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Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study

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Introduction

Approximately one out of three people in the United States suffers from chronic pain.[35] A family of conditions characterized in part by pain and varied constitutional symptoms, such as Fibromyalgia (FM), Temporomandibular Disorder (TMD), and Chronic Pelvic Pain, play a significant role in the societal burden of chronic pain as they are both prevalent and difficult to treat. These and other pain conditions are referred to as Chronic Overlapping Pain Conditions (COPCs) because they so often co-occur, in both individuals and families. [58] In COPCs, peripheral pathology corresponds poorly to the location and severity of pain[9; 59]. Many researchers favor a primary (but not exclusive) role for central nervous system (CNS) mechanisms in the etiology and maintenance of COPCs.[65] Functional, chemical, and structural neuroimaging studies reveal abnormalities in the brains of patients with COPCs,[20; 25; 27; 29; 34; 36; 37; 39; 45; 46; 53; 56] and the drugs that are effective in these conditions are thought to work primarily in the CNS.[7; 28] However, defining and describing the CNS pain phenotype is a challenge. As a result, health care providers often

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assume new onset pain or other symptoms to be a peripheral problem rather than yet another manifestation of an ongoing CNS issue.

Currently the term ‘centralized pain’ is used to encompass the theoretical and empirical basis for the CNS contribution to chronic pain states, but the term may also be used to describe the symptomology characteristic of COPCs with the greatest evidence of pain centralization.[8] Hallmark symptoms of centralized pain include widespread pain, fatigue, negative affect, unrefreshing sleep, and cognitive dysfunction. While these symptoms are assessed by promising instruments like the 2011 survey criteria for FM,[64] COPCs seem to involve additional symptom domains.[43] Namely, many patients with COPCs report sensitivity to non-painful environmental stimuli, including lights and sounds, and increased awareness of non-painful somatic sensations, suggesting aberrant sensory processing outside of the traditional nociceptive pathways.[18; 22; 26; 30; 31; 42; 48; 61] Understanding how these varied symptoms relate to one another will help us build simple methods for characterizing individuals who suffer from these conditions.

Urologic Chronic Pelvic Pain Syndrome (UCPPS) is a COPC characterized by pain in the pelvic region accompanied by urologic symptoms.[47] One of the goals of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, a multi-site project funded by the National Institute of Diabetes and Digestive and Kidney Diseases,[11; 40] is to define symptom patterns that UCPPS has in common with other COPCs. In its first phase, the MAPP Research Network measured several symptom domains relevant to centralized pain in cohorts with UCPPS, other COPCs, and controls free of COPCs. Our primary objective here was to determine if primary symptoms of centralized pain can be explained by a smaller number of latent factors or symptom clusters. Using factor analysis and structural equation modelling, we identified two factors, representing sensory sensitivity and symptom severity, and then examined their relationship to COPCs and other clinical outcomes.

Methods

Participants

The MAPP Research Network recruited three participant cohorts across six US discovery sites: UCPPS (n= 424), healthy controls without COPCs from the community (n = 415) and a mixed pain cohort comprised of individuals with other COPCs (i.e., FM, Irritable Bowel Syndrome [IBS], TMD, Chronic Fatigue Syndrome [CFS], Migraine; n = 200). The scientific aims of the network, recruitment strategy, and inclusion and exclusion criteria have been described in detail in previous publications.[11; 40]. The MAPP study is registered at [Clinicaltrials.gov](https://clinicaltrials.gov): “Chronic Pelvic Pain Study of Individuals with Diagnoses or Symptoms of Interstitial Cystitis and/or Chronic Prostatitis (MAPP-EP)”. All procedures were approved by Institutional Review Boards at the participating institutions and all subjects provided informed consent.

In brief, primary inclusion criteria for UCPPS was bladder and/or pelvic pain, pressure or discomfort present the majority of the time over the last three months. The mixed pain cohort met criteria for either IBS, CFS, or FM, though participants from both the UCPPS

and mixed pain cohorts could and did meet criteria for more than one condition. The presence of UCPPS symptoms (i.e., pelvic pain) was not exclusionary for the mixed pain cohort though mean levels were well below those of the UCPPS cohort (Table 1). The healthy controls had no UCPPS symptoms and no chronic pain conditions as assessed by the modules of the Complex Medical Symptoms Inventory (described below), but may have endorsed some pain on the body map as would be expected from a community sample. The UCPPS cohort was seen for in-clinic visits at baseline, 6 months, and at one year. The healthy controls and mixed pain cohorts were seen once at baseline.

Measures

Pain Severity—In the UCPPS and the mixed pain cohorts, pain severity was measured by the Symptom and health care utilization Questionnaire (SYM-Q), which was designed specifically for the MAPP Research Network.[40] The pain severity measure ranges from 0–10, and contains a question for genitourinary pain severity (SYM-Q #1), and an analogous question for non-genitourinary pain severity (SYM-Q #6). We chose this measure rather than that used in previous MAPP publications[24] so that a similar pain severity measure could be used in both the UCPPS and mixed pain cohorts.

Urinary Symptom Severity—Urinary symptom severity was assessed using a composite measure derived from the Genitourinary Pain Index (GUPI)[10] and Interstitial Cystitis Symptom Index (ICSI),[49] based on psychometric analyses performed on MAPP baseline data.[24] Individual items assess urinary urgency and frequency, nocturia, and bladder emptying. This results in a urinary severity score (range 0–25), with higher scores indicating greater symptom severity.

Sleep and Fatigue—Sleep disturbances and fatigue were each assessed with the Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires.[5]

Cognitive Dysfunction—Self-reported cognitive difficulties were assessed with the Multiple Ability Self-Report Questionnaire (MASQ). The 38-items of the MASQ cover 5 domains: language ability, attention, visuo-spatial, verbal memory, and visual memory. These domains have been validated against neuropsychological tasks.[55] The sum of the five domains represents the cumulative burden of self-reported cognitive dysfunction.[38]

Depression—Depression was measured using the Hospital Anxiety and Depression Scale (HADS).[66]

Spatial Extent of Pain—The extent or spatial distribution of pain was assessed using a 45-site body map [40] which has been used in previous MAPP studies and is associated with disease burden, immunological, and neuroanatomical findings.[39; 52; 54]

Disability and Quality of Life—Perceived physical and mental well-being were measured using the SF-12 physical components score (PCS; a composite of all physical health subscales), and mental health components score (MCS).[60]

Complex Medical Symptom Inventory (CMSI)—The CMSI provided an overall index of the symptom burden, as well as an assessment of the presence of COPCs.[62] The CMSI is composed of 41 items asking about the presence of functional symptoms for 3 months out of the last year.[62] Ten of the 41 questions act as “trigger” items, which, if answered affirmatively, lead to additional diagnostic modules being administered. For example, checking, “abdominal pain or discomfort,” automatically triggers the IBS module. For this version of the CMSI, possible diagnostic modules included FM,[64] CFS,[21] IBS,[14] TMD,[16] and MI[50]. Additional information about the diagnostic modules is given below. An additional nine items directly reference pain/tenderness or symptoms central to the definition of COPCs investigated in this study (e.g., items about impaired memory, attention, or urinary dysfunction). The remaining 22 items cover non-specific somatic or functional symptoms (18 items) or sensory sensitivity to non-painful environmental stimuli (e.g., to bright lights or odors; 4 items). All CMSI items are shown in Supplemental Table 1.

The 18 functional or somatic symptom items in the CMSI are highly similar to items used to measure a construct variously termed “somatic awareness,” “somatosensory amplification,” “anxious arousal” or “somatic arousal” which refers to heightened awareness of and attention to internal sensations and symptoms. Similarly, the four items representing sensory sensitivity in the CMSI are comparable to items used to measure sensitivity to external physical stimuli. These 22 CMSI items are compared to similar items used in validated measures of analogous constructs in Supplemental Table 2.

For the present analysis, we explored the use of the summed score of the 18 items as a *Somatic Awareness* subscale (range 0 –18), and the sum of the four sensory items (range 0–4) as a *Sensory Sensitivity* subscale. The adequacy of these scales was subsequently tested using confirmatory factor analysis (Methods and Results for this analysis are shown in Supplemental Figure 1). We also calculated Chronbach’s α for both Somatic Awareness and Sensory Sensitivity subscales for each cohort.

CMSI Diagnostic Modules—FM was assessed by an adaptation of the 2011 survey criteria for FM.[64] These criteria use a 19-site body index of pain distribution (referred to as the Widespread Pain Index, WPI) and several questions about symptoms of fatigue, cognitive issues, unrefreshing sleep, headache, depression, and gastrointestinal complaints. For each patient to receive a classification of FM, both multisite pain and non-specific symptoms must be present, the symptoms must have been present at similar levels three months or longer.

CFS was assessed by an adaptation of the 1994 Fukuda criteria.[21] These criteria assess fatigue that has been ongoing for at least six months in addition to domains for cognitive dysfunction, unrefreshing sleep, post-exertion malaise, interference with activities, and symptoms like headache, sore throat, and muscle pain. Fatigue relieved by rest or due to strenuous activity does not contribute to case status.

IBS was assessed by an adaptation of the ROME III criteria.[14] These criteria assess pain or discomfort in the abdomen in conjunction with change in the frequency of bowel

movements, and change in the appearance or consistency of bowel movements. Pain during menses does not contribute to case status. The pain must be ongoing at least six months.

TMD was assessed by an adaptation of the Research Diagnostic Criteria for TMD.[16] These criteria assess pain in the face, jaw, temple, ear, or in front of the ear, and measure severity and interference with activities during the past six months.

Migraine was assessed by an adaptation of the International classification of headache disorders criteria, 2nd edition.[50] These criteria assess frequency, severity, and symptoms accompanying headache, such as pain confined to one side of the head and vomiting.

The CMSI also included a triggered diagnostic module for vulvodynia. This COPC was not considered in this manuscript as it is female specific and we sought to only include COPCs that affect both sexes.

Data Analysis

Overview—We pursued three analytic aims: a) identify the number of latent factors that explain the centralized pain phenotype in UCPPS using exploratory factor analysis (EFA), b) confirm these factors through confirmatory factor analysis (CFA) in the UCPPS, mixed pain, and healthy control cohorts, and c) evaluate the stability of these factors over time in the UCPPS cohort. Because healthy controls were by definition without pain, we initially excluded the pain intensity/severity measures from the analyses of all groups. However, as pain severity is a critical component of the perceptual burden experienced by chronic pain patients,[12] pain measures were subsequently added to the CFA models in both the UCPPS and mixed pain cohorts.

We report model fit indices, including non-centrality fit indices (Comparative Fit Index [CFI; greater than .95 generally represents adequate fit]); Root Mean Square Error of Approximation and 90% confidence interval (RMSEA; <.06 generally represents adequate fit), and absolute measures of fit (Standardized Root Mean Square Residual [SRMR; < .08 generally represents adequate fit]; χ^2 test [where non-significant p values are seen as desirable, but in practice are rarely observed when sample size is greater than 200]). These guidelines are adopted from Hu & Bentler.[32]

The scales used for factor analysis were the total number of painful sites on the 45-site body map, the Somatic Awareness and Sensory Sensitivity subscales derived from the CMSI, the PROMIS-fatigue and PROMIS-sleep measures, the MASQ total score, and the HADS-depression scale. Together these reflect the primary elements of the 2011 FM survey criteria[64] and other posited measures of the centralized pain phenotype, with the addition of the somatic awareness and sensory sensitivity measures.

Exploratory Factor Analysis in UCPPS—The EFA model was fit by Maximum Likelihood robust (MLR) estimation. MLR is able to provide reliable estimates of model fit even when the underlying distribution of data does not meet assumptions embedded in the ML framework, such as normality.[19] We used the lower bound RMSEA (lb.RMSEA) criteria to select the optimal number of factors.[51] Lb.RMSEA is the smallest number of

factors that produces a lower bound 90% confidence interval for RMSEA below .05. In simulation studies this metric appears to result in the strongest likelihood of verisimilitude, or identifying the “true” underlying number of factors when compared to other model fit metrics like AIC, BIC, or the simple RMSEA estimate.[51] Using MPLUS v. 8.0 with Geomin, an oblique rotation method that allows identified factors to be correlated, was applied. This EFA was conducted both with and without the pain severity measure.

Confirmatory Factor Analysis in All Cohorts—Confirmatory factor analysis on the factor solution derived from the EFA was performed in the UCPPS, mixed pain, and healthy control cohorts using MLR estimation. CFA models were constructed both with and without the pain severity measures, to allow for analogous models to be fit in all three cohorts (i.e., without pain severity), and separately for the UCPPS and mixed pain cohorts (i.e., with pain severity – genitourinary pain severity for UCPPS, non-genitourinary pain severity for PC).

We then fit the same model to a subset UCPPS participants (n = 332) that completed all measures at baseline, six months, and one year to evaluate the stability of these factors over time.

Associations of Identified Factors with Measures of Disability and Urinary Symptom Severity—To determine if the identified factors were associated with severity of non-painful urinary symptoms (e.g., frequency and urgency) and perceived physical (PCS) and mental (MCS) well-being as measured by the SF-12, we constructed structural models with the identified factors as predictors of these measures controlling for age, sex, and BMI.

Supplemental Analyses

a) As a form of method validation, we also explored the association of the identified factors with individual COPC status and with the total number of COPCs in the full UCPPS and mixed pain cohorts. These analyses were intended to determine whether higher levels of these factors are associated with the presence or absence of COPCs

b) It is possible that while a latent factor may fit a particular dataset well, its association with other outcomes may be driven by a given indicator, rather than the latent construct itself. To evaluate this possibility, we compared the proportion of variance in number of COPCs explained (R^2) when the latent variable was used as a predictor, to each of its individual indicators alone.

Results

Participants

UCPPS participants were on average 43 years old and 55% of the sample was female. Healthy controls were 41 years old on average and 56% of the sample was female; mixed pain participants were 42 years old on average and 78% of the sample was female. See Table 1 for comparison of COPCs in the UCPPS and mixed pain cohorts.

Exploratory Factor Analysis in UCPPS

The optimal number of factors in the UCPPS cohort was two, in both models with and without pain severity. The rotated factor loadings are shown in Supplemental Table 3.

The two factors identified appeared to be readily interpretable – number of painful sites, somatic awareness, and sensory sensitivity loaded on the first factor; whereas fatigue, sleep, depression, and cognitive dysfunction, and pain severity loaded on the second factor. The first factor represents a broad amplification or awareness of sensory processes, both somatosensory (internal) and external. The second factor represents severity of clinical pain and non-specific CNS symptoms across multiple domains. All factor loadings were above .45 on the primary factor, and less than .2 on the second factor. Overall model fit was adequate (CFI = .998; RMSEA = .020, 90% CI = .000, .062; $\chi^2 = 9.342$, df = 8, p = .314).

Confirmatory Factor Analysis in All Cohorts

The resulting two-factor models displayed adequate fit in all three cohorts. The model for each cohort is shown in Figure 1A with fit statistics. Mean symptom levels for each cohort are shown in Figure 1B. The models that included pain severity measures for UCPPS and mixed pain cohorts similarly showed adequate fit to the data, with general loadings broadly similar between groups. These are shown in Figure 2 with fit statistics.

We refer to the first factor as *Generalized Sensory Sensitivity* or GSS, and the second factor by the acronym *SPACE* (Sleep, Pain, Affect, Cognition, Energy).

Factor loadings and overall model fit were similar for SPACE, if slightly worse, when the HADS-anxiety subscale was used in place of the HADS-depression subscale (data not shown).

In each cohort, GSS and SPACE were associated with one another (UCPPS standardized $\phi = .638$, 95% CI = .554, .721; Mixed pain standardized $\phi = .808$, 95% CI = .727, .888; Healthy control standardized $\phi = .503$, 95% CI = .395, .611).

Temporal Stability of GSS and SPACE

In the 332 UCPPS participants that completed symptom assessments at baseline, six months, and one year, the same two-factor model showed adequate fit to the data. These are shown in Figure 3 with fit statistics.

Relationships between GSS, SPACE, Disability, and Urinary Symptoms

Higher levels of SPACE were significantly associated with worse perceived physical well-being (SF-12 PCS; $\beta = -.175$, 95% CI = $-.300, -.050$, p = .006) and worse urinary symptom severity ($\beta = .181$, 95% CI = .223, .491, p < .001). SPACE was not associated with worse perceived mental well-being, and GSS was not associated with any of these outcomes (all p > .05).

Summary of Supplemental Analyses (See Supplemental Material)

- a) GSS showed strong relationships with each individual comorbid COPC as well as the number of comorbid COPCs in the UCPPS cohort; these results validated in the mixed pain cohort. GSS particularly showed strong “discrimination” on the probability of a patient having each COPC (See Supplemental Table 4 & Supplemental Figures 2–4).
- b) The variance explained in the number of COPCs was substantially greater using the entire GSS construct versus that explained by the indicator variables in isolation. This suggests that these associations cannot be reduced to a patient indicating more painful sites on the body map, or increased somatic awareness or sensory sensitivity (See Supplemental Table 5).
- c) Given the strong association of the GSS construct with the prevalence of COPCs, we created a preliminary brief form of the GSS from representative items. This form correlates well with the factor scores derived from entire GSS construct (Supplemental Material; Supplemental Figure 4).

Discussion

Because many chronic pain conditions overlap with one another it has long been assumed that they share common neurobiological mechanisms – these conditions are now collectively termed COPCs. We refer to the neurobiological substrate of COPCs as ‘centralized pain’ because of the overwhelming evidence for central neurobiological dysfunction in these conditions. Changes to the CNS provide the simplest explanation for the co-occurrence of symptoms like sensitivity to many different sensory experiences, widespread pain, and the memory, sleep, and mood issues observed in most COPCs.[8] These CNS changes may proceed from peripheral pathological processes, such as the presence of the Hunner’s ulcers in the wall of the bladder of some UCPPS patients.[57] More often than not however UCPPS patients do not show gross pathological features indicative of local nociceptive input, suggesting that in these patients the CNS changes are independently generated and/or maintained.[65] No matter the role of peripheral nociceptive input in these conditions, there is a clear aggregation of these symptoms into two factors in COPCs, and these primary self-reported symptoms of centralized pain need to be accurately and succinctly assessed in both research and clinical contexts. Here we have begun that work using one of the largest multi-site phenotyping studies of chronic pain patients ever conducted.

Conceptually, we have found that the myriad of COPC symptoms often studied in isolation can be described as part of distinct but closely related constructs. We have coined these Generalized Sensory Sensitivity (GSS) and SPACE (Sleep, Pain, Affect, Cognition, Energy). GSS may be best understood as a tendency to experience, notice, and report increased sensitivity to external stimuli across multiple sensory modalities, increased sensitivity to symptoms or sensations occurring within the body (somatic awareness), and pain or tenderness (hyperalgesia/allodynia) in multiple regions of the body. SPACE is an amalgamation of constitutional symptoms that often become disrupted in tandem. Symptom clusters similar to SPACE have been described in primary care,[12] cancer patients,[6] as well as other chronic diseases.

Exploratory and confirmatory factor analyses support a two-factor model of centralized pain, with strong associations between the two factors. This basic two-factor structure was apparent in each cohort (UCPSS; mixed pain such as FM, IBS, and CFS; and healthy community controls), despite the large differences in average levels of symptoms. Put simply, even when the severity range of each symptom differs enormously, the same symptoms tend to be co-expressed. This supports the idea of a symptom continuum present to some degree in all people, including those described nominally as healthy. This idea was first advanced by Wolfe, using the term ‘fibromyalgiansess’ to connote the fact that FM-like symptoms are not confined to FM patients, and that sub-syndromal levels of fibromyalgiansess contribute to pain and disability.[63] We previously showed that higher levels of fibromyalgiansess are associated with poorer post-surgical outcomes even at levels below criteria for FM.[3; 4; 33] The current analyses considerably expand and refine the concept of centralized pain by identifying additional critical aspects of COPC symptomology. The longitudinal analyses within the UCPPS cohort further demonstrate that the basic two-factor structure can be observed in the same sample over time, suggesting that the general co-expression of these patterns of symptoms is stable.

Recent work in rheumatoid arthritis has demonstrated that higher levels of fibromyalgia symptoms are associated with the same functional connectivity findings seen in centralized pain conditions like FM[46] – specifically, an increase in positive connections between the default mode network (DMN) and insular cortex as fibromyalgiansess increases. [2] This agreement, which echoes findings in chronic low back pain[41] and other mixed-pain cohorts [1], suggests that there may be identifiable neurobiological substrates of ‘centralized pain’ across pain conditions. The insula cortex plays an important role in integrating sensory information, monitoring interoceptive processes,[15] and determining their salience. Thus it is possible that the more closely the insula is incorporated into other neural processing streams the more likely it is that sensory information will attain an aversive valence. Recent work using a graph theory framework, which attempts to model patterns of connections across hundreds of brain regions, supports this view. In FM patients with high levels of pain, those brain regions with the greatest importance for relaying and integrating information – hubs – show reorganization that favors connections between the somatosensory cortices and both anterior and posterior insular cortices, compared to both healthy controls and FM patients with low levels of pain [Under Review]. In FM patients, recent work has shown that complex visual stimuli are judged to be more aversive, and that neural activation patterns evoked by these stimuli, particularly within the insula, distinguish these patients from healthy controls with remarkable accuracy.[30] Other studies of the neural response to non-painful sensory stimuli have confirmed augmented insular activation to visual, auditory and tactile stimulation in FM.[42] These findings support a model in which COPCs are characterized by enhanced coupling, or over-integration, of sensory signals with regions and networks that determine salience.

The present work also has implications for applied research in COPCs. COPCs are characterized by an increased prevalence of mood imbalances, cognitive difficulties, and fatigue. However, when we attempted to confirm the association between each factor and the presence of COPCs, we found that the GSS construct has a stronger relationship with the presence of COPCs measured by self-report criteria than SPACE. It may be then, that GSS is

a particularly important concept for assessing risk of developing a new COPC – we make this suggestion cautiously, as we do not yet have data suggesting that the relationship extends beyond the cross-sectional. However, the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study's findings support this idea. Higher scores on a measure of somatic awareness was the most robust predictor of new-onset TMD over an average observational period of 2.8 years.[17] Similarly, the somatic awareness construct predicted new-onset chronic widespread pain over a 12-month period of observation.[44] Previous research has found that the presence of COPCs is a good predictor of developing a new COPC,[61] but it is not currently simple or easy to comprehensively assess COPCs. A short version of GSS or similar construct, which we have developed a preliminary version of here, may be useful for assessing the broad vulnerability to COPCs. Similarly, the continuous nature of the construct may be helpful in assessing the impact of therapy or adverse events on the underlying vulnerability. For instance, pregabalin has been shown to reduce levels of excitatory neurotransmitter in the posterior insula of FM patients.[28] It is plausible that GSS, if shown to accurately reflect aberrant neurochemistry in sensory processing regions, could be used either to predict treatment response to pregabalin, or as a surrogate marker of the attenuation of multi-modal sensory hypersensitivity in responders.

Limitations

The absence of clinical outcomes over a long follow-up period is a limitation of the current study design. A larger set of items derived from focus groups may be helpful in better defining the sensory sensitivity and somatic awareness constructs. Some caution is warranted in interpreting these findings in the pain-free community sample, as the questions used to define somatic awareness and sensory sensitivity were intended for chronic pain patients – it is reasonable to wonder if the range of difficulty for these items is not broad enough for this group. While UCPPS is an important clinical category, it comprises several conditions (i.e., interstitial cystitis/bladder pain syndrome, chronic prostatitis/chronic pelvic pain syndrome) that may be distinct. Perceived stress and pain catastrophizing, for example, are closely related constructs that have been hypothesized to play critical roles in the development or presence of COPCs,[13; 23] and these should be investigated further in the context of SPACE.

Conclusions

Two constructs encompassing a large number of related symptoms in COPCs have been identified in one of the largest phenotyping studies of chronic pain patients yet undertaken. These constructs appear to be closely linked with one another and the strength of that association, or coupling, may reflect critical pathological processes undergirding the presence and development of COPCs. Generalized Sensory Sensitivity (GSS) and SPACE represent novel expansions of constructs for measuring the various aspects of sensory sensitivity and symptom severity that mark COPCs. Both of these aspects of the centralized pain continuum should be measured in studies of COPCs, and each should be considered in longitudinal studies that evaluate the trajectory of symptoms in COPCs and responses to treatment. Because the GSS construct has not been presented before, we offer a short form that appears to measure the construct well, in the hope that it will be useful to researchers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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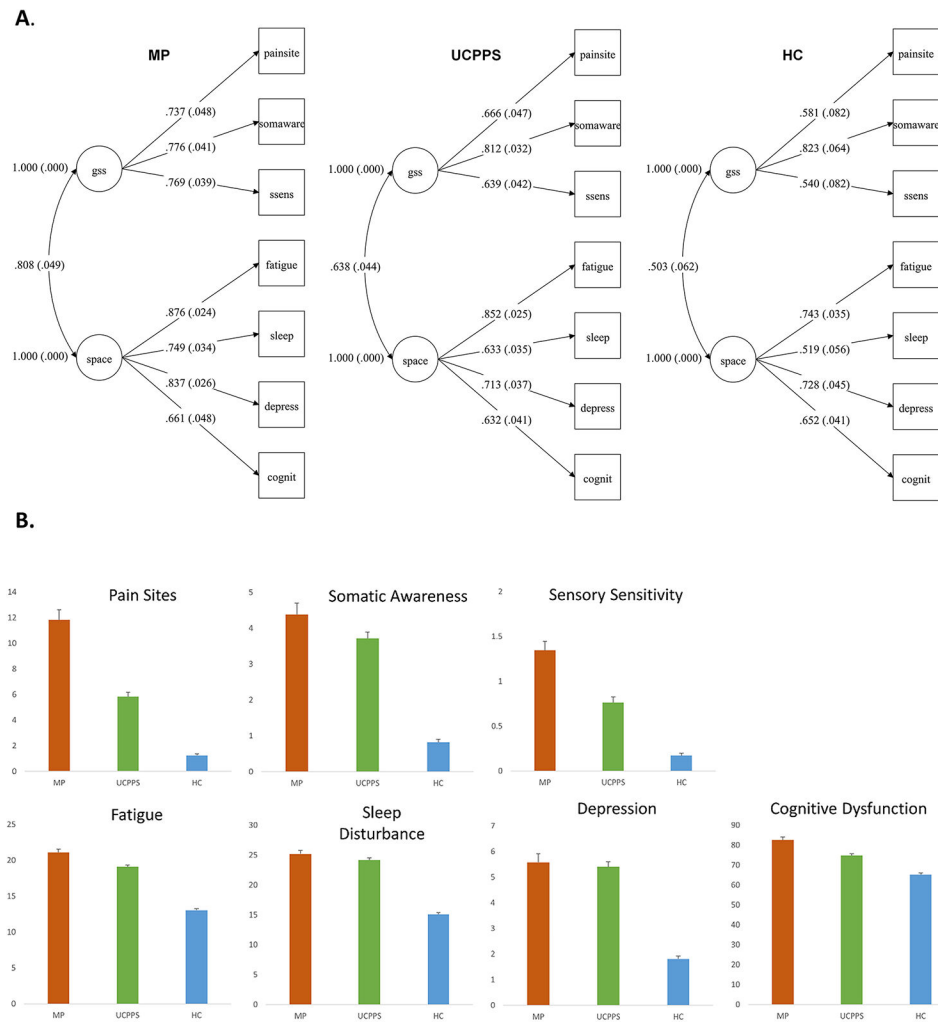
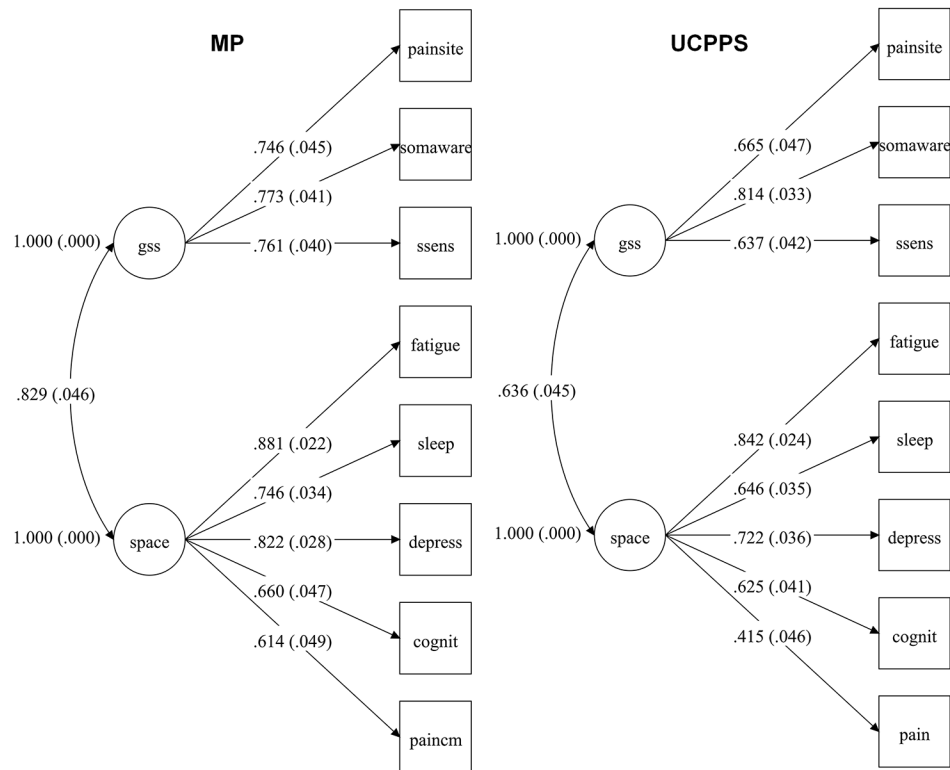


Figure 1. (A) Measurement models for symptoms of centralized pain in UCPPS, mixed pain (MP), and healthy controls (HC). Model fit for UCPPS: $X^2=20.512$, $df=13$, $p=.0832$. RMSEA = .037, 90% CI = .000, .066. CFI = .991. SRMR = .027; Model fit for MP: $X^2=18.014$, $df=13$, $p=.1570$. RMSEA = .044, 90% CI = .000, .088. CFI = .991. SRMR = .027;; Model fit for HC: $X^2=8.007$, $df=13$, $p=.8431$. RMSEA = .000, 90% CI = .000, .028. CFI = 1.000. SRMR = .023. Standardized loadings are shown. (B) Mean symptom levels by group with standard errors.

**Figure 2.**

Measurement models with pain severity for UCPPS and mixed pain (MP) cohorts. Model fit for UCPPS: $X^2 = 41.907$, $df = 19$, $p = .0018$. RMSEA = .053, 90% CI = .031, .075. CFI = .976. SRMR = .035; Model fit for MP: $X^2 = 37.285$, $df = 19$, $p = .0073$. RMSEA = .069, 90% CI = .035, 1.02. CFI = .972. SRMR = .039. Standardized loadings are shown.

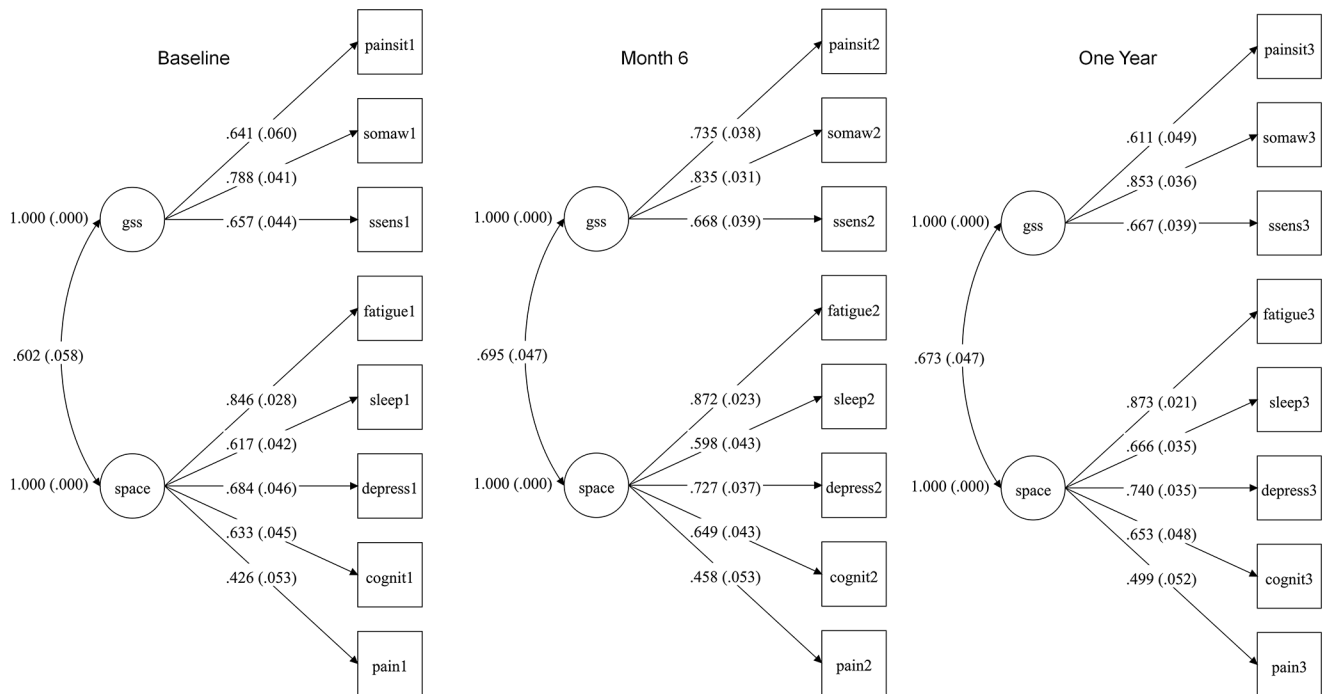


Figure 3.

Measurement model in the UCPPS cohort at baseline, 6 months and one year ($n = 332$).

Model fit for baseline: $X^2 = 37.378$, $df = 19$, $p = .0071$. RMSEA = .054, 90% CI = .027, .079.

CFI = .974. SRMR = .038; Model fit for month 6: $X^2 = 27.039$, $df = 19$, $p = .1038$. RMSEA = .036, 90% CI = .000, .064. CFI = .990. SRMR = .029; Model fit for year one: $X^2 = 35.551$, $df = 19$, $p = .0120$. RMSEA = .051, 90% CI = .024, .077. CFI = .981. SRMR = .032.

Table 1.

Type and number of COPCs in the UCPPS and mixed pain cohorts.

	UCPPS (n = 424)	Mixed Pain (n = 200)
Genitourinary Pain (SYM-Q # 1)	5.07 (2.20)	1.40 (2.20)*
Non-Genitourinary Pain (SYM-Q # 6)	3.25 (2.70)	4.64 (2.83)*
	frequency (%)	
IBS	127 (30)	146 (73)*
TMD	101 (24)	55 (28)
CFS	49 (12)	75 (38)*
FM	38 (9)	84 (42)*
MI	99 (23)	69 (35)*
Number of comorbid COPCs		
None	201 (47)	80 (40)
1	112 (26)	54 (27)
2	58 (14)	33 (17)
3 or more	53 (12)	33 (17)

COPCs = Chronic Overlapping Pain Conditions; UCPPS = Urological Chronic Pelvic Pain Syndrome; IBS = Irritable Bowel Syndrome; TMD = Temporomandibular Disorder; CFS = Chronic Fatigue Syndrome; FM = Fibromyalgia; MI=Migraine.

*
p < 0.01