Alterations in Resting State Oscillations and Connectivity in Sensory and Motor Networks in Women with Interstitial Cystitis/Painful Bladder Syndrome

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Purpose: The pathophysiology of interstitial cystitis/painful bladder syndrome remains incompletely understood but is thought to involve central disturbance in the processing of pain and viscerosensory signals. We identified differences in brain activity and connectivity between female patients with interstitial cystitis/painful bladder syndrome and healthy controls to advance clinical phenotyping and treatment efforts for interstitial cystitis/painful bladder syndrome.

Materials and Methods: We examined oscillation dynamics of intrinsic brain activity in a large sample of well phenotyped female patients with interstitial cystitis/painful bladder syndrome and female healthy controls. Data were collected during 10-minute resting functional magnetic resonance imaging as part of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network project. The blood oxygen level dependent signal was transformed to the frequency domain. Relative power was calculated for multiple frequency bands.

Results: Results demonstrated altered frequency distributions in viscerosensory (post insula), somatosensory (postcentral gyrus) and motor regions (anterior paracentral lobule, and medial and ventral supplementary motor areas) in patients with interstitial cystitis/painful bladder syndrome. Also, the anterior

Abbreviations and Acronyms

BOLD = blood oxygen level dependent
fMRI = functional magnetic resonance imaging
FWE = familywise error
GUPI = Genitourinary Pain Index
HF = high frequency
IC/PBS = interstitial cystitis/painful bladder syndrome
LF = low frequency
MAPP = Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MF = medium frequency
mINS = mid insula
MRI = magnetic resonance imaging
NWU = Northwestern University
pINS = posterior insula
RN = red nucleus
ROI = region of interest
SMA = supplementary motor area
SU = Stanford University
UAB = University of Alabama at Birmingham
UM = University of Michigan

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paracentral lobule, and medial and ventral supplementary motor areas showed increased functional connectivity to the midbrain (red nucleus) and cerebellum. This increased functional connectivity was greatest in patients who reported pain during bladder filling.

Conclusions: Findings suggest that women with interstitial cystitis/painful bladder syndrome have a sensorimotor component to the pathological condition involving an alteration in intrinsic oscillations and connectivity in a cortico-cerebellar network previously associated with bladder function.

Key Words: urinary bladder; cystitis, interstitial; magnetic resonance imaging; brain mapping; pain

INTERSTITIAL cystitis/painful bladder syndrome is a chronic pelvic pain condition associated with urinary urgency and frequency that may affect as many as 7.9 million women in the United States.[1] The specific pathophysiology remains incompletely understood but several lines of evidence suggest a role for central amplification of viscerosensory signals.[2,3]

The MAPP Research Network is a multisite endeavor to identify epidemiological and neuroimaging parameters to advance clinical phenotyping and treatment efforts for urological chronic pelvic pain, including IC/PBS (fig. 1). Standardized acquisition parameters for structural and resting scan fMRI were applied at 5 MAPP sites across the United States as part of the Trans-MAPP neuroimaging study.

Resting scan fMRI depends on the fact that a wealth of information can be extracted from intrinsic fluctuations in the BOLD signal without the need of an external stimulus. Advantages of resting scan fMRI over task based fMRI include the ability to achieve a greater degree of standardization across research centers. In addition, brain responses to acute experimental pain in the laboratory may have limited usefulness for understanding chronic pain. Monitoring how the brain processes ongoing signals from the body and environment may provide novel insights into altered neural circuitry in patients with chronic pain.

We examined intrinsic brain oscillations (resting state fMRI) in female patients with IC/PBS and healthy controls to determine alterations in frequency power distribution and functional connectivity patterns. Based on previous reports of other chronic pain conditions (Kutch et al, unpublished data)[3,4] we hypothesized that patients with IC/PBS would show altered oscillation frequency and functional connectivity in visceromotor and sensorimotor regions.

METHODS

Subjects

Subjects were recruited from urology clinics and community advertisements. To meet IC/PBS symptom criteria patients had to report an unpleasant sensation of pain, pressure or discomfort perceived to be related to the bladder and/or pelvic region that was associated with lower urinary tract symptoms. IC/PBS symptoms must have been present for most of the time during any 3 months in the previous 6 months and for most of the time during the most recent 3 months. Healthy controls reported absent current pain problems and no history of chronic pain in the pelvic or bladder region. The supplementary materials (http://jurology.com/) show additional subject criteria.

The current analysis included 85 healthy female controls and 82 patients with IC/PBS from a total of 5 MAPP discovery sites, including UCLA, NWU, UM, UAB and SU. This cohort represents all female control and IC/PBS subjects from the Trans-MAPP neuroimaging study with a resting scan that passed quality control for excessive motion except in 1 in whom normalization failed during fMRI preprocessing. Approval was received from the ethics committee at each site and consent was obtained from all participants.

Procedures

To quantify symptoms participants completed the female version of GUPI before resting fMRI was completed.[5] GUPI consists of pain, urinary and quality of life subscales.

fMRI Acquisition and Analysis

Acquisition. MRI was performed at multiple sites using various scanner technologies, including the 3 Tesla Trio (Siemens®) at NWU and UCLA, 3 Tesla Ingenia at UM, 3 Tesla Achieva (Philips®) at UAB and 3 Tesla Discovery (GE Healthcare, Pittsburgh, Pennsylvania) at SU. Trans-MAPP neuroimaging data were collected, quality controlled and archived according to multisite imaging procedures developed collaboratively between the MAPP Research Network, and the UCLA PAIN (Pain and Interoception Imaging Network) repository (http://pain.med.ucla.edu) and Laboratory of Neuroimaging. Scanner compatible acquisition parameters were developed based on recommendations from fBIRN (https://xwiki.nbirn.org:8443/bin/view/Function-BIRN/FBIRN_Best_Practices). All sites were required to complete and pass a site qualification including a set of pilot scans of a human volunteer. Initial scans were reviewed for quality control at the UCLA site with recommendations and adjustments made as needed before beginning study scans.

A high resolution structural image was acquired for each subject with a magnetization prepared rapid

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Figure 1.

gradient-echo sequence, repetition time 2,200 milliseconds, echo time 3.26 milliseconds, slice thickness 1 mm, 176 slices, 256 × 256 voxel matrices and 1^3 mm voxel size. Resting scans were acquired while subjects rested with eyes closed for 10 minutes in 40-slice whole brain volumes with slice thickness 4 mm, repetition time 2,000 milliseconds, echo time 28 milliseconds and flip angle 77 degrees. Before entering the scanner subjects were asked to empty the bladder.

Preprocessing. Using DPARSF (Data Processing Assistant for Resting-State) fMRI (http://www.restfmri.net/forum/DPARSF),[6] which is based on SPM8 (Welcome Department of Cognitive Neurology, London, United Kingdom) and the Resting-State fMRI Data Analysis Toolkit[7] data were slice-time and motion corrected. Nuisance covariate regression was then performed to minimize physiological noise using 6 head motion parameters, white matter signal and corticospinal fluid signal. Data were spatially normalized to

the MNI (Montreal Neurological Institute) template using structural scans. Spatial smoothing with a 3 mm^3 Gaussian kernel was done after calculation of frequency and connectivity maps.

Statistical Analysis

Frequency. Although frequency analyses of resting scan data typically calculate power within a 0.01 to 0.10 Hz band, the frequency spectrum can be further subdivided to better reflect the neural origin of the sources.[8] Using a previously developed framework[8,9] the BOLD signal time course data of each voxel was transformed to the frequency domain and subdivided into 3 frequency bands, referred to in the literature as slow-5 (0.01 to 0.027 Hz), slow-4 (0.027 to 0.073 Hz) and slow-3 (0.073 to 0.198 Hz). We refer to these 3 frequency bands as LF, MF and HF, respectively. The fractional amplitude of frequency fluctuation for each band was calculated for each grey matter voxel and normalized to the mean.[10] Group (control; IC) × band (LF; MF; HF) × site (NWU; UCLA; UAB; UM; SU) flexible factorial analysis was performed in SPM8 with subject age entered as a covariate. Contrasts were performed for each band to identify regions with altered frequency power distribution for IC/PBS cases vs controls. Regions at a cluster level FWE corrected $p < 0.05$ were considered significant.

We hypothesized that alterations would be seen in 1) the insular cortex, given the demonstration of insular structural and functional alterations in IC/PBS and chronic pain disorders comorbid with IC/PBS,[3,4,11] 2) the brainstem, given its role in bladder function,[12] and 3) the anterior paracentral lobule/SMA because these regions have consistently been shown to activate during pelvic floor contractions in women.[13–15] For these ROIs FWE correction was restricted to the specified region (ie small volume correction). The aal atlas in MRIcron (http://www.cabiatl.com/mricro/mricron/index.html) was used to aid in identifying the anatomical location of significant clusters.

Seed based functional connectivity. The SPM MarsBaR toolkit was used to create 5 seed functional ROIs of significant clusters from the described frequency analysis.[16] Preprocessed functional data were bandpass filtered using LF, MF and HF bands, and band specific Fisher transformed maps of the bivariate correlation between seed ROI time courses and all other voxels were created using DPARSF. Group differences in band specific functional connectivity for each seed were examined using a flexible factorial model in SPM8 with site and group factors, and age as a covariate.

RESULTS

Subject Characteristics

Table 1 lists average age, symptom duration, total GUPI scores and GUPI pain subscores. Table 2 shows drug use. Age showed a trend to be greater in patients with IC/PBS compared to controls ($t(165) = -1.875$, $p = 0.062$). At UAB patients had a significantly longer symptom history than at other sites (23.1 vs 7.6 years).

Table 1. *Participant characteristics*

	No. Pts	Mean ± SE Age	Mean ± SE Duration (yrs)	Mean ± SE GUPI Total	Mean ± SE GUPI Pain
Overall:					
CONTROL	85	35.3 ± 1.2	Not applicable	1.5 ± 0.3	0.4 ± 0.2
IC/PBS	82	38.8 ± 1.4	10.4 ± 1.3	26.2 ± 1.0	12.8 ± 0.5
UCLA:					
CONTROL	14	36.7 ± 3.6	Not applicable	1.3 ± 0.4	0.1 ± 0.1
IC/PBS	9	32.3 ± 2.6	6.9 ± 2.7	24.8 ± 2.8	11.8 ± 1.4
NWU:					
CONTROL	9	36.8 ± 4.8	Not applicable	0.9 ± 0.4	0.4 ± 0.4
IC/PBS	29	35.1 ± 2.7	8.1 ± 4.5	26.0 ± 2.7	13.6 ± 1.2
UM:					
CONTROL	18	32.8 ± 2.2	Not applicable	0.9 ± 0.2	0.1 ± 0.1
IC/PBS	14	36.7 ± 2.2	6.6 ± 1.5	25.9 ± 1.7	12.5 ± 0.9
UAB:					
CONTROL	9	32.3 ± 2.7	Not applicable	3.1 ± 2.5	1.4 ± 1.4
IC/PBS	9	36.8 ± 4.3	23.1 ± 3.4	27.2 ± 3.4	13.6 ± 1.8
SU:					
CONTROL	29	35.1 ± 3.1	Not applicable	2.0 ± 0.7	0.6 ± 0.3
IC/PBS	82	38.8 ± 2.7	9.1 ± 2.3	26.8 ± 1.8	13.0 ± 0.9

Group Differences

Oscillation frequency power. Female patients with IC/PBS and healthy controls were examined for regional brain differences in frequency power in 3 frequency bands (LF, MF and HF) thought to represent different neuronal oscillation classes.[8] Alterations were found exclusively in the lowest frequency band (LF, 0.01 to 0.027 Hz). Patients with IC/PBS showed significantly greater LF power in the postcentral gyrus (primary sensory cortex), anterior paracentral lobule (in the primary motor cortex), ventral SMA extending into the mid cingulate cortex (ventral SMA) and medial SMA/paracentral lobule (medial SMA) (table 3 and fig. 2, *A*). In addition, the right pINS demonstrated significantly less LF power in patients than in controls (table 3 and fig. 2, *B*).

Functional connectivity. Functional connectivity in the LF band of the 5 regions showing altered LF power was examined in patients and controls. We found increased connectivity in patients between 1) medial SMA and right midbrain, 2) ventral SMA and cerebellum, 3) ventral SMA and bilateral midbrain, 4) anterior paracentral lobule and superior parietal cortex, 5) anterior paracentral lobule

Table 2. *Drug treatments at time of scan*

	% IC/PBS	% Controls
None	40.2	88.2
Peripheral acting (nonsteroidal anti-inflammatory drugs, antimuscarinics)	18.3	8.2
Central acting (amitriptyline, Lyrica®, Neurontin®, Tegretol®, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, Valium®)	23.2	3.5
Opioids (oral narcotics, morphine)	18.3	0

Table 3. *Location, extent and significance of each cluster showing altered frequency distribution and altered functional connectivity by region of altered frequency distribution*

Region (hemisphere)	Peak Coordinates	Cluster Size	Z-Score	FWE p Value
	Altered frequency distribution			
Greater IC/PBS vs control LF power:				
Medial SMA, Brodmann area 4/6m (bilat)	−2, −16, 68	10	3.95	0.007
Ventral SMA, Brodmann areas 6m/23 (rt)	4, −22, 48	95	4.98	0.025
Paracentral, Brodmann area 4 (lt)	−16, −24, 58	80	5.13	0.025
Postcentral, Brodmann area 3 (rt)	44, −14, 30	295	5.43	<0.001
Less IC/PBS vs control LF power pINS (rt)	46, −10, 4	16	3.80	0.049
	Altered functional connectivity			
Greater IC/PBS vs control:				
Medial SMA to midbrain (rt)	8, −24, −8	66	4.30	0.007
Ventral SMA to midbrain (rt)	6, −24, −6	22	3.96	0.048
Ventral SMA to midbrain (lt)	−6, −24, −4	28	3.92	0.035
Ventral SMA to cerebellum (bilat)	2, −70, −30	240	3.98	0.002
Ventral SMA to cerebellum (rt)	20, −66, −18	173	4.16	0.011
Paracentral to midbrain (rt)	8, −26, −10	24	3.69	0.042
Paracentral to midbrain (bilat)	0, −26, −20	41	3.52	0.018
Paracentral to cerebellum (lt)	−34, −82, −18	536	4.27	<0.001
Paracentral to cerebellum (rt)	36, −64, −20	163	4.38	0.012
Paracentral to cerebellum (bilat)	0, −66, −24	260	4.08	0.001
Paracentral to superior parietal, Brodmann area 7 (lt)	−8, −70, 54	153	3.82	0.017
Paracentral to superior parietal, Brodmann area 7 (lt)	−30, −62, 44	230	4.49	0.002
Paracentral to precuneus, Brodmann area 5/7m (bilat)	0, −48, 58	373	4.08	<0.001
Less pINS to mINS (rt) IC/PBS vs control	46, 0, 6	32	3.93	0.027

and cerebellum, and 6) anterior paracentral lobule and right midbrain (table 3 and fig. 2, *A*). Decreased connectivity in patients compared to controls was found between the right pINS and right mINS (table 3). Notably 3 regions (medial SMA, ventral SMA and anterior paracentral lobule) demonstrated altered connectivity with the same region of the right midbrain in the RN area centered at 6, −24, −7 with a volume of 64 mm. Two regions (ventral SMA and anterior paracentral lobule) similarly showed increased LF functional connectivity with the same regions in the cerebellum located in vermis VII (centered at 5, −69, −27 with a volume of 712 mm) and in right lobule VI (centered at 28, −58, −20 with a volume of 432 mm). The medial SMA also showed increased LF functional connectivity with these cerebellar regions after small volume correction was applied to the cerebellum.

Clinical Correlates

The cortico-cerebellar and insular functional connectivity identified as altered in patients was evaluated for associations with symptom duration and

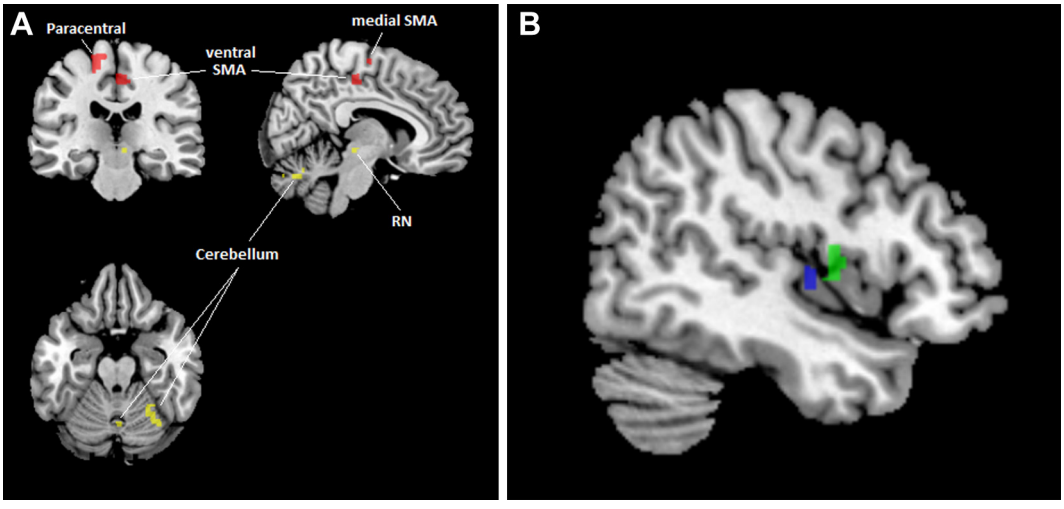

Figure 2. *A*, medial and ventral SMA, and anterior paracentral lobule (red areas) showed increased LF power and connectivity with region in right midbrain/RN, and regions in cerebellar vermis VI/VII and right lobule VI (yellow areas) in patients vs controls. *B*, pINS (blue area) showed decreased LF power and connectivity with mINS (green area) in patients vs controls.

GUPI scores in patients with IC/PBS, controlling for age and site. No functional connectivity measure correlated with the self-reported duration of urological symptoms or with composite GUPI scores (each $p > 0.05$). To further evaluate whether observed brain changes correlated with symptoms we tested for differences among patients using a general linear model controlling for age and site. Differences were based on yes/no responses to individual GUPI items regarding pain during urination (48% of patients) and pain during bladder filling (64%). Pain during urination did not modulate functional connectivity (each $p > 0.05$). However, compared to those who reported no pain during bladder filling those who reported such pain showed increased functional connectivity between 1) medial SMA and RN/cerebellum ($F(1,74) = 4.91$, $p = 0.03$), 2) ventral SMA and RN/cerebellum ($F(1,74) = 4.24$, $p = 0.043$), and 3) anterior paracentral lobule and RN/cerebellum ($F(1,74) = 6.41$, $p = 0.013$, figs. 3 and 4).

DISCUSSION

To our knowledge this is the first report of abnormalities in the intrinsic oscillation of the resting brain in a large sample of well phenotyped women with IC/PBS. Results reveal disease related alterations in frequency distributions. Patients showed decreased LF power in viscerosensory regions (pINS) and increased LF power in sensorimotor related cortices (postcentral gyrus, medial SMA, ventral SMA and anterior paracentral lobule). In addition, most clusters showing altered frequency distribution also demonstrated frequency specific alterations in functional connectivity. Strikingly

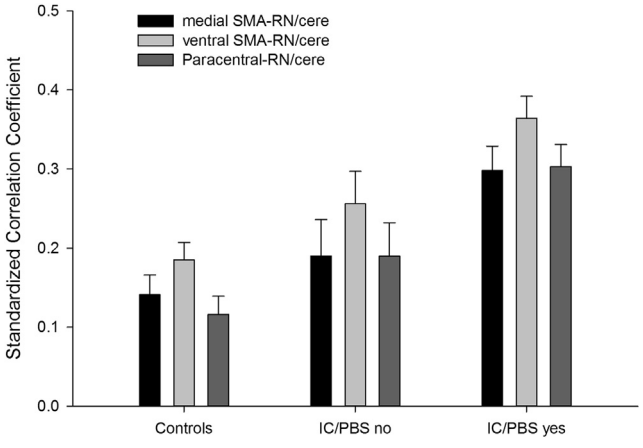

Figure 3. Estimated mean functional connectivity controlling for age for medial and ventral SMA, anterior paracentral lobule and RN/cerebellar regions (*RN/cere*) in controls, and in patients with IC/PBS with (*IC/PBS yes*) and without (*IC/PBS no*) pain during bladder filling.

3 increased LF frequency clusters (medial SMA, ventral SMA and anterior paracentral lobule) previously associated with pelvic muscle control[13–15] demonstrated increased LF functional connectivity with the same areas of the midbrain (right RN) and cerebellum (vermis VI/VII and right lobule VI) in the patient group. Increased functional connectivity between motor cortices and RN/cerebellum was greatest in patients who reported pain during bladder filling. These results suggest an alteration in the ongoing activity in known cortico-cerebellar pathways in women with IC/PBS that may relate to a particular aspect of IC/PBS symptomology, namely the experience of pain during bladder filling.

Bladder Functional Neuroanatomy

Preclinical and human imaging studies identified a number of cortical regions (insula, prefrontal, anterior cingulate, motor cortex and cerebellum), midbrain regions (hypothalamus, RN and periaqueductal gray) and brainstem regions (Barrington nucleus, locus coeruleus complex and inferior olive) that are directly involved in bladder function.[12] The voiding reflex is mediated by spinal and medullary pontine relay nuclei but in humans it receives strong input from cortical regions, including anterior cingulate, prefrontal and motor regions. Conscious perception of urinary sensation, including fullness, urgency and pain, involves activation of the anterior insula. In the current study alterations in the frequency power distribution of intrinsic oscillations were observed in several of these bladder related brain regions.

Alterations in viscerosensory regions. The insula has posterior-to-mid-to-anterior integration of interoceptive information with primary interoceptive representations located in pINS and subjective awareness of interoceptive information in the anterior insula.[17] Lower LF power in the pINS of women with IC/PBS compared to healthy controls may suggest increased neural activity in pINS, consistent with tonically increased viscerosensory input to the brain. However, there are other interpretations mentioned previously. Such input may come from increased afferent input from the bladder or from dorsal horn neurons, sensitized by descending facilitatory input from the brain. In addition, decreased connectivity between pINS and mINS suggests altered integration of interoceptive information into subjective awareness. However, no significant correlation was observed between insula and clinical symptoms.

Alterations in pelvic motor related cortical and subcortical regions and pathways. Several regions with known involvement in bladder function and

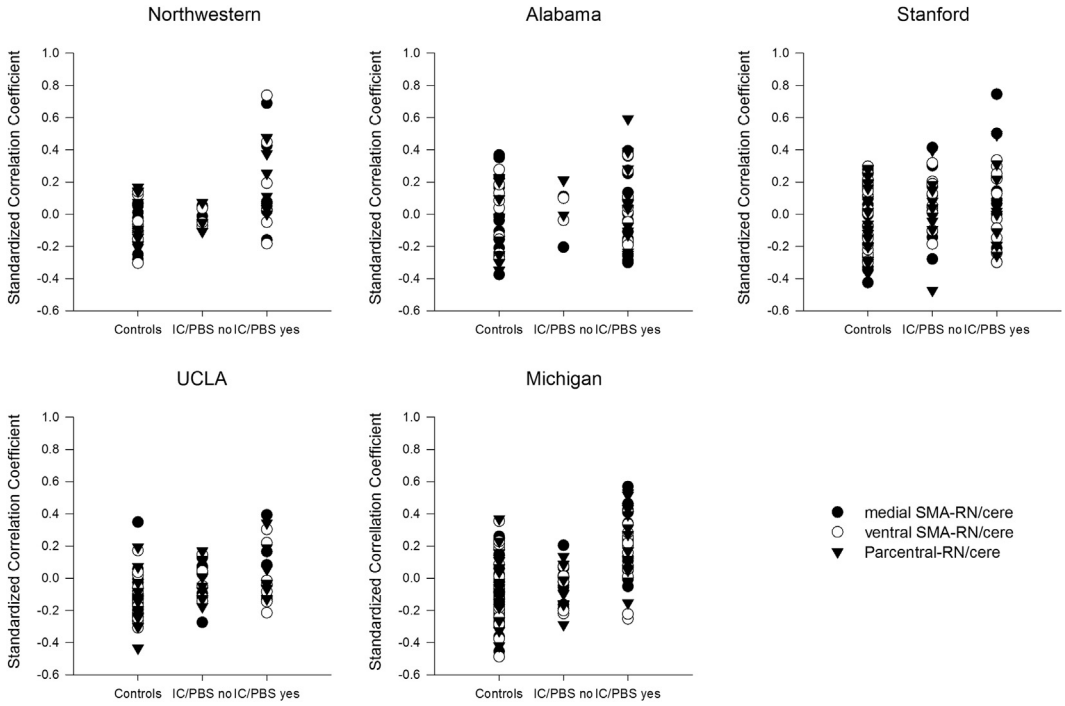

Figure 4. Functional connectivity values in each individual at each of 5 scanning sites. *RN/cere,* RN/cerebellar region.

pelvic motor control (medial SMA, ventral SMA, anterior paracentral lobule and postcentral gyrus) showed increased LF power in the patient group. A possible interpretation of this finding may be that these regions are less active in women with IC/PBS. However, other interpretations are possible, such as increased activity specifically in deep cortical layers, as mentioned previously.

The paracentral lobule and SMA have consistently been shown to be involved in pelvic floor contraction in females during periods of urge as well as during an empty bladder.[13–15] Thus, the noted altered activity and connectivity of pelvic floor cortical control regions in women with IC/PBS could be related to pelvic floor dysfunction. These cortical regions showed increased functional connectivity with the RN and cerebellum. The RN is a relay center whose functions include the integration of information from the motor cortex and cerebellum. Several observations imply a role in bladder motility. For example, tracer injection in the bladder revealed that the RN is a supraspinal center connected to the bladder.[18] Electrical stimulation of the RN resulted in inhibition of spontaneous bladder contractions during fluid instillation.[19] In addition, increased nerve growth factor levels in the RN were associated with the development of neuropathic pain after peripheral nerve injury in rats.[20] Thus, an alteration in coordination between the cerebellum and motor cortex involving the RN may have consequences for bladder function and pain.

Although cerebellar activation has often been observed in evoked brain responses to experimental pain stimuli, its specific role in pain processing/modulation remains unclear.[21] The cerebellum has an important role in motor learning[22] and central autonomic control, and it receives strong noradrenergic input from the pontine locus coeruleus complex (Barrington nucleus and locus coeruleus).[12]

Briefly, the results of the current study suggest that women with IC/PBS have altered sensorimotor cortical control of the cerebellum and brainstem structures known to be involved in bladder function. Altered sensorimotor function in IC/PBS is consistent with a previous study showing deficits in sensorimotor gating in women with IC/PBS.[23]

Our findings differ from findings in other persistent pain conditions such as irritable bowel syndrome, vulvodynia, fibromyalgia and low back pain, which revealed pain related abnormalities in classic pain regions, including the anterior insula, anterior cingulate cortex, periaqueductal gray and thalamus.[3,4] Altered activity of these classic regions are possibly only seen during evoked or spontaneous pain but not during resting conditions. Alternatively IC/PBS may be a different condition with different brain abnormalities. Future studies of intrinsic activity and connectivity during a pain eliciting condition, such as bladder filling compared

with an empty bladder, may help elucidate this matter.

Limitations

The separation of frequency bands used in this analysis was based on the observation that behaviorally relevant brain oscillations have linearly distributed center frequencies on the natural logarithmic scale.[9] However, little is known about the functional relevance of these bands. Given that activation of brain regions through a task shifts the frequency distribution towards higher frequencies,[24] a possible interpretation of increased LF power in motor cortical regions is that these regions are less active in women with IC/PBS. However, local field potential studies showed that lower frequency oscillations are found in deeper cortical layers.[25] Because the BOLD signal in a brain voxel combines signals from all layers of the cortex, another possibility is that the contribution of the signal from deeper cortical layers, including layer V where the corticorubral pathway originates, is enhanced in women with IC/PBS. This would be consistent with the observed increase in functional connectivity between motor cortices and RN. Additional limitations include variability across sites in the number of individuals per group. Also, to focus analysis on overall group differences in the resting state we did not examine the influence of psychological or other potential mediators, such as treatment.

Possible Clinical Implications

Although we did not assess pelvic floor dysfunction in the current study, several clinical observations support the concept of altered pelvic floor activity in IC/PBS. A high prevalence of pelvic floor dysfunction in IC/PBS in terms of pain during physical palpitation was reported.[26,27] In addition, pelvic MRI demonstrated a shorter puborectal distance and levator length in patients with IC/PBS, consistent with hypertonicity.[28] Finally, physical therapy of the pelvic floor has been successful for IC/PBS.[29] Thus, the demonstrated altered activity and connectivity of pelvic floor sensorimotor cortical control regions in women with IC/PBS may be related to pelvic floor dysfunction. However, this alteration could be a primary or a secondary abnormality.

CONCLUSIONS

Longitudinal studies are needed to determine whether therapy targeted at abnormal motor control, such as biofeedback, muscle relaxation and pelvic floor exercises, would normalize the central motor networks and whether this normalization would be associated with decreased symptoms. In addition, further brain imaging studies may help identify biologically distinct, symptom based subgroups, such as those with and without pain during bladder filling.

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