Increased Brain Gray Matter in the Primary Somatosensory Cortex is Associated with Increased Pain and Mood Disturbance in Patients with Interstitial Cystitis/Painful Bladder Syndrome

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Purpose: Interstitial cystitis is a highly prevalent pain condition estimated to affect 3% to 6% of women in the United States. Emerging data suggest there are central neurobiological components to the etiology of this disease. We report the first brain structural imaging findings from the MAPP network with data on more than 300 participants.

Materials and Methods: We used voxel based morphometry to determine whether human patients with chronic interstitial cystitis display changes in brain morphology compared to healthy controls. A total of 33 female patients with interstitial cystitis without comorbidities and 33 age and gender matched controls taken from the larger sample underwent structural magnetic resonance imaging at 5 MAPP sites across the United States.

Results: Compared to controls, females with interstitial cystitis displayed significant increased gray matter volume in several regions of the brain including the right primary somatosensory cortex, the superior parietal lobule bilaterally and the right supplementary motor area. Gray matter volume in the right primary somatosensory cortex was associated with greater pain, mood (anxiety) and urological symptoms. We explored these correlations in a linear regression model, and found independent effects of these 3 measures on primary somatosensory cortex gray matter volume, namely clinical pain (McGill pain sensory total), a measure of urgency and anxiety (HADS).

Abbreviations and Acronyms

CSF = cerebrospinal fluid
DMN = default mode network
FWE = family wise error
GM = gray matter
HADS = Hospital Anxiety and Depression Scale
HC = healthy control
IC = interstitial cystitis
MAPP = Multidisciplinary Approach to Pelvic Pain
MRI = magnetic resonance imaging
S1 = primary somatosensory cortex
SMA = supplementary motor area
SPL = superior parietal lobule
SVC = small volume correction
SYM-Q = Symptom and Health Care Utilization Questionnaire
TIV = total intracranial volume
VBM = voxel based morphometry
WM = white matter

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Conclusions: These data support the notion that changes in somatosensory gray matter may have an important role in pain sensitivity as well as affective and sensory aspects of interstitial cystitis. Further studies are needed to confirm the generalizability of these findings to other pain conditions.

Key Words: cystitis, interstitial; pain; somatosensory cortex

Interstitial cystitis, also known as painful bladder syndrome, is a prevalent pain condition, estimated to affect 3% to 6% of women in the U.S.[1] Symptoms include urinary frequency, urgency and pelvic pain, with no pathognomonic clinical findings in these patients.[2] Originally considered a disease of the bladder,[3] it is now recognized that some patients have a systemic condition involving pain outside the bladder and comorbid symptoms.[2] With no general agreement about the pathophysiology, a wide variety of management options includes dietary, behavioral, pharmacological and surgical therapies.[4]

Chronic pain disorders are considered partially mediated by a centralized pathology (ie pain is augmented/maintained by alterations in central nervous system processing). Neuroimaging is increasingly used to assess alterations in brain shape and function in chronic pain conditions.[5–8] Voxel based morphometry, an imaging technique used to assess changes in brain anatomy, has been used previously in pelvic pain conditions.[9–12] Compared to healthy controls, patients with chronic pelvic pain have increased and decreased regional GM volume in specific brain areas involved in nociceptive processing. These changes were associated with self-report measures of clinical symptoms.[10,11] Analogous structural neuroimaging studies have not been published for IC/bladder pain syndrome.

We present data from a multisite neuroimaging study of female patients with IC originating from the MAPP network (www.mappnetwork.org). We examined the relationship between GM volume and clinical symptoms in women with noncomorbid IC compared to HCs. We hypothesized patients with IC would show GM alterations in brain regions previously found to be involved in chronic pain conditions, and that these changes would be associated with clinical measures.

METHODS

Anatomical Data Acquisition

Anatomical MRI data were acquired across 5 MAPP discovery sites. Each site used a whole body scanner with an 8-channel phased array head coil, as previously described.[13] High resolution T1 structural images were acquired for each subject using the acquisition protocol of 2,200 ms repetition time, 3.26 ms echo time, 1 mm slice thickness, 256 × 256 voxel matrices and 1 mm^3 voxel size.

Trans-MAPP neuroimaging data were collected, quality controlled and archived according to multisite imaging procedures developed by the MAPP Research Network, UCLA PAIN (Pain and Interoception Imaging Network) repository and UCLA Laboratory of Neuroimaging. Scanner compatible acquisition parameters were developed and all sites passed a qualification test. Initial scans were reviewed for quality control by the UCLA site. Recommendations and adjustments were made as necessary before patient enrollment.

Subjects

Subjects included 33 female patients with noncomorbid IC (mean age ± SD 39.5 ± 12 years, mean symptom duration 9.1 ± 9 years) and 33 age and gender matched healthy controls (mean age 39 ± 11.6 years). Subjects were selected from 225 women in the MAPP network database as of July 2012 (see supplementary Appendix, http://jurology.com/). Because our primary research focus was brain GM in patients with noncomorbid IC, we selected patients with pure IC without fibromyalgia, irritable bowel syndrome or chronic fatigue syndrome. Subjects were from the 5 discovery sites of NWU (Northwestern University) (2 patients with IC, 5 HCs), UCLA (6 IC, 9 HCs), U of M (University of Michigan) (10 IC, 7 HCs), UAB (University of Alabama at Birmingham) (6 IC, 7 HCs) and Stanford University (9 IC, 5 HCs). This study was approved by the institutional review board of each site.

Assessment of IC Symptoms (Collected Day of Scan)

Subject MRI sessions were conducted within 14 days of a baseline visit. Symptom measure data analyzed in this study were restricted to those obtained on the day of the scan, which included the SYM-Q, Concomitant Medications (supplementary table 1, http://jurology.com/), the Female Genitourinary Pain Index, PROMIS (Patient-reported Outcomes Information System) sleep disturbance scale (www.nihpromis.org), SF-MPQ (Short Form McGill Pain Questionnaire),[14] HADS,[15] Positive and Negative Affect Scale,[16] and Gracely Box Scales to measure pain and unpleasantness during the scan (supplementary table 2, http://jurology.com/).

Data Processing − Voxel Based Morphometry

T1-weighted structural images were segmented into WM, GM and CSF using the new segment function in SPM8, under MATLAB® 7.6. Resulting GM segments were then processed using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) toolbox.[17] DARTEL increases the accuracy of inter-subject alignment by modeling the shape of each participant's brain using millions of parameters (3 parameters per voxel).