American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 11 (November), 2014: pp 1110-1119
*Available online at www.jpain.org and www.sciencedirect.com*

# White Matter Involvement in Chronic Musculoskeletal Pain

Gregory Lieberman,* Marina Shpaner,* Richard Watts,† Trevor Andrews,†,‡ Christopher G. Filippi,§ Marcia Davis,* and Magdalena R. Naylor*

**MindBody Medicine Clinic at Fletcher Allen Healthcare and Clinical Neuroscience Research Unit, University of Vermont, Burlington, Vermont.*
*†Department of Radiology and MRI Center for Biomedical Imaging, University of Vermont, Burlington, Vermont.*
*‡Philips Healthcare, Best, The Netherlands.*
*§Department of Radiology, Columbia University, 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 metrics of 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 was 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 as a cause, a predisposing factor, a consequence, or a 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.*



***Key words:** Diffusion tensor imaging (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 study[50] has used contemporary analysis approaches to compare measures of anisotropy and diffusion specifically between chronic musculoskeletal pain patients and healthy volunteers. Moayedi and colleagues showed that patients with temporomandibular disorder (TMD) have highly significant clusters of lower fractional anisotropy (FA) and higher radial diffusivity (RD) in the trigeminal nerves, in the right internal capsule, in the 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) grants R21-AR055716 and 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

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

other brain regions.[50] In another article, Buckalew and colleagues[11] 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 than 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 pancreatitis[25]), 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 Test[34] 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 (BDI).[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 Scale[71] and the Chronic Pain Self-Efficacy Scale.[3] Healthy volunteer participants were asked to complete a demographics questionnaire and the BDI. 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 $\times$ 2-mm in-plane resolution, b = 1,000 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.