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Multimodal nociceptive mechanisms underlying chronic pelvic pain

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Abstract

Objective—To evaluate candidate mechanisms underlying the pelvic floor dysfunction in women with chronic pelvic pain and/or painful bladder syndrome/interstitial cystitis. Notably, prior studies have not consistently controlled for potential confounding by psychological or anatomical factors.

Study Design—As part of a larger study on pelvic floor pain dysfunction and bladder pain sensitivity, we compared a measure of mechanical pain sensitivity, pressure pain thresholds, between women with pelvic pain and pain-free controls. We also assessed a novel pain measure using degree and duration of post-exam pain aftersensation, and conducted structural and functional assessments of the pelvic floor to account for any potential confounding. Phenotypic specificity of pelvic floor measures was assessed with receiver-operator characteristic curves adjusted for prevalence.

Results—A total of 23 women with chronic pelvic pain, 23 painful bladder syndrome, and 42 pain-free controls completed the study. Women with chronic pelvic pain or painful bladder syndrome exhibited enhanced pain sensitivity with lower pressure pain thresholds (1.18 [interquartile range: 0.87–1.41] kg/cm²) than pain-free participants (1.48 [1.11–1.76] kg/cm²; $p < 0.001$) and prolonged pain aftersensation (3.5 [0–9] vs 0 [0–1] minutes; $p < 0.001$). Although genital hiatus ($p < 0.01$) was wider in women with chronic pelvic pain there were no consistently

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observed group differences in pelvic floor anatomy, muscle tone or strength. The combination of pressure pain thresholds and aftersensation duration correlated with severity of pelvic floor tenderness ($R^2 = 41\text{--}51$, $p's < 0.01$). Even after adjustment for prevalence, the combined metrics discriminated pain-free controls from women with chronic pelvic pain or painful bladder syndrome (area under the curve=0.87).

Conclusion—Both experimental assessment of pelvic floor pain thresholds and measurement of sustained pain are independently associated with pelvic pain phenotypes. These findings suggest systematic clinical assessment of the time course of provoked pain symptoms, which occurs over seconds for mechanical pain thresholds vs. minutes for aftersensation pain, would be helpful in identifying the fundamental mechanisms of pelvic floor pain. Longitudinal studies of therapies differentially targeting these discrete mechanisms are needed to confirm their clinical significance.

Keywords

Pelvic Pain; Painful Bladder Syndrome; Pressure Pain Threshold; Quantitative Sensory Testing

Introduction

Chronic pelvic pain (CPP) is a highly prevalent (14–25%) condition, and pelvic floor myofascial dysfunction is increasingly recognized as a key contributor.^{1–3} Even among visceral CPP conditions such as painful bladder syndrome/interstitial cystitis (PBS) presumed bladder pain may actually arise from alterations in mechanical sensitivity of the pelvic floor musculature.⁴

Although diagnosis of CPP/PBS is primarily dependent on self-report of symptoms that are confounded by psychological factors, recent guidelines suggest that palpation can identify patients with pelvic floor dysfunction.⁵ Work by our group and others suggests CPP patients exhibit enhanced pelvic floor pain sensitivity, using transvaginal pressure pain threshold measurement.^{6–9} However, additional research is needed to verify whether palpation induced pain is related to pelvic mechanical thresholds and not confounded by psychological, anatomical and muscular factors. Indeed, gynecologists have been publicly challenged recently to prove the value of pelvic exam-based biomarkers following a Veterans Affairs panel report that questions the utility of routine pelvic examination.¹⁰

Since multiple nerve fiber types provide sensory innervation of the pelvic floor, identification of dysfunction within specific fiber types could identify dysfunctional mechanisms that can be used for diagnosis and evaluation with greater specificity. Prior reports of reduced pelvic floor pain thresholds may reflect reduced mechanical thresholds in type A-fibers (mechanoreceptive nerves).¹¹ However, differences in electrical and heat thresholds in male CPP suggested that CPP is associated with reduced thresholds in C-fibers (multimodal pain nerves).¹² Since A-fibers primarily mediate first pain and C-fibers mediate a delayed secondary pain, temporal characteristics of evoked pain may help resolve the distinct contribution of A vs. C fibers.¹³

Current guidelines for CPP/PBS recommend multidimensional management, which may include physical therapy in patients that have pelvic palpation pain.⁵ Indeed, a randomized

controlled trial combining external and pelvic floor manual physical therapy for PBS showed greater than two-fold reduction of global pain assessment compared with global therapeutic massage.¹⁴ Standardized examination of pelvic floor tenderness could improve appropriate identification of candidates for such physical therapy.¹³

The present study objective was to determine whether specific variations in myofascial anatomy, function, or sensitivity differentiate CPP, PBS, and pain-free patients and how these relate to the simple binary construct of clinical tenderness. These findings also extend our prior work on quantitative sensory testing in undifferentiated CPP to a primarily visceral condition, PBS, and for the first time are extrapolated to testing in the general population with Monte Carlo simulations.

Materials and Methods

Study design

To test our primary hypothesis, that pelvic floor pressure pain thresholds (PPTs) would be lower (indicative of increased pain sensitivity) in CPP and PBS patients versus pain-free controls, we conducted a cross-sectional study between July 2010 and September 2013. Secondary analyses subsequently estimated the discriminatory value of pelvic floor sensitivity for CPP and PBS, adjusting for potential epidemiological, anatomical, physiological, and psychological factors.

Setting and participants

Cases included women with a) CPP or b) PBS recruited from Chicagoland area clinics, community advertisements, and by mailed invitations to patients in our system's electronic health record databases. CPP was defined as pain lasting three months or longer in the area between the umbilicus and inguinal ligament. Symptoms could not solely be perceived on the skin (as in vulvodynia), only involve the hip or back, or only occur with menses (isolated dysmenorrhea). PBS patients met the CPP criteria and also reported urgency or frequency for at least three months' duration (see Supplemental Material for detailed criteria). Controls were healthy, pelvic pain-free, PBS cohort age-matched patients (± 5 years) recruited from the same population as above.

Cases were limited to ages 18–55 years old. Exclusion criteria included: pregnancy, active urogenital infection, prior urogenital malignancy, unexplained hematuria, active nephro/ureterolithiasis, vaginal prolapse exceeding second degree, refusal of vaginal examination, and unwillingness to avoid short-acting opioids prior to examination. All participants received a stipend of \$50. The NorthShore University Health System Institutional Review Board approved the study.

Study procedure

At the screening visit, one examiner (FT) conducted a complete abdominopelvic examination. We used the vaginal palpometer described below to calibrate exam palpation pressure to 0.4–0.6 kg/cm², and asked participants to rate tenderness at multiple palpation sites using a numeric rating scale (NRS, 0-no pain to 10-worst imaginable pain). Vaginal

tissue compliance, voluntary pelvic floor contractility, and pelvic floor gross muscle strength were quantified on exam using Likert scales (see clinical exam scoring criteria in Supplemental Material). We diagnosed pelvic organ prolapse using standard POP-Q criteria (except isolated cervical elongation exceeding 2 cm was not treated as prolapse).¹⁵

Participants completed medical history questionnaires covering prior surgery, medication use, other treatments, and menstrual history. They also completed the State-Trait Anxiety Inventory (STAI), Center for Epidemiologic Studies Depression (CES-D) survey, and Patient Reported Outcomes Measurement Information System (PROMIS) computer adaptive tests for fatigue, anxiety, depression, pain behavior, pain interference, and sleep impairment.^{16–18} Pain patients also completed the McGill Pain Questionnaire - short form.¹⁹

Experimental pain measurement was performed at two subsequent visits in a temperature-controlled research examination room. The sessions were planned for one month apart, although repeat sessions were adjusted due to personal circumstances in 4 participants (see participant flow chart, Figure 1). We assessed pelvic floor sensitivity at the bilateral iliococcygeus, anteriorly under the bladder and posteriorly against the anorectal raphe using our previously validated vaginal pressure algometer in a randomized order (see Supplemental Material, Algometer for details).⁶

Both post-PPT pain (NRS 0–10) and duration were recorded to evaluate the safety and comfort of PPT testing. Post hoc, we recognized this recorded safety data is a measure of sustained pain. Following prior work in neuropathic pain we conducted post-hoc analysis of these results in order to characterize sustained pain (hereafter referred to as *aftersensation pain*).^{20,21}

Study Size

Our initial sample size requirements were based on preliminary data suggesting a 0.5 kg/cm² difference between PBS patients and pain-free controls ($\alpha=0.01$, $\beta=0.2$), and were estimated at 22 participants per group. It was assumed the CPP group had similar size requirements. We specify three primary contrasts for formal hypothesis testing: determining if group differences exist for pelvic floor PPTs, self-reported pain with clinical palpation, and duration of time for pain to return to baseline after clinical assessment between the CPP/PBS and the HC population. All other contrasts are considered exploratory.

Statistical Analysis

STATA 13.1 (StataCorp LP, College Station, TX) was used for statistical analysis. We had complete case data for the first session of clinical palpation and PPT testing. Since the pain data was not normally distributed as confirmed by Shapiro-Wilk tests, group differences were evaluated with Dunn's test with Šidák's correction for multiple comparisons. Bonferroni adjustments were made for variables evaluated with chi square tests. We used Spearman correlations to identify potential confounders of the group and pressure-pain sensitivity relationship, among pain-free participants, and verified this with stepwise linear regression. Coefficients from this regression model were used to standardize PPT estimates, ultimately including age and genital hiatus for subsequent modeling. To further evaluate the

clinical significance of palpation pain, PPT and aftersensations in the general population, we adjusted for prevalence using a biased-bootstrap Monte Carlo resampling method.²² Biased resampling was performed such that the simulated population contained 15% pain subjects, assuming combined prevalence of 11% CPP only and 4% with PBS.^{2,23} The model also incorporated a 15% random Poisson noise to account for measurement error. As an alternative verification for correct prevalence adjustment, we performed binomial regression with sample weighting.²⁴ Receiver operating characteristics were tabulated to determine the area under the curve for both Monte Carlo simulations and sample weighting results.

Results

Initially, 93 study participants were recruited, with 42 pain-free controls and 46 patients with either CPP or PBS completing at least one PPT testing session (Figure 1). Women with CPP and PBS had comparable demographic factors, anatomy, and peripheral sensitivity (Table 1 and 2). However, women with PBS reported more pain when the bladder or adjacent regions were palpated ($p < 0.05$, Table 2). Women with and without CPP/PBS in the study had similar age, weight, and pregnancy history, and marital status (Table 1). Women with CPP were more likely to be college educated than pain-free women. As anticipated, higher levels of psychological distress and prior diagnosis of endometriosis and dysmenorrhea were also more common among CPP/PBS patients (Table 1). Significant differences in demographic factors were not observed between women with CPP and PBS.

Clinical tenderness and mechanical thresholds

On clinical examination, measures of pelvic floor flexibility, strength and tone did not differ between groups (Table 2). However, routine palpation elicited more self-reported pain (tenderness) in both CPP and PBS patients at almost every pelvic site (Table 2). Aside from genital hiatus (Table 2), there were no consistently observed group differences in myofascial anatomy or function between women with CPP or PBS and pain-free controls.

We next analyzed the PPT results to evaluate potential mechanisms underlying the pelvic floor tenderness reported by CPP and PBS patients. Since differences other than bladder sensitivity were not statistically significant between these two groups, they were grouped together (referred to collectively hereafter as CPP/PBS) for the remainder of the pelvic floor targeted analyses. Across all four pelvic floor sites, PPTs in women with CPP/PBS were lower (meaning higher pain sensitivity) than in pain-free participants (CPP/PBS: 1.18 [interquartile range: 0.87–1.41] kg/cm², pain-free participants: 1.48 [IQR 1.11–1.76] kg/cm²; individual sites are listed in Table 2, p 's < 0.001). Reports of pain aftersensation following completion of PPT testing were more intense and prolonged in women with CPP/PBS (Table 2, p 's < 0.001). We compared the cumulative sum of tenderness pain (all of the sites listed in Table 2) across participants to their average PPT and aftersensation duration with multivariate regression. Across all of the groups ($R^2 = 0.51$, $p < 0.001$) and within women with CPP/PBS ($R^2 = 0.41$, $p < 0.001$) increased tenderness was associated with lowered PPTs (p 's < 0.01) and longer aftersensation (p 's < 0.001).

To identify any potential confounders of pain sensitivity, we examined the correlation between candidate demographic, medical history and pelvic floor predictors of average

pelvic PPT in pain-free controls (Table 3). Age ($r=0.57$), genital hiatus (0.46), pelvic floor tone (-0.38), and introital flexibility (0.32) were significantly correlated with pelvic floor pain threshold. Forward stepwise regression confirmed the primary contributing factors to PPTs in pain-free participants were age and genital hiatus ($R^2=0.42$, $p<0.001$). A one cm increase in genital hiatus was associated with a 0.3 ± 0.1 kg/cm² increase in pelvic PPT ($p<0.01$). Increasing participant age was associated with a reduction of 0.016 ± 0.005 kg/cm²/yr in pelvic PPT ($p<0.01$). After adjusting for median age (32) and genital hiatus length (1.5 cm) PPT differences remained robust between women with CPP/PBS (IQR 0.98 [0.68–1.13] kg/cm²) and pain-free controls (1.36 [IQR 1.20–1.61] kg/cm², $p<0.001$). We also confirmed that the identity of the examiner (clinician vs. trained non-clinicians) had no contributing effect ($p=0.85$). Intraclass correlations of average PPTs across sessions were 0.86 (95% CI 0.72–0.92) for pain-free subjects and 0.81 (95% CI 0.64–0.90) for subjects with CPP/PBS suggesting PPTs were stable over a 1 month period.

Population Characteristics

To place the value of PPT and aftersensation testing in a clinical context, we used our data to model a hypothetical population using Monte Carlo simulation, adjusting for published estimates of CPP prevalence. In the simulation, again we observe significant differences in the distribution of pelvic floor tenderness, PPTs and aftersensation between the groups (Kolmogorov-Smirnov tests p 's <0.001 Figures 2a–c). Tenderness reasonably discriminates between women with CPP/PBS and those pain-free (area under the curve [AUC]=0.76, 95% CI 0.74 – 0.78). However, PPTs (AUC=0.84, 95% CI 0.82 – 0.85) provided better discrimination than tenderness ratings alone ($p <0.05$). Additionally, combined consideration of PPTs and aftersensation (AUC=0.87, 95% CI 0.86 – 0.88) was better than PPT alone ($p<0.05$). A similar improvement in discrimination was observed using an alternative adjustment technique, sample weighting (AUC=0.84 vs AUC=0.88). The independent contributions of mechanical thresholds and aftersensation can be observed on a margin plot (Figure 3). Inspecting the distribution on a histogram (Figure 2b) it is easily observed that one-third of women with CPP/PBS have a phenotype of substantially reduced mechanical sensitivity (0.8 kg/cm²) at a level rarely found in pain-free participants. In the remaining two-thirds of CPP/PBS participants who have more moderate mechanical sensitivity (>0.8 kg/cm²), one-third exhibit aftersensation duration exceeding five minutes. In contrast, aftersensation duration above five minutes is only observed in less than 10% of healthy controls (Figure 2c). Pain lasting longer than 10 minutes was observed in less than 2% pain-free participants, but in 20% of women with CPP/PBS. These findings imply the existence of two independent components mediating pelvic floor dysfunction: a rapid time scale component reflecting increased mechanical sensitivity, and another component involving prolonged pain.

Comment

Main findings

This study extends quantitative sensory profiling of pain mechanisms to the pelvic floor in CPP. Consistent with our hypothesis, and prior work in idiopathic pain disorders, we found enhanced pressure-pain sensitivity at the pelvic floor in both PBS and CPP compared to

pain-free controls, but not between pain groups. We extend our prior published findings conducted in a general CPP population,⁷ and show that genital hiatus and age are the key factors that should be controlled for when measuring pelvic floor mechanical sensitivity, even among pain-free participants. Moreover, we find that predictive models incorporating this mechanical sensitivity measure, along with the presence of prolonged pain following performance of these measures, accurately characterize CPP/PBS patients. Unlike clinical tenderness report, which is the final output of the brain considering all the inputs and contexts engaging the central nervous system, these constructs map to specific alterations in peripheral nociceptive mechanisms--reduced mechanical thresholds (measured by PPT), and increased aftersensation duration (measured by duration of pain sensation after PPT provocation). On the other hand, our results showed that magnitude of palpation pain correlates with PPTs and aftersensation, suggesting its utility in the clinic, where quantitative sensory testing is unavailable. Future studies could use our methods to determine if these measures can help refine selectivity of treatments, which presently are largely determined by symptoms alone.

Strengths and limitations

Our study's main strengths are an extensive characterization of the perineum and pelvic floor and repeated experimental measures to minimize residual confounding. Although it may be hypothesized that psychological effects, age, tone, flexibility at the introitus and vaginal anatomy could affect pelvic mechanical sensitivity, investigation of these factors are limited.^{9,25} In particular, further studies should consider that either a 0.5 cm reduction in genital hiatus, or a 10 year reduction in age, reduces pelvic floor PPTs by about 10% relative to our reported averages. This is a large difference, considering there is only a 25% difference in these factors between women with CPP and pain-free controls. Limitations include the cross-sectional nature of the study and lack of blinding of the primary examiner in the later stages of the study. The blinding issue was unavoidable as a mid-study IRB review mandated that only a clinician could perform PPTs. However, we showed no effect on PPTs by examiner (clinician vs. trained non-clinicians) suggesting minimal effect of any ascertainment bias, and we have previously shown the testing has adequate inter-rater reliability between examiners (Supplemental material).

Comparison with existing literature

Our results show local alterations in PPTs (mechanical sensitivity) and pain aftersensations are associated with a pain phenotype, even after controlling for potential morphological and demographic confounders. The observed AUC (0.85) for PPTs are comparable for facial PPTs in temporomandibular joint syndrome (TMD=0.84–0.92)²⁶, and paraspinal PPTs for chronic low back pain (0.87).²⁷ Prior studies have also shown that reduced PPTs and prolonged aftersensation are linked to chronic pain.^{28–30} Although in a recent study Lai and colleagues did not identify PPT differences in female PBS patients, we had more power to detect differences, included a positive control group, and included pelvic floor assessment.⁴ They did note patients with PBS report higher levels of pain following tonic pressure application (2 kg or 4 kg). Another study has shown women with PBS have reduced conditioned pain modulation, suggesting that mechanisms affecting pain sensitivity in PBS

can have effects on central pain processing.³¹ Thus, combinations of peripheral and central pain modulatory dysfunction could contribute to pain phenotypes.

Implications for mechanisms underlying CPP/PBS

The observed PPT and aftersensation pain differences imply two different alterations may occur in CPP/PBS. The decrease in PPTs likely reflects increased excitability in peripheral A-mechanically-sensitive nerve fibers (which respond on a rapid time scale) responsible for perception of “first pain”.^{32–34} In contrast, our observed aftersensation differences point to also aberrant C nerve fiber activity, which typically relays information about pain and temperature sensation. These C fibers are primarily implicated in sustained perception of pain, labelled “second pain.”^{35–37} As each class of fibers are differentially modulated by given treatment modalities (A-fibers are preferentially blocked by compression/ischemia, while C-fiber activity is reduced in animal models by DMSO or anticonvulsants), this points to the need to test our identified mechanistic classifications to determine if certain subtypes of CPP/PBS selectively respond to physical therapy (A-fiber predominant) vs. oral neuromodulating drugs (C-fiber predominant).^{38–41} However, we will need to validate these candidate subtypes in larger studies.⁵ Of note, this also points to a potential opportunity to explore longitudinally whether pain-free controls exhibiting either low PPTs or prolonged pain post-pelvic exam represent an at risk-cohort for future development of CPP/PBS. Our findings could be readily translated to the ambulatory clinic-based screening studies for CPP/PBS risk, if clinicians could consistently document pelvic floor tenderness ratings using calibrated clinical pelvic floor palpation (to mimic pressure pain testing), along with recording the presence of prolonged pain following pelvic exam.

Conclusion

Both pelvic floor experimental pressure pain sensitivity and aftersensation duration following pelvic floor stimulation are enhanced in CPP/PBS. Pelvic floor pain sensitivity assessment is influenced by both age and genital hiatus, which should be accounted for in future studies. In particular, more attention to women who report prolonged pain after intercourse or routine pelvic exam is warranted in light of the association of aftersensation pain and CPP/PBS, including longitudinal studies of incident CPP/PBS and treatment response.

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1 pain-free followup session done earlier than 4 weeks, 1 CPP/PBS followup session done before 3 weeks, and 2 CPP/PBS followup sessions done between 3-5 mths

Figure 1. Study recruitment flow chart

Initially, 93 study participants were recruited, with 42 pain-free controls and 46 patients with either CPP or PBS completing at least one PPT testing session. Subjects that participated in the initial visit, but failed to return for the follow up visit due to scheduling issues or because they experienced a pain flare are shown in the chart above.

Figure 2. Distribution of pain sensitivity profiles in pelvic pain phenotypes in Monte Carlo simulations

Monte Carlo simulations of pelvic floor pain sensitivity and palpation-related pain between CPP/PBS and pain-free controls modeled for a general population. Panels show a) histograms of palpation-induced pelvic floor tenderness (numeric rating scale [NRS] 0–10), b) pelvic floor pressure pain thresholds, and c) pain after-sensation duration, respectively with error bars indicating SEM.

Figure 3. The combined effects of alterations in pelvic floor mechanical thresholds and prolonged aftersensation on likelihood of being CPP/PBS

This margin plot shows the probability of being CPP/PBS (Y axis) at different pelvic floor mechanical thresholds (X axis) given shorter or longer duration of painful aftersensation. Aftersensation duration up to 5 minutes are shown in green, 5 and 10 minutes in black, and >10 minutes in red. The percent of the overall population with each aftersensation range are shown in parentheses. Women with below average levels of mechanical pain sensitivity (e.g. 1.5 kg/cm²) are still likely to have CPP/PBS if they exhibit prolonged aftersensations.

Table 1

Sociodemographic and medical history profiles between controls and women with chronic pelvic pain (CPP) or painful bladder syndrome (PBS).

	Controls n=42	CPP n=23	PBS n=23
Age	32 (23–44)	35 (29–44)	31 (27–39)
Weight (lb)	146 (127–192)	170 (140–199)	145 (128–183)
Marital Status			
Married/Committed	20/42 (48%)	15/23 (65%)	14/23 (61%)
Single	21/42 (50%)	5/23 (22%)	7/23 (30%)
Divorced/Separated/Widowed	1/42 (2%)	3/23 (13%)	2/23 (9%)
Race			
Caucasian	30/41 (73%)	15/23 (65%)	21/23 (91%)
African American	8/41 (20%)	4/23 (17%)	2/23 (9%)
Other	3/41 (7%)	4/23 (17%)	0/23 (0%)
Education level			
High school equivalent or less	4/41 (10%)	2/22 (9%)	3/23 (13%)
Some college	20/41 (49%)	3/22 (14%)	10/23 (43%)
Associate degree	2/41 (5%)	0/22 (0%)	1/23 (4%)
College/Bachelor's degree	12/41 (29%)	13/22 (59%)	7/23 (30%)
Post-graduate degree	3/41 (7%)	4/22 (18%)	2/23 (9%)
Parous	12/42 (29%)	10/23 (43%)	11/23 (48%)
PROMIS physical functioning	59 (56–62)	43 (38–54)	42 (38–48)
Depression	8/42 (19%)	10/23 (43%)	12/23 (52%)
CES-D Score	2 (0–4)	13 (3–21)	15 (8–23)
Anxiety	8/42 (19%)	8/23 (35%)	13/23 (57%)
STAI score	27 (24–32)	38 (29–48)	43 (36–50)
Abuse	6/42 (14%)	12/23 (52%)	15/23 (65%)
Dyspareunia	3/35 (9%)	8/13 (62%)	10/11 (91%)
Prior abdominal/pelvic surgeries	16/42 (38%)	17/23 (74%)	18/23 (78%)
Dysmenorrhea	15/35 (43%)	14/15 (93%)	18/19 (95%)
Endometriosis	0/42 (0%)	5/23 (22%)	8/23 (35%)
Fibromyalgia	0/42 (0%)	3/23 (13%)	2/23 (9%)
Chronic headaches	4/42 (10%)	2/23 (9%)	5/23 (22%)
Irritable bowel syndrome	1/42 (2%)	3/23 (13%)	9/23 (39%)
Duration of pelvic pain (years)		4 (2–7)	6 (1–9)

Data are specified as median (interquartile range), or as a proportion (percent) for controls, CPP and PBS subjects. Correction for 3 comparisons (Healthy vs CPP, Healthy vs PBS, and CPP vs PBS) for categorical variables were determined with chi-square Bonferroni adjustments or for continuous variables with Dunn's test with Šidák's correction. Significant differences ($p < 0.05$) between Healthy vs CPP or Healthy vs PBS are shown in bold. Significant differences between CPP and PBS were not observed. CESD - Center for Epidemiologic Studies Depression survey, STAI - State-Trait Anxiety Inventory.

Table 2

Physical exam and QST differences between controls and women with chronic pelvic pain (CPP) or painful bladder syndrome (PBS).

Variable	Healthy	CPP	PBS
Introitus Flexibility (0–3)	2 (1–2)	2 (1–2)	2 (2–2)
Pelvic Floor Relaxation (0–2)	0 (0–0)	0 (0–0)	0 (0–0)
Pelvic Floor Strength (0–5)	2 (1–3)	2 (1–3)	2 (2–3)
Pelvic Floor Tone (–9 – +9)	0 (0–2)	0 (–2–3)	0 (–2–2)
Genital Hiatus (cm)	1.5 (1.0–2.0)	2.0 (1.8–2.5)	2.0 (1.5–2)
POP-Q Stage			
0	32/42 (76%)	21/23 (91%)	19/23 (83%)
1	8/42 (19%)	1/23 (4%)	2/23 (9%)
2	2/42 (5%)	1/23 (4%)	2/23 (9%)
<i>Right SI Joint</i>	0.0 (0.0–0.0)	0.0 (0.0–1.5)	0.0 (0.0–1.5)
<i>Left SI Joint</i>	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.5)
<i>Right Pubococcygeus</i>	0.0 (0.0–0.0)	0.0 (0.0–3.0)	3.0 (1.0–5.5) *
<i>Left Pubococcygeus</i>	0.0 (0.0–0.0)	1.0 (0.0–3.0)	3.0 (0.5–5.0)
<i>Right Iliococcygeus</i>	0.0 (0.0–0.0)	0.0 (0.0–3.0)	1.0 (0.0–5.0)
<i>Left Iliococcygeus</i>	0.0 (0.0–0.0)	0.0 (0.0–3.0)	2.0 (0.5–5.0) *
<i>Right Obturator</i>	0.0 (0.0–0.0)	0.0 (0.0–1.5)	1.0 (0.0–4.5)
<i>Left Obturator</i>	0.0 (0.0–0.0)	1.0 (0.0–3.5)	2.0 (0.0–3.5)
<i>Bladder</i>	0.0 (0.0–0.0)	0.0 (0.0–2.5)	5.0 (3.0–6.0) *
<i>Urethra</i>	0.0 (0.0–0.0)	0.0 (0.0–1.0)	4.0 (0.0–5.0) *
<i>Uterus</i>	0.0 (0.0–0.0)	1.5 (0.0–5.0)	4.0 (0.0–6.0)
<i>Uterosacral Ligaments</i>	0.0 (0.0–0.0)	0.0 (0.0–4.0)	1.5 (0.0–5.0)
<i>Right Vaginal Fornix</i>	0.0 (0.0–0.0)	0.0 (0.0–4.5)	4.0 (0.0–6.5) *
<i>Left Vaginal Fornix</i>	0.0 (0.0–0.0)	2.0 (0.0–5.0)	4.0 (0.5–6.0)
<i>Vaginal tenderness</i>	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.8)
Vaginal PPT Values (kg/cm ²)			
<i>Right Sidewall</i>	1.5 (1.2–1.9)	1.2 (0.9–1.4)	1.4 (0.8–1.6)
<i>Left Sidewall</i>	1.2 (1.0–1.6)	1.1 (0.9–1.3)	0.9 (0.7–1.2)
<i>12 o'clock</i>	1.5 (1.1–1.8)	1.1 (0.8–1.3)	0.9 (0.7–1.2)
<i>6 o'clock</i>	1.5 (1.2–1.8)	1.2 (0.9–1.5)	1.2 (0.9–1.4)
<i>Aftersensation (NRS)</i>	0.0 (0.0–0.5)	1.0 (0.0–1.5)	1.0 (0.5–1.8)
<i>Aftersensation (minutes)</i>	0.0 (0.0–1.0)	2.0 (0.0–9.5)	1.0 (0.0–9.0)

Data are specified as median (interquartile range), or as a proportion (percent) for controls, CPP and PBS subjects. Significant differences ($p < 0.05$) after corrections for multiple comparisons between CPP and PBS vs healthy controls are shown in bold. Significant differences between subjects with CPP and PBS are designated with an *. NRS – numeric rating scale, PPT – pressure pain threshold

Table 3
Correlation between vaginal pressure pain threshold (PPT) and other factors in healthy controls

1. Average vaginal PPT Value	1	2	3	5	6	7	8	9	10	11	12
2. Education	0.05										
3. Age	0.57	0.12									
4. CESD Score	-0.03	-0.06	-0.22								
5. STAI Score	-0.14	0.05	0.04	0.63							
6. Prior vaginal delivery	0.27	-0.10	0.40	0.07	0.15						
7. Prolapse	0.07	0.24	0.26	-0.08	0.06	0.18					
8. Genital Hiatus	0.46	0.01	0.31	-0.19	-0.13	0.05	0.20				
9. Pelvic Floor Tone	-0.38	-0.02	-0.39	0.41	0.35	-0.10	-0.45	-0.48			
10. Introitus Flexibility	0.32	0.07	0.61	-0.34	-0.13	0.42	0.42	0.36	-0.38		
11. Pelvic Floor Relaxation	0.25	0.14	0.18	0.12	0.01	-0.16	0.00	-0.03	-0.03	-0.07	
12. Pelvic Floor Strength	0.00	0.00	0.10	0.00	0.09	0.11	0.11	-0.25	-0.12	0.10	0.25

CESD - Center for Epidemiologic Studies Depression survey, STAI -State-Trait Anxiety Inventory. The significance of correlation coefficients as follows: $|r| > .49 = p < 0.001$, $|r| > .39 = p < 0.01$, $|r| > .30 = p < 0.05$.