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Experimental pain and auditory sensitivity in overactive bladder syndrome: a Symptoms of the Lower Urinary Tract Dysfunction Research Network (LURN) Study

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Conflicts of Interest

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Clinical Trial and IRB Information

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Abstract

Purpose: Investigate the presence of non-bladder sensory abnormalities in participants with overactive bladder (OAB) syndrome.

Materials and Methods: Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) study participants with OAB symptoms and controls were recruited from six US tertiary referral centers. Quantitative sensory testing (QST) was performed to determine pressure pain sensitivity at the thumbnail bed and auditory sensitivity. Fixed and mixed effect multivariable linear regressions and Weibull models were used to compare QST responses between groups. Pearson correlations were used to assess the relationship between QST measures. Associations between QST and self-reported symptoms were explored with linear regression.

Results: 297 participants were analyzed (191 OAB, 106 controls; 76% white, 51% male). OAB cases were older than controls (57.4 vs. 52.2 years, p = 0.015). No significant differences in experimental thumbnail (non-bladder) pain or auditory sensitivity were detected between OAB cases and controls. Correlations between pressure and auditory derived metrics were weak to moderate overall for both groups, with some significantly stronger correlations for cases. Exploratory analyses indicated increased pressure pain and auditory sensitivity were modestly associated with greater self-reported bladder pain and pain interference with physical function.

Conclusions: As a group, no significant differences between OAB cases and controls were observed in experimental non-bladder pain or auditory sensitivity during QST. Associations between QST outcomes and clinical pain raise the possibility of centrally-mediated sensory amplification in some individuals with OAB.

Keywords

pressure pain threshold; pain tolerance; quantitative sensory testing; central sensitization; nociplastic pain

Introduction

Clinical management of lower urinary tract symptoms (LUTS) remains suboptimal because the biological and psychosocial factors that initiate, exacerbate, and modify this group of symptoms remain largely unknown. Among the most difficult LUTS to understand and manage is urinary urgency, an abnormal sensation defined as the sudden and compelling desire to void that is difficult to postpone.[1] Urinary urgency is the defining symptom of overactive bladder (OAB) syndrome and can cause significant impairment in quality of life.[2]

A significant proportion of OAB patients have bothersome urinary urgency but do not have involuntary bladder contractions and/or urgency urinary incontinence.[3] This raises the question as to whether some patients with OAB might have altered or amplified

central nervous system (CNS)-mediated perception of bladder sensations.[4] According to this hypothesis, these patients would be expected to demonstrate increased sensitivity to sensory stimulation compared to controls. Moreover, this sensory hypersensitivity could be generalized such that it occurs in body areas remote to the bladder and pelvic region, and may involve multiple sensory modalities, including increased sensitivity to pain, odors, lights, and sounds. Such findings would be consistent to those observed in patients with nociplastic chronic pain conditions, such as fibromyalgia, in which pain and sensory abnormalities are thought to be preferentially generated and/or maintained by aberrant CNS processing (e.g., central sensitization) rather than peripheral tissue injury or nerve damage.[5] In fact, fibromyalgia is associated with increased severity of OAB symptoms.[6–8] Examining for the presence of specific sensory abnormalities in OAB may lead to more mechanism-based categorization and treatment paradigms for LUTS, rather than relying upon nonspecific, symptom-based categorization.

The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) was established to address knowledge gaps in understanding and managing LUTS.[9] The LURN Neuroimaging and Sensory Testing (NIST) sub-study[10] examined sensory processing in participants with OAB using quantitative sensory testing (QST) of pressure pain and auditory sensitivity. The objective of this study was to investigate the presence of sensory abnormalities in participants with OAB relative to controls.

Methods

Study design and population

LURN NIST sub-study methods were described previously.[10] Briefly, participants with OAB, with or without urgency urinary incontinence, and controls without pelvic pain or LUTS were recruited to one of six US tertiary referral centers (see Supplemental Table 1 for a full list of inclusion/exclusion criteria). Male and female participants of at least 18 years of age were presenting for treatment of LUTS to a LURN physician in urology or urogynecology clinics. Demographic and symptom data were collected at baseline; participants underwent functional magnetic resonance imaging and QST within four weeks of their baseline visit.

Patient-reported outcomes

Patient-reported outcomes included assessments of LUTS severity and bother, functional comorbidities, bowel and pelvic floor symptoms, clinical pain severity and its interference with physical function, sensory sensitivity, somatic awareness, sexual function, childhood trauma, psychosocial symptoms, and general health-related quality of life (Supplemental Table 2).

Quantitative sensory testing

Pressure Pain.—Sensitivity to pressure pain was assessed using a Multimodal Automated Sensory Testing System (AMI, Ann Arbor, MI). An ascending series of discrete pressure stimuli were applied to the dominant thumbnail bed for five seconds (5-s), with an inter-stimulus rest interval of at least 20-s. Pressures started at an intensity of 0.5 kilograms of

force (kgf)/centimeter-squared(cm^2), and increased in steps of 0.5 kgf/cm^2, to a maximum of 10 kgf/cm^2. Participants rated the magnitude of pain evoked by each pressure on a digital 0–100 numerical rating scale (NRS; 0 = no pain, 100 = worst pain imaginable). Testing stopped when participants provided a rating of ≥ 80/100 or indicated they were unwilling to continue testing. Participants then underwent testing with pseudo-random sequence of tolerable pressures (ranging from 1–4.5 kgf/cm^2) presented two times each.

Ascending series data were used to derive single-point metrics of pressure pain sensitivity. *Pressure pain threshold* (PPT) was defined as the first pressure in a sequence of at least two consecutive pressures that elicited pain greater than zero. Pressure pain *tolerance* was defined as the last pressure recorded during testing before stopping. *Pain50* was calculated as an approximation of the pressure that evokes moderate pain halfway between threshold and tolerance.[11] Participant pain ratings at 2 kgf/cm^2 were assessed to compare evoked pain at a standardized stimulus intensity. Area under the curve (AUC) was calculated for each participant's stimulus-response profile.

Auditory sensitivity.—Assessment of auditory sensitivity[12,13] was conducted using an audiometer (MA41, Maico Diagnostics, Eden Prairie, MN) that produces pure tones at differing levels of intensity [calibrated as decibels (dB) hearing level]. Participants failing a standardized hearing screen were excluded from auditory analysis.

Participants first listened to a 2000 Hz tone presented at six intensity levels (starting at 40 dB, and increasing by 10 dB steps until 90 dB, with a 10-s inter-stimulus rest interval). After each stimulus, participants verbally rated intensity and unpleasantness, each on a 0–100 NRS (0 = no sound/not unpleasant; 100 = loudest sound imaginable/most unpleasant sound imaginable). If a participant was not able to tolerate or did not wish to continue testing above an intensity level, the ascending series was stopped. Participants were then presented with a pseudo-random sequence of up to six intensities (40–90 dB), three times each, depending on their personal tolerance. Ratings for each intensity level were averaged across repetitions for analysis. Single-point derived metrics of perceived auditory intensity and unpleasantness at *low*, *moderate*, and *high* dB intensity levels were calculated as the mean rating at 40/50, 60/70, and 80/90 dB levels, respectively.

Statistical analysis

For demographics and symptom data, sample means (with standard deviations) and frequencies (with percentages) are reported overall and separately for case and control groups, and compared using two-sample Wilcoxon and chi-square tests. Box-cox transformations were used for non-normal QST measures when appropriate.[14] Multivariable linear regressions with adjustments for age, sex, and clinical site were used to compare pressure Pain50 and tolerance (square-root transformed), AUC (square-root transformed), and low/moderate/high auditory intensity and unpleasantness ratings (separately for ascending and random data). Weibull models were fitted with similar adjustments to compare PPT and pain ratings at 2 kgf/cm^2. Pearson correlation coefficients were calculated for all QST metrics, and compared between groups using confidence intervals. Mixed effects linear regression models comparing cases versus control responses at each of the pressure

and auditory stimulus levels are described in the supplemental materials. In a series of exploratory analyses, potential QST profiles were investigated for OAB participants with varying levels of clinical pain or LUTS. For each pressure pain and auditory sensitivity outcome, separate models were fit using the following independent variables: Brief Pain Inventory (BPI) severity and interference scales; LURN Symptom Index (SI-29) urgency, incontinence, and bladder pain scales. Fixed effects for age, sex, race, and random effects for clinical site were included in the final models. All statistical analyses were completed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA), except for the comparison of correlations, which were completed using the R package cocor.[15] The significance level was corrected for multiple comparisons using the false discovery rate.

Power analyses were presented previously and determined that with at least 84 participants in each group, a medium effect size of 0.5 or a correlation coefficient of 0.25 could be detected with >90% statistical power.[10]

Results

Participants

Of the 319 participants enrolled, 297 (191 OAB cases, 106 controls) had analyzable QST data. No differences in QST were found between OAB with and without urgency urinary incontinence groups, so results are presented for collapsed OAB case and control groups (all p-values>0.05). Participant flow is shown Figure 1. Participants were predominantly white (76%) with an even split between sexes for cases and controls (51% and 50%, respectively) by design (Table 1). Cases were older than controls (57.4 vs. 52.2, p-value=0.0147), and scored significantly higher on measures of urinary symptom severity and bother, genitourinary pain, overall pain severity and interference, sensory sensitivity and somatic awareness,[16] hyperacusis, sleep disturbance, and nearly all other psychosocial factors.

Comparison of pressure pain and auditory sensitivity metrics between OAB and controls

Ratings of evoked pressure pain, auditory intensity, and auditory unpleasantness increased on average for both cases and controls as stimulus intensity increased (Figure 2; Supplemental Figures 1–3). Unadjusted error bars in Figure 2 for mean case and control responses overlap at nearly every stimulus level for each response, indicating no difference in these responses between OAB and controls. Post-hoc analyses using mixed effects linear regression models confirmed these results when controlling for age, sex, clinical site, and within-participant variation (Supplemental Tables 3–5).

Derived pressure pain metrics were similar between OAB and controls (Table 2). Cases showed nominally lower mean Pain50 and significantly lower pain tolerance, indicating increased pain sensitivity. However, after adjusting for age, sex, and clinical site, and correcting for multiple comparisons, none of these comparisons remained significant. Pain50 and pain tolerance values were significantly higher, and AUC was significantly lower, for males compared to females after adjusting for age, site, and OAB status (p-values=0.001, <0.001, and <0.001, respectively), indicating increased pain sensitivity in females regardless of case or control status (not shown).

Comparisons of auditory intensity (Table 3a) and unpleasantness (Table 3b) ratings between cases and controls are shown separately for ascending and pseudo-random data. After adjusting for age, sex, and clinical site, and correcting for multiple comparisons, none of the auditory ratings significantly differed between cases and controls at any level (all p-values>0.05). These results indicate there is no difference in auditory sensitivity between OAB cases and controls.

Correlations between pressure pain and auditory sensitivity

Correlations between auditory intensity (low and moderate level tones - ascending) and PPT, Pain50, pain tolerance, and pain rating at 2 kgf/cm^2 were significantly stronger in OAB cases compared to controls (Table 4). Correlations between these pressure pain metrics and auditory intensity for high level tones and pseudo-random series data showed similar trends, but the majority of comparisons were not statistically significant (p-value range=0.001 to 0.806).

Association between pressure pain and auditory sensitivity with OAB symptoms

Increases in BPI-severity, BPI-interference, and LURN SI-29 bladder pain were associated with significant decreases in Pain50 (linear regression coefficients per 10% increase of the scale range: −0.175 to −0.017) and pain tolerance (−0.038 to −0.004) (Table 5). Associations between Pain50 with BPI-interference and LURN SI-29 bladder pain, and tolerance with BPI-interference, remained significant following correction for multiple comparisons (p-values<0.05). Increases in BPI-interference, BPI-severity, and LURN SI-29 urgency and bladder pain were associated with significant increases in auditory unpleasantness ratings of moderate level tones (ascending series; 0.23 to 3.92 increase per 10% of scale) (Table 6). In addition, increases in LURN SI-29 bladder pain were associated with significant increases in auditory unpleasantness ratings of ascending low tones and pseudo-random moderate tones. After correction for multiple comparisons, only the association between ascending moderate tones and LURN SI-29 bladder pain remained statistically significant (p-value<0.05). No other QST metric was significantly associated with clinical outcomes following correction for multiple comparisons.

Discussion

The present study investigated whether central alterations in afferent signaling contributes to urinary symptoms in OAB. To examine this hypothesis, we measured provoked pain at the thumbnail bed – an asymptomatic body site in OAB remote from the bladder referral areas – and sensitivity to auditory stimuli that bypass the peripheral nervous system. Findings of increased sensitivity in either modality would suggest CNS-mediated sensory amplification, presumably at the supraspinal level of the neuraxis.[17,18] Although as a group, significant case-control differences in QST were not detected, we found some support for our hypothesis in the associations between QST and clinical pain. Lower Pain50 and tolerance levels (i.e., more sensitive) were associated with increased pain interference and bladder pain. Increased ratings of unpleasantness to moderately loud tones were also associated with increased bladder pain. Said differently, participants with greater self-reported pain interference and bladder pain were more sensitive to painful

pressure stimuli and rated auditory tones more unpleasant. These findings are consistent with observations of increased pain sensitivity at the thumbnail in patients with chronic pelvic pain,[19] vulvodynia,[20] and most notably, urological chronic pelvic pain syndrome (UCPPS).[11] Increased auditory sensitivity also occurs in nociplastic pain conditions, such as irritable bowel syndrome, fibromyalgia, and tempomandibular joint disorders.[12,13,21,22] Together these findings suggest that perceptual amplification of sensory processing within the CNS may contribute to abnormal bladder sensations in a subset of OAB patients with pain. In support of this interpretation, recent studies showed increased temporal summation of pain – a QST measure of CNS excitability – in women with OAB.[4] A higher degree of temporal summation was also noted in OAB patients undergoing third line therapy compared to those who were not undergoing third-line therapy.[23]

Reynolds and colleagues[8,24] previously reported the presence of comorbid multifocal pain and somatic symptoms in a substantial portion of individuals with OAB. These findings were confirmed in the present analysis. OAB cases scored significantly higher on measures of overall pain severity and interference, pain distribution on a body map, bladder pain, fatigue, poor sleep, depression, and anxiety. This constellation of symptoms, commonly reported in UCPPS[25] and other nociplastic pain conditions, underscores the probable involvement of centrally-mediated factors in a subset of OAB patients.

Two distinct sensory modalities – cutaneous pressure pain and audition – were more strongly correlated in OAB patients than in controls. Similar relationships between painful/nociceptive and non-painful/non-nociceptive stimuli exist in individuals with nociplastic pain[13,26,27] and may suggest altered multisensory integration. According to this hypothesis, central sensitization causes alterations in brain sites implicated in sensory integration, such as the insula, that leads to maladaptive perceptions of pain or unpleasantness to innocuous stimuli.[26,28,29] Of note, compared to controls, OAB cases reported increased sensitivity to environmental stimuli (e.g., sounds, lights, chemicals) and to sensations occurring within the body (somatic awareness) – important features of nociplastic pain.[16] The implication of altered sensory integration in OAB, though speculative, warrants further investigation.

This study has limitations. The relationships between QST and clinical variables were modest, and many were not statistically significant suggesting small effect sizes that would require an even larger sample to detect. As such, the present findings should be viewed as hypothesis generating rather than definitive. Assessment of pain sensitivity was limited to a single body site and modality. This limitation is being partially addressed in the second phase of the LURN with assessments of pressure pain and temporal summation in the suprapubic bladder referral area. Investigation of hypersensitivity in this body site may help to clarify whether there are subgroups of OAB cases with localized hypersensitivity and spinally-mediated central sensitization.[30]

Conclusions

Experimental sensory sensitivity was assessed in individuals with OAB. Individuals with OAB were not hypersensitive to painful pressure stimuli delivered to the thumbnail bed or auditory stimuli, but exhibited stronger correlations between these sensory modalities compared to controls. Exploratory analyses revealed that increased sensory sensitivity was

associated with greater clinical pain. These findings suggest that OAB patients may exist on a sensory continuum in that those with increased pain exhibit increased sensory sensitivity and subsequently a greater burden of OAB symptoms.[24] This study emphasizes the need for additional studies examining how pain and sensory information is processed and integrated in individuals suffering LUTS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support

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Abbreviations

AUC	Area under the curve
BPI	Brief Pain Inventory
CNS	Central nervous system
LURN	Lower Urinary Tract Dysfunction Research Network
LURN SI-29	LURN Symptom Index
LUTS	Lower urinary tract symptoms
NIST	Neuroimaging and Sensory Testing
OAB	Overactive bladder
PPT	Pressure pain threshold
QC	Quality control
QST	Quantitative sensory testing
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UCPPS	Urological chronic pelvic pain syndrome

Supplemental Abbs:

AUA-SI	American Urological Association Symptom Index
BPI	Brief Pain Inventory
CMSI	Complex Medical Symptom Inventory
CTES	Childhood Traumatic Events Scale
FCI	Functional Comorbidity Index
GUPI	Genitourinary Pain Index
HRQOL	Health-related quality of life
ICIQ-OAB	International Consultation on Incontinence Modular Questionnaire - Overactive Bladder
ICIQ-UI	ICIQ - International Consultation on Incontinence Modular Questionnaire -Urinary Incontinence
I-PAQ	International Physical Activity Questionnaire
LURN SI-29	LURN Symptom Index-29

MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
NRS	Numerical rating scale
OAB-q SF	Overactive Bladder Questionnaire Short Form
PROMIS	Patient-Reported Outcomes Measurement Information System
PSS	Perceived Stress Scale
SA	Somatic awareness
SS	Sensory sensitivity
UDI-6	Urogenital Distress Inventory

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 2002;187:116–26. [PubMed: 12114899]
2. Coyne KS, Payne C, Bhattacharyya SK, et al. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey. Value Health 2004;7:455–63. [PubMed: 15449637]
3. Steers WD. Pathophysiology of overactive bladder and urge urinary incontinence. Rev Urol 2002;4 Suppl 4:S7–S18. [PubMed: 16986023]
4. Reynolds WS, Brown ET, Danford J, et al. Temporal summation to thermal stimuli is elevated in women with overactive bladder syndrome. Neurourol Urodyn 2017;36:1108–12. [PubMed: 27434229]
5. Fitzcharles MA, Cohen SP, Clauw DJ, et al. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021;397:2098–110. [PubMed: 34062144]
6. Chung JH, Kim SA, Choi BY, et al. The association between overactive bladder and fibromyalgia syndrome: a community survey. Neurourol Urodyn 2013;32:66–9. [PubMed: 22674758]
7. Puri BK, Lee GS. Overactive Bladder Symptoms in Patients with Fibromyalgia: A Systematic Case-Controlled Study. Rev Recent Clin Trials 2021;16:202–5. [PubMed: 33023435]
8. Reynolds WS, Mock S, Zhang X, et al. Somatic syndromes and chronic pain in women with overactive bladder. Neurourol Urodyn 2017;36:1113–8. [PubMed: 27367486]
9. Yang CC, Weinfurt KP, Merion RM, et al. Symptoms of Lower Urinary Tract Dysfunction Research Network. J Urol 2016;196:146–52. [PubMed: 26784646]
10. Lai HH, Naliboff B, Liu AB, et al. The LURN Research Network Neuroimaging and Sensory Testing (NIST) Study: Design, protocols, and operations. Contemp Clin Trials 2018;74:76–87. [PubMed: 30248454]
11. Harte SE, Schrepf A, Gallop R, et al. Quantitative assessment of nonpelvic pressure pain sensitivity in urologic chronic pelvic pain syndrome: a MAPP Research Network study. Pain 2019;160:1270–80. [PubMed: 31050659]
12. Hollins M, Harper D, Gallagher S, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215–21. [PubMed: 19121558]
13. Geisser ME, Glass JM, Rajcevska LD, et al. A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. J Pain 2008;9:417–22. [PubMed: 18280211]

14. Box GEP, Cox DR. An Analysis of Transformations. Journal of the Royal Statistical Society Series B (Methodological) 1964;26:211–52.
15. Diedenhofen B, Musch J. cocor: a comprehensive solution for the statistical comparison of correlations. PLoS One 2015;10:e0121945. [PubMed: 25835001]
16. Schrepf A, Williams DA, Gallop R, et al. Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study. Pain 2018;159:2002–11. [PubMed: 29863527]
17. Arendt-Nielsen L Central sensitization in humans: assessment and pharmacology. Handb Exp Pharmacol 2015;227:79–102. [PubMed: 25846615]
18. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–43. [PubMed: 12115241]
19. As-Sanie S, Harris RE, Harte SE, et al. Increased pressure pain sensitivity in women with chronic pelvic pain. Obstet Gynecol 2013;122:1047–55. [PubMed: 24104772]
20. Reed BD, Sen A, Harlow SD, et al. Multimodal Vulvar and Peripheral Sensitivity Among Women With Vulvodynia: A Case-Control Study. J Low Genit Tract Dis 2017;21:78–84. [PubMed: 27753704]
21. Blomhoff S, Jacobsen MB, Spetalen S, et al. Perceptual hyperreactivity to auditory stimuli in patients with irritable bowel syndrome. Scand J Gastroenterol 2000;35:583–9. [PubMed: 10912657]
22. Berman SM, Naliboff BD, Chang L, et al. Enhanced preattentive central nervous system reactivity in irritable bowel syndrome. Am J Gastroenterol 2002;97:2791–7. [PubMed: 12425550]
23. Reynolds WS, Kowalik C, Cohn J, et al. Women Undergoing Third Line Overactive Bladder Treatment Demonstrate Elevated Thermal Temporal Summation. J Urol 2018;200:856–61. [PubMed: 29746857]
24. Kowalik CG, Cohn JA, Delpe S, et al. Painful Bladder Symptoms Related to Somatic Syndromes in a Convenience Sample of Community Women with Overactive Bladder Symptoms. J Urol 2018;200:1332–7. [PubMed: 30017963]
25. Clemens JQ, Mullins C, Ackerman AL, et al. Urologic chronic pelvic pain syndrome: insights from the MAPP Research Network. Nat Rev Urol 2019;16:187–200. [PubMed: 30560936]
26. Harte SE, Ichesco E, Hampson JP, et al. Pharmacologic attenuation of cross-modal sensory augmentation within the chronic pain insula. Pain 2016;157:1933–45. [PubMed: 27101425]
27. Martenson ME, Halawa OI, Tonsfeldt KJ, et al. A possible neural mechanism for photosensitivity in chronic pain. Pain 2016;157:868–78. [PubMed: 26785323]
28. Suhnan AP, Finch PM, Drummond PD. Hyperacusis in chronic pain: neural interactions between the auditory and nociceptive systems. Int J Audiol 2017;56:801–9. [PubMed: 28685627]
29. Mouraux A, Diukova A, Lee MC, et al. A multisensory investigation of the functional significance of the “pain matrix”. Neuroimage 2011;54:2237–49. [PubMed: 20932917]
30. Lai HH, Gardner V, Ness TJ, et al. Segmental hyperalgesia to mechanical stimulus in interstitial cystitis/bladder pain syndrome: evidence of central sensitization. J Urol 2014;191:1294–9. [PubMed: 24316091]

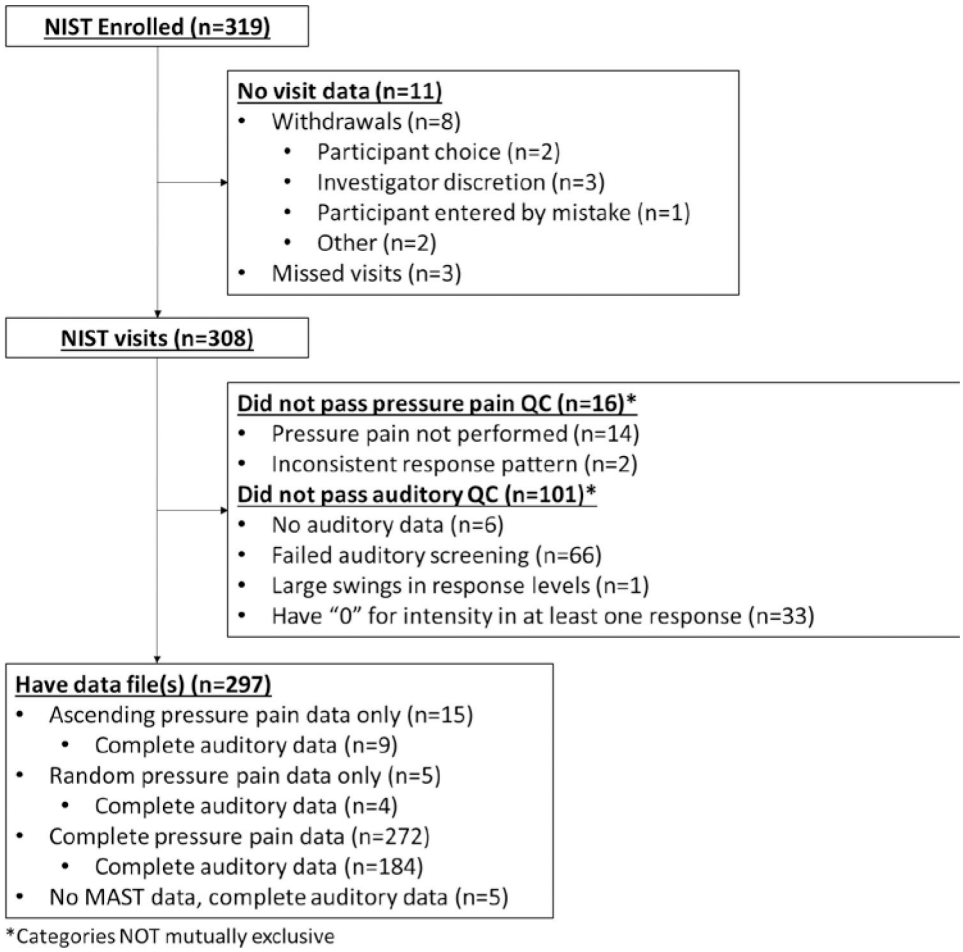

Figure 1.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram for participant flow of Quantitative Sensory testing (QST) data in the Neuroimaging and Sensory Testing (NIST) study. Flow chart begins in topmost rectangle with the number of total enrolled participants and shows number (and reasons) for not having a NIST visit or for QST data not passing quality control (QC). The bottommost rectangle shows the number of participants with available and valid data for analysis.

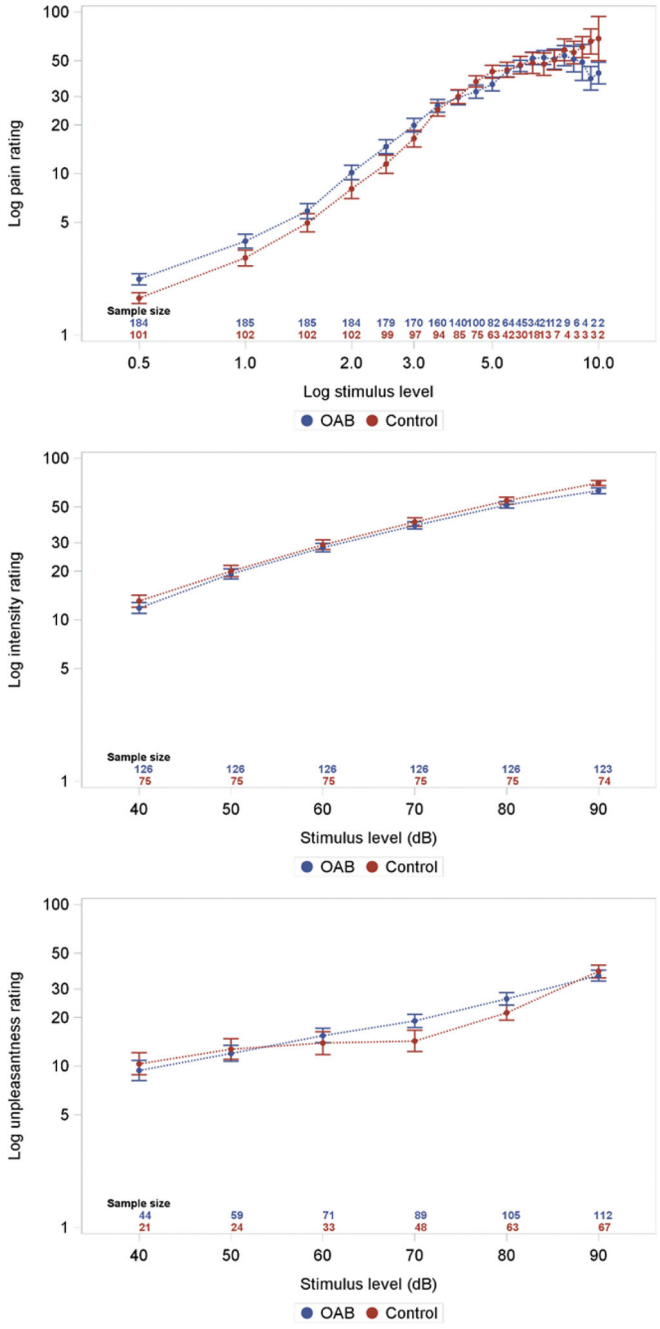

Figure 2.

Paneled graphic of log-transformed overactive bladder syndrome case vs. control ratings of pressure pain (top panel), auditory intensity (middle panel), and auditory unpleasantness (bottom panel). Only ascending series data are presented. In each panel, the stimulus applied is shown on the x-axis (kgf/cm^2 for pressure and db HL for auditory testing), and the response is shown on the y-axis. At each stimulus level applied, the mean rating for case (blue dots) and control (red dots) participants are shown with corresponding unadjusted error bars.

Table 1.

Demographics, clinical characteristics, and patient-reported outcome data by overactive bladder syndrome (OAB) cases and controls.

	Total (n = 297)	OAB (n = 191)	Controls (n = 106)	p-value*
Age	55.5 (14.9)	57.4 (14)	52.2 (15.9)	**0.0147**
Sex (% male)	150 (51%)	97 (51%)	53 (50%)	0.8968
Race				**0.0241**
White	227 (76%)	137 (72%)	90 (85%)	
Black	40 (13%)	29 (15%)	11 (10%)	
Multi-racial/other	30 (10%)	25 (13%)	5 (5%)	
Obese (% yes)	109 (37%)	76 (41%)	33 (31%)	0.0984
Diabetes Type I or II (% yes)	23 (8%)	19 (10%)	4 (4%)	0.0536
Functional comorbidity index	1.7 (1.9)	2.1 (2.0)	1 (1.2)	**<.0001**
AUA-SI total score**	10.2 (8.4)	14.8 (6.8)	1.8 (2.3)	**<.0001**
LURN SI-29 Incontinence scale†	5 (11.4)	8 (13.9)	0.3 (1.7)	**<.0001**
LURN SI-29 Pain scale‡	9 (13.9)	13.9 (15.7)	1.8 (4.9)	**<.0001**
LURN SI-29 Voiding scale‡	8.8 (13.9)	13.7 (15.9)	1.8 (5.0)	**<.0001**
LURN SI-29 Urgency scale‡	25.1 (24.2)	39.2 (21)	3.8 (7.0)	**<.0001**
LURN SI-29 Nocturia scale‡	46.3 (34.4)	62.8 (29.6)	20.5 (24.1)	**<.0001**
ICIQ-UI total score	3.9 (4.7)	5.7 (4.9)	0.6 (1.3)	**<.0001**
ICIQ-OAB total score	4.7 (3.5)	6.7 (2.7)	1.2 (1.2)	**<.0001**
UDI-6 total score	28.7 (26.5)	43 (22.2)	3 (6.7)	**<.0001**
IIQ-7 total score	15.5 (23.2)	23.7 (25.4)	0.7 (3.5)	**<.0001**
OAB-q SF symptom score	28.2 (26.3)	41.9 (22.9)	3.4 (6.7)	**<.0001**
OAB-q SF HRQL score	21.2 (24.0)	32.2 (23.5)	1.5 (3.7)	**<.0001**
BPI severity scale**	10.4 (9.7)	15.7 (8.4)	1.1 (1.6)	**<.0001**
BPI interference scale**	5.9 (7.8)	7.7 (8.6)	2.6 (4.8)	**<.0001**
GUPI overall score‡	8.8 (14.0)	12.4 (15.8)	2.9 (7.3)	**<.0001**
MAPP Body map (% endorsed areas)	6.2 (9.4)	8.3 (10.6)	2.4 (4.6)	**<.0001**
Khalfa hyperacusis questionnaire total score	8.7 (7.1)	10.5 (7.3)	5.5 (5.5)	**<.0001**
CMSI Somatic Awareness (3-month)	2.9 (3.4)	3.9 (3.7)	1.3 (1.9)	**<.0001**
CMSI Sensory Sensitivity (3-month)	0.6 (1.1)	0.8 (1.2)	0.2 (0.6)	**<.0001**
CTES (% any traumatic event) †	165 (64%)	99 (63%)	66 (64%)	0.9196
PROMIS Depression T-score**	46.7 (8.6)	48.6 (9.1)	43.6 (6.6)	**<.0001**
PROMIS Anxiety T-score**	47.2 (9.1)	49.5 (9.4)	43.4 (7.2)	**<.0001**
PROMIS Sleep Dist. T-Score**	49.9 (9.3)	52.3 (8.5)	45.9 (9.2)	**<.0001**
PSS total score†	10.9 (7.0)	12.7 (7.0)	7.9 (5.8)	**<.0001**
PROMIS Phys. function T-score**	51.6 (8.6)	49.7 (9.1)	54.9 (6.5)	**<.0001**
IPAQ category**				0.4762

	Total (n = 297)	OAB (n = 191)	Controls (n = 106)	p-value*
Low activity	128 (46%)	84 (48%)	44 (42%)	
Moderate activity	40 (14%)	22 (13%)	18 (17%)	
High activity	112 (40%)	70 (40%)	42 (40%)	

*p-values for comparison of Cases and Controls from chi-square test or Wilcoxon two-sample test

Missingness is less than 2% for all variables except where noted:

**Missingness 4 to <10%

†Missingness 10% to <20%

‡Missingness 20 to <25%

Table 2.

Comparison of pressure pain metrics across overactive bladder syndrome (OAB) cases and controls.

	OAB Median (IQR)	Controls Median (IQR)	Raw p-value*	FDR corrected p-value*
Pressure pain threshold (kgf/cm^2)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	0.9798	0.9798
Pain50 (kgf/cm^2)	3.1 (2.3–4.1)	3.7 (2.7–4.3)	0.0642	0.1293
Pain Tolerance (kgf/cm^2)[a]	4.5 (4.0–5.5)	5.0 (4.0–6.0)	**0.0409**	0.1293
Area under the curve	107.5 (62.5–153.5)	113.3 (77.8–149.5)	0.4053	0.6079
Pain rating at 2 kgf/cm^2 (0–100 NRS)	12.0 (2.0–30.0)	9.0 (3.0–20.0)	0.6087	0.7304

[a] square-root transformation (note: values back transformed for presentation)

* p-value for comparison OAB vs. controls, adjusted for age, sex, and clinical site.

Abbreviations: NRS = numerical rating scale.

Table 3a.

Comparison of auditory intensity ratings across overactive bladder syndrome (OAB) cases and controls.

	OAB Median (IQR)	Controls Median (IQR)	Raw p-value*	FDR corrected p-value*
Ascending Series				
Low tones	15 (10–25)	15 (10–25)	0.949	0.971
Moderate tones	35 (25–50)	35 (25–50)	0.971	0.971
High tones	52.5 (42.5–70)	57.5 (42.5–72.5)	0.257	0.514
Pseudo-Random Series (mean)				
Low tones	6.9 (5–10.8)	6.7 (4.8–8.3)	0.099	0.477
Moderate tones	17.3 (10.8–24.2)	15 (10.3–21.7)	0.159	0.477
High tones	53.8 (36.7–65)	50.8 (41.5–66.7)	0.663	0.971

Table 3b.

Comparison of auditory unpleasantness ratings across OAB cases and controls.

	OAB Median (IQR)	Controls Median (IQR)	Raw p-value*	FDR corrected p-value*
Ascending Series				
Low tones	0 (0–10)	0 (0–5)	0.224	0.416
Moderate tones	10 (0–20)	5 (0–15)	0.135	0.416
High tones	31.3 (12.5–60)	30 (14–57.5)	0.596	0.596
Pseudo-Random Series (mean)				
Low tones	0 (0–5)	0 (0–0.8)	0.338	0.473
Moderate tones	3.3 (0–11.7)	1.7 (0–10)	0.125	0.416
High tones	23.8 (10–48.3)	24.2 (12–42.5)	0.484	0.565

* p-value for comparison cases vs. controls, adjusted for age, sex, and site

Table 4a.

Pearson correlation coefficients between pressure pain metrics and ratings of auditory intensity (Controls only).

	low tones (asc)	moderate tones (asc)	high tones (asc)	low tones (p-ran)	moderate tones (p-ran)	high tones (p-ran)
Pressure pain threshold	0.20	0.13	0.09	−0.09	−0.07	0.00
Pain50	0.00	−0.07	−0.21	0.02	−0.03	−0.19
Tolerance[a]	−0.07	−0.13	−0.24	0.04	−0.01	−0.21
AUC[a]	−0.21	−0.13	−0.06	0.08	0.12	0.04
Pain rating at 2 kgf/cm^2	−0.07	0.01	0.15	−0.05	0.00	0.21

[a]square-root transformation

Abbreviations: asc = ascending series data; p-ran = pseudo-random series data

Table 4b.

Pearson correlation coefficients between pressure pain metrics and ratings of auditory intensity (OAB Cases only).

	low tones (asc)	moderate tones (asc)	high tones (asc)	low tones (p-ran)	moderate tones (p-ran)	high tones (p-ran)
Pressure pain threshold	−0.25 *	−0.31 *	−0.24 *	−0.06	−0.18	−0.23
Pain50	−0.38 *	−0.48 *	−0.45	−0.24	−0.45 *	−0.44 *
Tolerance [a]	−0.39 *	−0.48 *	−0.44	−0.21 *	−0.41	−0.42 *
AUC [a]	−0.05	−0.01	−0.01	−0.05	−0.05	−0.02
Pain rating at 2 kgf/cm^2	0.36 *	0.44 *	0.33	0.17	0.37 *	0.35

[a] square-root transformation

* Significantly different compared to controls (FDR corrected p-value < 0.05)

Abbreviations: asc = ascending series data; p-ran = pseudo-random series data

Table 5.

Mean pressure pain linear regression coefficients (95% CI) for Brief Pain Inventory (BPI) and LURN Symptom Index-29 (SI-29) scales (model adjusted).

Independent variable	Pain50	Tolerance
BPI-severity, per unit increase (scale is 0–10)	**−0.021 [−0.040, −0.002]**	**−0.005 [−0.010, −0.000]**
BPI-interference, per unit increase (scale is 0–10)	**−0.017 [−0.028, −0.006]** *	**−0.004 [−0.007, −0.001]** *
LURN SI-29 urgency, per 10 pt increase (scale is 0–100)	−0.045 [−0.114, 0.023]	−0.010 [−0.028, 0.008]
LURN SI-29 incontinence, per 10 pt increase (scale is 0–100)	−0.085 [−0.235, 0.066]	−0.021 [−0.061, 0.018]
LURN SI-29 bladder pain, per 10 pt increase (scale is 0–100)	**−0.175 [−0.287, −0.063]** *	**−0.038 [−0.067, −0.008]**

Bold indicates raw p-value < 0.05

* indicates FDR corrected p-value < 0.05

Table 6.

Mean auditory unpleasantness linear regression coefficients 95% CI) for Brief Pain Inventory (BPI) and LURN Symptom Index-29 (SI-29) scales (model adjusted).

Independent variable	Auditory unpleasantness ratings (low tones, ascending series)	Auditory unpleasantness ratings (low tones, pseudo-random series)	Auditory unpleasantness ratings (moderate tones, ascending series)	Auditory unpleasantness ratings (moderate tones, pseudo-random series)
BPI-severity, per unit increase (scale is 0–10)	**0.22 [0.02, 0.43]**	0.09 [−0.03, 0.21]	**0.41 [0.08, 0.74]**	0.20 [−0.03, 0.43]
BPI-interference, per unit increase (scale is 0–10)	0.08 [−0.04, 0.19]	0.02 [−0.05, 0.09]	**0.23 [0.05, 0.41]**	0.06 [−0.06, 0.19]
LURN SI-29 urgency, per 10 pt increase (scale is 0–100)	0.94 [0.29, 1.60]	0.41 [0.01, 0.82]	**1.46 [0.36, 2.57]**	**0.80 [0.04, 1.57]**
LURN SI-29 incontinence, per 10 pt increase (scale is 0–100)	1.07 [−0.57, 2.72]	**1.10 [0.10, 2.09]**	1.68 [−1.06, 4.43]	1.58 [−0.30, 3.46]
LURN SI-29 bladder pain, per 10 pt increase (scale is 0–100)	**1.85 [0.63, 3.08]**	0.54 [−0.22, 1.31]	**3.92 [1.90, 5.95]** *	**1.66 [0.23, 3.09]**

Bold indicates raw p-value < 0.05

* indicates FDR corrected p-value < 0.05