Brain white matter changes associated with urological chronic pelvic pain syndrome: multisite neuroimaging from a MAPP case–control study

Lejian Huang[a], Jason J. Kutch[b], Benjamin M. Ellingson[c], Katherine T. Martucci[d], Richard E. Harris[e],
Daniel J. Clauw[e], Sean Mackey[d], Emeran A. Mayer[c], Anthony J. Schaeffer[f], A. Vania Apkarian[a,g],
Melissa A. Farmer[a,*], on behalf of the MAPP Research Network

Abstract

Clinical phenotyping of urological chronic pelvic pain syndromes (UCPPSs) in men and women have focused on end organ abnormalities to identify putative clinical subtypes. Initial evidence of abnormal brain function and structure in male pelvic pain has necessitated large-scale, multisite investigations into potential UCPPS brain biomarkers. We present the first evidence of regional white matter (axonal) abnormalities in men and women with UCPPS, compared with positive (irritable bowel syndrome, IBS) and healthy controls. Epidemiological and neuroimaging data were collected from participants with UCPPS (n = 52), IBS (n = 39), and healthy sex- and age-matched controls (n = 61). White matter microstructure, measured as fractional anisotropy (FA), was examined by diffusion tensor imaging. Group differences in regional FA positively correlated with pain severity, including segments of the right corticospinal tract and right anterior thalamic radiation. Increased corticospinal FA was specific and sensitive to UCPPS, positively correlated with pain severity, and reflected sensory (not affective) features of pain. Reduced anterior thalamic radiation FA distinguished patients with IBS from those with UCPPS and controls, suggesting greater microstructural divergence from normal tract organization. Findings confirm that regional white matter abnormalities characterize UCPPS and can distinguish between visceral diagnoses, suggesting that regional axonal microstructure is either altered with ongoing pain or predisposes its development.

Keywords: Pain, Urological, Pelvic, Irritable bowel syndrome, Diffusion tensor imaging

1. Introduction

Urological chronic pelvic pain syndrome (UCPPS) comprises genital and bladder symptoms that persist in the absence of identifiable pathology, presenting as chronic prostatitis (CP) or CPPS in men and interstitial cystitis/bladder pain syndrome (IC/BPS) in men and women. Traditionally, CP/CPPS and IC/BPS have been considered distinct clinical syndromes triggered by end organ pathology, such as occult inflammation, pelvic floor muscle dysfunction, and/or urinary dysfunction.[24] However, their common pelvic localization and significant symptom overlap suggest that parallel peripheral and central nervous system processes, and potentially similar genetic vulnerabilities, may mutually mediate their chronification.[14,24,56] Because UCPPS can impair multiple aspects of daily function, from affective, interpersonal, and sexual function, to work productivity and quality of life, it poses a substantial economic burden on the individual and society.[6,13,44] Clinical and experimental efforts to understand physiological mechanisms leading to UCPPS are therefore of urgent importance to progress phenotyping, diagnosis, and treatment of these syndromes.

The recent focus on supraspinal processing in the development and maintenance of UCPPS is a critical step in this progression. Women with IC/BPS exhibited increased primary somatosensory cortex gray matter volume and colocalization of increased low-frequency oscillations and greater regional microstructural coherence primary motor cortex corticospinal white matter.[23,35,36] These functional and structural changes suggest that UCPPS may be centrally characterized by a unique pattern of brain activity and anatomical changes that are unlike "signatures" of other chronic pain conditions.[21] Furthermore, these findings collectively suggest that widespread shifts in local and whole-brain function and structure may uncover neuropathological markers and mechanisms of UCPPS.

Regional brain function correlates with anatomy, both developmentally[62] and in neurodegenerative disease states.[61] For instance, functional activity is influenced by neurons' axonal and dendritic morphology, interactions with resident glia, synaptic connections made with a neighbor and long-distance neurons, and properties of white (axonal) matter that mediate these synaptic connections. White matter microstructure is assessed using diffusion tensor imaging (DTI), which is used to deduce the microstructure of axonal tracts by measuring the direction of water flow within known structural barriers, like myelin sheaths surrounding axons.[4] Therefore, DTI provides a gross measure of the organization of white matter fiber bundles—the structural pathways by which brain regions communicate—throughout the brain and can reliably detect white matter abnormalities across multiple clinical pain populations and neurological disease processes.[10,11,26,41,56]

To evaluate the degree and clinical relevance of white matter abnormalities in UCPPS, we report the first white matter characterization of UCPPS in men and women using human noninvasive brain imaging technology. Diffusion tensor imaging was used to indirectly measure brain white matter properties in a multisite sample of patients with UCPPS, in relation to positive visceral (irritable bowel syndrome [IBS]) and healthy controls. We hypothesized that microstructural abnormalities would be evident in UCPPS and IBS, yet UCPPS-specific white matter biomarkers would emerge as intermediate phenotypes for urological chronic pelvic pain.

2. Methods

Between December 2009 and December 2013, the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network enrolled 1039 men and women in an Epidemiology/Phenotyping (EP) prospective, observational multisite study, including 415 healthy controls, 424 UCPPS participants, and 200 positive controls, including individuals with IBS, fibromyalgia, and chronic fatigue syndrome.[15,38] Epidemiology/Phenotyping participants who met all magnetic resonance imaging (MRI) inclusion/exclusion criteria underwent functional and structural neuroimaging, including DTI (n = 201), T1 anatomical scans (n = 301), and resting-state functional scans (n = 297). Here, we report DTI data (n = 152) across 3 MAPP sites, including Northwestern University (NU), University of California at Los Angeles (UCLA), and Stanford University (SU). Epidemiology/Phenotyping and neuroimaging procedures were approved by Institutional Review Boards at each site, and written informed consent was obtained before participant enrollment.

2.1. Participants

Diffusion-weighted and high-resolution T1-weighted images were acquired in 52 patients with UCPPS(23 women and 29 men), 39 positive visceral pain controls with IBS (24 women and 15 men), and 61 healthy controls (32 women and 29 men). Positive and healthy controls were age- (±3 years) and sex-matched to the UCPPS group.

Primary inclusion criteria for UCPPS included either IC/BPS diagnosis with urologic symptoms present for the previous 3 months, or CP/CPPS diagnosis with urologic symptoms present most of the time during 3 of the previous 6 months; ≥1/10 mean intensity of pelvic pain, pressure, or discomfort in the previous 2 weeks (with 0 indicating no pain and 10 indicating worst imaginable pain/pressure/discomfort) (refer to[38] for complete inclusion/exclusion criteria, by group). To determine whether white matter differences were specific to urological pelvic pain or visceral pain in general, a positive IBS control group with chronic abdominal visceral pain (and no concurrent pelvic pain) was identified using the Complex Multi-Symptom Inventory[59] (n = 39). Healthy control men and women who reported no pelvic, bladder, or nonpelvic pain were selected as the comparison group for UCPPS and IBS participants. Although the EP study permitted controls to have no more than 1 nonurologic chronic pain, only pain-free controls were included in these analyses. Groups were continuously recruited throughout the MAPP scanning period to guard against effects of time, testing order, and potential technical biases due to scanner software upgrades.

2.2. Experimental design

Neuroimaging was conducted during a single visit that took place within 2 weeks of the EP study baseline visit, 6-month follow-up, or 12-month follow-up. On the day of scanning, the following questionnaires were administered: Symptom and Health Care Utilization Questionnaire (SYM-Q; designed for the MAPP study), Gracely Box Scales (pain unpleasantness and intensity, scores ranging from 0-20),[29] McGill Pain Questionnaire–Short Form (SF-MPQ),[40] Hospital Anxiety and Depression Scale (HADS),[53] Positive and Negative Affect Schedule (PANAS),[58] sleep scale of the Patient Reported Outcome Measurement Information System (PROMIS) and male and female versions of the Genitourinary Pain Index (GUPI),[12] including a pain symptom subscale (score range: 0-23), urinary symptom scale (score range: 0-10), and quality of life (score range: 0-12) subscale.

2.3. Diffusion tensor imaging and anatomical data acquisition

Magnetic resonance imaging was performed at multiple sites using different scanner technologies (3 Tesla [T] Siemens Trio [NU and UCLA], and 3T GE Discovery [SU]). Neuroimaging data were collected, quality controlled, and archived according to multisite imaging procedures developed collaboratively among the MAPP Research Network, the UCLA PAIN repository, and the UCLA Laboratory of Neuroimaging. Detailed procedures and description of the repository are available at PAINrepository.org. Scanner-compatible acquisition parameters were developed based on recommendations from Functional Biomedical Informatics Research Network (fBIRN) (https://xwiki.nbirn.org:8443/bin/view/Function-BIRN/FBIRN_Best_Practices), and all sites were required to complete and pass a site qualification based on data from pilot scans of a human volunteer.

Diffusion-weighted data at NU and UCLA were acquired using echo planar imaging (voxel size, 2 × 2 × 2 mm; TR, 8500-9500 milliseconds; TE, 83-88 milliseconds; flip angle, 90°; in-plane matrix resolution, 128 × 128; field of view [FOV], 256 mm). Diffusion weighting was isotropically distributed along 60 and 69 directions, respectively, using b value sets of 0 and 1000 s/mm^2. At SU, acquisition used echo planar imaging (voxel size, 0.85 × 0.85 × 2 mm; TR, 9600 milliseconds; TE, minimum; flip angle, 90°; in-plane matrix resolution, 128 × 128; FOV, 256 mm) with isotropically distributed weighting along 69 directions using b value sets of 0 and 1000 s/mm^2. All subject space data were resampled to 1-mm isotropic resolution for analyses in standard space.

The 3D MP-RAGE pulse sequences at NU and UCLA acquired T1-weighted anatomical images (voxel size, 1 × 1 × 1 mm; TR, 2200 milliseconds; TE, minimum; flip angle = 9°, in-plane matrix resolution, 256 × 256; FOV, 220 × 220 mm; slices, 176; slice thickness, 1 mm). T1 images from SU were acquired with similar parameters (voxel size, 0.86 × 0.86 × 1 mm; TR, 2200 milliseconds; TE, minimum; flip angle = 11°;

in-plane matrix resolution, 256 × 256; FOV, 220 × 220 mm; slices, 170; slice thickness, 1 mm).

2.4. Data analysis

2.4.1. Image preprocessing

Analysis was performed using tools from the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) and custom software. Diffusion tensor imaging data were manually checked volume by volume for obvious artifacts and distortions. FMRIB's Diffusion Toolbox (FDT) was used to correct for eddy currents (which cause stretches and shears in images) and head motion, and images were affinely registered to the first no-diffusion weighted ($b = 0$ s/mm^2) image of each subject. After skull extraction with Brain Extraction Tool (BET),[52] a diffusion tensor model was fit at each voxel to determine the voxelwise fractional anisotropy (FA), which reflects the degree of water diffusion along a principle axis (diffusion anisotropy). Neuronal axons are insulated with myelin sheaths that physically constrain water flow within the myelin sheath, along the length of the axon (resulting in high FA). Fractional anisotropy values range from 0 to 1.0; larger values indicate directional dependence of Brownian motion in the presence of white matter tracts, whereas smaller values indicate more isotropic diffusion and less directional coherence[4]

2.4.2. Analysis of diffusion tensor imaging and T1 images

Voxelwise statistical analysis of FA data was executed with the tract-based spatial statistics (TBSS) package.[51] Fractional anisotropy data were nonlinearly realigned to a high-resolution (1 mm^3) standard space, and mean FA images were then generated and thinned to create a mean FA skeleton mask (FA > 0.25), which represents the spatial distribution of white matter that is common to all subjects (including patients and controls). Each subject's aligned FA data were projected back onto this group skeleton. Significant group differences between UCPPS, IBS, and controls were determined using permutation methods, which apply inference (thresholding) on statistical maps when the null distribution is not known (N = 5000 permutations, $P < 0.01$ corrected for multiple comparisons using threshold-free cluster enhancement and a 30-voxel cluster threshold). The resulting FA regions of interest (ROIs) that significantly differed between groups were extracted, and group differences in mean FA were reconfirmed with posthoc one-way analyses of variance (ANOVAs), or Kruskall–Wallis one-way ANOVAs for nonnormally distributed data. To further evaluate the diffusion properties of significant FA ROIs, water diffusion is examined along the principle direction of diffusion (axial diffusivity, AD $\lambda1$), away from (perpendicular to) the principle diffusion direction (radial diffusivity, RD ($\lambda2 + \lambda3$)/2), and average diffusion in all directions (mean diffusivity, ($\lambda1 + \lambda2 + \lambda3$)/3). Finally, to confirm that results are independent of potential artifacts/selection bias in the control group, we used permutation methods repeated 10 times (N = 1000, $P < 0.05$, corrected for multiple comparisons using threshold-free cluster enhancement) to assess between-group differences in randomly shuffled subgroups of controls (n = 20, 20, and 21). For visualization purposes only, ROIs were plotted with the Johns Hopkins University (JHU) DTI-based white matter tractography atlas based on the mean tractography from 28 healthy individuals.

High-resolution T1-weighted anatomical brain images were visually examined for artifacts, skull extracted, and normalized to a standard brain to control for body mass. Next, we conducted a whole-brain analysis of regional gray matter differences between CP/CPPS and controls using an optimized method of voxel-based morphometry and nonparametric statistical contrasts described by Ashburner and Friston[2] and Good et al.[28] To evaluate potential gray matter anatomical changes in DTI-derived ROIs, ROI masks were used to extract mean grey matter density values specific to those regions. Group differences were investigated using one-way ANOVA ($P < 0.05$).

2.4.3. Statistical corrections for site effects

Large-scale, multisite collaborations are frequently faced with site differences in neuroimaging data. Fractional anisotropy values show the excellent consistency (0.96 concordance)[25] and comparable rates of test–retest reproducibility errors[34] across magnets and manufacturers, yet between-site variability is common. No gold-standard method has been developed for statistical correction of FA site differences, although normalization within-site (ie, subject-specific corrections within an institution) and cross-site (ie, normalization with Grand mean across sites) is common.

Each participant's mean skeletal FA value was calculated as a global index of diffusion in white matter[27] by averaging FA values over each subject's white matter skeleton. Mean FA values were then used to assess and correct for site differences based on a previously described method.[23] Briefly, a linear correction for site effect was applied, (Mean$_a$ − Mean$_b$) + FA$_c$, where a = a subject's uncorrected FA value, b = the mean FA value of each subject's site, and c = mean FA value of all sites. This correction accounts for the impact of site mean on a subject's data (thereby correcting for individual site effect), and adds this corrected value to the grand mean of all sites. This correction method normalized sites means with one another.

2.4.4. Assessment of convergent validity

The identification of diagnostically accurate and sensitive brain biomarkers of disease, such as abnormalities in brain white matter integrity, requires corroborating evidence to confirm that the biomarker(s) indeed measures the construct of interest. For example, evidence may include correlations between biomarker properties and clinical symptoms that uniquely characterize the disease. Similarly, the convergence of multiple measures, such as complementary findings from previous functional and structural imaging studies, may further support biomarker status. The white matter ROIs identified from our analyses in men and women with UCPPS were therefore examined in relation to published neuroimaging findings from the MAPP Network conducted in women with UCPPS and using an ROI identified in non-MAPP healthy men but analyzed within a male MAPP cohort:

Published MAPP MRI papers conducted in female UCPPS populations:

Farmer MA, Huang L, Martucci K, Yang CC, Maravilla KR, Harris RE, Clauw DJ, Mackey S, Ellingson BM, Mayer EA, Schaeffer AJ, Apkarian AV; Network MR. Brain white matter abnormalities in female interstitial cystitis/bladder pain syndrome: a MAPP network neuroimaging study. J Urol 2015;194: 118–26. *Pooled NU, UCLA, and SU sample.*

Kairys AE, Schmidt-Wilcke T, Puiu T, Ichesco E, Labus JS, Martucci K, Farmer MA, Ness TJ, Deutsch G, Mayer EA, Mackey S, Apkarian AV, Maravilla K, Clauw DJ, Harris RE. Increased brain gray matter in the primary somatosensory cortex is associated with increased pain and mood disturbance in interstitial cystitis/painful bladder syndrome patients. J Urol

2014. *Pooled UCLA, NU, SU, University of Michigan, and University of Alabama sample.*

Kilpatrick LA, Kutch JJ, Tillisch K, Naliboff BD, Labus JS, Jiang Z, Farmer MA, Apkarian AV, Mackey S, Martucci KT, Clauw DJ, Harris RE, Deutsch G, Ness TJ, Yang CC, Maravilla K, Mullins C, Mayer EA. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. J Urol 2014;192: 947–55. *Pooled UCLA, NU, SU, University of Michigan, and University of Alabama sample.*

Published MAPP MRI paper conducted in a male UCPPS population:

Kutch JJ, Yani MS, Asavasopon S, Kirages DJ, Rana M, Cosand L, Labus JS, Kilpatrick LA, Ashe-McNalley C, Farmer MA, Johnson KA, Ness TJ, Deutsch G, Harris RE, Apkarian AV, Clauw DJ, Mackey SC, Mullins C, Mayer EA. Altered resting state neuro-motor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: a MAPP: research network neuroimaging study. Neuroimage Clin 2015;8:493–502. *Pooled UCLA and University of Southern California sample.*

Specifically, the primary somatosensory region showing significantly increased gray matter density in Kairys' MAPP sample of women with IC/BPS was plotted (with contralateral coordinates −17, −43, 61[35]), along with regions of altered low-frequency oscillations described by Kilpatrick and colleagues in women with IC/BPS (with coordinates at −16, −24, 58,[36]). Furthermore, a pelvic–motor region showing abnormal brain connectivity in a MAPP sample of men with UCPPS published by Kutch was also examined,[37] with center of the 10-mm radius ROI located at 4, −26, 66. Overlap between white matter abnormalities and previous descriptions of regions with altered brain activity and gray matter distribution were visualized to determine the extent of convergence between multimodal results. Original papers varied substantially in sample sizes, composition of participants because of site differences in types of neuroimaging data collection, analytic strategy (eg, use of á priori-derived ROIs from an independent sample vs exploratory analyses), and previous publications had not investigated alterations in both sexes. Moreover, functional MRI, T1-weighted, and DTI images are collected using independent methods with independent sources of noise. Therefore, inflation of type-I error remains possible but unlikely given these numerous potential confounds.

2.4.5. Behavioral data analysis

Mean FA values for each ROI were extracted and evaluated in relation to behavioral data from questionnaires. Pearson correlations assessed the degree of association between behavioral variables and regional white matter FA to determine particular ROIs-reflected clinically relevant parameters. These ROIs were first identified by their correlation with UCPP pain severity across a pooled sample of UCPPS and IBS participants. Subsequent exploratory correlations were conducted within the respective patient groups and included an á priori-defined subset of questionnaire measures as follows: MPQ pain and affective subscale scores, Hospital Anxiety and Depression subscale scores, GUPI pain, urinary, and quality of life subscales, Positive and Negative Affect Schedule, and 2 items about urinary urgency and frequency (Bonferroni corrected for 10 comparisons, $P \leq 0.005$). For parametric data, one-way ANOVAs with Tukey posthoc tests were used. For nonparametric data, Kruskall–Wallis one-way ANOVAs were applied, and pairwise comparisons were generated using Dunn's Method, where applicable.

3. Results

3.1. Description of clinical sample

Groups differed on all clinical questionnaire measures indicating a broad range of sensory, psychological, and functional impairments in UCPPS (**Table 1**). Planned posthoc t tests revealed that compared with the IBS and control groups, the UCPPS group reported greatest pelvic pain severity (eg, pain intensity and unpleasantness, MPQ sensory and affective pain scales, and GUPI pain subscale) and urinary symptom severity (eg, GUPI urinary subscale). Similarly, the UCPPS group reported greater mood disturbances (eg, depression, anxiety, and negative affect scales), more sleep difficulties (eg, PROMIS sleep scale), and poorer quality of life (eg, GUPI quality of life subscale), compared with positive and healthy controls. Across all clinical measures, the IBS group exhibited greater symptom impairment compared with the control group and significantly less severe symptoms than the UCPPS group. No group effects of age were found, yet a small age × sex interaction was identified (F = 4.02, $P < 0.05$). We repeated the above analyses in male and female cohorts separately and found no change in the observed group differences (data not shown).

3.2. Regional white matter fractional anisotropy differences in urological chronic pelvic pain syndrome

We first examined subjects' FA skeletons using a one-way ANOVA to evaluate FA differences among 3 groups (UCPPS, IBS, and controls). Permutation testing identified 7 regional FA clusters that yielded group differences, and group differences were confirmed with one-way ANOVAs. These clusters included the following: (1) a portion of the left corticospinal tract projecting through the precentral gyrus adjacent to the motor homunculus ($F_{2,149} = 6.82, P = 0.001$), (2) aspects of left forceps major ($H_{2,149} = 16.71, P < 0.001$), (3) left superior longitudinal fasciculus tracts within the precentral gyrus, just posterior to the pars opercularis of the inferior frontal gyrus ($H_{2,149} = 20.04, P < 0.001$), (4) aspects of the left superior corona radiata, just lateral to the anterior cingulate cortex ($H_{2,149} = 15.19, P < 0.001$), (5) tracts located in the precuneous cortex that include right forceps major, right inferior fronto–occipital fasciculus, and the border of the cingulum bundle that projects to parahippocampal gyri ($H_{2,149} = 19.61, P < 0.001$), (6) aspects of the right inferior longitudinal fasciculus bordering the cingulum bundle that projects to parahippocampal gyri, located within the temporal occipital fusiform cortex ($F_{2,149} = 5.86, P = 0.004$), and (7) right anterior thalamic radiation (ATR) tracts ($F_{2,149} = 5.80, P = 0.004$). Permutation testing confirmed that randomly shuffled subgroups of control participants exhibited no significant between-group FA differences, which strongly suggests the DTI results are not attributable to artifacts in control participant data. Diffusivities of all regions are presented in supplementary Figure 1 (available online at http://links.lww.com/PAIN/A335).

3.3. Clinical relevance of regional white matter abnormalities

Of the 7 identified ROIs, FA of 2 regions—including the corticospinal tract passing through the precentral gyrus and ATR tracts—was significantly correlated with UCPPS pain severity (measured with the GUPI pain scale). Further, inspection revealed corticospinal and ATR ROIs were significantly correlated with the sensory and affective domain scores of the MPQ, as well as pain, urinary, and quality of life domain scores of the GUPI. Within each patient group, these ROIs were further evaluated for directional dependence and related clinical parameters in planned posthoc analyses.

Table 1

Clinical characteristics of UCPPS, IBS, and control groups collected on the day of scanning.

Clinical parameters	UCPPS	IBS	Controls	Group effect	Gender effect	Group × gender
	Mean (SEM)	Mean (SEM)	Mean (SEM)			
Age	39.96 (1.83)	36.69 (2.10)	37.55 (1.63)	0.80	4.02*	1.61
Genitourinary pain index						
Total Score	23.78[ab] (0.79)	7.15[bc] (0.92)	1.31[ac] (0.72)	231.18**	1.06	1.09
Pain	11.40[ab] (0.39)	2.53[bc] (0.45)	0.20[ac] (0.35)	243.52**	0.90	2.17
Urinary	4.90[ab] (0.26)	1.71[bc] (0.30)	0.74[ac] (0.23)	74.53**	1.58	1.09
Quality of life	7.23[ab] (0.32)	3.02[bc] (0.37)	0.37[ac] (0.29)	129.10**	0.11	0.54
McGill Pain Questionnaire						
Total Score	10.92 (0.57)	5.85 (0.66)	0.24 (0.52)	97.67**	0.60	0.07
Sensory	8.32[ab] (0.46)	4.86[bc] (0.53)	0.19[ac] (0.41)	89.00**	1.17	0.54
Affective	2.18[ab] (0.23)	0.98[bc] (0.27)	0.05[ac] (0.21)	23.50**	0.16	0.11
Hospital Anxiety and Depression Scale						
Anxiety	8.17[ab] (0.47)	5.15[bc] (0.55)	3.15[ac] (0.42)	31.61**	1.51	0.06
Depression	5.78[ab] (0.32)	3.29[bc] (0.37)	2.05[ac] (0.29)	37.54**	3.01	1.11
Gracely Pain Scale						
Pain intensity	9.17[ab] (0.46)	6.78[bc] (0.53)	0.20[ac] (0.42)	113.83**	0.58	1.77
Unpleasantness	8.10[ab] (0.45)	5.68[bc] (0.52)	0.48[ac] (0.41)	81.26**	0.09	1.33
Sleep quality (PROMIS)	−1.19[ab] (0.74)	−5.47[bc] (0.86)	−10.28[ac] (0.67)	41.92**	0.00	1.71
Positive and Negative Affect Schedule						
Positive affect	28.41[ab] (0.98)	33.69[b] (0.79)	35.46[a] (0.88)	14.82**	0.17	1.19
Negative affect	18.60[ab] (0.69)	15.87[bc] (0.81)	12.33[ac] (0.63)	22.81**	4.47*	0.62
Symptom and health care utilization questionnaire						
Pain	4.05[ab] (0.22)	1.12[bc] (0.26)	0.01[ac] (0.20)	95.66**	0.13	0.46
Urgency	3.77[ab] (0.26)	1.69[bc] (0.30)	0.31[ac] (0.23)	49.29**	0.09	0.08
Frequency	4.09[ab] (0.27)	1.77[bc] (0.31)	0.50[ac] (0.24)	50.14**	0.32	0.02
Voiding	2.21[ab] (0.10)	1.40[bc] (0.12)	1.01[ac] (0.09)	40.29**	0.22	0.57
Overall severity	3.98[ab] (0.21)	0.91[bc] (0.25)	0.01[ac] (0.19)	101.18**	0.01	0.35

Asterisks indicate significance levels (**$P < 0.01$ and *$P < 0.05$). Planned posthoc group comparisons ($P < 0.05$) included the following: [a]UCPPS vs controls, [b]UCPPS vs IBS, and [c]IBS vs controls.
IBS, irritable bowel syndrome; UCPPS, urological chronic pelvic pain syndrome; PROMIS, Patient Reported Outcomes Measurement Information System.

The first white matter region that correlated with pelvic pain severity was a portion of the corticospinal tract for which patients with UCPPS exhibited higher FA compared with that by positive visceral controls (IBS) and healthy controls ($P < 0.001$ and $P = 0.04$, respectively), shown in **Figure 1**. No group differences in mean diffusivity images were identified for this region ($F_{2,147} = 1.65$, $P > 0.05$). Although no group differences in mean diffusivity (average diffusion across all directions of water flow) were found, patients with UCPPS exhibited greater axial diffusivity (diffusion along the principle direction of water flow) compared with controls, with a similar trend observed in the patients with IBS. In contrast, greater radial diffusivity (diffusion away from the principle tract direction) was identified in patients with IBS compared with those with UCPPS ($H_{2,149} = 7.49$, $P = 0.02$), indicating microstructural divergence from normal tract orientation within this region in IBS despite the comparable FA values with controls. Within the IBS group, a trend toward significance was found between greater corticospinal radial diffusivity and fewer pain sensory descriptors from the MPQ ($r = -0.33$, $P = 0.04$). More specifically, women with IBS with greater RD endorsed greater pain intensity ($r = 0.50$, $P = 0.069$), fewer GUPI urinary symptoms ($r = -0.48$, $P = 0.085$), and less urinary frequency ($r = -0.54$, $P = 0.047$). Across patients groups, regional FA positively correlated with pelvic pain severity ($r = 0.35$, $P < 0.001$) and MPQ sensory characteristics of pain ($r = 0.30$, $P = 0.003$) but not with MPQ affective appraisal of pain (**Fig. 1**). Trends toward significance were identified for urinary urgency

($r = 0.23$, $P = 0.02$), pelvic pain–related quality of life ($r = 0.25$, $P = 0.01$), and anxiety ($r = 0.25$, $P = 0.01$).

The anterior thalamic radiation contained the second region of altered FA that correlated with clinical parameters, with significantly greater FA identified in healthy controls and patients with UCPPS, compared with that in patients with IBS ($P = 0.006$ and $P = 0.008$, respectively). No group differences in mean diffusivity images were identified for this region ($F_{2,149} = 2.18$, $P > 0.05$). Increased radial diffusivity in the IBS group ($H_{2,149} = 7.24$, $P = 0.02$), compared with controls, again indicated an IBS-related microstructural divergence from normal tract organization that was also observed in the corticospinal white matter region. In the IBS group, a correlation between greater radial diffusivity and less pelvic pain severity trended toward significance ($r = -0.29$, $P = 0.05$). No group differences in mean or axial diffusivity were found. Across visceral pain patients, regional FA significantly correlated with pelvic pain severity ($r = 0.29$, $P = 0.005$) and trended toward significance with urinary symptoms ($r = 0.25$, $P = 0.01$), pelvic pain–related quality of life ($r = 0.29$, $P = 0.006$), and negative affect on the day of scanning ($r = 0.26$, $P = 0.01$) (**Fig. 2**). Taken together, the diffusion and clinical profiles of the identified white matter clusters uniquely discriminated between UCPPS, IBS, and control groups.

3.4. Gray matter properties of diffusion tensor imaging regions

Voxel-based morphometry–derived metrics of gray matter density for the 2 primary white matter ROIs yielded no
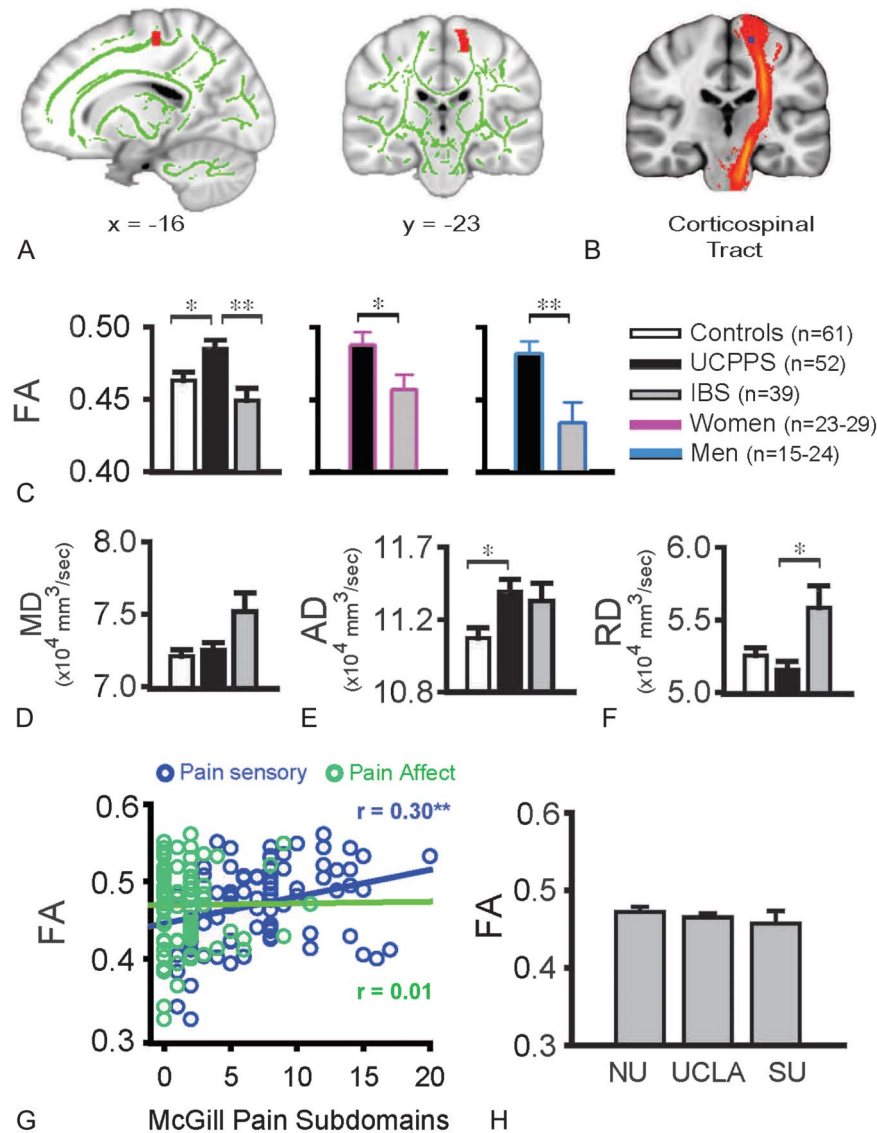
Figure 1. Corticospinal white matter abnormalities discriminate patients with urological chronic pelvic pain syndrome (UCPPS) from irritable bowel syndrome (IBS) and control groups. (A) The peak voxels of the corticospinal cluster (red) are overlaid on the mean fractional anisotropy (FA) image from all participants (green). (B) This cluster (now in blue) is projected onto axonal tracts derived from the Johns Hopkins University diffusion tensor imaging–based white matter tractography atlas, which depicts corticospinal fiber pathways (red–yellow) that originate from the precentral gyrus of M1, postcentral gyrus of S1, and supplementary motor area/premotor cortex and project to the ventral horn (for the primary motor cortex, SMA, and premotor) or the dorsal horn (for S1 projections) of the spinal cord. (C) Patients with UCPPS exhibited increased FA in this corticospinal tract region, compared with IBS and control groups (left panel), and this result was consistent in women and men with UCPPS (middle and right panels outlined in pink and blue, respectively). Whereas, no significant group differences emerged for (D) mean diffusivity (mean diffusion across all directions of water flow), (E) the UCPPS group exhibited increased axial diffusivity (diffusion along the principle direction of water flow), compared with healthy controls. (F) Radial diffusivity (diffusion away from the principle tract direction) was increased in patients with IBS, which may account for the group's low FA values in (C). (G) In patients with UCPPS, corticospinal regional FA correlated with the sensory subscale of the McGill Pain Questionnaire (MPQ) (blue), yet no relationship emerged for the MPQ-affective subscale (green) (Bonferroni-corrected Pearson correlations were used with $P \leq 0.007$). (H) No site differences were evident in regional FA. McGill Pain Questionnaire evaluated sensory vs affective/emotional aspects of pain perception. NU, Northwestern University; UCLA, University of California at Los Angeles; SU, Stanford University. For C-D, $* p < 0.05$, $** p < 0.01$. For G, $**$ Bonferroni-corrected $p < 0.005$.

significant differences for the corticospinal tract region ($F_{2,139} = 1.25$, $P > 0.05$) or the anterior thalamic radiation region ($F_{2,149}$ 0.63, $P > 0.05$).

3.5. Convergence with previously described MAPP imaging results

Substantial spatial overlap was found when comparing coordinates of this study's corticospinal white matter ROI with previous findings from functional and gray matter anatomical studies (**Fig. 3**). Specifically, the corticospinal ROI exhibiting UCPPS-specific increases in FA overlapped with the premotor region thought to encode voluntary pelvic floor muscle activity[1] and the primary motor cortex region displaying altered whole-brain functional connectivity in men with UCPPS.[37] Furthermore, this tract directly traversed an area associated with heightened low-frequency power in women with IC/BPS, based on resting-state functional scan data.[36] Whereas the aforementioned regions were confined to the motor cortex, the primary somatosensory region showing increased gray matter density in women with IC/BPS was more posterior[35] and overlapped with the genitalia representation Penfield somatosensory homunculus.[46]
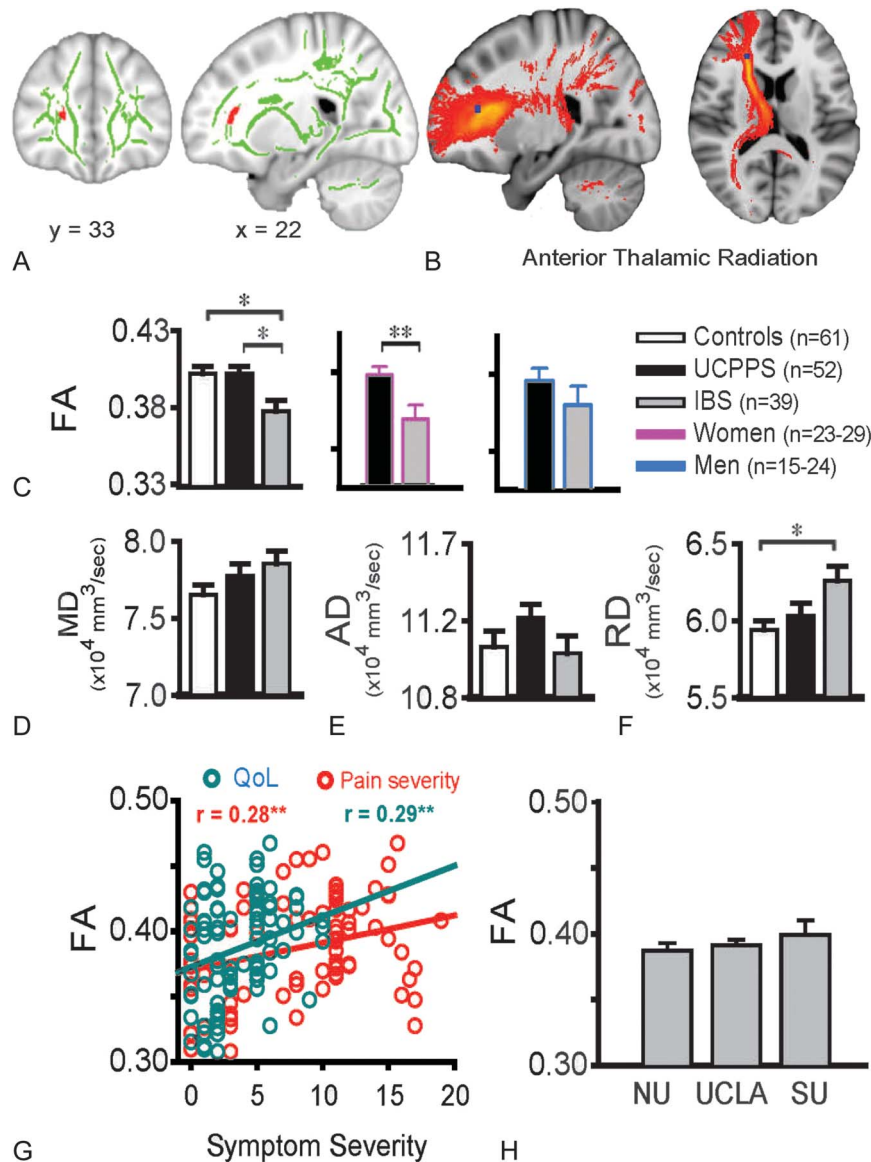
Figure 2. White matter abnormalities in the anterior thalamic radiation (ATR) discriminate visceral pain patients from healthy controls. (A) The peak voxels of the ATR cluster (red) are localized on the white matter skeleton (green) common to patient and control groups. (B) This cluster (now in blue) is projected onto tracts derived from the Johns Hopkins University diffusion tensor imaging–based white matter tractography atlas, which depicts ATR fiber pathways (red–yellow) that originate in the anterior and medial thalamic nuclei and project to the primary and secondary somatosensory regions. (C) Patients with irritable bowel syndrome (IBS) exhibited significantly reduced fractional anisotropy (FA) in this portion of the ATR region, compared with urological chronic pelvic pain syndrome (UCPPS) and control groups (left panel). This result was preserved for women, but not men, with IBS (middle and right panels outlined in pink and blue, respectively). Whereas, no significant group differences emerged for (D) mean diffusivity (mean diffusion across all directions of water flow), (E) axial diffusivity (diffusion along the principle direction of water flow), or (F) increased radial diffusivity (diffusion away from the principle tract direction) in patients with IBS was identified. (G) In patients with UCPPS, ATR regional FA correlated with pain severity (red) and quality of life (teal), thereby reinforcing that this segment of white matter tract reflects clinically relevant symptoms of UCPPS (Bonferroni-corrected Pearson correlations were used with $P \leq 0.007$). (H) No site differences were evident in regional FA. Genitourinary Pain Index was used to assess pelvic pain severity and quality of life. NU, Northwestern University; UCLA, University of California at Los Angeles; SU, Stanford University.

4. Discussion

Using diffusion imaging techniques, we have, for the first time, described clinically relevant brain white matter abnormalities uniquely related to UCPPS. Increased FA was localized to aspects of the corticospinal and anterior thalamic radiation tracts, with the former region demonstrating specificity and sensitivity to female and male patients with UCPPS, and the latter region distinguishing patients with IBS from healthy controls. Moreover, these regional changes were independent of local gray matter FA and density. These findings strongly suggest that ongoing urological pelvic pain is associated with highly localized, condition-specific patterns of axonal reorganization reflecting either a predisposition for developing UCPPS or a consequence of living with persistent pelvic pain. When considered with previous evidence of UCPPS-specific regional gray matter properties in men[22] and women,[36] these data collectively point to brain white and gray matter changes associated with the reorganization of local and global brain circuitry in UCPPS.

The identification of condition-specific biomarkers for CPPS and IC/BPS requires an understanding of how central mechanisms
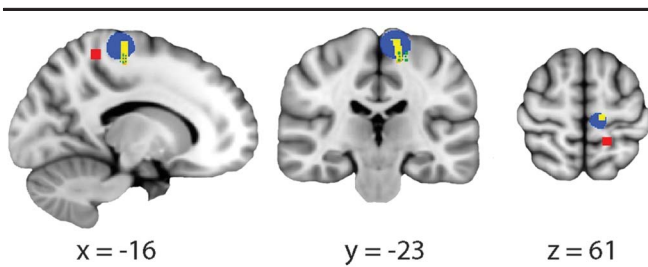
Figure 3. Colocalization of urological chronic pelvic pain syndrome(UCPPS)–related corticospinal white matter region and functional and structural brain changes in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain–derived UCPPS populations. The aspect of the corticospinal tract showing increased fractional anisotropy (FA) in men and women with UCPPS (yellow) was visualized. This region greatly overlapped with the pelvic floor motor region identified by Kutch that yielded whole-brain functional connectivity differences in men with UCPPS.[37] Furthermore, our corticospinal region directly intersected a region characterized by low-power frequency oscillations in women with UCPPS (green[35]). Notably, these regions are located anterior to the S1 region of increased gray matter density identified in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain patients with interstitial cystitis or bladder pain syndrome.[36]

underlying UCPPS differ from those found in other types of visceral pain, which motivated our inclusion of a positive control group (IBS) exhibiting visceral pain in a nonpelvic region. Visceral pain is perceived as diffuse, dull, or throbbing, with associated negative affect (ie, "aching," "sickening" pain), and autonomic changes, and pain neuroimaging has yet to identify reliable differences between brain functional representations of somatic vs visceral pain, or between types of visceral pain.[18,19] For instance, acute visceral discomfort and pain in the bladder, bowel, and esophagus are associated with similar patterns of regional brain activity that greatly overlap with the activity related to cutaneous (somatic) pain perception.[18,30,45,55,57] Visceral and somatic pain recruit common attentional and emotional processes that are widely distributed across networks of brain regions.[21] Similarly, the spinal cord contains no known neurons that solely convey visceral input, given the spinal convergence of overlapping visceral and somatic afferent nerve fibers.[8] However, the primary supraspinal region that initially receives nociceptive input, the ventral posterolateral nucleus of the thalamus, distinguishes abdominal from pelvic visceral input, although it lacks visceral topography from pelvic viscera.[7] If regional patterns of brain activity are insufficient to distinguish types of visceral pain, as these studies suggest, it is feasible that cortical representations of visceral pain are mediated by other features of neural information processing, such as the microstructure of axonal tracts that communicate pain-related information. This hypothesis is supported by UCPPS-specific abnormalities in FA in a portion of the corticospinal tract permeating the precentral gyrus (primary motor cortex or M1). Corticospinal neurons (ie, upper motor neurons) modulate voluntary, fine muscle movements and posture, and approximately 30% of these neuronal processes originate in the precentral gyrus, where the UCPPS-related increases in FA were localized. Elevated FA is typically thought to result from numerous, denser axon concentrations, greater axonal orientation in the same direction, and/or increased myelination (although myelin is not necessary), such that high FA values are interpreted as properties of healthy white matter. For instance, diffuse increases in corticospinal FA are observed throughout childhood and adolescence as part of normal neural development.[49,60] Reduced corticospinal FA, however, is common in diseases associated with loss of motor and executive function, including Huntington disease,[47] multiple sclerosis,[32]

cerebral palsy in children,[48] multiple system atrophy,[33] and amyotrophic lateral sclerosis.[9] In contrast, increased corticospinal FA is observed with recovery of motor function following diffuse axonal injury,[31] and more commonly with motor learning. Across species, learning repetitive motor tasks is associated with increased corticospinal FA, whether it be a human juggling or playing the piano, or song production during a songbird's mating season.[17,20,50] Urological chronic pelvic pain syndrome–related corticospinal abnormalities may therefore reflect an ongoing refinement and strengthening of motor connections that are relevant to pelvic pain, rather than a selective sparing of this tract. In particular, the correlations between corticospinal FA in M1, pelvic pain severity, and sensory qualities of pain, as well as the close proximity of this tract segment to a region strongly implicated in voluntary pelvic floor motor control,[1] implies that increased regional FA may be the product of experience-dependent reinforcement (or perhaps overuse) of pain-related pelvic motor responses. Given that motor learning requires the presence of newly myelinated axons,[39] it can be reasoned that pelvic pain–related motor learning is also accompanied by enhanced myelination of axons (and therefore FA) in the activated neural circuit. These observations support the hypothesis that elevated corticospinal FA in UCPPS reflects increased myelination accompanying learned motor responses that are intended to physically adapt to or relieve pelvic pain. Ultimately, these changes in corticospinal microstructure may facilitate sensorimotor processing of pelvic pain–related information.

Axonal tracts within the anterior thalamic radiation seem to serve multiple functions in the communication of visceral pain information. The ATR links the dorsomedial thalamus and anterior thalamic nuclei to the medial prefrontal cortex, ventral periaqueductal gray, and retrocommissural hippocampus, making this pathway critical in memory, emotional reactivity to autonomic arousal, and emotional expression.[16] Across visceral pain populations, ATR regional FA correlated with greater pain severity and poorer quality of life, implying that this tract relays sensory and cognitive–emotional information used to appraise the global impact of visceral pain, in general. The reorganization of ATR axonal tracts plays a prominent role in IBS pain, in particular. These tracts were characterized by greater radial diffusivity away from the primary tract direction with no concurrent changes in axial diffusivity, thereby yielding reduced FA values. Radial diffusivity may reflect degradation of axonal morphology (eg, demyelination in multiple sclerosis), reduction of the number of axons (ie, axonal membranes[5] or changes in the organization of tracts (ie, with new axonal branching and/or crossing of fibers)). Furthermore, women but not men with IBS exhibited more extensive radial diffusivity related to greater pain intensity and low urinary frequency. As a result, ATR radial diffusivity helps to discriminate abdominal visceral pain from the UCPPS urinary phenotype. Collectively, these findings point to the possibility that distinct types of chronic visceral pain may differentially reorganize common axonal tracts, therefore implying that the modulation of common neural circuitry occur in condition-specific patterns.

As diagnoses of exclusion, IC/CPPS and IC/BPS share substantial symptom overlap, including voiding difficulties, dyspareunia/painful ejaculation, and abnormal bladder and urethral findings. However, distinct physiological mechanisms underlying urinary symptoms, as well as variable pelvic and bladder pain, may account for the broad symptom variability within UCPPS. Although the current investigation focused on two white matter regions that did not exhibit sex dependence, it is acknowledged that sex differences in pain perception[3,42] and nociceptive processing[43,54] may prove to be critical in UCPPS

clinical phenotyping. Furthermore, it is feasible that CPPS and IC/BPS are heterogeneous diagnoses that consist of etiologically distinct subtypes that are yet to be identified.[24]

We have observed regional white matter abnormalities that seem to reflect white matter microstructural changes that are specific to UCPPS, and these alterations are anatomically distinct from white matter changes associated with visceral abdominal pain from IBS. It is unclear whether these differences reflect predispositions, previous pain experiences, factors driving pain onset, and/or mechanisms of pelvic pain maintenance. To tease apart the mechanistic roles of brain functional and structural changes observed in UCPPS,[22,35,36] the MAPP Network is currently expanding on these findings with longitudinal epidemiological and neuroimaging studies to temporally track the neural biomarkers that can differentiate UCPPS phenotypes.

Conflict of interest statement

Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A335.

References

[1] Asavasopon S, Rana M, Kirages DJ, Yani MS, Fisher BE, Hwang DH, Lohman EB, Berk LS, Kutch JJ. Cortical activation associated with muscle synergies of the human male pelvic floor. J Neurosci 2014;34: 13811–18.

[2] Ashburner J, Friston KJ. Voxel-based morphometry–the methods. Neuroimage 2000;11(6 pt 1):805–21.

[3] Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth 2013;111:52–8.

[4] Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 2002;15:435–55.

[5] Beaulieu C. The biological basis of diffusion anisotropy. In: Johansen-Berg H, Behrens TEJ, editors. diffusion MRI: from quantitative measurement to in-vivo neuroanatomy. London: Elsevier, 2009.

[6] Beckett MK, Elliott MN, Clemens JQ, Ewing B, Berry SH. Consequences of interstitial cystitis/bladder pain symptoms on women's work participation and income: results from a national household sample. J Urol 2014;191:83–8.

[7] Bruggemann J, Shi T, Apkarian AV. Squirrel monkey lateral thalamus. II. Viscerosomatic convergent representation of urinary bladder, colon, and esophagus. J Neurosci 1994;14(11 pt 2):6796–814.

[8] Brumovsky PR, Gebhart GF. Visceral organ cross-sensitization - an integrated perspective. Auton Neurosci 2010;153:106–15.

[9] Cardenas-Blanco A, Machts J, Acosta-Cabronero J, Kaufmann J, Abdulla S, Kollewe K, Petri S, Heinze HJ, Dengler R, Vielhaber S, Nestor PJ. Central white matter degeneration in bulbar- and limb-onset amyotrophic lateral sclerosis. J Neurol 2014;261:1961–7.

[10] Chanraud S, Zahr N, Sullivan EV, Pfefferbaum A. MR diffusion tensor imaging: a window into white matter integrity of the working brain. Neuropsychol Rev 2010;20:209–25.

[11] Chen JY, Blankstein U, Diamant NE, Davis KD. White matter abnormalities in irritable bowel syndrome and relation to individual factors. Brain Res 2011;1392:121–31.

[12] Clemens JQ, Calhoun EA, Litwin MS, McNaughton-Collins M, Kusek JW, Crowley EM, Landis JR; Urologic Pelvic Pain Collaborative Research N. Validation of a modified national institutes of health chronic prostatitis symptom index to assess genitourinary pain in both men and women. Urology 2009;74:983–7, quiz 987. e981–983.

[13] Clemens JQ, Markossian T, Calhoun EA. Comparison of economic impact of chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/painful bladder syndrome. Urology 2009;73:743–6.

[14] Clemens JQ, Markossian TW, Meenan RT, O'Keeffe Rosetti MC, Calhoun EA. Overlap of voiding symptoms, storage symptoms and pain in men and women. J Urol 2007;178(4 pt 1):1354–8, discussion 1358.

[15] Clemens JQ, Mullins C, Kusek JW, Kirkali Z, Mayer EA, Rodriguez LV, Klumpp DJ, Schaeffer AJ, Kreder KJ, Buchwald D, Androle GL, Lucia MS, Landis JR, Clauw DJ; Group MRNS. The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. BMC Urol 2014; 14:57.

[16] Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci 2012;24:223–36.

[17] De Groof G, Verhoye M, Van Meir V, Balthazart J, Van der Linden A. Seasonal rewiring of the songbird brain: an in vivo MRI study. Eur J Neurosci 2008;28:2475–85, discussion 2474.

[18] Derbyshire SW. Imaging visceral pain. Curr Pain Headache Rep 2007;11: 178–82.

[19] Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, Tracey I. A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. J Neurosci 2005;25:7333–41.

[20] Engel A, Hijmans BS, Cerliani L, Bangert M, Nanetti L, Keller PE, Keysers C. Inter-individual differences in audio-motor learning of piano melodies and white matter fiber tract architecture. Hum Brain Mapp 2014;35:2483–97.

[21] Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. Neurosci Lett 2012;520:197–203.

[22] Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. J Urol 2011;186:117–24.

[23] Farmer MA, Huang L, Martucci K, Yang CC, Maravilla KR, Harris RE, Clauw DJ, Mackey S, Ellingson BM, Mayer EA, Schaeffer AJ, Apkarian AV; Network MR. Brain white matter abnormalities in female interstitial cystitis/bladder pain syndrome: a MAPP network neuroimaging study. J Urol 2015;194:118–26.

[24] Forrest JB, Nickel JC, Moldwin RM. Chronic prostatitis/chronic pelvic pain syndrome and male interstitial cystitis: enigmas and opportunities. Urology 2007;69(suppl 4):60–3.

[25] Fox RJ, Sakaie K, Lee JC, Debbins JP, Liu Y, Arnold DL, Melhem ER, Smith CH, Philips MD, Lowe M, Fisher E. A validation study of multicenter diffusion tensor imaging: reliability of fractional anisotropy and diffusivity values. AJNR Am J Neuroradiol 2012;33:695–700.

[26] Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008;60:570–81.

[27] Giorgio A, Watkins KE, Douaud G, James AC, James S, De Stefano N, Matthews PM, Smith SM, Johansen-Berg H. Changes in white matter microstructure during adolescence. Neuroimage 2008;39:52–61.

[28] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14(1 pt 1):21–36.

[29] Gracely RH, Kwilosz DM. The descriptor differential scale: applying psychophysical principles to clinical pain assessment. PAIN 1988;35: 279–88.

[30] Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn 2008;27: 466–74.

[31] Han BS, Kim SH, Kim OL, Cho SH, Kim YH, Jang SH. Recovery of corticospinal tract with diffuse axonal injury: a diffusion tensor image study. NeuroRehabilitation 2007;22:151–5.

[32] Hulst HE, Steenwijk MD, Versteeg A, Pouwels PJ, Vrenken H, Uitdehaag BM, Polman CH, Geurts JJ, Barkhof F. Cognitive impairment in MS: impact of white matter integrity, gray matter volume, and lesions. Neurology 2013;80:1025–32.

[33] Ji L, Zhu D, Xiao C, Shi J. Tract based spatial statistics in multiple system atrophy: a comparison between clinical subtypes. Parkinsonism Relat Disord 2014;20:1050–5.

[34] Jovicich J, Marizzoni M, Bosch B, Bartres-Faz D, Arnold J, Benninghoff J, Wiltfang J, Roccatagliata L, Picco A, Nobili F, Blin O, Bombois S, Lopes R, Bordet R, Chanoine V, Ranjeva JP, Didic M, Gros-Dagnac H, Payoux P, Zoccatelli G, Alessandrini F, Beltramello A, Bargallo N, Ferretti A, Caulo M, Aiello M, Ragucci M, Soricelli A, Salvadori N, Tarducci R, Floridi P, Tsolaki M, Constantinidis M, Drevelegas A, Rossini PM, Marra C, Otto J, Reiss-Zimmermann M, Hoffmann KT, Galluzzi S, Frisoni GB, PharmaCog C. Multisite longitudinal reliability of tract-based spatial statistics in diffusion tensor imaging of healthy elderly subjects. Neuroimage 2014;101:390–403.

[35] Kairys AE, Schmidt-Wilcke T, Puiu T, Ichesco E, Labus JS, Martucci K, Farmer MA, Ness TJ, Deutsch G, Mayer EA, Mackey S, Apkarian AV, Maravilla K, Clauw DJ, Harris RE. Increased brain gray matter in the primary somatosensory cortex is associated with increased pain and mood disturbance in interstitial cystitis/painful bladder syndrome patients. J Urol 2015;193:131–7.

[36] Kilpatrick LA, Kutch JJ, Tillisch K, Naliboff BD, Labus JS, Jiang Z, Farmer MA, Apkarian AV, Mackey S, Martucci KT, Clauw DJ, Harris RE, Deutsch G, Ness TJ, Yang CC, Maravilla K, Mullins C, Mayer EA. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. J Urol 2014;192:947–55.

[37] Kutch JJ, Yani MS, Asavasopon S, Kirages DJ, Rana M, Cosand L, Labus JS, Kilpatrick LA, Ashe-McNalley C, Farmer MA, Johnson KA, Ness TJ, Deutsch G, Harris RE, Apkarian AV, Clauw DJ, Mackey SC, Mullins C, Mayer EA. Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: a MAPP: research network neuroimaging study. Neuroimage Clin 2015;8:493–502.

[38] Landis JR, Williams DA, Lucia MS, Clauw DJ, Naliboff BD, Robinson NA, van Bokhoven A, Sutcliffe S, Schaeffer AJ, Rodriguez LV, Mayer EA, Lai HH, Krieger JN, Kreder KJ, Afari N, Andriole GL, Bradley CS, Griffith JW, Klumpp DJ, Hong BA, Lutgendorf SK, Buchwald D, Yang CC, Mackey S, Pontari MA, Hanno P, Kusek JW, Mullins C, Clemens JQ, Group MRNS. The MAPP research network: design, patient characterization and operations. BMC Urol 2014;14:58.

[39] McKenzie IA, Ohayon D, Li H, de Faria JP, Emery B, Tohyama K, Richardson WD. Motor skill learning requires active central myelination. Science 2014;346:318–22.

[40] Melzack R. The short-form McGill pain questionnaire. PAIN 1987;30: 191–7.

[41] Moayedi M, Weissman-Fogel I, Salomons TV, Crawley AP, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. White matter brain and trigeminal nerve abnormalities in temporomandibular disorder. PAIN 2012;153:1467–77.

[42] Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci 2012;13:859–66.

[43] Mogil JS, Richards SP, O'Toole LA, Helms ML, Mitchell SR, Kest B, Belknap JK. Identification of a sex-specific quantitative trait locus mediating nonopioid stress-induced analgesia in female mice. J Neurosci 1997;17:7995–8002.

[44] Muller A, Mulhall JP. Sexual dysfunction in the patient with prostatitis. Curr Urol Rep 2006;7:307–12.

[45] Naliboff BD, Berman S, Suyenobu B, Labus JS, Chang L, Stains J, Mandelkern MA, Mayer EA. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. Gastroenterology 2006;131:352–65.

[46] Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 1937;60: 389–443.

[47] Phillips O, Squitieri F, Sanchez-Castaneda C, Elifani F, Griguoli A, Maglione V, Caltagirone C, Sabatini U, Di Paola M. The corticospinal tract in Huntington's disease. Cereb Cortex 2015;25:2670–82.

[48] Scheck SM, Boyd RN, Rose SE. New insights into the pathology of white matter tracts in cerebral palsy from diffusion magnetic resonance imaging: a systematic review. Dev Med Child Neurol 2012;54:684–96.

[49] Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. Radiology 2002;222:212–18.

[50] Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. Nat Neurosci 2009;12:1370–1.

[51] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487–505.

[52] Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479–89.

[53] Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed) 1986;292:344.

[54] Sorge RE, LaCroix-Fralish ML, Tuttle AH, Sotocinal SG, Austin JS, Ritchie J, Chanda ML, Graham AC, Topham L, Beggs S, Salter MW, Mogil JS. Spinal cord Toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice. J Neurosci 2011;31:15450–4.

[55] Strigo IA, Duncan GH, Boivin M, Bushnell MC. Differentiation of visceral and cutaneous pain in the human brain. J Neurophysiol 2003;89: 3294–303.

[56] Szabo N, Kincses ZT, Pardutz A, Toth E, Szok D, Csete G, Vecsei L. White matter disintegration in cluster headache. J Headache Pain 2013; 14:64.

[57] Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, Price DD. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. PAIN 2003;103:99–110.

[58] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.

[59] Williams DA, Schilling S. Advances in the assessment of fibromyalgia. Rheum Dis Clin North Am 2009;35:339–57.

[60] Yeo SS, Jang SH, Son SM. The different maturation of the corticospinal tract and corticoreticular pathway in normal brain development: diffusion tensor imaging study. Front Hum Neurosci 2014;8:573.

[61] Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain 2010;133(pt 5):1352–67.

[62] Zielinski BA, Gennatas ED, Zhou J, Seeley WW. Network-level structural covariance in the developing brain. Proc Natl Acad Sci U S A 2010;107: 18191–6.