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White matter microstructure predicts measures of clinical symptoms in chronic back pain patients

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ABSTRACT

Chronic back pain (CBP) has extensive clinical and social implications for its sufferers and is a major source of disability. Chronic pain has previously been shown to have central neural factors underpinning it, including the loss of white matter (WM), however traditional methods of analyzing WM microstructure have produced mixed and unclear results. To better understand these factors, we assessed the WM microstructure of 50 patients and 40 healthy controls (HC) using diffusion-weighted imaging. The data were analyzed using fixel-based analysis (FBA), a higher-order diffusion modelling technique applied to CBP for the first time here. Subjects also answered questionnaires relating to pain, disability, catastrophizing, and mood disorders, to establish the relationship between fixelwise metrics and clinical symptoms. FBA determined that, compared to HC, CBP patients had: 1) lower fibre density (FD) in several tracts, specifically the right anterior and bilateral superior thalamic radiations, right spinothalamic tract, right middle cerebellar peduncle, and the body and splenium of corpus callosum; 2) higher FD in the genu of corpus callosum; and 3) lower FDC – a combined fibre density and cross-section measure – in the bilateral spinothalamic tracts and right anterior thalamic radiation. Exploratory correlations showed strong negative relationships between fixelwise metrics and clinical questionnaire scores, especially pain catastrophizing. These results have important implications for the intake and processing of sensory data in CBP that warrant further investigation.

1. Introduction

Chronic pain (CP) is a major clinical and social problem worldwide: an estimated one in five Canadians suffer from CP (Reitsma et al., 2011; Schopflocher et al., 2011), with chronic back pain (CBP) being the most commonly reported disorder (Schopflocher et al., 2011). Most CP sufferers report that their pain has prevented them from performing at least some activities of daily living (Reitsma et al., 2011), while a number of studies have shown relationships between CP and secondary mood disorders, especially depression (Agüera-Ortiz et al., 2011; Gerrits et al., 2015; Gerrits et al., 2014; Sheng et al., 2017). The pathology of CBP is generally viewed primarily through the lens of peripheral causes (Freiwald et al., 2021), and as such is often treated directly at the site of peripheral pain, for example using electrical stimulation (Gilmore et al., 2020), heat therapy (Freiwald et al., 2021), or non-steroidal anti-inflammatory drugs (NSAIDs; Enthoven et al., 2016).

While some of these peripherally-targeted treatments do show moderate efficacy, this conception of CBP misses the growing body of evidence from neuroimaging showing functional and structural plastic changes in the brain alongside CP development, irrespective of any tissue damage or insult (Henry et al., 2011; Kuner and Flor, 2017). For example, functional studies in CP patients have shown evidence of reorganization in the primary somatosensory cortex that increases with disease duration (Flor, 2003; Flor et al., 1997). There is also evidence of altered descending pain modulation facilitating nociception in CP patients (Seifert et al., 2009). Meanwhile, it has also been demonstrated in a small sample that successful surgical intervention can reverse CBP-related functional and structural changes (Seminowicz et al., 2011).

We are particularly interested in analyzing white matter (WM) microstructure because of its relationship with neuropathology: for example, dysfunctional glial activation has been documented in CBP patients (Loggia et al., 2015), resulting in a telltale neuroinflammatory signature (Grachev et al., 2000; Torrado-Carvajal et al., 2021). This neuroinflammation, in turn, would result in increased neuronal death and reduced neuronal regeneration (Mutso et al., 2012; Rao et al., 2012), and thus a corresponding loss of WM. Many studies have

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examined WM microstructure in CBP patients using diffusion tensor imaging (DTI) with mixed results. One notable study (Mansour et al., 2013) compared DTI metrics in subacute back pain patients who recovered versus those who developed CBP and found powerful evidence of weakened WM microstructure in persisting pain patients across numerous regions. However, several others found few or no differences, which were generally isolated to one or two regions of the brain if they existed at all (Buckalew et al., 2010; Čeko et al., 2015; Li et al., 2021a).

This inconsistency may arise in part from flaws inherent to DTI analysis. In principle, FA may be combined with additional metrics based on fluid movement along or perpendicular to the primary eigenvector of the tensor to contextualize the change in anisotropy (Song et al., 2002). However, DTI interpretation remains complicated for several reasons. First, multiple nerve bundle properties can contribute to anisotropy, including myelination, fibre packing, and membrane integrity (Beaulieu, 2002). Second, because of this, different clinical mechanisms may produce similar anisotropy and diffusivity outcomes, limiting the ability to draw physiological conclusions (Wheeler-Kingshott and Cercignani, 2009). Third, DTI metrics cannot distinguish damaged axons from intact fibres running in multiple directions (Jones et al., 2013). Given that most voxels are likely to contain crossing WM fibres (Jeurissen et al., 2013), this in turn is likely to produce misleading findings (Grazioplene et al., 2018).

These issues sparked the development of alternative analyses, including fixel-based analysis (FBA), where *fixels* are calculated to describe one or more fibre populations within each voxel (Raffelt et al., 2015). These fixels, importantly, may have distinct orientations from one another despite sharing a voxel, allowing the analysis of crossing or interacting fibres. Because of this utility, FBA has become increasingly popular in recent years for studying a wide variety of neurological and neuropsychological phenomena (reviewed in Dhollander et al., 2021). Indeed, it has proven robust to the effect of inflammation and glial dysfunction as severe as that observed in HIV^+ brains, whereas DTI has not (Finkelstein et al., 2021). Despite this, to our knowledge, it has not yet been used to study CBP specifically, however it has been applied more broadly to chronic musculoskeletal pains in general (Bishop et al., 2018) and to neuropathic pain secondary to spinal cord injury (SCI; Black et al., 2022). We have recently reported that FBA can provide novel insights regarding the role of structural pathways in pain modulation in healthy individuals (Aristi et al., 2022b) and in the development of unexplained, injury-induced headaches (Aristi et al., 2022a).

Thus, the present study was undertaken with the aim of describing differences in WM microstructure between CBP patients and healthy controls using the FBA framework. Additionally, because of the relationships between CP, disability, and neuropsychiatric symptoms, we sought to determine whether these fixelwise measures predicted patient characteristics such as pain intensity, pain disability, pain catastrophizing, and mood disorders. We hypothesized that we would see weakening of the WM microstructure in the brains of the CBP patients along tracts related to pain processing, and that these findings would in turn correlate with clinical manifestations of CBP.

2. Material and methods

These data were collected as part of a larger study on biomarkers in chronic back pain (clinicaltrials.gov RCT #NCT02991625), some aspects of which have previously been reported (Lim et al., 2020; Wang et al., 2022). The experimental protocol was approved by the Nova Scotia Health Authority (NSHA) Research Ethics Board. All subjects reported to the Biomedical Translational Imaging Centre (BIOTIC) at the Veterans' Memorial Building of the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. There, they provided written, informed consent, during which time they were informed that they were permitted to withdraw from the study at any point for any reason.

2.1. Subjects

2.1.1. Recruitment and Inclusion/Exclusion criteria

All subjects, healthy or patient, were required to be 18–75 years of age; right-handed; comfortable completing questionnaires and tasks with English-language instruction; and able to get onto an MRI table with minimal support. Subjects were excluded for having a history of any cardiac, respiratory, or nervous disorder that could prevent entry into the MRI chamber (*e.g.*, claustrophobia); contraindications to safe MRI participation (*e.g.*, embedded metal in their bodies); or sensory loss, including vision loss beyond the scope of corrective lenses. Subjects could be removed post-enrolment due to self-reported substance use; unstable or erratic pain readings; or the development of MRI contraindications (*e.g.*, pregnancy).

Healthy control subjects (HC; N = 44) answered advertisements in the community near Dalhousie University and the Victoria General Hospital complex in Halifax. In addition to the above criteria, potential healthy controls were also excluded if they demonstrated acute or chronic pain.

Chronic back pain patients (CBP; N = 61) were also recruited through advertising, as well as the Pain Management Unit of the Victoria General Hospital and other clinical centres in the community in accordance with provincial regulations. Besides the general inclusion criteria, CBP patients also required low back pain for six or more months and an average of at least 4/10 clinical pain on the Brief Pain Inventory Scale (Cleeland, 1989) in the two weeks prior to enrolment.

2.1.2. Clinical parameters

After consenting, subjects provided demographic information and answered a series of questionnaires related to their health, pain, disability, and mood. All subjects answered the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995), the Beck Depression Inventory-II (BDI; Beck et al., 1996), and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). Chronic back pain patients additionally answered the McGill Pain Questionnaire short form (MPQ; Melzack, 1987), the Oswestry Disability Index (Fairbank et al.), and the Neuropathic Pain Scale (NPS; Galer and Jensen, 1997). They also reported their clinical back pain diagnoses, if known, and a list of active medications and past treatments. After answering these questionnaires, subjects underwent a series of MRI scans, described below.

2.2. Imaging procedures

2.2.1. Acquisition

Images were acquired using a 3 T MRI scanner (Discovery MR750, GE Healthcare, Waukesha, WI) with a 32-channel head coil (MR Instruments, Inc.; Minneapolis, MN, USA). T_1-weighted images were collected for anatomical reference (voxel size: 1x1x1 mm; resolution: 184x224x224 voxels; echo time: 1.9 ms; repetition time: 4.4 ms; inversion time: 450 ms; flip angle: 9°), followed by the diffusion-weighted images (DWI). Single-shell data were acquired at $b = 1000$ s/mm^2 in 60 directions, with seven interleaved volumes at $b = 0$ s/mm^2 (voxel size: 2x2x2 mm; resolution: 108x108x77 voxels; echo time: 66 ms; repetition time: 8 s; flip angle: 90°), followed by eight reverse-phase images, also at b = 0 s/mm^2, to allow distortion correction.

2.2.2. Preprocessing

The T_1 anatomical image was preprocessed predominantly using the FreeSurfer (Fischl, 2012) autorecon1 sequence, which includes motion correction, intensity normalization, and Talairach transformation. A mask was then generated for stripping the skull away from the image, leaving only brain; this mask was reoriented to match the original scan then used to crop it. The skull-stripped image was retained for registration purposes.

The diffusion pre-processing pipeline followed the procedure outlined by the developers of MRTrix (Dhollander et al., 2021), and

includes elements from FSL (Jenkinson et al., 2012) and ANTS (Avants et al., 2011). First, the raw data files were denoised (Veraart et al., 2016), and ringing artifacts were removed (Kellner et al., 2016). The $b = 0$ slices were then extracted to allow the removal of susceptibility-induced distortions and eddy currents (Andersson et al., 2003), with outliers replaced using a Gaussian process (Andersson et al., 2016). The undistorted data then underwent field inhomogeneity correction using ANTS before being intensity normalized.

Next, white matter response functions were estimated per subject (Tournier et al., 2013a), then averaged to produce a global mean response. After this, the diffusion images were upsampled from the raw 2x2x2 mm voxels to 1.3x1.3x1.3 mm voxels, to allow better registration and template-building (Raffelt et al., 2012b).At this point, the WM fibre orientation density (FOD) values are calculated using single-shell, single-tissue constrained spherical deconvolution (SSST-CSD) (Tournier et al., 2013b).

2.2.3. Fixel-Based analysis

Using these normalized FOD files, a population-level FOD template can be calculated, to which all individual subject FOD files are then registered (Raffelt et al., 2012a; Raffelt et al., 2011). This template also allows us to create the WM analysis mask, which contains the areas in which the apparent fibre density (FD) – the amplitude of the FOD, representing the amount of axonal content per voxel (Raffelt et al., 2012b) – has at least a certain minimum value, to reduce superfluous comparisons (Raffelt et al., 2015); for this experiment, the mask was generated at an FD threshold of 0.75.

The individual FOD images were then warped to the group template using the previously calculated registration (Raffelt et al., 2011) and segmented to allow the estimation of subject fixels (Smith et al., 2013). These subject fixels were then reoriented onto the group template (Raffelt et al., 2012a) and assigned to template fixels (Raffelt et al., 2015) so that individual fixelwise values could be computed for FD and fibre cross-section (FC), a metric representing the thickness of WM tracts (Raffelt et al., 2017). The FD and FC values were then multiplied to create the combined metric FDC, representing the full, measurable changes in axonal matter within a tract (Raffelt et al., 2017). Additionally, FC was converted to logarithmic space (*i.e.*, log(FC)) for ease of analysis (Dhollander et al., 2021).

Groupwise, whole-brain FBA comparisons were performed using connectivity-based fixel enhancement (CFE; Raffelt et al., 2015). To enable this, it was necessary to first calculate fixel-to-fixel connectivity using whole-brain probabilistic tractography: 20 million streamlines were generated, then filtered down to 2 million using spherical-deconvolution informed filtering of tractograms (SIFT) to reduce biases (Smith et al., 2013). Then, the fixel-to-fixel connectivity matrix was calculated, and the metrics of interest – FD, log(FC), and FDC – were smoothed based on said connectivity (Raffelt et al., 2015).

2.3. Statistics

Statistical comparisons of FD, log(FC), and FDC between groups were performed using CFE across all WM fixels within the previously-described brain masks, *i.e.*, for all fixels with at least a certain population-level FD value. The procedure is fundamentally similar to traditional voxel-based analysis: a design matrix containing group designations and group-normalized regressors of no interest (in this case, age and sex), and a contrast matrix specifying the comparisons of interest (in this case, HC > CBP and CBP > HC), were used to create a generalized linear model, which is tested using 5000 permutations. Significant differences were corrected for family-wise error (FWE) and reported at the $p < 0.05$ level. Regions highlighted by these comparisons were then separated based on the tracts they represented using the MRViewer region of interest (ROI) editor. Mean values of the relevant parameter (*i.e.*, FD, log(FC), or FDC) were extracted for each subject from the significant fixels within each tract.

Questionnaire responses and demographic data were compared groupwise between HC and CBP subjects. Categorical variables (*i.e.*, sex and ethnicity) were compared using Fisher's exact test. Comparisons for continuous variables varied depending on the normality of the distribution: this was established using the Shapiro-Wilk test, with non-normality assumed at $p < 0.05$. Based on this, groupwise comparisons of age were performed using Student's *t*-test, while all others were performed using the Mann-Whitney *U* test, because the distributions were found to be non-normal for at least the HC participants. To determine whether FBA produced clinically predictive data, Spearman partial correlations were computed with 5000-iteration permutation testing, controlling for age, head motion, and – for CBP subjects only – medication usage based on the Medication Quantification Scale III (MQS; Harden et al., 2005). All groupwise comparisons and correlations were regarded as significant at $p < 0.05$.

While age was used as a regressor of no interest in several of our statistical tests, we ran additional, separate groupwise comparisons using a subset of sex- and age-matched HC and CBP subjects to ensure that it was not a meaningful factor. These results are detailed in Supplement #1 and described where appropriate. Additionally, while SSST-CSD has been used for many years in fixel-based analysis, it has more recently been determined that multi-tissue analysis is possible not only with multiple shells, but indeed even with a single shell; therefore, a secondary analysis has been performed using single-shell, three-tissue CSD (SS3T-CSD) (Dhollander and Connelly, 2016) using a fork of MRTrix called MRTrix3Tissue (http://3tissue.github.io/). The changes to the analysis procedure and all findings are reported in Supplement #2, with select results again described where appropriate.

3. Results

3.1. Subjects

From the initial pool, subjects were removed due to withdrawal (HC: 1, CBP: 6), medical considerations (HC: 2, CBP: 2), difficulty with instructions (CBP: 1), undisclosed contraindications for MRI (CBP: 1), or technical difficulties (HC: 1, CBP: 1). This left us with diffusion scans for 40 healthy controls and 50 CBP patients. Two of those CBP patients completed all scans but did not provide any questionnaire data.

Table 1
Comparison of demographic characteristics and questionnaire scores for healthy controls and chronic back pain patients.

Measure	HC (N = 40) Mean ± SEM	95 % CI	CBP (N = 50) Mean ± SEM	95 % CI	P
Age (yrs)	31.9 ± 1.6	(28.7, 35.1)	43.1 ± 1.9	(39.3, 47.0)	< **0.001**
Pain Catastrophizing Scale:					
Rumination	5.0 ± 0.6	(3.8, 6.2)	7.5 ± 0.6	(6.3, 8.6)	**0.004**
Magnification	2.8 ± 0.4	(2.0, 3.5)	4.4 ± 0.4	(3.7, 5.2)	**0.002**
Helplessness	4.7 ± 0.7	(3.2, 6.2)	8.9 ± 0.7	(7.4, 10.3)	< **0.001**
Total	12.5 ± 1.6	(9.3, 15.7)	20.8 ± 1.5	(17.8, 23.7)	< **0.001**
Beck Depression Inventory	6.1 ± 0.9	(4.3, 7.8)	15.1 ± 1.5	(12.1, 18.1)	< **0.001**
State-Trait Anxiety Inventory:					
State Anxiety	32.7 ± 1.5	(29.7, 35.7)	41.2 ± 1.5	(38.2, 44.2)	< **0.001**
Trait Anxiety	36.6 ± 1.7	(33.2, 40.1)	43.6 ± 1.7	(40.1, 47.1)	**0.007**
Sex (% female)	22/40 (55.0 %)		36/50 (72.0 %)		0.122
Ethnicity (% White)	29/40 (72.5 %)		39/48 (81.3 %)		0.444

CI: confidence interval; SEM: Standard error of the mean.

Subject demographics are summarized in Table 1. While CBP patients were significantly older, the sex and ethnicity distributions were not significantly different. The three questionnaires filled out by both groups – PCS, BDI, and STAI – all showed significantly higher response totals, indicating greater dysfunction, in CBP patients compared to HC. The CBP-specific questionnaire scores and clinical parameters appear in Table 2, while the medication classifications used to determine the MQS values are summarized in Table 3. Clinical back pain diagnoses appear in Table 4; note that most subjects (62 %) did not report a specific, physical diagnosis.

The age- and sex-matched cohort contained 24 subjects for each group; their specific characteristics are described in Supplement #1, Supplementary Tables A1–A4, which correspond in content to Tables 1–4, respectively. Age and sex were, by design, not significantly different; no other changes in groupwise significance were observed in the demographics nor questionnaire scores.

3.2. FBA results

Fixel-based analysis found several large areas where FD significantly differed between HC and CBP subjects, and a smaller number where FDC was significantly different. No significant differences were observed in log(FC).

Several regions were found to have greater FD in HC compared to CBP patients (Fig. 1). These significant regions include a large part of the body and splenium of the corpus callosum (CC); left and right superior thalamic radiations; right spinothalamic tract and anterior thalamic radiation; and a small area of white matter in the right middle cerebellar peduncle. Conversely, only one region – the genu of the CC – was found to have greater FD in CBP patients than HCs (Fig. 2). Three regions – the left and right spinothalamic tracts and the right anterior thalamic radiation – had greater FDC values in the HC group versus CBP (Fig. 3), while the reverse comparison found no significances.

These differences remained intact when the extracted mean FD values were compared only between subjects in the age- and sex-matched cohort (Supplementary Fig. A1). However, when the extracted mean FDC values were compared for the age- and sex-matched cohort, FDC in the bilateral spinothalamic tracts ceased to be significantly different between groups, while FDC in the right anterior thalamic radiation remained significant (Supplementary Fig. A2).

When repeating this analysis using SS3T-CSD, far fewer and smaller segments of white matter were found to have significantly different fixelwise metrics. Only two small chunks of the right body of the corpus callosum – one further anterior and one further posterior – and a piece of the right spinothalamic tract were found to have significantly greater FD in HC compared to CBP (Supplementary Fig. B1). Meanwhile, instead of the genu of the corpus callosum, the left unciate fasciculus was found to have greater FD in CBP compared to HC (Supplementary Fig. B2). However, unlike the SSST-CSD analysis, SS3T-CSD found a substantial portion of the posterior forceps had significantly lower FC in HC compared to CBP (Supplementary Fig.B3).

Table 2
Summary statistics for clinical parameters and questionnaires exclusive to chronic back pain patients.

Questionnaire	CBP Patient Score Mean ± SEM	95 % CI
Time Since Diagnosis (yrs)	7.5 ± 1.1	(5.2, 9.7)
Treatment Duration (yrs)	6.9 ± 0.9	(5.0, 8.8)
McGill Pain Questionnaire:		
Affective	4.8 ± 0.4	(3.9, 5.7)
Sensory	15.2 ± 0.9	(13.4, 17.0)
Total	20.0 ± 1.2	(17.6, 22.5)
VAS Pain Rating	50.0 ± 3.4	(43.1, 57.0)
Medication Quantification Scale	6.7 ± 0.9	(4.8, 8.6)
Neuropathic Pain Scale	45.1 ± 1.9	(41.2, 48.9)
Oswestry Disability Index	16.1 ± 1.0	(14.0, 18.1)

CI: confidence interval; SEM: standard error of the mean; VAS: Visual-Analogue Scale.

Table 3
Medication usage by type in chronic back pain patients. Categories are based on those used to calculate the Medication Quantification Scale. Note that any medications not used by any subject were omitted.

Medication	Number of Patients (%)
Acetaminophen	11 (22 %)
Analgesics (miscellaneous)	2 (4 %)
Antidepressants:	
SSRIs	8 (16 %)
Tricyclic/tetracyclic	1 (2 %)
Other	9 (18 %)
Anticonvulsants:	
GABAergic	3 (6 %)
Sodium-channel blockers	1 (2 %)
Benzodiazepines	3 (6 %)
Cyclooxygenase-2 inhibitors	4 (8 %)
Muscle relaxants (non-dependency producing)	6 (12 %)
NSAIDs	8 (16 %)
Opioids:	
Schedule II	13 (26 %)
Schedule III	1 (2 %)

NSAIDs: non-steroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitors.

Table 4
Clinical back pain diagnoses reported by CBP subjects.

Diagnosis	Number of Patients (%)
Unspecified Back Pain	16 (32 %)
Fibromyalgia	4 (8 %)
Arthritis	3 (6 %)
Nerve Compression	3 (6 %)
Disc Herniation	3 (6 %)
Radiculopathy	3 (6 %)
Degenerative Disc Disease	2 (4 %)
Ehlers Danlos Syndrome	1 (2 %)
Bulging Disc	1 (2 %)
Sacroiliac Joint Dysfunction	1 (2 %)
Pars Defect/Spondylosis	1 (2 %)
Diagnosis Not Reported	15 (30 %)

Note: Values do not add up to 100%, due to some subjects reporting multiple diagnoses.

3.3. Predicting clinical characteristics

The correlations between questionnaire scores and FD or FDC values extracted from significant regions returned many significant results, most of which involved PCS subscale or total scores. These associations, summarized in Fig. 4, indicate a putative connection between PCS and altered microstructure. Note that for CBP patients, FDC in the bilateral spinothalamic tracts predicted three of the four PCS scores, and that FD in CC body/splenium predicted two of the four PCS scores; in controls, FD in right superior thalamic radiation strongly predicted two of the four PCS scores. Furthermore, except for FD in the right middle cerebellar peduncle in CBP patients, all associations between PCS and FD/FDC were negative.

Negative correlations were also observed between FD in both ROIs of the CC and MPQ sensory subscale and total scores (Fig. 5A and 5B). FD in the genu also showed a negative relationship with Oswestry Disability Index, BDI, and STAI trait anxiety scores (Fig. 5C). Additionally, negative correlations were observed between time since CBP diagnosis and FD in the bilateral superior thalamic radiations, as well as FDC in the right anterior thalamic radiation (Fig. 6).

Fixelwise metrics in areas identified using SS3T-CSD also predicted a small number of clinical outcome measures (Supplementary Fig. B8). FD in the right spinothalamic tract correlated positively with neuropathic

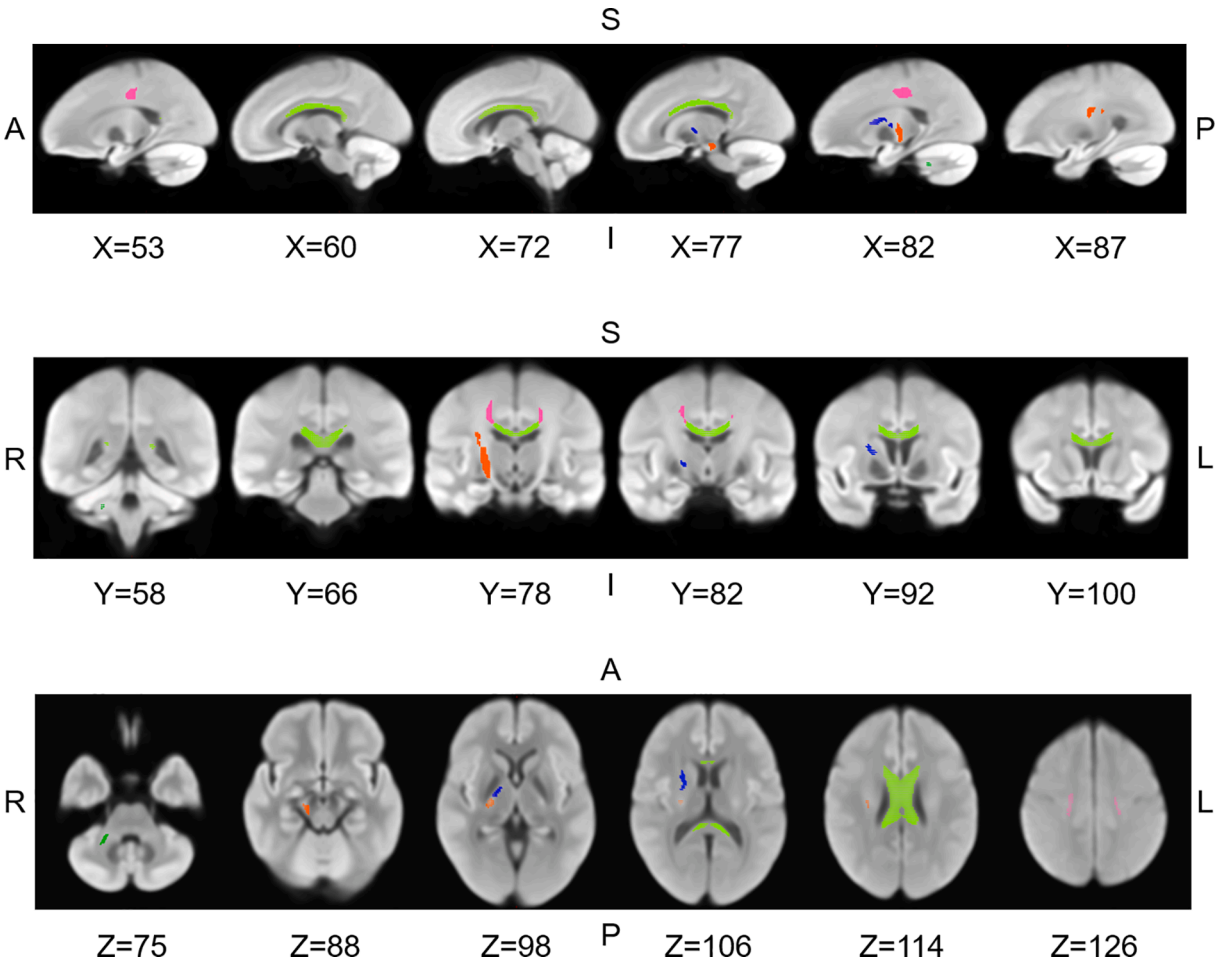

Fig. 1. Sagittal (top), coronal (middle), and axial (bottom) sections of the white matter FOD template for the study population. Overlaid are fixels where FD is significantly greater in healthy controls than chronic back pain patients ($P < 0.05$), colour-coded by tract: right middle cerebellar peduncle (green), corpus callosum (yellow), right anterior thalamic radiation (blue), right spinothalamic tract (orange), left and right superior thalamic radiations (pink).

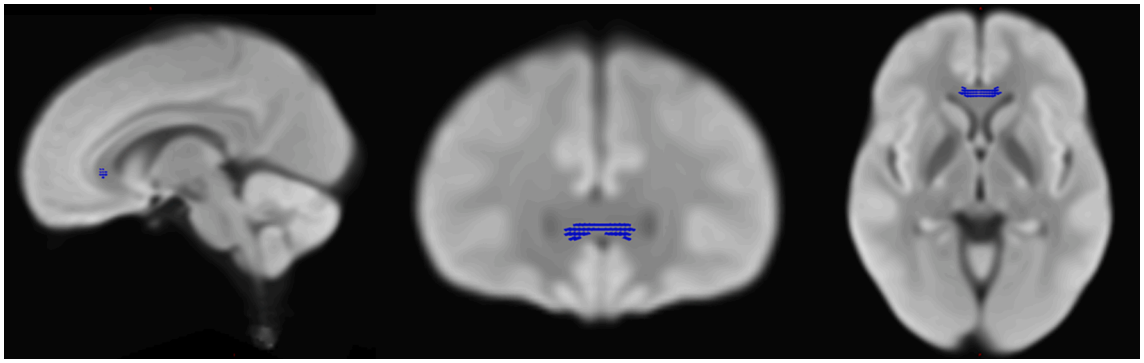

Fig. 2. Slices of the white matter FOD template, highlighting the fixels in which FD is significantly greater in CBP patients compared to healthy controls ($P < 0.05$), which occur exclusively in the genu of the corpus callosum. Top left: sagittal section ($x = 72$); top right: coronal section ($y = 111$); bottom left: axial section ($z = 96$).

pain, while FD in the left unciate fasciculus negatively correlated with both PCS rumination and PCS total.

4. Discussion

The objective of this study was to use FBA to better understand the differences in WM microstructure between CBP patients and healthy controls, and how these differences relate to clinical outcome measures. Significant weakening in WM microstructure was observed in many tracts, especially those involving the thalamus and the corpus callosum. Fixelwise measures in several regions were found to correlate with pain catastrophizing and, to a lesser degree, time since CBP diagnosis, while FD in the CC was related to pain, disability, and mood scores in CBP patients. Our results imply a major and clinically relevant loss of WM microstructure in tracts important for perception and cognition with CP.

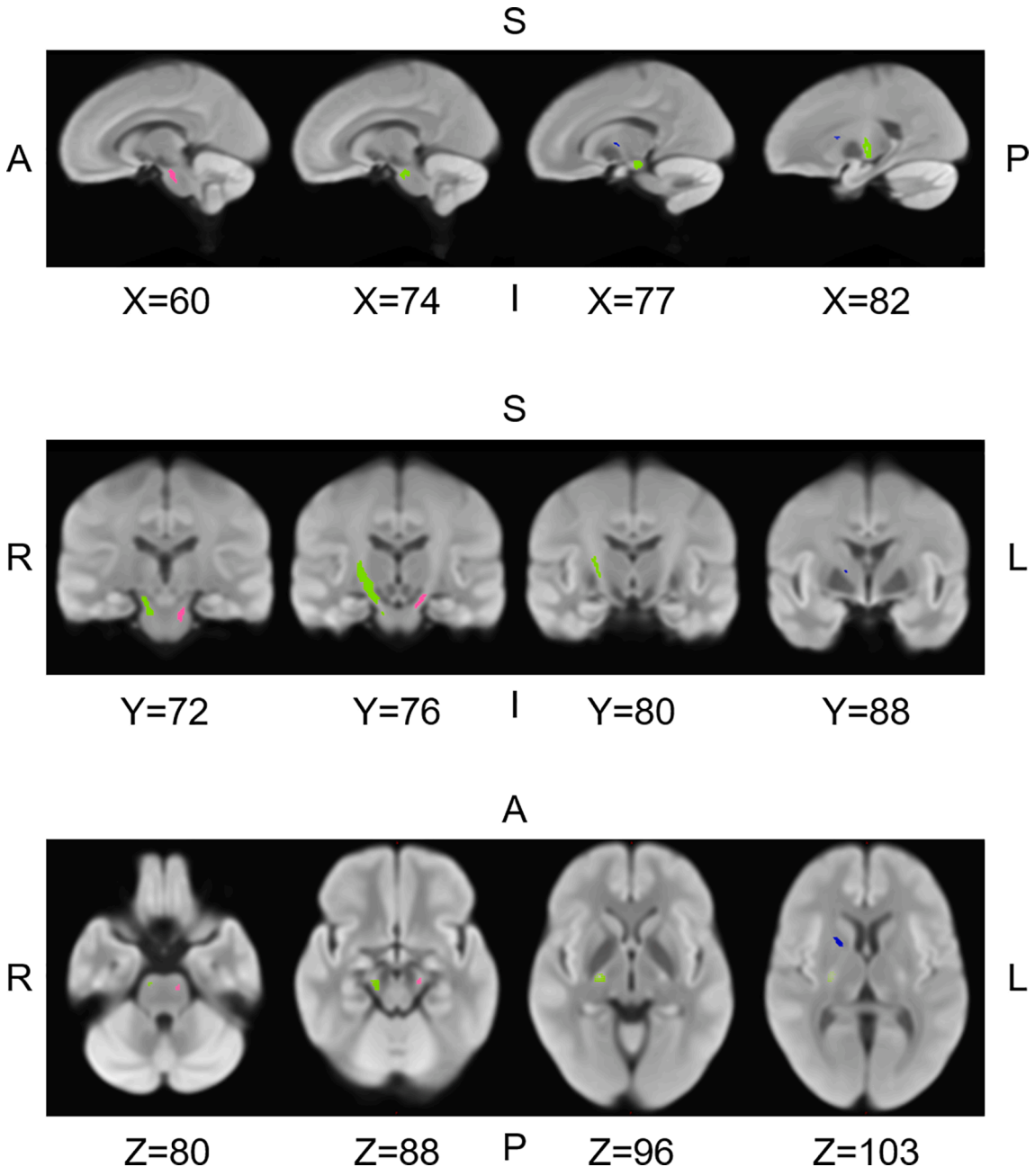

Fig. 3. Sagittal (top), coronal (middle), and axial (bottom) sections of the white matter FOD template for the study population. Overlaid are fixels where FDC is significantly greater in healthy controls than chronic back pain patients ($P < 0.05$), colour-coded by tract: left spinothalamic tract (pink), right spinothalamic tract (yellow), and right anterior thalamic radiation (blue).

4.1. Interpreting FBA results

While the interpretation of fixelwise measures requires some degree of nuance, it can broadly be said that FD, as a measure of axonal matter per voxel, represents microscopic changes in WM tract structure, while FC, as a measure of tract thickness, represents macroscopic changes; FDC, therefore, represents the overall changes in axonal matter throughout the tract (Dhollander et al., 2021). Based on this, the most probable interpretation of our SSST-CSD results is that axonal thickness and/or count is lower in CBP, even as overall tract volume remains the same. A recent study showed elevated markers of neuroinflammation in the thalamus of CBP patients (Torrado-Carvajal et al., 2021). Inflammation has long been known to cause increased cell death and decreased neuroregeneration in animal models of pain (Mutso et al., 2012; Rao et al., 2012); the loss of cellular matter implied here would agree with this model of CP.

Previous papers investigating pain produced some similar results to ours, and some differences. Bishop et al. (2018) examined chronic musculoskeletal pain generally and found reduced FD in the right inferior fronto-occipital fasciculus and splenium of pain patients versus controls; we, too, found reduced FD in the splenium of CBP patients, but no significant changes in inferior fronto-occipital fasciculus (Fig. 1). Black et al. (2022) investigated potential sites for deep brain stimulation for the relief of neuropathic pain in in SCI patients with neuropathic pain and found greater FC in the splenium, affecting connectivity to several regions of the pain network, including the prefrontal cortex, the cingulate, and the thalamus. We did not observe any changes in FC using SSST-CSD, instead finding a decreased FD in the splenium. These two findings are potentially compatible if one again takes a neuroinflammatory view of chronic pain: swelling in a tract may result in an

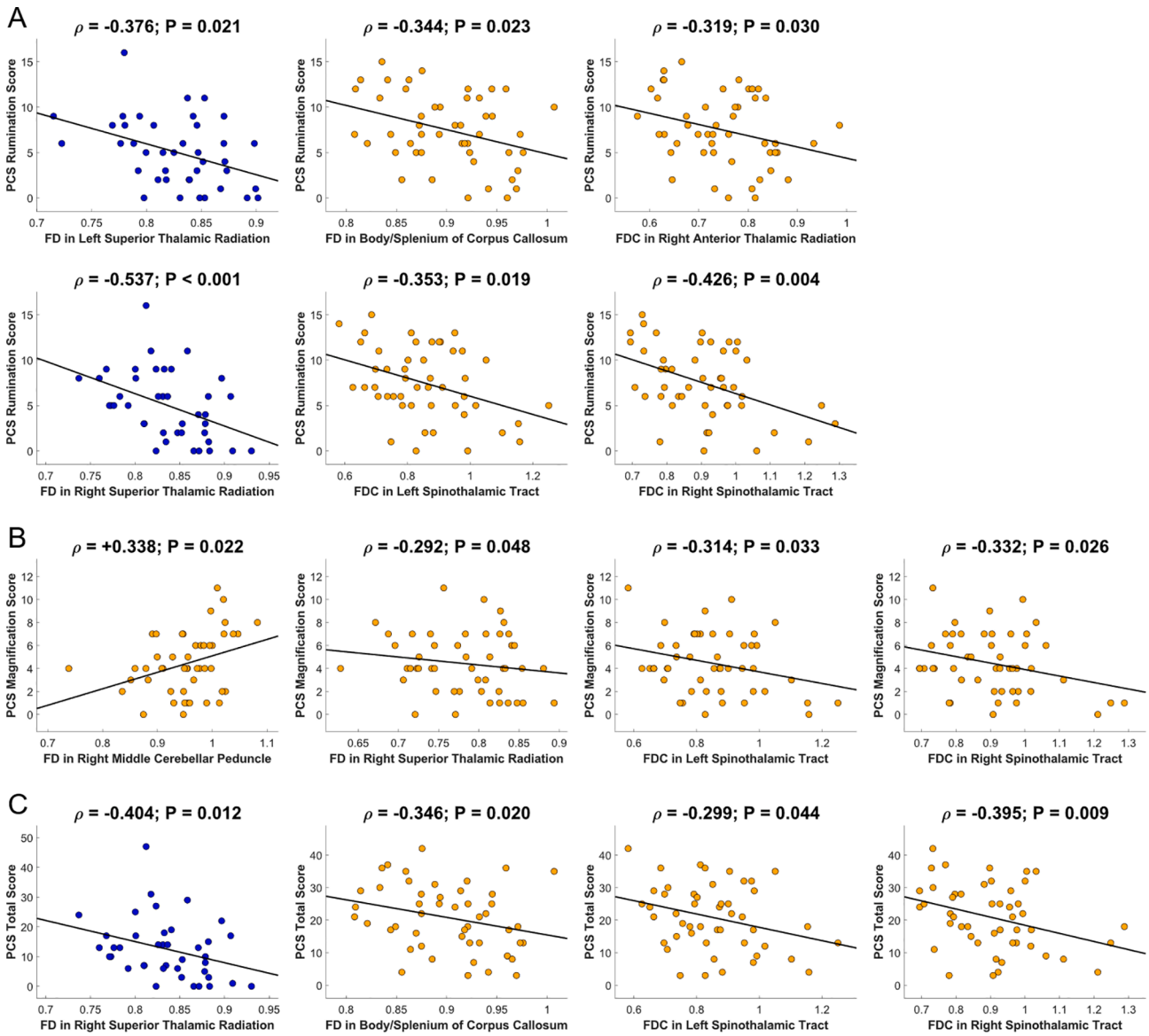

Fig. 4. Significant correlations between PCS subscale or total score (vertical axis) and the FD or FDC values from the tracts highlighted by the fixelwise comparisons between HC and CBP (horizontal axis). Blue points represent correlations for HC subjects; orange points represent correlations for CBP subjects. A) Significant correlations with PCS rumination score. B) Significant correlations between PCS magnification score. C) Significant correlations with PCS total score. All significances derived from permutation-tested partial Spearman correlations controlled for age, relative head motion, and (CBP subjects only) medication usage.

increased FC alongside a decrease in FD due to the decreased concentration of axonal matter per unit volume (Dhollander et al., 2021). However, using SS3T-CSD, we did find significantly increased FC in the posterior forceps, which Black et al. (2022) observed as an extension of their splenium finding at the $p < 0.10$ level, suggesting a general compatibility in our findings.

4.2. Tract-Specific outcomes

Given the vital role of the thalamus in the human pain system (Groh et al., 2018; Yen and Lu, 2013), it is unsurprising that our analysis highlighted several related tracts. Damage to the spinothalamic tract, which carries noxious stimuli and other sensory information to the thalamus, has been found to be crucial to the development of CP in SCI patients (Cruz-Almeida et al., 2012; Defrin et al., 2001). Additionally, studies in neuropathic pain syndromes (Maier et al., 2010) and SCI (Cruz-Almeida et al., 2012) have observed reduced sensory sensitivity alongside CP. Our findings also show a prominent relationship between weakened spinothalamic tract WM and pain catastrophizing; thus, it is plausible that reduced spinothalamic tract WM also contributes to the development or maintenance of CBP.I.

The significant regions of the superior thalamic radiations terminate in the posterior cingulate (PCC), a key node within the default-mode network (DMN), a system of connected regions that mediate self-referential thinking and rumination (Mak et al., 2017). While the anterior cingulate is more commonly implicated in pain processing (Tsuda et al., 2017; Xiao et al., 2021), some studies have specifically targeted PCC. A weaker connection between PCC and the rest of the DMN has been found to predict a stronger pain experience in both CP patients and HCs (Alshelh et al., 2018; Loggia et al., 2013). The thalamus and PCC are well-integrated, with reciprocal connectivity and shared metabolic failure in disease states (Leech and Sharp, 2014); a weakened connection between them has been observed in migraineurs without aura versus HCs (Wang et al., 2016).

The anterior thalamic radiation connects through the anterior limb of the internal capsule to the prefrontal cortex (PFC), particularly the

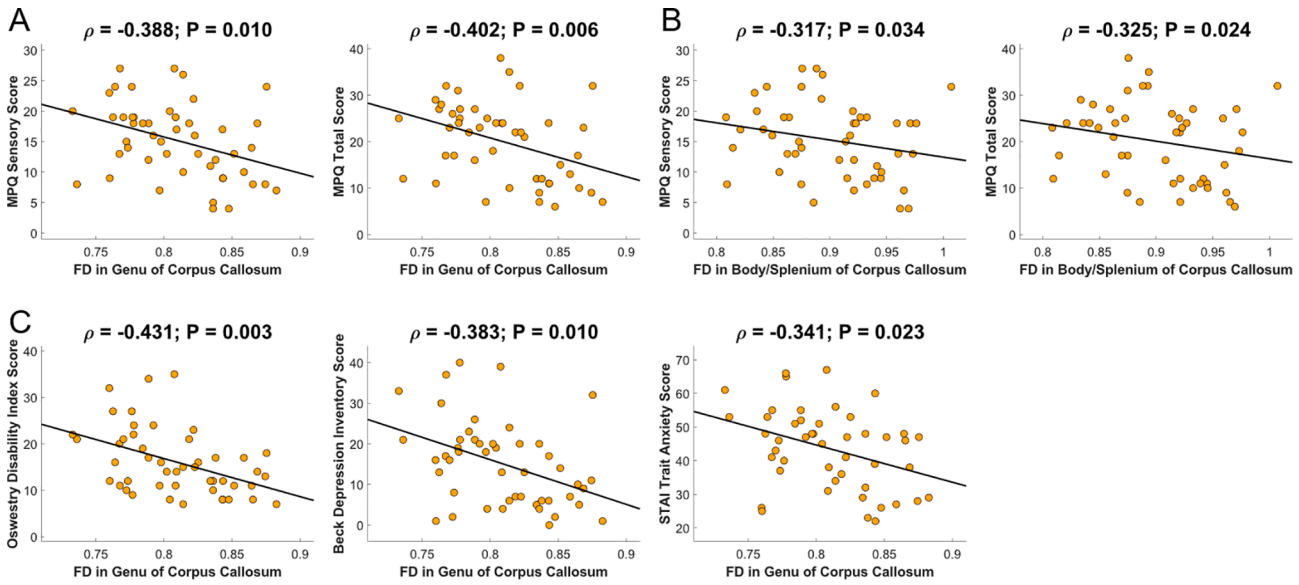

Fig. 5. Significant correlations between FD in the corpus callosum and non-PCS clinical questionnaire results in CBP subjects. A) Correlations between FD in the genu and MPQ sensory and total scores. B) Correlations between FD in the body/splenium and MPQ sensory and total scores. C) Correlations between FD in the genu and the Oswestry Disability Index, Beck Depression Inventory, and STAI trait anxiety scores. All significances derived from permutation-tested partial Spearman correlations controlled for age, relative head motion, and medication usage.

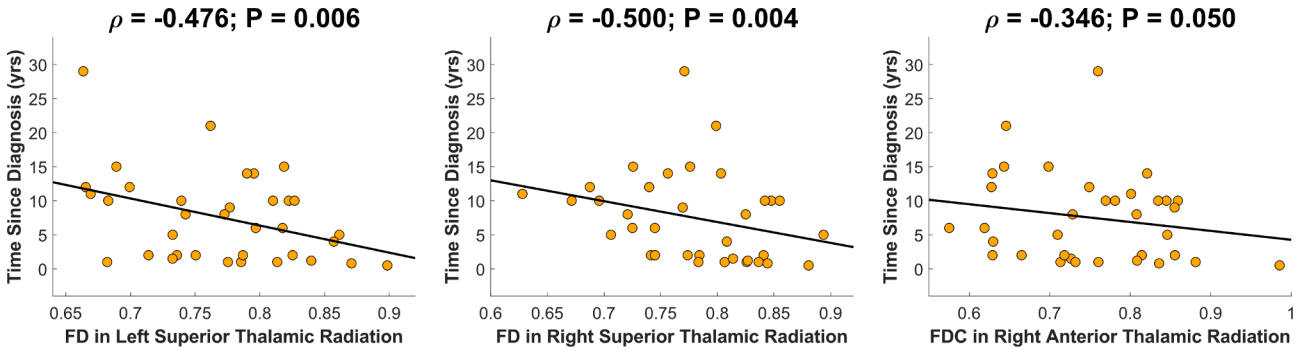

Fig. 6. Significant correlations between fixelwise metrics and time since CBP diagnosis. From left to right: FD in left superior thalamic radiation; FD in right superior thalamic radiation; FDC in right anterior thalamic radiation. All significances derived from permutation-tested partial Spearman correlations controlled for age, relative head motion, and medication usage.

dorsolateral prefrontal cortex (dlPFC). There is ample evidence tying dlPFC to pain processing (Seminowicz and Moayedi, 2017), with both structural and functional analyses demonstrating roles in pain inhibition and control (Brighina et al., 2011; Brighina et al., 2004; Moens et al., 2012; Sampson et al., 2006; Wang et al., 2016). Additionally, markers of reduced neuronal viability have been observed using magnetic resonance spectroscopy in PFC generally (Siddall et al., 2006) and dlPFC specifically (Grachev et al., 2000) in CBP. Studies of both acute and chronic pain have found the connection between dlPFC and the thalamus to be inhibitory in nature (Bräscher et al., 2016; Grachev et al., 2000; Li et al., 2021a; Lorenz et al., 2003); thus, it follows that this connection would be weaker in CBP.

The corpus callosum is a major WM throughfare connecting the hemispheres of the brain. DTI has typically shown decreased FA in various parts of the CC with chronic pain, which varied by study (Buckalew et al., 2010; Geha et al., 2008; Im et al., 2021; Kim et al., 2014; Li et al., 2021b; Moayedi et al., 2012); in migraine, by contrast, multiple studies found lower FA in all regions of CC (Li et al., 2011; Yu et al., 2013). Some of these FA changes have been correlated with clinical measures: decreased FA in the CC body of fibromyalgia patients (Kim et al., 2014) and the genu of trigeminal neuralgia patients (Li et al., 2021b) were both negatively associated with pain intensity, mirroring our results (Fig. 5).

All of the regions highlighted above were found to be significant using SSST-CSD, with some remaining significant – and most of the others showing at least a trend toward significance – using SS3T-CSD. However, there are some clear discrepancies, most notably the regions that have stronger WM microstructure in CBP patients. The SSST-CSD analysis found that only the genu of the CC was stronger in CBP patients compared to controls. While this may appear incongruous, the bilateral PFCs are connected directly by the genu (Baynes, 2002). Thus, a stronger genu may be a compensatory neuroplastic mechanism to mitigate other CP-related changes. However, this finding was not corroborated using SS3T-CSD; instead, it was found that a tiny portion of the left uncinate fasciculus – a tract in the anterior frontal lobe found to be affected in a number of disorders (Briggs et al., 2018) – was significantly stronger in CBP patients compared to healthy controls. This, too, is contrary to previous findings: Bishop et al. (2018) observed weakening in the right uncinate fasciculus in chronic musculoskeletal pain patients and tied this weakening to dysfunctional emotional processing and anxiety, which would potentially contribute to pain catastrophizing.

A brief word should also be said about the posterior forceps, aka the forceps major, which was found to have significantly greater FC in CBP patients compared to healthy controls using SS3T-CSD. While there is an

extensive literature connecting the splenium – through which the posterior forceps passes – to chronic pain, very few papers have found the same for the posterior forceps. Indeed, the trend toward significantly greater FC in CBP observed by Black et al. (2022) was the only result we could find based on either DTI or FBA. Furthermore, there is no obvious functional connection between posterior forceps and chronic pain, either: it connects the occipital lobes bilaterally, facilitating binocular vision and visual processing (Baker et al., 2018). The functional and mechanical significance of this finding and its relationship, if any, to results in the splenium are thus unclear, but do warrant further investigation.

4.3. Clinical questionnaire outcomes

The most prominent correlations between fixelwise metrics and questionnaire results involved PCS subscale scores. Pain catastrophizing refers to excessive negative thinking regarding pain and has been found to exacerbate chronic pain, including CBP (Wertli et al., 2014). Previous studies of CP and catastrophizing have found that PCS rumination (Sullivan et al., 2002) or helplessness (Craner et al., 2016; Sullivan et al., 2005) best predict pain and disability. Pain catastrophizing is also connected to depression and anxiety (Arteta et al., 2016; Linton et al., 2011; Scott et al., 2016; Wood et al., 2016), which in turn are strongly associated with CP (Agüera-Ortiz et al., 2011; Gerrits et al., 2015; Gerrits et al., 2014; Sheng et al., 2017). Unsurprisingly, catastrophizing, depression, and anxiety are all significantly greater in CBP compared to HC (Table 1), however only genu in CBP patients was negatively associated with depression or anxiety scores (Fig. 5C), again suggesting a possible compensatory effect at work.

The relationship between WM microstructure and pain catastrophizing has seldom been investigated, though one recent DTI study in complex regional pain syndrome (CRPS) found weakening in the PFC of patients versus controls, which in turn correlated with pain catastrophizing (Im et al., 2021). Functional studies, meanwhile, have found that connectivity between medial PFC or PCC and the rest of the DMN were related to pain catastrophizing and rumination (Kucyi et al., 2014; Lee et al., 2018). Our study found that the integrity of several WM tracts predicted PCS in both CBP and HC subject groups (Fig. 4); furthermore, the integrity of the same tract often predicted multiple PCS subscale scores. This is particularly true of the spinothalamic tract, suggesting a role for sensory feedback specifically in the affective dimension of CBP.

A key part of understanding CP is to understand structural changes that occur in the brain as CP progresses. There is evidence that neuroinflammatory responses to glial abnormalities are time-dependent (Loggia et al., 2015), which would in turn have consequences for WM microstructure over time. Multiple studies (Li et al., 2021b; Li et al., 2011) have found that FA in the genu of the CC decreases with CP duration. Our results did not show this, and indeed it would seem contrary to our supposition that genu WM strengthening is an adaptive response to CBP, however it should be noted that neither of those studies were in CBP specifically. Their findings may represent disorder-specific developments, the long-term decline of a positive adaptation, or differences due to analytical technique: the fact that the genu finding does not replicate between the SSST-CSD and SS3T-CSD analyses points toward the latter. Most other studies have found no correlation between FA in the rest of the CC and CP duration (Kim et al., 2014; Li et al., 2021b; Li et al., 2011), with the exception of Buckalew et al. (2010), who observed strong correlations between FA in both the splenium and the right centrum semiovale and CBP duration. At least one study (Im et al., 2021) reported no relationship between FA in any part of the brain and CP duration. Our own findings – an association between CBP duration and FD in the bilateral superior thalamic radiations and FDC in the right anterior thalamic radiation – are seemingly unique in this context and thus warrant a more targeted follow-up.

4.4. Limitations and future directions

While FBA more clearly illustrates WM microstructure changes in the brain than DTI, limitations remain. Importantly, there are few studies that have explicitly replicated FBA findings and/or directly related them to gold-standard histological data (Dhollander et al., 2021). Additionally, our scans used clinical diffusion imaging parameters, including a *b*-value of 1000 s/mm^2. While these parameters produce a good signal-to-noise ratio for clinical and DTI analyses, higher *b*-values provide several advantages for FBA. Greater *b*-values improve the angular precision of the FOD data (Tournier et al., 2007) by mitigating extracellular signals (Raffelt et al., 2012b): the optimal *b*-value for CSD is, in fact, closer to 3000 s/mm^2 (Tournier et al., 2013a). This extracellular signal captured at lower *b*-values weakens the interpretability of FD specifically by providing superfluous information can be erroneously included in FD calculations (Dhollander et al., 2021). Despite this, crossing fibres can still be resolved at the $b = 1000$ s/mm^2 level (Tournier et al., 2007; Tournier et al., 2008), and studies have successfully used values in the range of $b = 1000$ s/mm^2 for FBA (Bishop et al., 2018; Sang et al., 2022), especially with the aid of multi-tissue CSD techniques (Choy et al., 2020; Grazioplene et al., 2018; Luo et al., 2021; Verhelst et al., 2019). Multi-tissue CSD is particularly valuable for mitigating the problems introduced by extracellular signal – because it can be categorized with the CSF- and GM-like data rather than the WM – and has been shown to have good test–retest reliability (Newman et al., 2020).

On a related note, we must also state that the use of SS3T-CSD did produce fewer significant results than SSST-CSD (Supplement #2), however many of the regions observed to be significant using SSST-CSD did show trends toward significance using SS3T-CSD (*i.e.*, $p < 0.10$; see Supplementary Fig. B5). This makes interpretation of the SS3T-CSD findings less clear and suggests a need for more data. A validation set is currently being collected to both verify the present results and – in combination with the present data – better determine whether some of these regions are truly significantly different using a greater sample size.

The CBP dataset does contain some heterogeneity in both medication usage and back pain diagnoses. We controlled for medication usage by using MQS as a nuisance covariate. Meanwhile, separating subjects based on their diagnosis type produced no differences in clinical or fixelwise metrics save one (Supplement #3 and Supplementary Table C1), consistent with the general understanding that CBP symptoms are not necessarily related to tissue damage (Henry et al., 2011; Kuner and Flor, 2017). Therefore, this variability was not a significant factor in the main outcomes. Finally, while age was significantly different between HC and CBP groups, all comparisons were age-controlled, while separate analyses on the age- and sex-matched cohort produced few differences from the main outcomes.

The results of this study provide numerous opportunities for follow-up, the most obvious being to apply FBA to other, specific CP populations like migraine, fibromyalgia, or CRPS, none of which have been studied with FBA to date. Similarly, FBA could provide new insights on the chronification of pain (Mansour et al., 2013; Vachon-Presseau et al., 2016). Finally, both the present findings and the literature suggest that weakened spinothalamic tract WM begets continued pain generation and sensory desensitization. Previous work with this dataset has investigated top-down and bottom-up sensory processing in healthy controls (Lim et al., 2020); repeating this analysis for CBP patients could better inform this supposition.

5. Conclusions

This study investigated differences in white matter structure between healthy controls and CBP patients using fixel-based analysis. Our findings of substantially weaker WM microstructure in tracts connecting to the thalamus of CBP patients – especially the spinothalamic tract – correlated with measures of pain catastrophizing. In the corpus callosum, WM fibre density was found to be lower in the body and

splenium, but higher in the genu, in CBP patients. Based on the regions connected, and the associations of CC fibre density with mood, pain, and disability, we propose that the thickening of the genu serves as a compensatory response to the losses elsewhere. As the first study to examine CBP using FBA, we have demonstrated that this is a potentially valuable technique in identifying future avenues for larger-scale research.

CRediT authorship contribution statement

Jason W. Robertson: Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Guillermo Aristi:** Methodology, Software, Investigation, Data curation, Writing – review & editing. **Javeria A. Hashmi:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103309.

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