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Quantitative Assessment of Non-Pelvic Pressure Pain Sensitivity in Urological Chronic Pelvic Pain Syndrome: A MAPP Research Network Study

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Conflicts of Interest

Dr. Harte reports grants from National Institutes of Health (NIH) during the conduct of the study; and grants from NIH, Veterans Affairs, Cerephex, Eli Lilly, American Cancer Society, grants and personal fees from Aptinyx, personal fees from SUFU, Longitudinal Capital Management, University of North Carolina - Chapel Hill, and Arbor Medical Innovations (AMI) outside the submitted work. In addition, Dr. Harte has a patent (US 9307906) for the MAST System with royalties paid to Arbor Medical Innovations. Dr. Schrepf reports grants from NIH during the conduct of the study. Dr. Gallop has nothing to disclose. Dr. Kruger reports grants from NIH during the conduct of the study; grants and personal fees from AMI outside the submitted work. In addition, Dr. Kruger has a patent (US9307906) with royalties paid to AMI. Dr. Lai reports grants from NIH during the conduct of the study; other support from Medtronic, Allergan, Teva, and Aquinox outside the submitted work. Dr. Sutcliffe has nothing to disclose. Mrs. Halvorson has nothing to disclose. Mr. Ichesco has nothing to disclose. Dr. Naliboff has nothing to disclose. Dr. Afari reports grants from NIH during the conduct of the study. Dr. Harris reports grants and other support from Pfizer and Aptinyx outside the submitted work. Dr. Farrar reports personal fees from Pfizer, Daiichi Sankyo, Cara Therapeutics, Biogen, Aptinyx, Campbell Alliance, NIH-NIAMS, Analgesic Solutions, Novartis, DepoMed, Jansen, Evadera, and Wolhers Kluwer Health all outside the submitted work. Dr. Tu reports personal fees from AbbVie outside the submitted work. Dr. Landis has nothing to disclose. Dr. Clauw reports grants and personal fees from Aptinyx and Pfizer, and personal fees from Daiichi Sankyo, Intec Pharma, Eli Lilly and Company, Samumed, Theravance, Tonix, Williams & Connolly LLP, and Zynerba outside the submitted work.

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INTRODUCTION

Urologic chronic pelvic pain syndrome (UCPPS) is characterized by persistent pain in the pelvic region and lower urinary tract symptoms.[63] It encompasses men and women with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS), both of which are prevalent and debilitating.[3; 5; 58] Although UCPPS was previously considered to be the result of damage and inflammation in the bladder and pelvic region,[39] emerging evidence suggests multiple inter-related underlying mechanisms that extend beyond local pathophysiology to encompass central nervous system (CNS) processes. Functional, morphological, and neurochemical brain alterations have been identified in UCPPS.[12; 17; 29; 37; 41-43; 46; 47; 57; 94] Many UCPPS patients also report widespread pain and constitutional symptoms such as fatigue and cognitive dysfunction.[49; 50; 80] Similar brain abnormalities and symptoms occur in chronic overlapping pain conditions (COPCs) that are frequently comorbid with UCPPS,[8] including fibromyalgia and irritable bowel syndrome (IBS), where CNS mechanisms are also believed to play a prominent role.[53; 56] Together these findings indicate that altered CNS mechanisms likely contribute to UCPPS symptoms in at least a subset of patients.

Central sensitization is a potential mechanism driving the pain experience in UCPPS. Broadly defined as a CNS-mediated amplification of nociceptive processing,[95; 96] central sensitization can be inferred clinically by evidence of pain hypersensitivity (i.e., allodynia and hyperalgesia) on quantitative sensory testing (QST). Whereas primary hyperalgesia at a symptomatic or injured body site implicates local factors such as inflammation and peripheral sensitization, hyperalgesia at remote and asymptomatic body sites suggests pain amplification organized within the CNS.[1] Several studies have found increased pain sensitivity at remote body sites in UCPPS patients, although these were limited by primarily small and only female samples. In an early study, female IC/BPS patients were shown to have significantly decreased pressure pain thresholds (PPT) and pain tolerance throughout the body at traditional fibromyalgia tender points compared to healthy controls.[9] Similar findings of diffuse hyperalgesia were shown in some subsequent studies,[36; 60; 61; 72] but results have been inconsistent.[19; 48] The heterogeneity of these findings underscores the need to more thoroughly characterize pain sensitivity in UCPPS.

The objective of the present study was to assess experimental pressure pain sensitivity in a large sample of males and females with UCPPS. This work was carried out as part of the *Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network* -- a major initiative of the National Institute of Diabetes and Digestive and Kidney Diseases to investigate clinical and mechanistic characteristics of UCPPS.[11; 51] Our primary aim was to determine whether pain sensitivity at an asymptomatic, remote body site (i.e., thumbnail bed) differed between UCPPS participants, healthy controls, and a comparator group of individuals with a mix of COPCs. Our secondary aim was to explore relationships

between pain sensitivity and UCPPS symptoms cross-sectionally, during flares, and over a one-year period. We hypothesized that UCPPS participants would exhibit remote hyperalgesia consistent with central sensitization, and that this finding would be driven by the subset of UCPPS participants with more widespread symptoms.

METHODS

Study Design and Population

The primary objectives of the MAPP Network, recruitment strategy, and inclusion and exclusion criteria have been previously described in detail.[11; 51] Briefly, in the first phase of the MAPP Network (MAPP I, 2009-2014), a network-wide Epidemiology/Phenotyping (EP) Study recruited a total of 1039 participants in three groups from nine U.S. academic medical centers: UCPPS (n= 424), healthy controls from the community (n = 415), and a mixed pain comparison group comprised of individuals with other COPCs (i.e., FM, Irritable Bowel Syndrome [IBS], Temporomandibular Disorder [TMD], Chronic Fatigue Syndrome [CFS], Vulvodynia, Migraine; n = 200). Although these conditions may have different etiologies, they share a common set of clinical features and are hypothesized to also share similar central mechanisms.[56] Participants with UCPPS completed in-clinic visits at baseline, six months and one year; healthy controls and mixed pain participants were assessed at baseline only. UCPPS participants also completed biweekly online assessments to document their urologic and pelvic pain symptoms over the one year study follow-up.[51]

Primary inclusion criteria for UCPPS was a clinical diagnosis of IC/BPS or CP/CPPS, pain severity of at least 1 out of 10 on a numerical rating scale (NRS), and urinary symptoms the majority of the time over the last three months. Participants in the mixed pain group met criteria for at least one COPC, though participants from both the UCPPS and mixed pain groups could and did meet criteria for more than one condition. Healthy controls were required to not have UCPPS symptoms, a chronic pain condition, pain in more than one body region, or psychiatric or medical condition that would interfere with study participation. All participants were age 18 or greater and were allowed to continue their standard medications during the study.

A subset of participants underwent pressure-based QST as one of several secondary aims of the MAPP Network. A pressure pain sensitivity protocol was implemented at six participating MAPP sites in phases after the parent EP Study began. The implementation timeline varied by site based on testing equipment availability, Institutional Review Board (IRB) and other regularity approvals, and completion of research staff training in experimental pain testing procedures. Following approval and training, pressure pain sensitivity assessments were conducted at the remaining in-person visits. Healthy control and mixed pain groups were only tested at baseline, while UCPPS participants underwent up to three assessments: baseline, six months, and one year depending on their timing of enrollment. Participants were excluded from testing if they frequently or habitually used artificial fingernails or fingernail enhancements that would interfere with assessments performed on the thumbnail (n = 4 participants). Tolerability for the procedure was high among eligible participants: only 10 individuals opted out of one or more sessions. The remaining 288 participants (n = 153 UCPPS; n = 100 healthy controls; n = 35 mixed pain)

provided at least one pressure pain record suitable for analysis. For UCPPS participants, 62 had measurements beginning at baseline, 52 had measurements beginning at the six month visit, and 39 had only one measurement at the one year visit

All procedures were approved by the IRB at each participating institution and all participants provided written informed consent.

Self-Reported Outcome Measures

Urinary Symptoms and Genitourinary Pain—Urinary symptoms and genitourinary pain were assessed in the UCPPS group using two separate composite measures derived from a combination of components of the Genitourinary Pain Index (GUPI),[10] and Interstitial Cystitis Symptom Index (ICSI),[65] based on psychometric analyses performed on MAPP I baseline data.[25] Individual urinary items assess urgency and frequency, nocturia, and bladder emptying combined into a Urinary Symptom score (range 0-25) with higher scores indicating greater symptom severity. Individual pain items assess bladder pain and burning, pain or discomfort during urination, during/after sexual climax, and bladder filling, and pain relieved by voiding combined into a Genitourinary Pain score (range 0-28), with higher scores indicating greater pain.

Pain Severity and Pain-related Interference—The Brief Pain Inventory (BPI) was used to assess overall clinical pain in the UCPPS and mixed pain groups. It consists of two subscales: Pain Severity and Pain Interference. Pain Severity is calculated as the mean of four items which assess worst, least, and average pain for the last week, and current pain on 0–10 scales. Pain Interference is calculated as the mean of seven items, also on 0-10 scales, which measure the degree to which pain interferes with life activities (general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) over the previous week.[87] Higher scores indicate increased pain severity and interference.

Spatial Extent of Pain—The spatial extent or distribution of pain was assessed using the total number of sites from a 45-site body map [51] which has been associated with disease burden, immunological, and neuroanatomical findings in previous MAPP studies.[46; 77; 79]

Catastrophizing—Catastrophizing refers to the belief that one's pain is overwhelmingly awful and burdensome. The 6-item catastrophizing subscale from the Coping Strategies Questionnaire (CSQ) was used to measure this characteristic.[76] Total scores range from 0 −36, and higher scores are indicative of greater catastrophizing when a person feels pain.

Anxiety and Depression—Anxiety (7 items, range 0-21) and depression (7 items, range 0-21) were measured using the Hospital Anxiety and Depression Scale (HADS).[98] Individual responses range from 0 (e.g., "Not at all") to 3 (e.g., "Most of the time") for each item experienced over the last week. Higher scores indicate greater depression and anxiety.

Generalized Sensory Sensitivity and SPACE—A recent MAPP Network study using exploratory and confirmatory factor analysis identified two general factors or symptom clusters expressed in individuals with UCPPS and other COPCs.[80] One factor, termed

Generalized Sensory Sensitivity (GSS), is characterized by a tendency to experience, notice, and/or report increased sensitivity to external stimuli across multiple sensory modalities, and to symptoms or sensations occurring within the body (somatic awareness), and widespread pain or tenderness. The other cluster is characterized by an amalgamation of constitutional symptoms that often become disrupted in tandem in COPCs - Sleep, Pain, Affect, Cognition, and Energy (SPACE). Higher GSS and SPACE factor scores indicate greater sensitivity or symptom severity.

Physical Well-Being—Perceived physical well-being was measured using a composite measure of all physical health items of the Short Form (SF)-12 Health Survey, referred to as the Physical Components Summary (PCS).[89] Responses range from 1 (“All of the time”) to 4 (“None of the time”). Higher scores indicate better physical well-being.

One year UCPPS symptom trajectories—Previous MAPP efforts have used functional clustering techniques to identify pattern of change in UCPPS symptoms over a 48-week period of observation [59]. This algorithm was applied to the Urinary Symptom and Genitourinary Pain scores in the MAPP I longitudinal cohort.[25] Because substantial regression-to-the-mean or enrollment effects were observed in MAPP I,[82] the analysis selectively used weeks 4-48, which resulted in three broad categories of symptom change: “improved,” “stable,” and “worsened.” Initially, Ward’s minimum variance was used to classify a participant’s trajectory, and in the second iterative classification step, one participant was removed and new mixed effects models were estimated by K-mixture functional mixed effects models.[27] The posterior probability of the excluded participant belonging to one of the groups was then calculated, and the steps were repeated until group assignments for each participant were stable, as previously reported.[27; 78] The number of clusters was selected based on Kullback-Leibler (KL) criterion.[45] These outcomes were then used in logistic regression models to determine if pressure pain sensitivity at baseline was associated with the likelihood of improvement or worsening in the subsequent 48-week period.

Flare Status—Flares refer to self-reported, time-limited amplification of UCPPS symptoms. The Symptom and Health Care Utilization Questionnaire developed for the MAPP Network contains a binary (yes/no) question about symptom flare status (i.e., “. . .are you currently experiencing urologic or pelvic pain symptoms that are much worse than usual?”). Positive responses indicate that the participant reports currently experiencing a symptoms flare.

COPC Classification—COPC status (yes/no) was assessed using standardized self-report classification criteria for FM,[93] CFS,[21] IBS,[14] migraines,[66] TMD,[15] and vulvodynia (females only).[92]

Pressure Pain Sensitivity

Pressure pain sensitivity was assessed using the University of Michigan-developed Multimodal Automated Sensory Testing (MAST) system (Arbor Medical Innovations, Ann Arbor, MI).[30; 34; 62; 77; 90] The MAST system is an investigational-use QST platform

that consists of a wireless, hand-held stimulator able to provide controlled mechanical stimulation, a touchscreen-based rating scale to capture participant feedback, and another computer to configure and control the test. The design and validation of the pressure stimulator was described previously.[35]

During testing, an ascending sequence of pressures starting at 0.5 kgf/cm^2 and increasing in 0.5 kgf/cm^2 steps were delivered by a 1 cm^2 rubber probe to the participants' dominant thumbnail. A ramp rate of 4.0 kgf/cm^2/s was used to reach each pressure level prior to maintaining a constant pressure for 5-s. After each stimulus, a 20-s inter-stimulus interval allowed stimulation site tissue to equilibrate between stimuli. Participants rated perceived pain intensity after each stimulus using a digital 0–100 NRS displayed on the touchscreen (0 = no pain; 100 = pain as bad as you could imagine). The test was completed when one of three stopping criteria were satisfied: a) the participant reached his/her pain tolerance and asked that the test be stopped, b) the participant reported a pain intensity of ≥ 80/100, or c) a maximum possible pressure intensity of 10 kgf/cm^2 was delivered. Average time to test completion was 5.1 minutes after which the data were automatically uploaded by the system to the MAPP Network Data Coordinating Center via a secure file transfer protocol for storage and analysis.

Captured pain ratings were used to generate a psychophysical function of each participant's pain sensitivity with pressure intensity and response magnitude represented on the x- and y-axes, respectively. Several metrics of pressure pain sensitivity were derived from these stimulus-response curves for analysis. *Pressure pain threshold (PPT)* was defined as the first pressure in a series of at least two consecutive pressures that evoked a sensation rated > 0/100. Pressure pain *tolerance* was defined as the last pressure delivered and rated. A three parameter logistic model was used to estimate the within-person inflection point on the stimulus-response curve between PPT and tolerance, referred to as *Pain50* (See Supplementary Fig. 1 for details on the calculation of Pain50).[26; 34; 40; 71; 73] The pain rating (0-100 NRS) evoked by 2.0 kgf/cm^2 was also extracted for analysis. This variable permitted analyses of a subjective response to a standardized physical stimulus tolerated by most participants.

Participants first underwent a MAST familiarization procedure and practice test prior to data collection on their non-dominant thumb. The purpose of familiarization was to teach participants how to perform the test correctly and reduce testing anxiety. Following task completion, research staff reviewed the participant's understanding of the procedure and provided additional guidance as necessary. Data from the familiarization task was not used for analysis. To ensure standardization across sites, scripted participant instructions were used and research staff completed in-person training prior to implementing the pressure pain sensitivity protocol. Supplemental training and technical assistance was provided multiple times per year in-person during MAPP Network meetings and as-needed by phone or webinar.

Data Analysis

Data cleaning and preparation—All pressure pain sensitivity data were independently visually inspected by three of the authors (SH, AS, RG). The purpose of this inspection was

to identify particular anomalous data-points likely to be the result of a technical error. In eight cases, pain ratings at one or more initial stimuli in the testing sequence (0.5-1.5 kgf/cm^2) were between 25-100, but were followed by several very low pain ratings (e.g., ratings of 0-3/100) before gradually increasing again as pressure intensity increased. In three additional cases, a ratings drop occurred later in the testing sequence in which a single low pain rating (0-3/100) occurred within a series of pain ratings at least 20 NRS units higher. Each of these instances were flagged for further discussion and it was determined by consensus that these were very likely user or device errors – these values were subsequently set to missing.

Normality of data was assessed for each group by visual inspection of histograms and boxplots, and formally through the Shapiro-Wilk test statistic (range 0-1; distributions with values ≥ 0.98 were considered normal). Box and Cox[6] power transformations were subsequently applied to any variable whose distribution showed deviation from normality in any of the three groups. As a result, log transformations were applied to the PPT and pain rating at 2 kg/cm^2 variables, and square-root transformations were applied to the tolerance and Pain50 variables. Analyses were performed using SPSS 24, SAS, and R 3.5. Two-tailed *P*-values ≤ 0.05 were considered significant.

Comparison of pressure pain sensitivity by group—For comparisons of pressure pain sensitivity by group, baseline data were used for healthy control and mixed pain groups, whereas the first available value was used for UCPPS participants (n = 153). Estimated mean differences adjusted for covariates were compared between groups for each of the four transformed pressure pain sensitivity measures using mixed-effects linear models. Fixed effects were group and a priori covariates age and sex. [4; 52; 74] Random intercept terms were included for clinical site performing the assessment. Overall omnibus testing was conducted followed by pairwise contrasts to detect group differences.

Association of pressure pain sensitivity with current UCPPS symptoms and clinical pain—Associations of pressure pain sensitivity measures with symptoms and clinical pain were limited to UCPPS participants with baseline pressure pain data (n = 62). This restriction was made because the MAPP I longitudinal cohort showed substantial evidence of regression-to-the-mean or enrollment effects[82] that would make the association of pressure pain sensitivity with symptom and pain measures acquired at six months or one year difficult to compare to the same relationships at baseline. Associations were analyzed by partial correlation coefficients controlling for age and sex.

Exploratory Analyses

Association of pressure pain sensitivity with symptom trajectories.: An exploratory analysis of pressure pain sensitivity with one year UCPPS symptom trajectories was performed among participants with baseline pressure pain values and sufficient longitudinal symptom data to be classified according to the clustering algorithm (n = 55). In this analysis, the transformed continuous Pain50 outcome was used. Binary logistic regression models were used to examine the contrast of improvement versus stable/worsened, and worsened versus stable/improvement for each symptom pattern. Models were adjusted for variables

found to be associated with symptom trajectories in a previous and larger analysis of MAPP I participants,[59] including age, levels of the relevant symptom (urinary severity or genitourinary pain) at week four, and the SF-12 PCS score.

Associations of pressure pain sensitivity with UCPPS symptom flares.: As an additional exploratory analysis, we assessed the possible relationships between pressure pain sensitivity measures and symptom flares in a sample of 22 participants who underwent experimental pain testing during a symptom flare and also during a time when they did not report a symptom flare. We compared the transformed Pain50 measure by paired-sample t-test to determine if pressure pain sensitivity changed during the experience of a symptom flare.

RESULTS

Participants

In this analysis, UCPPS participants were on average 44.2 (SD 16.3) years old and 49% of the sample was male. Healthy controls were 39.7 (SD 13.2) years old on average and 41% of the sample was male; mixed pain participants were 40.6 (SD 14.5) years old on average and 22.9% of the sample was male. Baseline demographics are shown in Table 1 for each group. Symptom measures and the prevalence of individual COPCs for the UCPPS and mixed pain groups are shown in Supplementary Table 1. Overall clinical pain severity was similar between groups (UCPPS mean 3.68, SD 1.81; mixed pain mean 3.90, SD 1.85; $p = 0.54$). However, the mixed pain group (mean 12.89, SD 11.12) reported significantly more non-pelvic body sites with pain compared to the UCPPS group (mean 3.93, SD 5.60; $p < 0.001$). The two most common COPCs in the mixed pain group were fibromyalgia (60%) and IBS (62.9%). Symptom measures for the subset of UCPPS participants tested at baseline are shown in Supplementary Table 2.

Group comparisons

Table 2 shows the results of the group comparisons on each pressure pain sensitivity measure, including the estimated transformed mean adjusting for the effects of age, sex, and site, and for ease of interpretation, the back-transformed estimated means (kgf/cm^2) and 95% confidence interval (CI) for each group.

There were significant group differences in all four pressure pain sensitivity outcomes (all omnibus tests $p < 0.01$). The mixed pain group showed the highest pain sensitivity, followed by the UCPPS and healthy control groups. For all pressure pain sensitivity variables, pairwise contrasts showed significantly increased pain sensitivity in UCPPS and mixed pain groups compared to healthy controls (all $p < 0.05$). Additionally, the mixed pain group showed greater sensitivity than UCPPS on Pain50 and pain rating at 2 kgf/cm^2 (both $p < .05$) and greater sensitivity on PPT and tolerance, though these contrasts were not statistically significant (both $p < 0.09$). There were no significant effects of testing site or participant age on any pressure pain sensitivity variable as well as no significant effect of sex on PPT, Pain50, or pain rating at 2 kgf/cm^2. There was a significant effect of sex on pressure pain tolerance ($p = 0.015$). See Fig. 1 for density plots depicting the distribution and median

values of all four unadjusted pressure pain sensitivity variables for each group. Supplementary Fig. 2 shows all 288 raw stimulus-response profiles with smoothed trajectories for each group. Both of these figures highlight that despite significant group differences in pain sensitivity, there is considerable overlap between groups and inter-individual variability in these responses.

Associations of pressure pain sensitivity measures with UCPPS symptoms and clinical pain

In UCPPS participants, higher PPT (lower pain sensitivity) was associated with fewer painful non-pelvic sites endorsed on the body map ($p = 0.027$), while higher Pain50 and tolerance values were associated with less overall pain severity (both $p < 0.05$). Additionally, higher tolerance was associated with a lower GSS factor score ($p = 0.045$). No other clinical symptom or psychological factor was associated with pressure pain sensitivity. See Table 3.

Associations of pressure pain sensitivity measures with symptom trajectories

Of the 55 participants with pressure pain sensitivity data and corresponding longitudinal symptom trajectories, 17 (31%) were classified as improved, 24 (44%) as stable, and 14 (25%) as worse at one year on urinary symptoms; whereas 15 (27%) were classified as improved, 24 (44%) as stable, and 15 (27%) as worse at one year on genitourinary pain. In the multivariate logistic regression model, higher transformed values of baseline Pain50 (indicating less pain sensitivity) were associated with a greater likelihood of genitourinary pain improvement at one year, controlling for age, week-4 genitourinary pain severity, and SF-12 PCS scores ($p = 0.049$). Specifically, each one standard deviation increase in Pain50 on the transformed scale was associated with a 2.16 greater odds of improvement (95% CI, 1.00, 4.65). No other longitudinal outcome was associated with baseline pressure pain sensitivity (all $p > 0.05$). Parameter estimates for each model are shown in Table 4.

Associations of pressure pain sensitivity measures with flares

In the 22 participants who were tested during discordant flare reports, seven participants were experiencing a flare at the first pressure pain assessment but not at the second, while 15 were not experiencing a flare at the first assessment but subsequently were in a symptom flare at a later assessment point. Transformed Pain50 values were significantly lower, indicating greater pain sensitivity, during a symptom flare ($t = 2.12$, $p = 0.046$). The back-transformed mean for the non-flare condition was 4.04 kg/cm^2 (95% CI, 3.44, 4.69) versus 3.62 kg/cm^2 (95% CI, 3.10, 4.20) in the flare condition. See Fig. 2.

DISCUSSION

This is the largest investigation of experimental pain ever undertaken in UCPPS. The primary finding is that UCPPS is characterized by increased pressure pain sensitivity in comparison to healthy controls, but less pain sensitivity than participants with a mix of other COPCs such as fibromyalgia and IBS. In many ways, this finding confirms the initial investigation of experimental pain sensitivity in IC/BPS, where Clauw et al.[9] demonstrated that female IC/BPS patients have lower pain thresholds at a number of body sites than healthy individuals, but less sensitivity than fibromyalgia patients.

The current protocol was designed to assess evoked pain responses at a site considered asymptomatic for UCPPS and other COPCs. As such, it is believed to represent the central sensitization component of chronic pain.[1] One primary assumption is that increased pain sensitivity at an asymptomatic site, in this case the bed of the thumbnail, reflects CNS-mediated mechanisms of pain amplification rather than local tissue damage or inflammation.[22; 24; 32; 34; 62] For that reason, we hypothesized that participants with more generalized pain hypersensitivity or a “centralized” phenotype of UCPPS would show greater pain sensitivity at this site, similar to other conditions characterized by pain centralization (e.g., fibromyalgia).[2; 69] We found some support for this hypothesis: a modest association between lower PPTs (increased sensitivity) and a greater number of non-pelvic painful body sites. Likewise, lower pressure pain tolerance was modestly associated with higher GSS -- a novel construct that is an amalgamation of widespread pain, non-painful somatic symptoms, and sensitivity to environmental stimuli (e.g., lights, sounds, chemicals).[80] We recently showed that the aggregation of these symptoms, which are features of central amplification,[8] is apparent in the full sample of MAPP I UCPPS participants (n=424) as well as the mixed COPC participants (n=200), and appears to be strongly associated with the presence and number of comorbid COPCs in UCPPS.[80] Lower Pain50 and pressure pain tolerance levels were also related to increased overall clinical pain severity, which represents another important aspect of centralized chronic pain conditions.[26; 31] Together these findings suggest that increased pressure pain sensitivity measured at the thumbnail is consistent with the presence of a centrally amplified pain phenotype in UCPPS. In support of this view, recent studies have shown that conditioned pain modulation (CPM), where two painful stimuli are administered simultaneously in an effort to assess CNS-mediated endogenous pain inhibition, is deficient in UCPPS.[26; 60]

QST provides standardized procedures to characterize pain and sensory mechanisms. Data from QST studies indicate considerable inter-individual variability in responsivity to painful stimulation in the general population – consistent with the wide distribution and substantial overlap between groups observed in the present study on all four components of pressure pain sensitivity that were measured.[18; 64] Previous QST studies in UCPPS have generally found patterns of hypersensitivity to pressure, though study methods and outcomes have been heterogeneous. An early study demonstrated that UCPPS was characterized by heightened pain sensitivity in a sample of 60 fibromyalgia patients with 30 age-matched IC/BPS patients and 30 controls.[9] As mentioned above, IC/BPS patients and fibromyalgia patients were more sensitive than controls at both fibromyalgia tender points and control areas such as the thumbnail and forehead, and IC/BPS patients showed less sensitivity than those with fibromyalgia. These findings are supported by the current study, where we found that the mixed pain group, which showed substantially more widespread pain and a higher proportion fibromyalgia, was more sensitive to pressure stimuli than the UCPPS cohort. Ness and colleagues [61] subsequently showed diffuse hypersensitivity to pressure stimulation in a sample of 13 IC/BPS patients and 13 controls. Lai[48] conversely reported hypersensitivity in a sample of 10 IC/BPS patients in response only to fixed pressures applied to the suprapubic area (T11), while remote site fixed pressure at the forearm and PPTs at both suprapubic and forearm sites showed no differences compared to controls. In

our view, the current study resolves these discordant findings in favor of non-pelvic hyperalgesia as a common feature of UCPPS.

The MAST system used in the present study was originally designed for the MAPP Network to provide a brief QST procedure that could be easily implemented and standardized across multiple testing sites comprised of diverse and alternating technical staff. We did not note significant differences related to testing site in the current study. This would appear to be a strength of the automated stimulus delivery and data capture features of this system, which are designed to reduce potential operator and site influences on the assessment of pain sensitivity. We used an asymptomatic site for pain testing to allow for comparisons across groups and to other studies that have shown sensitization at the thumbnail in chronic pain [2; 23; 69; 75]. Experimental pain evoked by thumbnail pressure is associated with overall body tenderness,[70] measures of clinical pain,[31] and neuroimaging markers of pain processing.[24; 32; 40] The potential for experimental pain testing to capture central neurobiological vulnerabilities that are not easily discerned through symptom reports is one promising application of QST.

We found increased pain sensitivity was associated with a lower likelihood of improvement in genitourinary pain over a 48-week period of observation, controlling for relevant covariates derived from a larger longitudinal study of MAPP I participants.[59] However, this was the only significant association of four outcomes that were tested, so we caution that these findings are preliminary and exploratory. In other studies, QST has been associated with a variety of treatment outcomes, including pain and analgesic requirements following surgery, and the effectiveness of some analgesics.[16; 38; 54; 67; 68; 91; 97] However, many prospective studies examining the ability of QST to predict clinical trajectories have not found these associations.[7; 28; 81; 88] Additional research is needed before the prognostic value of QST for clinical pain management can be evaluated.

Pain sensitization in UCPPS is presumed to occur as a result of both nociceptive input from the periphery and the dysregulation of central mechanisms that augment and maintain painful sensations.[11] Nociceptive input may come from environmental insults, such as infection, impacting spinal and supraspinal amplification mechanisms as described in a recent review of neuroimmune contributions to visceral pain.[13] Alternately, some patients may experience fluctuations in CNS pain processes that are not affected by local bladder or pelvic pathology – the pure “top down” central augmentation pathway.[33; 96] Both of these broad pathways likely play a role in the transient increases in pain sensitivity and urological symptoms that are part of the symptom flares that characterize UCPPS and that can impair day to day life.[83-85] To our knowledge, this is the first study to suggest that psychophysical pain responses indicative of global hyperalgesia are altered during symptom flares. Recent work within the MAPP Network demonstrated that recent sexual activity may be a trigger for flare onset in UCPPS.[86] Animal models of UCPPS have shown that the introduction of gram-negative bacterial components into the lower urinary tract at subnoxious levels hastens the onset of UCPPS symptoms, suggesting that previous subclinical infections may act as a sensitizing agent for flares.[44] In the short-term, experimental stress tasks provoke urinary urgency and pain in women with IC/BPS, and it has long been postulated that certain environmental triggers, especially diet, can provoke

symptom flares in UCPPS.[20; 55]. Our findings highlight the potential multifactorial nature of symptom flares and are worthy of further investigation.

Limitations

This study has limitations. The staggered rollout of the pressure pain protocol reduced the number of participants available to partake in this assessment and resulted in an unequal distribution of data from across the network. Because this was an observational study, participants continued their medications and other treatments during the evaluation period. Dosages and frequency of treatments were not captured and patients were not restricted from changing treatments during the study, which may have impacted the results. The heterogeneity of the mixed pain group precluded analysis of individual COPCs. The relatively small number of UCPPS participants tested at baseline limited our ability to examine phenotypes within this group and longitudinal outcomes. Assessment of pain sensitivity was limited to a single body site and modality. The measures of pressure pain sensitivity reported are associated with one another and do not reflect independent aspects of the phenomenon. No power calculations were performed for pain sensitivity outcomes in MAPP I, as this was considered an ancillary aim. Instead we have used the largest available sample size for each analysis in the current manuscript and therefore caution the reader that these results, particularly those for smaller exploratory analyses, should not be taken as definitive. Some of the relationships between clinical variables (e.g., genitourinary pain) and pressure pain sensitivity were in the hypothesized directions but not statistically significant – this may indicate smaller effects that would require an even larger sample to confirm. These limitations are being partially addressed in the second phase of the MAPP Network (MAPP II), where a larger sample of UCPPS participants are assessed multiple times over 36-months with a more comprehensive QST battery, including assessments of pelvic/suprapubic pain sensitivity, CPM, and temporal summation.

Conclusions

Experimental pain sensitivity was assessed in individuals with UCPPS as part of the MAPP Network. Results showed that UCPPS participants were hypersensitive to painful pressure stimuli delivered to the thumbnail bed. Increased pressure pain sensitivity in UCPPS was associated with greater clinical pain, more non-pelvic body areas endorsed as painful, and increased levels of GSS. Exploratory analyses revealed that pain sensitivity increased during periods of UCPPS symptom flare and that lower pressure pain sensitivity at baseline was associated with a greater likelihood of genitourinary pain improvement one year later. These findings support a role for central sensitization in UCPPS as measured through pressure pain sensitivity testing. The MAPP Network is poised to expand on these findings with a comprehensive, longitudinal evaluation of QST in UCPPS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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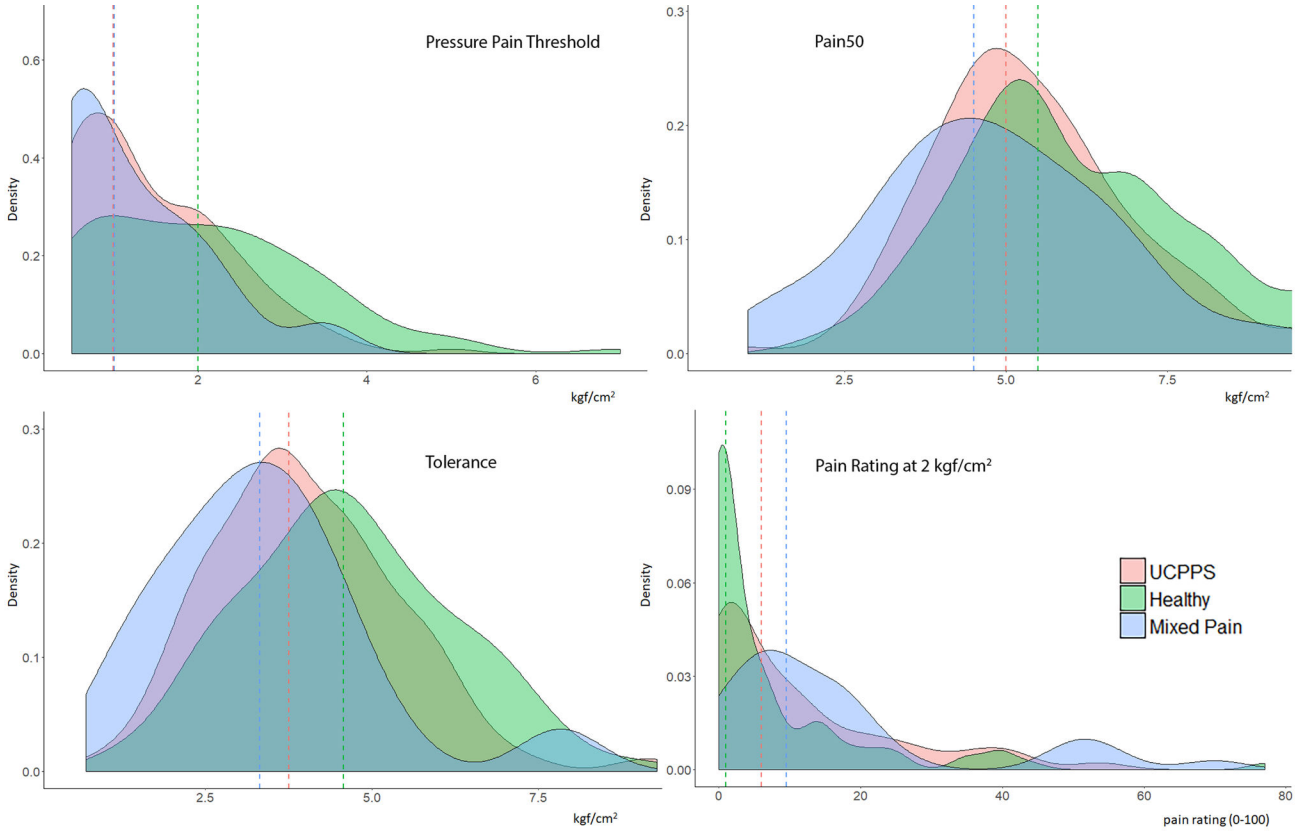

Fig. 1.

Density plots depicting the distribution of unadjusted pressure pain sensitivity values for each group. Density (y-axis) refers to the proportion of values at each pressure level (x-axis). The peaks of each plot indicate where values are most concentrated, with median values shown as dashed lines.

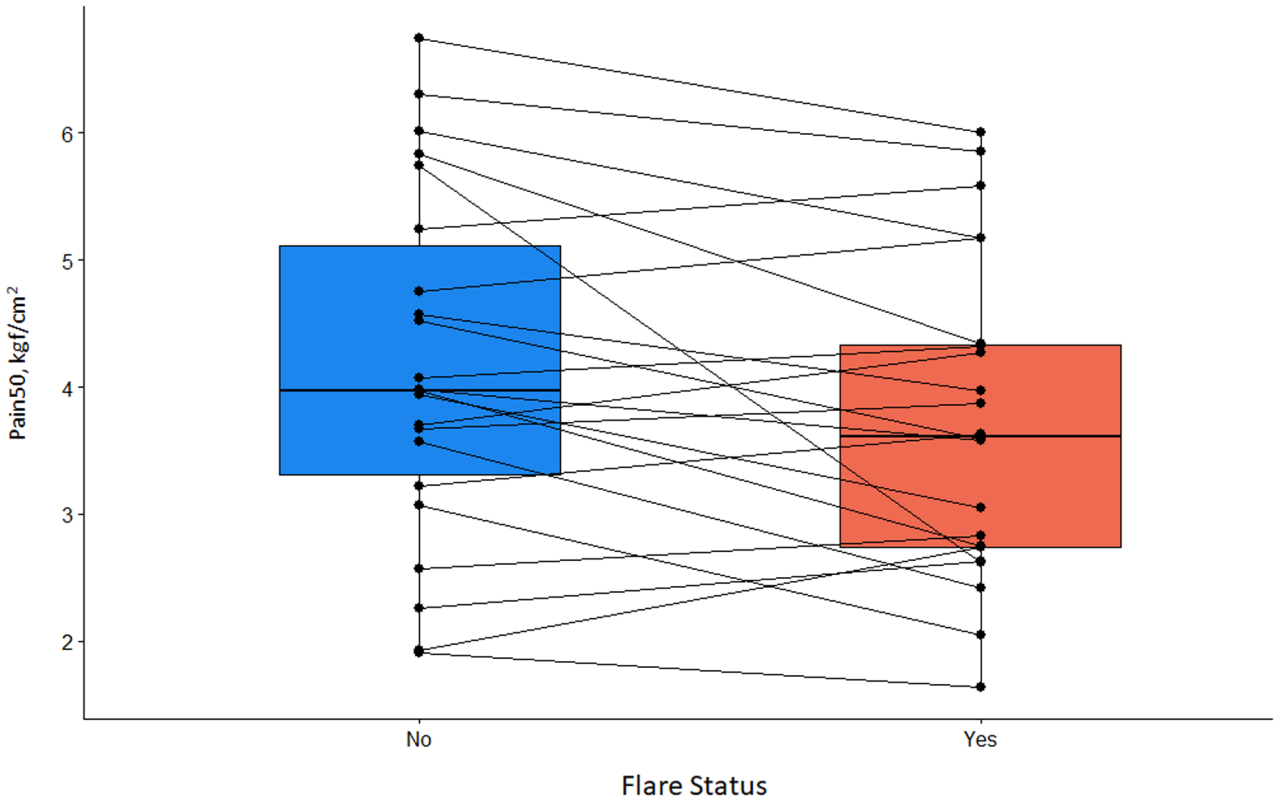

Fig. 2.

Box plots and unadjusted Pain50 values for 22 participants with discordant flare data. Middle lines are median values, lower edge shows 25th percentile, upper edge shows 75th percentile. Blue box is no flare; red box is flare.

Table 1

Distribution (n %) and demographic characteristics (mean, SD) of participants completing pressure pain sensitivity testing across MAPP Network sites.

		UCPPS (n = 153)	Healthy Controls (n = 100)	Mixed Pain (n = 35)	Total (n = 288)	Test Statistic	*P*
Site:	UCLA	16 (10.5%)	10 (10.0%)	4 (11.4%)	30 (10.4%)	$\chi^2(10) = 34.38$	< **0.001**
	Iowa	29 (19.0%)	5 (5.0%)	8 (22.9%)	42 (14.6%)		
	UM	69 (45.1%)	67 (67.0%)	16 (45.7%)	152 (52.8%)		
	UW	27 (17.7%)	7 (7.0%)	4 (11.4%)	38 (13.2%)		
	WashU	9 (5.9%)	1 (1.0%)	0 (0%)	10 (3.5%)		
	Stanford	3 (2.0%)	10 (10.0%)	3 (8.6%)	16 (5.6%)		
Sex (% Males)		75 (49.0%)	41 (41.0%)	8 (22.9%)	124 (43.1%)	$\chi^2(1) = 8.22$	**0.016**
Ethnicity (% Hispanic)		6 (3.9%)	6 (6.0%)	0 (0%)	12 (4.2%)	$\chi^2(2) = 2.39$	0.30
Race (% White)		141 (92.2%)	83 (83.0%)	30 (85.7%)	254 (88.2%)	$\chi^2(2) = 5.11$	0.078
Age (years)		44.2 (16.3)	39.7 (13.2)	40.6 (14.5)	42.2 (15.2)	F(2,285) = 2.97	0.053

UCPPS = urological chronic pelvic pain syndrome; UCLA = University of California – Los Angeles (Los Angeles, CA); Iowa = University of Iowa (Iowa City, IA); UM = University of Michigan (Ann Arbor, MI); UW = University of Washington (Seattle, WA); WashU = Washington University in St. Louis (St. Louis, MO); Stanford = Stanford University (Stanford, CA)

Table 2

Comparison of pressure pain sensitivity outcomes across participant groups.

	UCPPS (n = 153)		Healthy Controls (n = 100)		Mixed Pain (n = 35)		Omnibus	Adjusted *P* (age, sex, and site)		
	T Mean (95% CI)	BT Mean (95% CI)	T Mean (95% CI)	BT Mean (95% CI)	T Mean (95% CI)	BT Mean (95% CI)	*F (df)*	UCPPS vs. HC	UCPPS vs. MP	HC vs. MP
PPT[a]	0.19 (0.05-0.32)	1.20 (1.05-1.38)	0.48 (0.31-0.64)	1.61 (1.37-1.89)	−0.03 (−0.27-0.21)	0.97 (0.76-1.23)	**9.28 (2, 278)**	**0.001**	0.089	< **0.001**
Pain50[b]	1.94 (1.83-2.06)	3.78 (3.34-4.25)	2.08 (1.96-2.21)	4.34 (3.83-4.89)	1.78 (1.62-1.94)	3.16 (2.62-3.76)	**9.47 (2, 278)**	**0.005**	**0.017**	< **0.001**
Tolerance[b]	2.29 (2.16-2.43)	5.25 (4.66-5.89)	2.40 (2.25-2.54)	5.75 (5.08-6.46)	2.16 (1.99-2.34)	4.69 (3.97-5.46)	**5.76 (2, 278)**	**0.029**	0.0615	**0.001**
2 kgf rating[a]	1.73 (1.27-2.20)	5.17 3.05-8.55)	1.06 (0.55-1.58)	2.40 (1.23-4.35)	2.34 (1.68-3.00)	9.85 (4.86-19.5)	**10.42 (2, 272)**	< **0.001**	**0.04**	< **0.001**

UCPPS = urological chronic pelvic pain syndrome; PPT = pressure pain threshold; T Mean = transformed mean adjusted for age, sex, and MAPP site; BT Mean = back-transformed adjusted mean to original scale: kgf/cm^2 for PPT, Pain50, Tolerance; 0-100 numerical rating scale for 2 kgf/cm^2 rating

[a] log transformation

[b] square-root transformation

Table 3

Partial correlations (age and sex adjusted) between baseline clinical features and transformed pressure pain sensitivity outcomes in participants with urological chronic pelvic pain syndrome.

	n	Pressure Pain Threshold	Pain50	Tolerance	2 kgf Rating
Urinary Symptoms	62	0.125	−0.1	−0.11	−0.088
Genitourinary Pain	62	0.03	−0.189	−0.202	0.025
BPI Pain Severity	59	−0.241	**−0.306**[a]	**−0.309**[a]	0.197
BPI Pain Interference	60	−0.157	−0.206	−0.243	0.076
Number of non-pelvic sites with pain	62	**−0.286**[a]	−0.099	−0.098	0.108
CSQ	62	−0.004	−0.096	−0.163	−0.002
HADS anxiety	62	−0.061	−0.049	−0.145	−0.007
HADS depression	62	0.097	−0.064	−0.131	−0.012
GSS	62	−0.207	−0.201	**−0.26**[a]	0.136
SPACE	61	0.028	−0.042	−0.134	−0.029

BPI = Brief Pain Inventory; CSQ = Coping Strategies Questionnaire; HADS = Hospital Anxiety and Depression Scale; GSS = generalized sensory sensitivity; SPACE = Sleep, Pain, Affect, Cognition, and Energy

[a] $P < 0.05$

Table 4

Logistic regression for longitudinal urinary symptoms and genitourinary pain outcomes in urological chronic pelvic pain syndrome participants (n = 55) at one year with Pain50 (square root transformation) as a baseline predictor, controlling for age, SF-12 PCS score, and week 4 symptom levels. Odds Ratios (OR) are for a one standard deviation increase in Pain50 on the transformed scale.

Outcome	Estimate	S.E.	Wald	*P*	OR	95 % CI LL	95 % CI UL
Urinary Improvement	−0.0855	0.8925	0.0092	0.9237	0.918	0.16	5.279
Urinary Worsening	−0.7708	0.9783	0.6207	0.4308	0.763	0.389	1.496
Pain Improvement	2.1913	1.1155	3.8587	**0.0495**	2.159	1.002	4.652
Pain Worsening	0.2725	0.9237	0.0871	0.768	1.313	0.215	8.027