Brain Functional and Anatomical Changes in Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Melissa A. Farmer, Mona L. Chanda, Elle L. Parks, Marwan N. Baliki,
A. Vania Apkarian,*,† and Anthony J. Schaeffer‡,§,‖

From the Departments of Physiology (MAF, MLC, ELP, MNB, AVA), Urology (AJS), Anesthesia (AVA) and Surgery (AVA), Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Purpose: Research into the pathophysiology of chronic prostatitis/chronic pelvic pain syndrome has primarily focused on markers of peripheral dysfunction. We present the first neuroimaging investigation to our knowledge to characterize brain function and anatomy in chronic prostatitis/chronic pelvic pain syndrome.

Materials and Methods: We collected data from 19 male patients with chronic prostatitis/chronic pelvic pain syndrome, and 16 healthy age and gender matched controls. Functional magnetic resonance imaging data were obtained from 14 patients with chronic prostatitis/chronic pelvic pain syndrome as they rated spontaneous pain inside the scanner. Group differences (16 patients per group) in gray matter total volume and regional density were evaluated using voxel-based morphometry, and white matter integrity was studied with diffusion tensor imaging to measure fractional anisotropy. Functional and anatomical imaging outcomes were correlated with the clinical characteristics of chronic prostatitis/chronic pelvic pain syndrome.

Results: Spontaneous pelvic pain was uniquely characterized by functional activation within the right anterior insula, which correlated with clinical pain intensity. No group differences were found in regional gray matter volume, yet density of gray matter in pain relevant regions (anterior insula and anterior cingulate cortices) positively correlated with pain intensity and extent of pain chronicity. Moreover the correlation between white matter anisotropy and neocortical gray matter volume was disrupted in chronic prostatitis/chronic pelvic pain syndrome.

Conclusions: We provide novel evidence that the pain of chronic prostatitis/chronic pelvic pain syndrome is associated with a chronic pelvic pain syndrome specific pattern of functional brain activation and brain anatomical reorganization. These findings necessitate further investigations into the role of central mechanisms in the initiation and maintenance of chronic prostatitis/chronic pelvic pain syndrome.

Key Words: magnetic resonance imaging, image cytometry, diffusion tensor imaging, cerebral cortex

Abbreviations and Acronyms

ACC = anterior cingulate cortex

ant INS = anterior insula

CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome

DTI = diffusion tensor imaging

FA = fractional anisotropy

fMRI = functional magnetic resonance imaging

INS = insula

MPQ = McGill Pain Questionnaire

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index

NPS = Neuropathic Pain Scale

QOL = quality of life

ROI = region of interest

VBM = voxel-based morphometry

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CHRONIC prostatitis/chronic pelvic pain syndrome is an enigmatic pain disorder characterized by persistent genitourinary discomfort and occurs in 5% to 10% of the male population.[1] Pain and concomitant urinary and sexual dysfunction lead to diminished QOL as well as impairments in primary intimate relationships.[2] The study of CP/CPPS is complicated by the heterogeneity of the disorder. Patients with CP/CPPS differ in presumed etiology, configuration of clinical symptoms, course of disease and pain characteristics. As a result, efforts to treat this condition are critically limited by our tentative knowledge of mechanisms.[2]

Known pathophysiological correlates of CP/CPPS include local inflammation, endocrine involvement, pelvic floor muscle irregularities and voiding dysfunction, yet nothing is known about the role of the brain in CP/CPPS pain. This is surprising given the long accepted view that chronic pain results from a combination of peripheral and central processes.[3] Brain activity associated with acute pain is well characterized,[4] yet mounting evidence indicates that different chronic pain conditions show distinct patterns of pain related brain activation,[5] suggesting that chronic pain produces long-term changes in how and where pain is processed by the brain. Recent brain imaging studies show unique functional and anatomical brain abnormalities in patients with varieties of musculoskeletal and neuropathic pain, including chronic low back pain, postherpetic neuralgia, complex regional pain syndrome and knee osteoarthritis.[5] However, it is unclear how CP/CPPS compares to other chronic pain, given that this condition can include spontaneous visceral and referred somatic pain characteristics (ie pelvic visceral and referred perineal pain), and unknown involvement of central alterations in pain processing (eg central sensitization). Consequently it is unknown how brain function and anatomy characterize persistent, spontaneous CP/CPPS pain.

We report the first functional and anatomical characterization of CP/CPPS using human noninvasive brain imaging technology. fMRI was used to indirectly measure brain neuronal activity related to spontaneous pelvic pain. Brain anatomy was examined through the evaluation of whole brain, and regional gray matter (where neuronal bodies are located) and white matter (location of axonal tracts) characteristics. In a limited group of patients with CP/CPPS we show unique brain activity in response to pelvic pain that differs from previous chronic pain populations studied, describe brain anatomy correlates with clinical parameters, and suggest CP/CPPS specific changes in brain structure and function.

MATERIALS AND METHODS

Subjects
We recruited 19 right-handed male patients with CP/CPPS (diagnosed by AJS) from the Northwestern University urology clinic, and 16 healthy gender and age matched control subjects. All patients with CP/CPPS had negative prostate cultures, an overall score of 15 or greater of 43 points on the NIH-CPSI[6] including 1 or more on the pain subscale of this index or current pain, symptoms of pelvic discomfort/pain for 3 or more months within the last 6 months, and they fulfilled condition specific inclusion and exclusion criteria.[7] Participants provided informed consent and were financially compensated. All procedures were approved by the Northwestern University institutional review board.

Experimental Design
Functional imaging data were collected from 14 patients with CP/CPPS with 2 spontaneous pain functional scans, T1-weighted imaging data were collected from 16 and DTI data were collected from 10. T1 and DTI data were also collected for matched controls. During the spontaneous pain scans patients were instructed to rate pelvic pain fluctuations (in the absence of an external stimulus) using a finger-span logging device.[8] Spontaneous pain was rated on a visual analog scale of 0 to 10 (0—no pain and 10—worst pain imaginable, fig. 1). A visual control task scan was also conducted and the visual feedback stimulus was matched to each patient's respective spontaneous pain rating output. Clinical parameters collected on the day of scanning included demographic information, pain intensity (0 to 10), duration, total scores from the MPQ, NPS[9] and NIH-CPSI, which included a NIH-CPSI total score (0 to 43), and subscores for pain (0 to 21), voiding (0 to 10) and QOL (0 to 12). Mood was assessed with the Beck Depression Inventory.

fMRI and Anatomical Data Acquisition
Functional and anatomical imaging data were acquired using a 3T Siemens Trio® whole-body scanner with echo planar imaging capability and a standard 8-channel head coil. The fMRI parameters were identical to those described by Baliki et al.[10] T1-weighted and DTI images were obtained using a protocol described in detail by Geha et al.[11]

Data Analysis
Analysis of fMRI. We used fMRI data collected from 14 patients with CP/CPPS to investigate brain regions activated for spontaneous pain, matched visual rating tasks, and contrasts between the 2 tasks using described methods.[8] Post hoc correlations of clinical parameters to regions of interest were conducted. ROIs were derived from the contrast of pain and visual tasks, and were located in right anterior insula and right secondary somatosensory
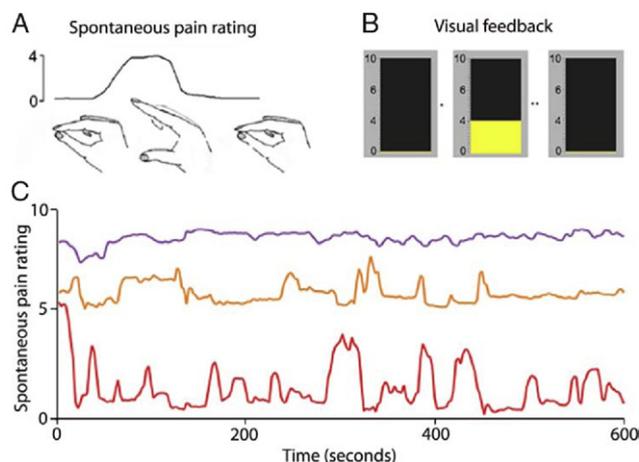
Figure 1. Spontaneous pain rating task in patients with CP/CPPS. *A*, patients used finger-span logging device to continuously rate fluctuations in spontaneous pelvic pain (in absence of external stimulus) on scale from 0 to 10 by opening and closing fingers. *B*, inside scanner patients received feedback of pain ratings in real time, presented as visual bar projected onto screen that fluctuated on scale from 0 to 10. *C*, examples of spontaneous pain ratings from 3 patients with CP/CPPS. Individual patients exhibited distinct overall pain magnitudes and varying levels of fluctuations around mean spontaneous pain. Ratings were used as explanatory variables in fMRI analyses to identify related brain activity.

cortex. Peak ROI activity (averaged for 27 voxels) was extracted from each subject and related to clinical parameters.

Analysis of global and regional anatomical differences. We investigated global and regional gray differences based on the T1-weighted anatomical images obtained from 16 patients with CP/CPPS and 16 matched controls using described methods.[11] Brain white matter properties were studied based on the DTI images obtained from 10 patients with CP/CPPS and 10 matched controls using described methods.

## RESULTS

Participant Characteristics
Men with CP/CPPS (mean age 36.94 years old) reported pelvic pain for an average of 3 years with a mean 4.5/10 current pain intensity. Global NIH-CPSI scores ranged from 19 to 35 (mean 28.56, SE 1.17) with an average pain subscore of 13.56 (SE 0.81). Participants reported pelvic (100%), penis tip (75%), perineal (66%) and testicle (58%) pain with no history of other chronic pain. Of the 16 men 7 were taking medication and none used tricyclics or gabapentinoids.

Brain Activity for Spontaneous Pain in CP/CPPS
Conscious subjective rating of spontaneous fluctuations of CP/CPPS pain during a period of 10 minutes resulted in the group averaged brain activity shown

in figure 2, *A*. The brain regions activated, their coordinates in standard space and magnitude of activity are shown in the table. In addition to the pain of CP/CPPS, this task required attention, motor control and evaluation of magnitudes. The visual control task contained all of these same cognitive demands without being related to CP/CPPS pain. Therefore, the activity for visual control identified brain areas activated in the task but not related to CP/CPPS (fig. 2, *A*). More importantly by contrasting activity between the pain task and visual task (spontaneous pain – visual), we pinpointed brain regions where activity was preferentially and, thus, more specifically, related to the perception of CP/CPPS pain. This result is shown in figure 2, *B*, and included ant INS and secondary somatosensory cortex. The opposite contrast (visual – spontaneous pain) revealed visual task related activity. Age and depression scores were used as covariates of no interest (eg confounding variables) in all functional analyses.

To determine the clinical relevance of these findings, average brain activity from regions preferentially involved in CP/CPPS pain were extracted and correlated with predetermined clinical variables. Ant INS activity was significantly positively correlated with self-reported spontaneous pelvic pain intensity ($r = 0.57$, $p < 0.05$; fig. 3, *A*), indicating that brain activity characterizing the spontaneous pain experienced by men with CP/CPPS was related to
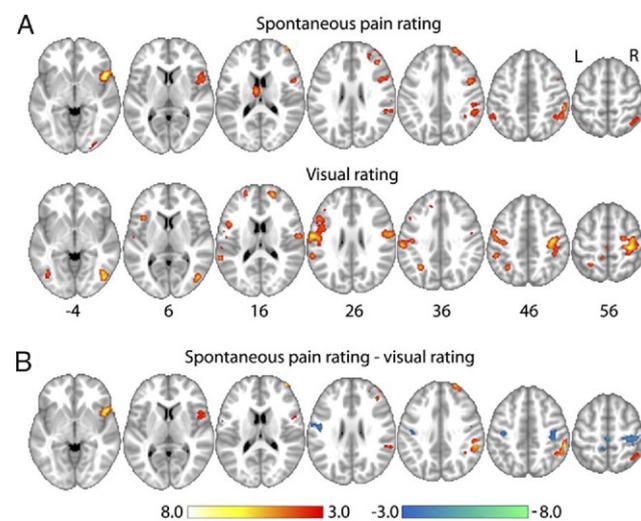
Figure 2. Group brain activity maps for spontaneous pain and visual rating tasks in CP/CPPS. *A*, group average brain activity for spontaneous pain rating task and for visual rating task. *B*, contrast between pain and visual tasks shows areas that were more specifically active during spontaneous pain of CP/CPPS (red-yellow), and included right anterior insula and parietal regions. Regions with higher activity during visual task (visual – pain) are shown as negative activity (blue-green).

Peak foci for activations for pain rating and visual rating, and their contrast

Brain Region (Brodmann area)	Pain Rating		Visual Rating		Pain − Visual	
	Coordinates x, y, z (mm)	Z Score	Coordinates x, y, z (mm)	Z Score	Coordinates x, y, z (mm)	Z Score
Rt ant INS	44, 14, −4	7.00	38, 30, 28	4.40	46, 12, −4	6.22
Rt DLPFC (9)	40, 36, 28	5.18			40, 36, 28	3.80
Rt VPC (6)	46, 6, 36	4.81				
Rt PPC (40)	52, −48, 48	4.72			50, −48, 48	4.33
Lt PPC (40)	−52, −48, 50	4.12	−30, −60, −2	5.81		
Lt TH	−6, −10, 16	5.28				
Rt M1 (4)			36, −30, 30	3.05		
Lt VPC (6)			−48, 8, 18	4.88		
Rt S1 (3)			36, −18, 44	5.19	36, −28, 58	−4.54
Lt S1 (3)			−34, 4, 48	3.56		
Lt MT (19)			−42, −68, −6	4.11		
Rt MT (19)			46, −72, −2	6.10		
Lt ant INS			−38, −20, 6	4.86		
Lt M1 (4)			−52, −4, 46	4.18	−38, −18, 46	−4.10
Rt frontal (10)			18, 56, 16	5.12		
Lt frontal (10)			−22, 60, 16	4.02		
Lt PreCu (5)			−8, −42, 60	4.37	−8, −44, 58	4.17

In contrast (pain − visual), positive Z scores indicated pain greater than visual, while negative Z scores indicated visual greater than pain contrasts.

  DLPFC, dorsolateral prefrontal cortex; M1, primary motor area; S1, primary somatosensory cortex; PPC, posterior parietal cortex; VPC, ventral premotor cortex; MT, mid temporal cortex; PreCu, precuneus; TH, thalamus.

the subjective intensity of their clinical pain. In addition to pain intensity, activity in the ant INS showed a significant positive correlation with the MPQ score (p <0.01) and a borderline correlation with the NPS score (p = 0.06; fig. 3, *B*).

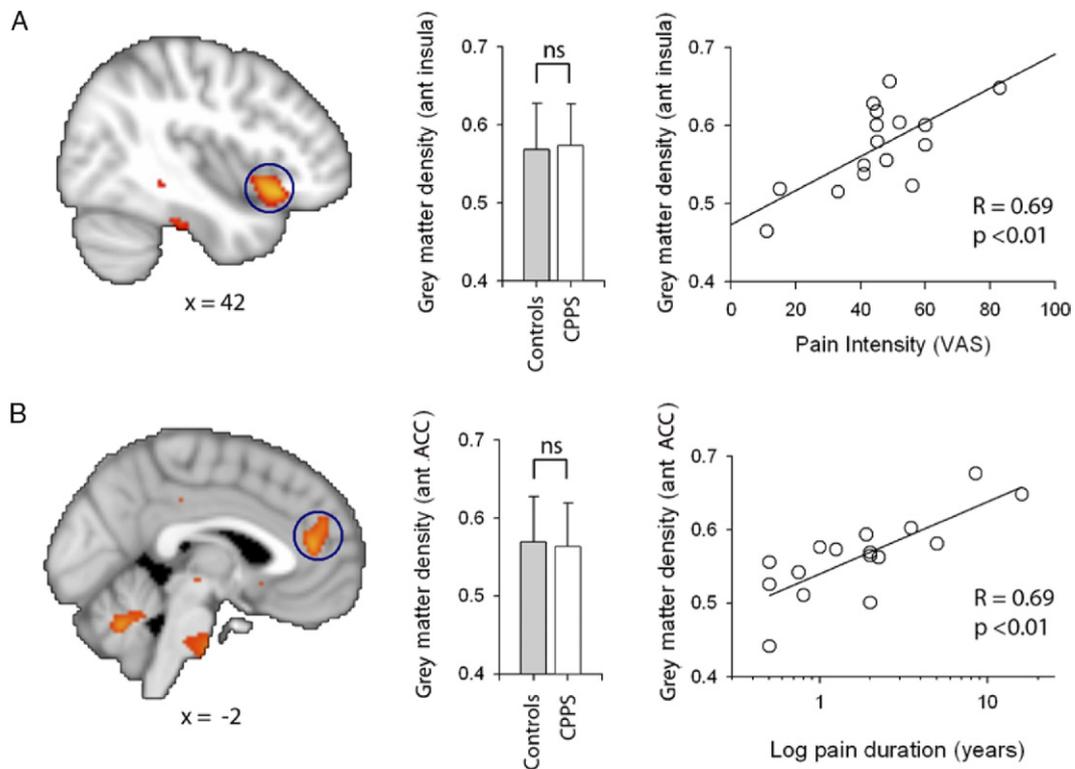### Relating Regional Gray Matter Density to CP/CPPS Characteristics

A whole brain covariate analysis of voxel-wise gray matter volume was conducted to determine the relationship between gray matter density and CP/CPPS

pain intensity (fig. 4, *A*). Of the regional clusters that were associated with pain intensity, the ant INS showed a highly significant correlation with pain intensity and was used as an ROI for further analyses. Ant INS density in patients with CP/CPPS was significantly correlated with pain intensity (r = 0.69, p <0.01), indicating that ant INS density increased with increasing self-reported pain intensity.

An additional whole brain covariate analysis of voxel-wise gray matter volume determined the rela-
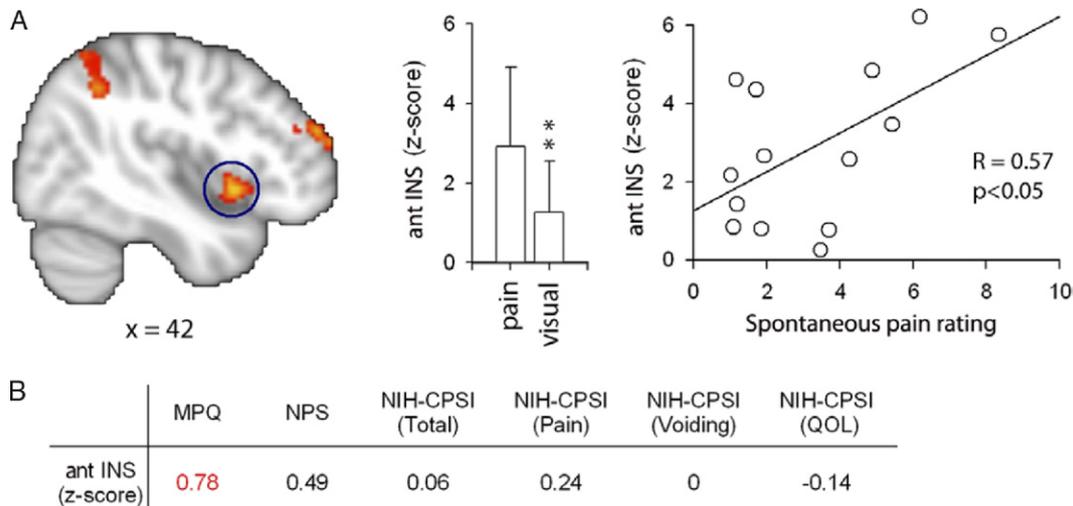
Figure 3. Anterior insula activity is related to CP/CPPS pain intensity. *A*, peak activity from anterior insula (blue circle) identified from pain − visual contrast shows significantly larger activity in pain task vs visual task (bar graph), and shows significant positive relationship between activity and CP/CPPS pain intensity (each symbol is individual subject in scatterplot). *B*, correlation of peak activity from anterior insula with clinical parameters of CP/CPPS. In addition to spontaneous pain intensity MPQ exhibited significant correlation with insular activity.

Figure 4. Distinct regional gray matter densities reflect different clinical parameters of CP/CPPS. *A*, whole brain covariate map of voxel-wise gray matter density and pain intensity in patients with CP/CPPS shows positively correlated regions. Right anterior insula was main region identified (ant insula, blue circle) and further analyzed (bar graph and scatterplot). Peak right anterior insula gray matter density shows no difference between patients with CP/CPPS and healthy controls (bar graph), and significant positive correlation between density and pain intensity in patients with CP/CPPS (scatterplot). *VAS*, visual analog scale. *ns*, not significant. *B*, whole brain covariate map of voxel-wise gray matter density and pain duration (in log units) shows regions positively correlated with pain chronicity, identifying mainly anterior cingulate cortex (blue circle). Bar graph shows no difference for peak ACC gray matter density between patients with CP/CPPS and healthy controls. Scatterplot depicts significant positive correlation between ACC density and pain chronicity in patients with CP/CPPS.

tionship between gray matter and pain duration (fig. 4, *B*). Multiple significant clusters emerged, including the ACC. Closer examination of this ROI revealed that ACC gray matter volume in patients was significantly positively correlated with logarithmic transformations of chronic pelvic pain duration (r = 0.69, p <0.01). Thus, patients with CP/CPPS with greater pain chronicity likely have increased ACC gray matter density.

Whole Brain Gray to White Matter Relationship in CP/CPPS
We found no group differences in total neocortical gray matter volume (before or after normalization with intracranial volume). Age was negatively correlated with total neocortical gray matter volume in patients with CP/CPPS (r = 0.71, p <0.01) and in controls (r = 0.75, p <0.01). Both groups showed comparable rates of gray matter loss with age, with patients with CP/CPPS losing 2.94 cc per year and controls losing 3.82 cc per year (fig. 5, *A*).

There was no group difference in mean whole brain FA between patients with CP/CPPS and con-

trols (fig. 5, *B*). To determine the global relationship between gray and white matter in patients with CP/CPPS and controls, whole brain mean skeletal FA was correlated with age corrected total neocortical gray matter volume. In healthy controls a strong positive correlation emerged between whole brain FA and whole brain gray matter volume (r = 0.87, p <0.01), indicating a congruent structural relationship between gray and white matter. In contrast, in patients with CP/CPPS no relationship was found between whole brain FA and age corrected neocortical gray matter volume (r = 0.01, p = 0.97). These results indicate a global structural disorganization of the relationship between white and gray matter in the CP/CPPS brain.

DISCUSSION
Using multimodal brain imaging techniques we have for the first time described clinically relevant functional and structural brain changes in a limited group of men with CP/CPPS. These changes are

Figure 5. Relationship between whole brain gray matter volume and white matter anisotropy is disrupted in patients with CP/CPPS. *A*, bar graph shows no difference in total neocortical gray matter volume (cc) between patients with CP/CPPS and controls. Scatterplots show degree of association between gray matter volume and age for controls (solid triangles) and patients (open circles). Both groups exhibited equivalent significant negative correlations between gray matter volume and age. *B*, bar graph shows no difference in mean whole brain white matter FA between patients with CP/CPPS and controls. Scatterplots show divergent correlations between whole brain FA and total gray matter volume (corrected for age). Whereas significant positive association between these parameters was found in healthy controls, relationship is absent in patients with CP/CPPS.

evident on regional and global scales, suggesting an ongoing reorganization of brain circuitry similar to recent observations in other chronic pain populations.[5] These findings suggest that the chronic presence of pelvic pain leaves specific neural imprints on the brain that persist for years. Alternatively some of these neural abnormalities may be predisposing factors for CP/CPPS.

The unique constellation of regional brain activity that characterizes pelvic pain represents a distinct CP/CPPS brain signature. The CP/CPPS functional brain signature differs from those of previously studied chronic pain conditions, including complex regional pain syndrome, interstitial cystitis, irritable bowel syndrome, knee osteoarthritis, low back pain and postherpetic neuralgia.[4,5] Specifically self-reported ongoing pelvic pain intensity was proportional to pain related anterior insula activity, which suggests this brain activity is relevant to the daily pain experienced by patients with CP/CPPS. These findings are also consistent with the hypothesized role of the anterior insula in encoding the magnitude of pain intensity,[12] and is further supported by the transient activation of the anterior insula in chronic back pain.[8] Additionally, anterior insula activity

correlates with the magnitude of bladder infusion in patients with varying levels of bladder voiding dysfunction.[13] Anterior insula gray matter density was robustly correlated with CP/CPPS pain intensity, indicating a convergence of insula structure and function with ongoing pain intensity. The anterior insula is implicated in the conscious perception of internal bodily processes including visceral[14] and somatic sensations.[15] This structure participates in a broad range of motor, cognitive and emotional functions,[16] suggesting that the impact of pain on the anterior insula may influence brain activity that surpasses the core clinical manifestations of CP/CPPS. Additionally, the central role of anterior insula activity in the spontaneous pain of CP/CPPS is distinct from the configuration of brain regions showing a functional association with spontaneous fluctuations of pain in other chronic pain conditions studied with a similar approach, eg chronic back pain (ie medial prefrontal cortex)[8] and postherpetic neuralgia (ie ventral striatum, amygdala, orbital frontal cortex, ventral tegmental area).[17] The latter is consistent with the notion that chronic pain conditions show distinct patterns of pain related brain activation.[5]

The CP/CPPS functional brain signature shares some similarities with brain activity observed during innocuous and painful visceral stimulation of the rectum, esophagus and bladder in pain-free controls,[13,18] particularly in the ant INS and ACC. However, brain activation patterns in healthy subjects may differ from those observed in chronic visceral pain populations. For example, patients with irritable bowel syndrome show abnormal processing of rectal distention pain within the insula,[19] prefrontal cortex,[19,20] ACC[19,21] and amygdala.[19] Further investigations of brain activity related to pelvic pain using larger sample sizes and uniform experimental designs are critical to tease apart activity that uniquely characterizes CP/CPPS compared to other visceral pain. Pelvic pain may be differentiated from other visceral pain conditions in the type of pain (ie spontaneous vs experimentally induced), impact and location of referred pain, factors related to pain onset (ie anxiety, sexual activity), comorbid regional vs systemic conditions, underlying pathophysiology and/or the existence of unidentified clinical subtypes.

Surprisingly we did not find reductions in global or regional gray matter volume which have been reported for numerous chronic pain conditions.[22] Given the small sample size and increasing evidence that CP/CPPS may consist of multiple clinical phenotypes,[2] we cannot conclusively rule out the contribution of gray matter atrophy. The significance of altered regional gray matter depends on what the volume loss reflects (ie neurodegeneration, nonneuronal tissue changes) and which structures (and their functions) are affected. Our data strongly suggest that anatomical changes (in ant INS and ACC) reflect the unique ongoing experience of pelvic pain, which appears to reshape local brain anatomy throughout the course of the disease (and perhaps also predisposes individuals to CP/CPPS). Importantly, the functions of these brain regions are likely altered, potentially impacting regional pain processing and regional processing of other types of nonpain related information. Relatedly, the disruption of the global relationship between gray and white matter in patients indicates large-scale anatomical reorganization due to pelvic pain and its consequences. We have previously described similar global changes in patients with complex regional pain syndrome.[11] This global cortical reorganization may reflect how the brain adapts to chronic pain in general, including the presence of pain as well as daily behavioral and psychological responses to pain.

CONCLUSIONS

We provide the first evidence of CP/CPPS specific pain related brain activation in the absence of an external stimulus and anatomical brain abnormalities related to the clinical features of CP/CPPS. Given the variability in clinical presentations of CP/CPPS, the small sample size used in our analyses may have been insufficient to capture the full extent of central changes associated with this condition. Larger samples and careful clinical phenotyping are necessary to reveal a more detailed picture of the functional and anatomical profile of patients with CP/CPPS, and to determine whether these changes are causes or consequences of disease progression.

REFERENCES

1. Clemens JQ, Calhoun EA, Litwin MS et al: 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.

2. Nickel JC, Krieger JN, McNaughton-Collins M et al: Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. N Engl J Med 2008; **359:** 2663.

3. Melzack R and Wall PD: Textbook of Pain. London: Churchill Livingston 1999; pp 1125–1250.

4. Apkarian AV, Bushnell MC, Treede RD et al: Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005; **9:** 463.

5. Apkarian AV, Baliki MN and Geha PY: Towards a theory of chronic pain. Prog Neurobiol 2009; **87:** 81.

6. Litwin MS, McNaughton-Collins M, Fowler FJ Jr et al: The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999; **162:** 369.

7. FitzGerald MP, Anderson RU, Potts J et al: Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol 2009; **182:** 570.

8. Baliki MN, Chialvo DR, Geha PY et al: Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 2006; **26:** 12165.

9. Galer BS and Jensen MP: Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology 1997; **48:** 332.

10. Baliki MN, Geha PY, Fields HL et al: Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 2010; **66:** 149.

11. Geha PY, Baliki MN, Harden RN et al: The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008; **60:** 570.

12. Baliki MN, Geha PY and Apkarian AV: Parsing pain perception between nociceptive representation and magnitude estimation. J Neurophysiol 2009; **101:** 875.

13. Griffiths D, Derbyshire S, Stenger A et al: Brain control of normal and overactive bladder. J Urol 2005; **174:** 1862.

14. Critchley HD, Wiens S, Rotshtein P et al: Neural systems supporting interoceptive awareness. Nat Neurosci 2004; **7:** 189.

15. Eickhoff SB, Lotze M, Wietek B et al: Segregation of visceral and somatosensory afferents: an fMRI and cytoarchitectonic mapping study. Neuroimage 2006; **31:** 1004.

16. Kurth F, Zilles K, Fox PT et al: A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 2010; **214:** 519.

17. Geha PY, Baliki MN, Chialvo DR et al: Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. Pain 2007; **128:** 88.

18. Yágüez L, Coen S, Gregory LJ et al: Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. Gastroenterology 2005; **128:** 1819.

19. Wilder-Smith CH, Schindler D, Lovblad K et al: Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 2004; **53:** 1595.

20. Silverman DH, Munakata JA, Ennes H et al: Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 1997; **112:** 64.

21. Mertz H, Morgan V, Tanner G et al: Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology 2000; **118:** 842.

22. May A: Chronic pain may change the structure of the brain. Pain 2008; **137:** 7.