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CNS changes in interstitial cystitis/painful bladder syndrome

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Abstract

Brain white matter (axonal) abnormalities associated with interstitial cystitis/bladder pain syndrome in women suggest that neuropathological brain alterations exist in, and might contribute to, chronic pelvic pain syndromes. Advancing our knowledge of central neuropathic mechanisms, which might initiate and/or maintain these syndromes, will help target pain-related neuroplasticity and identify future treatments.

Accurate diagnosis and treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) has evaded and frustrated physicians for over 50 years, creating a substantial quality of life burden for patients affected by this disorder. Despite vast improvements in diagnostic tools for, and treatments of, other pelvic floor disorders, such as incontinence, BPH and prolapse, very little in the way of biomarkers or targeted therapy has been developed for chronic pelvic pain. Over the past two decades, clinicians and researchers have started to investigate beyond the affected pelvic organs, in order to find other potential treatments for this complex syndrome. Farmer and colleagues¹ have shared their findings regarding the brains of patients with IC/BPS in a recent article published in the *Journal of Urology*, to help us better understand some new and different manifestations of this disorder. The authors investigated white matter fractional anisotropy (an indicator of nerve fibre density, axonal density and myelination of white matter) using diffusion tensor imaging (DTI) to characterize the brain white matter microstructure of women with IC/BPS as a part of the Multidisciplinary Approach to the Study of Chronic pelvic pain (MAPP) Research Network.¹ DTI is an MRI technique that uses fractional anisotropy to provide structural information on the integrity of tissues with intrinsic fibrous material such as brain white matter axons, cardiac muscle, and even prostate, by evaluating the restricted diffusion of water molecules along these tracts.² Fractional anisotropy with DTI is used to model directional water flow along axons, in order to assess white matter integrity.

In Farmer and colleagues' study, data from 22 women with IC/BPS from three centres in the USA were compared to 32 healthy age-matched women. Investigators used a 3 Tesla MRI scanner to obtain T1-weighted images and DTI to compare the brain white matter regions of

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Competing interests

The authors declare no competing interests.

interest in two well-characterized patient groups. By pooling fractional anisotropy data from normal and interstitial cystitis/PBS patients, a white matter template or ‘skeleton’ was created. In addition, the team performed a rigorous statistical correction to minimize the centre variability in their data, and demonstrated for the first time that women with IC/BPS have white matter alterations that include a decrease in integrity in several regions of interest: the right anterior thalamic radiation, which connects parts of thalamic nuclei to the frontal cortex; the left forceps major, connecting bilateral occipital lobes; and the right inferior longitudinal fasciculus, which connects the temporal and occipital lobes. Furthermore, these neurological abnormalities seemed to be closely related to the bothersome symptoms that affect every aspect of the patients’ quality of life such as pain, mood, daily function and urinary dysfunction. Interestingly, the authors also identified increased integrity in multiple regions of interest including left and right longitudinal fasciculi. These investigators were able to successfully characterize a tightly screened, highly homogenous group of women with IC/BPS and describe alterations to the microstructure of their brain white matter axonal tracts.

Chronic pain has long been suspected to create structural changes in the CNS and technical advances in brain imaging have enabled investigators to evaluate this hypothesis. In 2011 Farmer *et al.*³ reported their first experience in evaluating brain grey and white matter in 19 male patients with chronic prostatitis and chronic pelvic pain syndrome using resting fMRI and fractional anisotropy, and showed distinct anatomical and regional areas of abnormality.³

Preliminary data has also suggested limited recovery of the abnormal pathways in regions of insula and prefrontal cortex in 16 male patients with chronic lower back pain 6 months after treatment.⁴ Another interesting study, by Mansour and co-workers,⁵ used the brain white matter integrity data obtained in 24 patients with single subacute back pain and monitored them for 1 year in order to predict the transition of these patients to chronic lower back pain. 12 patients in this group had resolution of their back pain and 12 evolved to develop persistent chronic lower back pain. The investigators were able to show structural and anatomical differences in the functional connectivity and white matter integrity of the patients who transitioned to chronic pain compared to the recovered group, suggesting the ability of CNS neuroimaging to phenotype patients who are predisposed to developing chronic pain.⁵

Despite this diligent attempt by Farmer *et al.*¹ to correct the noise, variability still exists in the analysis of neuroimaging data. The authors reported a decrease in white matter integrity of the right inferior longitudinal fasciculus and an increase in the left inferior longitudinal fasciculus. We wonder if this is a compensatory mechanism of the brain attempting to restore its overall integrity. Furthermore, considerable individual axonal variability exists amongst individuals, based on their prior motor learning experiences—such as right versus left handedness and ability to play a musical instrument—creating distinct axonal tracts. With these inherent intrinsic variabilities from brain to brain, neuroimaging data has to be interpreted with caution, especially when small sample sizes are used. Alternatively, comparing each patient to their own imaging over time will be a valuable tool to decrease

this variability and add to causal or coincidental implications for brain structural alteration in chronic pain syndromes.

In conclusion, the current study by Farmer *et al.*¹ is a key landmark study, helping to establish the neuropathic pathways involved in female patients with IC/BPS, encouraging future research to characterize and phenotype patients with IC/BPS with regard to their diagnoses, progression and treatment modulation. We hope the MAPP Investigators will maintain their research by continuing to monitor and evaluate the patient in this study during their treatment, in order to further characterize and phenotype patients with IC/BPS.

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FIGURE.