD compared with healthy controls and in other musculoskeletal pain disorders using different experimental approaches: the splenium of the corpus callosum,^{11,45,50} the anterior and posterior limbs of the internal capsule,^{45,50} the cingulum bundle,⁵⁰ the temporal lobe branch of the cingulum,¹² the external capsule adjacent to the insular cortex,⁴⁵ and the superior longitudinal fasciculus.^{12,45} Additional exploratory analyses were performed on the uncinate fasciculus and the cerebral peduncles because of their involvement in emotional processing and descending motor signaling and pain inhibition, respectively.

Identifying WM abnormalities in a broad sample of chronic musculoskeletal pain patients that overlap with reported differences in TMD and/or nonmusculoskeletal pain disorders may provide insight into which fiber pathways play a role specifically in chronic musculoskeletal pain. Additionally, because abnormalities in WM pathways reflect changes in tract integrity between brain regions known to process the somatosensory, affective, and cognitive components of pain perception, we predicted that FA within these tracts would correlate with specific representative clinical measures of pain symptom severity.

Methods

Participant Recruitment and Initial Evaluation

All research protocols were reviewed and approved by the University's institutional review board. Forty-six patients between the ages of 18 and 65 years with primary chronic musculoskeletal pain diagnoses and 33 age-matched healthy volunteers were analyzed for this cross-sectional study. These participants were pulled from a larger pool of participants recruited for a series of longitudinal experiments.

Participants were evaluated in person for study eligibility; they provided informed consent and underwent a comprehensive clinical assessment of chronic pain symptoms, demographics, and cognitive eligibility based on the Wide Range Achievement Test³⁴ and the Mini-Mental State Examination.²⁴ Eligibility requirements included at least 1 year of self-reported chronic musculoskeletal pain symptoms scored at 4 or higher on a scale from 0 to 10 (where 0 represented no pain and 10 the worst pain). Exclusion criteria included inability to participate in magnetic resonance imaging (eg, claustrophobia, ferrous metal in the body), opiate medication use, previous history of traumatic brain injury, uncontrolled/unmedicated diabetes or hypertension, and comorbid diagnoses of psychiatric disorders (eg, current major depression, bipolar disorder, and schizophrenia). Primary chronic musculoskeletal pain diagnoses included osteoarthritis and postinjury back, neck, shoulder, knee/leg, and abdominal muscle pain. Several patients had a medical history containing more than 1 chronic musculoskeletal pain diagnosis.

Clinical Assessment

A preliminary phone screening, an initial in-person clinical evaluation, and a series of formal, self-administered, previously validated questionnaires were used to assess measures of pain, function, disability, and mental health for all patients. The initial clinical evaluation included questions regarding demographics, diagnoses, current and typical levels of pain, medical history, and treatment/medication management. Pain, function, and disability were assessed using the short form of the McGill Pain Questionnaire (MPQ)^{46,48} and the pain symptoms subscale of the Treatment Outcomes in Pain Survey (TOPS).^{58,59} Depression was assessed using the Beck Depression Inventory.¹⁰ Additional measures of coping skills use, ability to control pain, ability to decrease pain, and degree of pain catastrophizing were collected using the Pain Catastrophizing Scale⁷¹ and the Chronic Pain Self-Efficacy Scale.³ Healthy volunteer participants were asked to complete a demographics questionnaire and the Beck Depression Inventory. Clinical data were double-entered and reconciled, scored according to the instructions for each questionnaire, and stored and managed using REDCap electronic data capture tools.²⁹

DTI Acquisition

DTI data were acquired using a Philips Achieva 3T magnet (Philips Healthcare, Best, the Netherlands) with an 8-channel head coil, utilizing the following parameters: axial 2-dimensional spin echo echo-planar imaging sequence with 46 diffusion directions, 59 slices, 2-mm slice thickness, 10,000-ms repetition time, 68 ms echo time, 2×2 -mm in-plane resolution, $b = 1,000 \text{ s/mm}^2$, flip angle of 90° , and an echo planar imaging factor of 63. An axial T2-weighted gradient spin echo sequence was also acquired for radiological review in order to rule out neurologically significant abnormalities and pathology.

DTI Analysis

DTI data were processed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library's^{35,70,79} Diffusion Toolbox. Data underwent eddy current correction, brain extraction,⁶⁸ and fitting with a diffusion tensor model at each voxel in order to calculate FA, RD, and axial diffusivity (AD) maps. All raw images and processed FA maps were visually inspected for artifacts, excessive motion, and anatomic abnormalities that might interfere with registration such as lesions or enlarged cerebral ventricles due to cortical atrophy.³⁷ FA maps were nonlinearly registered^{5,6,36} into $1 \times 1 \times 1$ -mm standard space (FMRIB58_FA) and affine-aligned into MNI152 space. FA data were projected onto an alignment-invariant mean FA skeleton representing the centers of each tract in the brain before voxelwise cross-subject statistics were applied using tract-based spatial statistics (TBSS).⁶⁹ Skeletonization was carried out using an FA threshold of .2 in order to exclude GM and cerebrospinal fluid.

[Q5] Between-group voxelwise comparisons were performed using *randomize*,^{4,14,31} a nonparametric permutation test that utilizes threshold-free cluster enhancement to correct for multiple comparisons. Ten thousand permutations were performed per t-test. RD and AD images were processed using the same nonlinear registration steps and mean WM skeleton derived for FA. Participant ages were de-meant and input into the model as covariates. To improve visualization of thresholded TBSS results, clusters were thickened into local WM tracts.

DTI data from specific regions of interest were also analyzed individually. Binary WM masks were created from the Johns Hopkins University ICBM-DTI-81 atlas of WM labels,^{32,51,52} which was produced from average DTI maps from 81 participants with a mean age of 39 years. Specific tracts selected for analysis based on the existing literature included the splenium of the corpus callosum, the anterior and posterior limbs of the internal capsule, the external capsule adjacent to the insular cortex, the cingulum bundle, the temporal lobe branch of the cingulum bundle adjacent to the hippocampus, the superior longitudinal fasciculus, and the uncinate fasciculus. Additionally, post hoc region-of-interest analyses were performed on the cerebral peduncles after clusters of significantly higher RD were observed there in patients using TBSS. Mean FA, RD, and AD values were extracted from whole brain and from specific tracts by applying the binary masks to each volume (specific participant) of the skeletonized TBSS output. Skeletonized output was used rather than nonskeletonized in order to improve consistency across subjects and to ensure that only voxels from the WM were compared. Correlations between DTI data and clinical measures were performed using predetermined clinical measures thought to best represent pain severity and negative impact on life: pain duration, MPQ typical level of pain, TOPS total pain experience, and the Pain Catastrophizing Scale.

All region-of-interest DTI analyses and clinical comparisons were performed using SPSS Statistics for Windows,

version 20 (IBM Corporation, Armonk, NY). Graphs were created using Microsoft Excel and GraphPad Prism for Windows, version 6.00 (GraphPad Software, La Jolla, CA).

Results

Clinical Assessment of Chronic Musculoskeletal Pain Severity

Forty-six patients with chronic musculoskeletal pain (12 male, 34 female) were compared to 33 age-matched healthy control volunteers (14 male, 19 female). There was no significant difference in age ($P = .45$) between patients (mean = 45.8, standard deviation [SD] = 12.9) and healthy controls (mean = 44.5, SD = 13.3). Patients reported a mean chronic pain duration of 9.85 years (SD = 8.12) and a mean typical pain level of 5.5 (SD = 2.12) on a Likert-type scale ranging from 0 = no pain to 10 = the worst pain. Patients also reported a mean current pain level of 5.2 (SD = 2.4) at the time of questionnaire administration. Total pain experience and perceived family disability (a measure of pain interference) composite scores from TOPS were reported as 52.17 (SD = 16.39) and 49.97 (SD = 18.84), respectively, on a scale from 0 to 100, whereas the mean Pain Catastrophizing Scale score across the patient group was 19.47 (SD = 11.47) on a scale from 0 to 50. The mean score on the Beck Depression Inventory was 14.28 (SD = 9.88) on a scale from 0 to 63, which is considered to be mild depression.^{10,64} These measures fall within ranges that would be expected in a sample of chronic pain patients.^{53,54,64} Healthy volunteers did not report current chronic pain and were not depressed (BDI mean = 3.4, SD = 4.50).

Whole-Brain TBSS Analyses

TBSS analysis of skeletonized FA and AD data yielded no statistically significant differences between chronic musculoskeletal pain patients and healthy controls at a significance level of $P < .05$ using threshold-free cluster enhancement to correct for multiple comparisons. A number of regions did exhibit nonsignificantly lower FA ($P < .10$) in patients than controls, however, including several of the a priori regions of interest discussed below.

TBSS analysis of skeletonized RD data yielded a number of statistically significant differences between groups. Clusters of higher RD in patients were present in the body of corpus callosum, right superior longitudinal fasciculus, anterior and posterior limbs of the internal capsule, and the external capsule (Fig 1) as well as in the splenium of the corpus callosum, the right cingulum adjacent to the hippocampus, and the right cerebral peduncle (Fig 2). Each of these clusters was significant at a threshold of $P = .05$, fully corrected for multiple comparisons using threshold-free cluster enhancement. No clusters were identified that exhibited lower RD in patients than in controls. Specific region-of-interest analyses were also used to investigate the relationship between RD within specific tracts in chronic musculoskeletal pain and clinical measures. FA and AD values were

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Figure 1. Coronal (left) and axial view (right) of TBSS analysis of RD differences between chronic musculoskeletal pain patients and healthy control participants, at the level of the thalamus. A large cluster of higher RD contained fibers of the corpus callosum, right superior longitudinal fasciculus, right anterior and posterior limbs of the internal capsule, and right external capsule adjacent to the insular cortex. Clusters are significant at a level of $P < .05$ after correcting for multiple comparisons using threshold-free cluster enhancement.

also extracted and analyzed in order to provide further insight into the local microstructural properties of pain-related fiber pathways.

Region-of-Interest Analyses

Analysis of mean FA, RD, and AD values extracted from binary masks of specific WM tracts revealed a number of differences between chronic musculoskeletal pain patients and healthy volunteers. Because there were significant effects of age and gender on many of the diffusion measures, both measures were entered into the general linear model as covariates. All statistics reported below were generated by analyzing the effect of group after controlling for both age and gender.

Several tracts were identified that exhibited lower FA in chronic musculoskeletal pain patients compared with healthy controls, whereas no regions were identified that exhibited higher FA in patients (Fig 3). Specific tracts that exhibited lower FA in patients included the splenium of the corpus callosum ($F = 4.647$, $P = .034$) and the left temporal lobe branch of the cingulum bundle adjacent to the hippocampus ($F = 4.450$, $P = .038$).

Consistent with the TBSS results reported above, several tracts exhibited higher RD in patients compared

with healthy volunteers, and no tracts exhibited lower RD in patients (Fig 4). Higher RD was observed in patients in the splenium of the corpus callosum ($F = 6.499$, $P = .013$) and in the right anterior ($F = 4.018$, $P = .049$) and posterior ($F = 6.346$, $P = .014$) limbs of the internal capsule, the external capsule adjacent to the insular cortex ($F = 7.400$, $P = .008$), the superior longitudinal fasciculus ($F = 7.946$, $P = .006$), and the cerebral peduncle ($F = 5.652$, $P = .020$). No difference was observed in the region-of-interest analysis of the body of the corpus callosum, possibly because the cluster observed there using TBSS was relatively small in relation to the volume of the entire tract.

Finally (Fig 5), the left temporal lobe branch of the cingulum exhibited lower AD in patients than controls ($F = 4.404$, $P = .039$), and 3 specific tracts demonstrated higher AD in chronic musculoskeletal pain patients: the right cerebral peduncle ($F = 4.423$, $P = .039$) and both the right ($F = 17.430$, $P < .001$) and left ($F = 5.528$, $P = .021$) anterior limbs of the internal capsule.

Clinical Correlations

Exploratory correlational analyses were performed comparing representative measures of pain severity

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Figure 2. Coronal (left) and axial view (right) of TBSS analysis of RD differences between chronic musculoskeletal pain patients and healthy control participants, at the level of the thalamus. Cluster of higher RD contained fibers of the splenium of the corpus callosum, right superior longitudinal fasciculus, right cingulum bundle adjacent to the hippocampus, and right cerebral peduncle. Clusters are significant at a level of $P < .05$ after correcting for multiple comparisons using threshold-free cluster enhancement.

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Figure 3. Comparison of mean FA values extracted from specific pain-related cognitive, limbic, and sensory tracts between chronic musculoskeletal pain patients and healthy volunteers. Contrasts designated with an asterisk were significant at a level of $P < .05$ after correcting for both age and gender. Error bars signify the SEMs. Abbreviations: SEM, standard error of the mean; Splen, splenium of the corpus callosum; L, left; AIC, anterior limb of the internal capsule; CP, cerebral peduncle; Cing, cingulum bundle; Cing_Hipp, temporal lobe branch of the cingulum bundle adjacent to the hippocampus; EC, external capsule; PIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; Unc, uncinate fasciculus; R, right; Whole, whole brain.

and negative impact on life with mean FA, RD, and AD values extracted from specific regions of interest in the brains of chronic musculoskeletal pain patients. Because of the exploratory nature of this analysis and lack of correction for multiple comparisons, only correlations that were significant at a $P < .01$ level are reported.

Despite there being no significant between-group difference, significant positive correlations (Fig 6) were found between FA in the left uncinate fasciculus and the TOPS total pain experience composite score ($r = .399$, $P = .006$) and self-reported typical pain levels ($r = .415$, $P = .004$).

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Figure 4. Comparison of mean RD values extracted from specific pain-related cognitive, limbic, and sensory tracts between chronic musculoskeletal pain patients and healthy volunteers. Contrasts designated with an asterisk were significant at a level of $P < .05$ after correcting for both age and gender. Error bars signify the SEMs. Abbreviations: SEM, standard error of the mean; Splen, splenium of the corpus callosum; L, left; AIC, anterior limb of the internal capsule; CP, cerebral peduncle; Cing, cingulum bundle; Cing_Hipp, temporal lobe branch of the cingulum bundle adjacent to the hippocampus; EC, external capsule; PIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; Unc, uncinate fasciculus; R, right; Whole, whole brain.

Figure 5. Comparison of mean AD values extracted from specific pain-related cognitive, limbic, and sensory tracts between chronic musculoskeletal pain patients and healthy volunteers. Contrasts designated with an asterisk were significant at a level of $P < .05$ after correcting for both age and gender. Error bars signify the SEMs. Abbreviations: SEM, standard error of the mean; Splen, splenium of the corpus callosum; L, left; AIC, anterior limb of the internal capsule; CP, cerebral peduncle; Cing, cingulum bundle; Cing_Hipp, temporal lobe branch of the cingulum bundle adjacent to the hippocampus; EC, external capsule; PIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; Unc, uncinate fasciculus; R, right; Whole, whole brain.

No correlations were observed between clinical measures and RD at a significance level of .01, though 6 significant positive correlations were observed between clinical measures and AD (Fig 7). TOPS total pain experience was correlated with AD in the left uncinate fasciculus ($r = .393$, $P = .007$) and the left anterior limb of the internal capsule ($r = .398$, $P = .006$). AD in the left posterior limb of the internal capsule also demonstrated a correlation with total pain experience, though not at a significance level of $P < .01$ ($r = .373$, $P = .011$). MPQ typical pain demonstrated significant correlations with AD in the same 2 regions: left uncinate ($r = .480$, $P = .001$), left anterior limb ($r = .380$, $P = .009$), as well as the right uncinate fasciculus ($r = .451$, $P = .002$). Finally, AD in the right uncinate also was correlated with pain catastrophizing ($r = .381$, $P = .010$).

Discussion

In this study, we demonstrate that patients with chronic musculoskeletal pain exhibit significant WM differences in FA, RD, and AD compared with healthy volunteers and that the several differences in measures of diffusion are correlated with symptom severity. It has been known for some time that abnormal GM organization and altered patterns of functional activity are associated with chronic pain, and the results presented here show that WM plays an important role in chronic musculoskeletal pain, as well. The majority of the tracts that exhibited abnormal WM properties in this study convey information regarding specific components of pain perception—somatosensory, cognitive, and/or emotional—whereas others seem to be related to motor pathways and tracts involved in descending inhibition of pain.

Assessing not only FA but also RD and AD within specific tracts is important because these measures reflect

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Figure 6. Exploratory correlational relationships between FA and clinical measures. FA in the left uncinate fasciculus positively correlated with both (A) TOPS total pain experience and (B) MPQ typical pain rating.

microstructural properties that represent different aspects of tract integrity. Specifically, WM neuropathology is frequently associated with decreased FA within specific tracts,² but it is unclear whether lower FA is due to differences in fiber density, axon thickness, plasticity-related degree of myelination, or something else entirely. Because FA is a function of the amount of AD in relation to the amount of RD, it is important to determine whether FA differences are driven by differences in RD, AD, or both. For example, the lower FA observed in the splenium of the corpus callosum in chronic musculoskeletal pain patients is associated with lower RD (and no significant difference in AD), whereas the lower FA observed in the left cingulum adjacent to the hippocampus is associated with higher AD (and no difference in RD). It is equally important to note that the lack of significant difference observed in FA in the right anterior limb of the internal capsule may be due to the observation that both RD and AD are higher in this tract in patients than in healthy volunteers. It has been suggested that changes in RD likely reflect degree of myelination (as myelin restricts radial diffusion), whereas changes in AD are less well understood and might reflect anything from axon thickness to fiber density. Although much additional work is needed in order to understand the mechanisms behind these differences and the nature of any causative relationships that may exist, it seems clear that pain-related abnormalities in

FA can be a consequence of changes in diffusion both axially and radially within specific tracts (Table 1). Especially considering that clinical correlations were observed with multiple measures of diffusion within various tracts, additional work is needed in order to understand the mechanisms by which RD and AD are involved in chronic musculoskeletal pain as well as the implications for diagnosis, prevention, and/or treatment of chronic musculoskeletal pain disorders.

The splenium of the corpus callosum contains fibers that connect regions of the parietal cortex that process somatosensory information and several temporal lobe structures¹⁷ in addition to visual information. Our finding that FA is lower (and RD is higher) in this region may reflect abnormal processing of somatosensory or nociceptive input from the periphery. This result is supported by previous research demonstrating lower splenium WM integrity in patients with migraine⁴² as well as patients with disabling chronic back pain compared with patients with nondisabling chronic back pain.¹¹

The temporal lobe branch of the cingulum conveys fibers from the cingulate cortex, one of the principal processing centers of the cognitive dimensions of chronic pain, to the entorhinal cortex and then to the hippocampus, possibly playing a role in the emotional memories and learned behaviors associated with chronic pain.^{56,67,77,78} Neurons in the cingulate cortex have been shown to respond to both thermal and mechanical pain.³³ Our finding of lower FA and AD in this tract may reflect abnormal structural connectivity between pain-processing centers in the anterior cingulate cortex and temporal lobe memory/limbic regions, contributing to or resulting from chronic pain-related neuropathology.

The anterior limbs of the internal capsule contain fibers that project from the medial thalamus (which receives ascending nociceptive information from the periphery) to the prefrontal cortex, a tract likely involved in processing the cognitive and attention-related components of pain perception. Our finding that RD is higher in this region in patients with chronic musculoskeletal pain (interestingly in conjunction with higher AD) is consistent with findings in TMD,⁵⁰ supporting conclusions by Mansour and colleagues that it can serve as a predictor of development of chronic pain after back injury.⁴⁵

The external capsule provides some of the input to the insular cortex and conveys information pertaining to the emotional component of pain perception.^{18,63,75} The present demonstration of elevated RD in this region in chronic musculoskeletal pain is consistent with previous research^{45,50} and bolsters the argument that decreased tract integrity of insular inputs may play a role in pathologic perception of pain. Contradictory to these results, FA in the external capsule has been shown to be elevated in irritable bowel syndrome, a chronic visceral pain disorder, and correlated with bowel pain duration.¹⁸ It is unclear whether these differences are anomalies due to different measurement techniques or unique properties of specific subtypes of chronic pain.

Figure 7. Exploratory correlational relationships between AD and clinical measures. AD in the left uncinate anterior limb of the internal capsule positively correlated with both (A) TOPS total pain experience and (B) MPQ typical pain rating, as did AD within the left uncinate fasciculus (C, D). AD within the right uncinate fasciculus also positively correlated with both (E) Pain Catastrophizing Scale score and (F) MPQ typical pain rating.

The exact functions of the uncinate fasciculus are not yet fully known, but it has been shown to connect temporal lobe structures such as the amygdala and hippocampus with cognitive processing centers in the prefrontal cortex.³⁰ The uncinate demonstrates abnormal diffusion properties in a number of psychological

disorders⁶⁶ ranging from schizophrenia,³⁹ generalized anxiety,⁵⁵ and depression⁷⁴ to temporal lobe epilepsy memory loss²⁰ and Alzheimer's disease.⁸⁰ Although the current study did not find statistically significant differences in uncinate FA, RD, or AD between chronic musculoskeletal pain patients and healthy volunteers, the role that it clearly plays in processing emotion and memory makes it unsurprising that left uncinate FA was found to be correlated with both TOPS total pain experience and MPQ typical pain rating.

The posterior limb of the internal capsule conveys both ascending somatosensory and descending motor information.^{1,11,23} The cluster of elevated RD reported above in this tract encompassed both sets of fibers. This increase may be attributable to abnormal processing of somatosensory input or pain-related behaviors such as decreased physical activity. Some evidence suggests that this pathway also contains descending frontal corticopontine fibers that play a role in pain inhibition.^{1,23}

The superior longitudinal fasciculus and the cerebral peduncles (which also contain the descending corticospinal tracts) do not have an obvious role in the processing of chronic pain perception. However, both of these pathways are known to convey motor-related information, and changes in tract integrity in these pathways may reflect pain-related behavioral changes such as decreased physical activity.^{41,76} The cerebral peduncle was not selected a priori as a region of interest, but

Table 1. Patterns of FA, RD, and AD: Chronic Musculoskeletal Pain Patients Versus Healthy Controls

REGION OF INTEREST	FA	RD	AD
Splenium of the corpus callosum	↓	↑	
Left cingulum, temporal	↓		↓
Left anterior limb, internal capsule		↑	↑
Right anterior limb, internal capsule		↑	↑
Right posterior limb, internal capsule		↑	
Right external capsule		↑	
Right superior longitudinal fasciculus		↑	
Right cerebral peduncle		↑	↑

NOTE. The table demonstrates the relationship between FA, RD, and AD within specific cognitive, limbic, and sensory pathways of the pain matrix. Upward-pointing arrows indicate metrics that are higher in chronic musculoskeletal pain patients than healthy control participants, and downward-pointing arrows indicate the reverse. In most cases, lower levels of FA appear to be driven by either higher levels of RD or lower levels of AD, and when RD and AD are both higher, no effect is observed in FA. Further research is required in order to more deeply understand this relationship in vivo. Sample size: chronic musculoskeletal pain patients $n = 46$; healthy controls $n = 33$.

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analyzed post hoc after a highly significant cluster of increased RD was observed there using TBSS. It is possible that like the posterior limbs of the internal capsule, the cerebral peduncles contain descending pain-inhibiting fibers, the properties of which may be affected in chronic pain.

Perhaps the most intriguing and novel findings reported here are the relationships between clinical measures and RD and AD. Based on theories of RD's role in neuroplasticity, we expected to find that RD was the most highly correlated measure of diffusion, yet no significant RD correlations were found. Perhaps even more interestingly, the most correlations between metrics of diffusion and clinical measures involved AD. As it is not yet understood what factors influence AD within a tract, the implications of these findings are unknown. Additional research is needed in order to determine how abnormalities in WM integrity contribute to and/or result from chronic pain.

There are a few limitations that must be considered in interpreting our results. First, sample size is relatively small. Also, the demographic composition is skewed because the sample is predominantly female and ages are not perfectly balanced between groups. A broad sample of musculoskeletal pain diagnoses might be

considered as a strength, as it increases the generalizability of findings, but it might also prevent identification of phenomena specific to individual chronic pain diagnoses. Finally, additional confounds exist in the nature of our patient sample: Despite the fact that our patients were medically stable, even treated diabetes and hypertension may have influenced the properties of WM. It is also possible that stronger effects might have been observed if exclusion criteria did not render some patients with severe symptoms ineligible for analysis in this study (eg, for comorbid diagnoses of depression and anxiety disorders).

Acknowledgments

The authors would like to thank Jay Gonyea and Scott Hipko of the University of Vermont MRI Center for Biomedical Imaging for their assistance with scheduling and running scans, Dr. Shelly Naud for statistical advice, and the following individuals for their help acquiring, entering, and reconciling data: James Bishop, Nina La Rosa, Elizabeth McCallion, Hayley Perelman, Samuel Kellner, Emily Eck, Jenna Macarewicz, Alan French, and Dr. Asif Kalim.

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