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The LURN Research Network Neuroimaging and Sensory Testing (NIST) Study: Design, Protocols, and Operations.

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Abstract

The Neuroimaging and Sensory Testing (NIST) Study of the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) is a cross-sectional, case-control study designed to investigate whether disrupted brain connectivity and sensory processing are associated with abnormal lower urinary tract symptoms (LUTS) in patients with overactive bladder syndrome (OAB). The NIST Study tests the hypotheses that patients with urinary urgency will demonstrate: (1) abnormal functional and structural connectivity of brain regions involved in urinary sensation

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Conflict of Interest

Cindy L. Amundsen, Victor P. Andreev, Robin L. Gilliam, Margaret E. Helmuth, Ziya Kirkali, H. Henry Lai, Alice B Liu, Vincent A. Magnotta, Bruce Naliboff, Joseph J. Shaffer Jr., Joshua S. Shimony, and Jonathan B. Wiseman have no conflicts of interest to declare. Steven E. Harte reports grants from the NIH for the conduct of this study. In addition, Dr. Harte is co-inventor with royalty rights on the patent for the MAST pain testing device (US 9307906) used in this study, and he has equity membership with Arbor Medical Innovations (Ann Arbor, MI), the licensee of this technology. Steven E. Harte reports grants from NIH, VA, Cerephex, Eli Lilly, American Cancer Society, AAOG; grants and personal fees from Aptinyx; personal fees from SUFU and Longitudinal Capital Management; personal fees and non-financial support from University of North Carolina - Chapel Hill, all outside the submitted work.

on magnetic resonance imaging (MRI), and (2) hypersensitivity to painful (pressure) and non-painful (auditory) sensory stimuli on quantitative sensory testing (QST), compared to controls. Male and female adults (18 years or older) who present at one of the six participating LURN clinical centers for clinical care of their LUTS, with symptoms of urinary urgency with or without urgency urinary incontinence, are eligible to participate. The NIST Study is the largest MRI and QST study of its kind, yielding a neuroimaging and sensory testing dataset unprecedented in OAB research. Advanced multi-modal techniques are used to understand brain functional and structural connectivity, including gray matter volume, and sensory function. Unlike previous MRI studies which involved invasive catheterization and repeated cycles of non-physiologic bladder filling and emptying via a catheter, we use a water ingestion protocol to mimic more physiological bladder filling through natural diuresis. Furthermore, these data will be used in concert with other phenotyping data to improve our understanding of clinically meaningful subtypes of patients with LUTS in order to improve patient care and management outcomes.

Keywords

lower urinary tract symptoms; urgency incontinence; overactive bladder; functional MRI; quantitative sensory testing; Study Design; Statistical Design; Study Protocol

Introduction:

Lower urinary tract symptoms (LUTS) is a term used to describe a range of urinary symptoms believed to be related to lower urinary tract dysfunction. Among them, urinary urgency is one of the most difficult symptoms to understand and to manage. Urinary urgency refers to the abnormal sensation of a sudden compelling desire to pass urine which is difficult to defer.[1] Urinary urgency is the defining symptom of overactive bladder syndrome (OAB).[1] An estimated 16.6% of the US population (33 million) and 10.7% of the worldwide population (546 million) suffer from OAB.[2, 3] The prevalence is predicted to increase 20% by 2018.[2] The personal, societal, and economic cost of OAB is enormous. It is estimated that by 2020, the economic cost of OAB in the US alone will exceed \$82 billion.[4] The etiology and pathophysiology of urinary urgency remains elusive and treatment remains suboptimal.[5]

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) to address knowledge gaps in our understanding and management of LUTS. LUTS are being examined at the levels of patient reported experience, systemic factors, local genitourinary and tissue factors, and cellular/molecular mechanisms (Figure 1).[6] Sensations of the body, including sensations associated with the lower urinary tract (e.g., urinary urgency), engage the central nervous system (CNS) in processing, interpreting and modulating the sensation. To better characterize urinary sensations associated with LUTS, the LURN Neuroimaging and Sensory Testing (NIST) Study, described here, will examine neural connectivity and sensory processing abnormalities among patients with urinary urgency, with and without urgency urinary incontinence (UUI).

Previous neuroimaging studies of urinary urgency were small, enrolling only 20 patients or less from a single clinical site,[7–13] enrolled mostly women,[7–15] and recruited only patients with urgency incontinence.[7, 8, 10, 12–15] In addition, many studies did not have a control group.[11, 12, 14, 15] To our knowledge, only one study used quantitative sensory testing (QST) to measure sensory processing in a small sample of females with urinary urgency.[16] The NIST Study is designed to overcome these limitations by being the first study to enroll a large population of both men and women from multiple clinical centers, and to compare urinary urgency, urgency incontinent, and control participants using both brain magnetic resonance imaging (MRI) and QST.

The objective of the NIST Study is to investigate whether abnormal brain connectivity and sensory processing patterns are associated with urinary urgency. We will perform multi-modal MRI (resting state functional connectivity MRI, diffusion tensor imaging for structural connectivity, high resolution anatomical scans for volumetrics) and QST (pressure and auditory sensitivity assessments) in OAB participants with urinary urgency, with and without UUI, and compare the results to age and sex matched controls.

Materials and Methods:

The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

The LURN is a multi-center NIH/NIDDK sponsored research network consisting of six US clinical sites and a data coordinating center (DCC), with the primary objectives of identifying and explaining clinically relevant important subtypes of patients with LUTS, and improving the measurement of patient experiences of LUTS. The six clinical sites involved are: Washington University in St Louis, University of Michigan, Duke University, University of Washington, University of Iowa, and Northwestern University. Arbor Research Collaborative for Health (Ann Arbor, MI) serves as the DCC for LURN. The clinicaltrials.gov identifier number of this study is NCT02485808.

Overview of the Neuroimaging and Sensory Testing (NIST) Study Design

The NIST Study is a cross-sectional, case-control study that consists of two major components – brain MRI and QST. The MRI component consists of (1) resting state functional connectivity MRI (RS-fcMRI) that examines *functional connectivity* between brain regions implicated in sensory processing or motor control of the lower urinary tract, (2) diffusion tensor imaging (DTI) that examines *white matter structural connectivity* between these brain regions, and (3) high resolution T1 (MP-RAGE) scans that assess *anatomic* abnormalities of the brain *gray matter* using 3T MRI scanners. The second major component of the NIST Study uses QST to test the hypothesis that patients with urgency and/or urgency incontinence demonstrate evidence of generalized or global sensory hypersensitivity compared to controls. Standardized QST procedures are used to characterize participant responses to pressure and auditory stimulation. These methods are complimentary in that neuroimaging explores the brain networks that underlie the subjective sensory percepts evoked and measured in QST.

In addition to demographics and clinical and physical examination data, participants complete validated questionnaires to assess urinary, bowel and pelvic floor symptoms, and psychosocial health. Biological samples are collected and banked at the NIDDK Central Repository for future studies by the LURN investigators and the broader research community (<https://repository.niddk.nih.gov/home/>). A flow diagram of the NIST study visit is depicted in Figure 2

All study procedures occur on the same day, as this allows correlation between the various datasets – urologic symptoms, non-urologic symptoms, psychosocial measures, biomarkers, neuroimaging, and sensory testing – without large temporal gaps between them. MRI scanning is performed prior to QST, as the potential residual effects of QST (e.g., lingering pain) could interfere with resting state fMRI results.

Overarching Hypotheses

The objective of the NIST Study is to investigate whether disrupted brain connectivity and sensory processing are associated with abnormal urinary sensation or urinary urgency associated with OAB. The NIST Study tests the overarching hypotheses that patients with urinary urgency and/or urgency incontinence will demonstrate: (1) abnormal functional and structural connectivity of brain regions involved in urinary sensation on MRI scans, and (2) hypersensitivity to painful (pressure) and non-painful (auditory) sensory stimuli on QST, compared to control participants who do not have urinary urgency and/or UUI.

Specific Hypotheses

The specific neuroimaging hypotheses that will be tested in NIST include:

Hypothesis 1a: Patients with urinary urgency will demonstrate different brain functional connectivity (RSfMRI), including changes in inter- and intra-network connectivity of the control and salience networks, compared to controls.

Hypothesis 1b: Patients with urinary urgency will demonstrate altered brain white matter tract integrity (DTI), including reduced anisotropy within the prefrontal cortex and in the limbic region, compared to controls. The alteration in brain white matter tract integrity (DTI) will further correlate with changes in brain functional connectivity (RSfMRI) in patients with urinary urgency.

Hypothesis 1c: The degree of MRI abnormalities (RSfMRI, DTI) will have a positive correlation to the severity of urgency incontinence in patients.

The RSfMRI regions of interest (ROI) will include areas such as the insular cortex, anterior cingulate gyrus, frontal cortex, cerebellum, and pre-optic hypothalamus. DTI ROI will include white matter tracts such as the ATR (anterior thalamic radiation), UNC (uncinate fasciculus), IFO (inferior fronto-occipital fasciculus), SFO (superior longitudinal fasciculus), IFO (inferior longitudinal fasciculus).

The specific QST hypotheses that will be tested in NIST include:

Hypothesis 2a: Patients with urinary urgency will demonstrate increased sensitivity to non-pelvic somatic pressure stimuli and auditory stimuli compared to controls.

Hypothesis 2b: Global sensory abnormalities will be less common in patients with urinary urgency than in pelvic pain patients recruited through the NIDDK MAPP Research Network.

Hypothesis 2c: The degree of sensory sensitivity will have a positive correlation to the severity of urgency incontinence in patients.

Eligibility and Study Population

Male and female adult patients (18 years or older) presenting to a LURN physician in a urology or urogynecology clinic at one of the six participating LURN clinical centers, seeking clinical care of their LUTS, who complain of symptoms of urinary urgency, with or without UUI, are invited to participate.[5]

To be eligible, all cases have to answer “sometime”, “often”, or “always”, on question 6 of the LUTS Tool[17] (“*During the past month, how often have you had a sudden need to rush to urinate?*”). Cases are further assigned to the subgroup **urgency with UUI** if they answer “sometimes”, “often”, or “always” on question 16b of the LUTS Tool (“*How often in the past month have you... leaked urine in connection with a sudden need to rush to urinate?*”). Those answering “never” or “rarely” to this question are assigned to the subgroup **urgency without UUI**. Cases also have to fulfill the eligibility of the LURN Observational Cohort Study (see Cameron et al).[18] Age and sex matched controls without significant urgency or UUI are recruited for comparison. The full list of inclusion and exclusion criteria for cases and controls are listed in Table 1. The overall recruitment target was 252 participants across the six LURN clinical sites with an approximately equal proportion of males and females. Recruitment began in May 2016 and was completed in April 2018. The actual number of NIST Study participants enrolled was 265 (51% female): 85 with urgency and urgency incontinence (40 males, 45 females), 81 with urgency but without urgency incontinence (43 males, 38 females), and 99 controls (48 males, 51 females). Specific information on enrolled participants will be presented in future papers.

Prior to NIST Study initiation, institutional review board approval for study of human subjects is obtained separately from each of the participating clinical centers, and at the DCC. Written informed consent is obtained from all participants prior to enrollment.

Sample Size Calculation

T-tests and linear regression models are used to compare functional connectivity, diffusivity and anisotropy, and sensitivity thresholds between groups of patients. Power calculations based on these tests are performed to determine an appropriate sample size. The target was 1:1 for male to female and OAB wet and dry. Our estimates show that a sample size of n=84 for each of the three groups (urgency without UUI, urgency with UUI, and matched healthy controls) allows us to detect a medium effect size of 0.5 with >90% statistical power, using two-tailed tests with alpha=0.05. Additionally, using correlation coefficients as a proxy for

linear regression, we estimate that a sample size of $n=84$ for each of the subgroups would allow us to detect a correlation coefficient of 0.25 with >90% statistical power, assuming $\alpha=0.05$. These power calculations assume that associations are unadjusted for confounding factors, but adjusting analyses for age, sex, or other patient characteristics that can alter neuroimaging and QST findings will provide at least as much power as the unadjusted analyses, but in many cases the power would be increased.

Study Procedures and Data Collection

A) Questionnaires, Clinical Data and Biosample Collection—The NIST study visit includes the collection of demographics; past medical and surgical history; family history; medical comorbidities; all current prescription and over-the counter medications; a standardized physical and pelvic examination; and participants' self-report of urinary symptoms, pelvic floor symptoms, bowel symptoms and sexual function; psychosocial health (depression, anxiety, stress); health-related quality of life; a 3-day bladder diary; dipstick urine analysis; a pregnancy test if indicated; and biosample (serum, urine, saliva, vaginal swabs for women and perineal swabs for men), as previously described by Cameron et al.[18] With the exceptions of pelvic examination data and the bladder diary, these variables are also collected from controls. Control participants are asked to complete a dipstick urine test while urine culture results are obtained from the medical record of cases at their initial clinical encounter. Urodynamic testing was not performed as part of the NIST protocol.

The various questionnaires administered to NIST participants are described in Table 2. Briefly, the International Consultation on Incontinence Modular Questionnaire - Urinary Incontinence Short Form (ICIQ-SF)[20], and Incontinence Impact Questionnaire (IIQ-7)[21] are used to assess symptom severity and disease specific quality of life; International Consultation on Incontinence Modular Questionnaire – Overactive bladder (ICIQ-OAB)[22] and OAB Questionnaire Short Form (OAB-q)[23] to assess severity and impact of OAB; Urogenital Distress Inventory (UDI-6)[21] to assess the degree of bother of urinary symptoms; Hyperacusis Questionnaire (HQ)[24] to assess auditory hypersensitivity; Brief Pain Inventory (BPI)[25] and the MAPP Research Network Body Map[26] to assess systemic pain; Poly-Symptomatic Poly-Syndromic Questionnaire (PSPS-Q)[27] and Complex Medical Symptom Inventory (CMSI)[28] to assess somatic symptom burden; and Urgency Catastrophizing Scale (UCS), a questionnaire modified from the Pain Catastrophizing Scale[29] to assess catastrophizing due to urinary urgency. In addition, participants are also asked to complete questionnaires used in the LURN Observational Cohort Study described by Cameron et al to assess measures such as pelvic floor function, bowel function, anxiety, depression, perceived stress, and quality of life.[18] The questionnaires are completed on the day of MRI scans prior to brain scanning.

B) Brain MRI Scans—After the questionnaires are completed, two sets of resting state functional connectivity MRI scans (RS-fcMRI) - a high-resolution TI (MP-RAGE) scan and a diffusion tensor imaging (DTI) scan - are collected from each participant using 3T MRI scanners. The MRI study procedure is depicted in Figure 3.

The participant is first asked to void, if possible (“V” in Figure 3). Then 350 cc (12 oz) of water (W) are consumed by each participant 40 minutes before the first RS-fcMRI scan (RS1). The participant is asked to rate their bladder urgency and bladder pain levels on 0–10 scales (0 = no pain; 10 = worst pain imaginable) at 0 minute post ingestion, 20 minutes post-ingestion, and pre and post the individual scans (Q). The first RS-fcMRI scan (RS1) is performed after natural diuresis of the ingested water with a relatively *distended bladder*. The subject then exits the scanner and completes a measured void (V), and returns to the scanner for the second RS-fcMRI scan (RS2) with an *empty bladder*. Comparison of the RS1 and RS2 scans permits examination of resting state brain networks when the bladder is empty (RS2) versus when the bladder is relatively distended (RS1). A high resolution T1 (MP-RAGE) scan and a DTI scan follows the two RS-fcMRI scans. Again, the participant is asked to rate their bladder urgency and bladder pain levels on 0–10 scales (Q) at the beginning and conclusion of T1 and DTI. The specific data elements collected during the MRI scans are presented in Supplemental Material 1.

C) Quantitative Sensory Testing (QST)—QST refers to experimental methods in which sensations are evoked by quantifiable stimuli applied in a systematic manner to one or more body regions.[41] Participant responses to these stimuli, such as ratings of perceived intensity and unpleasantness, are correlated to stimulus intensity to provide a quantifiable index of experimental sensory sensitivity. The NIST QST protocol consists of two components: pressure pain sensitivity testing using the University of Michigan-designed Multimodal Automated Sensory Testing (MAST) System (Arbor Medical Innovations, Ann Arbor, MI)[42] and auditory sensitivity testing using a clinical-grade audiometer (MA41, Maico Diagnostics, Eden Prairie, MN). Scripted instructions are used for all QST procedures to maintain consistency across testing sites (see Supplemental Material 2 for the scripts). The sequential order of QST procedures (listed below) is designed to minimize participant burden by separating the painful tests (i.e., MAST Ascending and Random tests) with the non-painful Auditory tests.

- (1) MAST training and familiarization procedures (L thumb, non-dominant hand)
- (2) MAST Ascending Series (R thumb, dominant hand)
- (3) Short break (3–5 minutes)
- (4) Hearing screening (L and R ear separately)
- (5) Auditory Ascending Series (L and R ears together)
- (6) Auditory Random Series (L and R ears together)
- (7) Short break (3–5 minutes)
- (8) MAST Random Series (R thumb, dominant hand)

Pressure Pain Sensitivity

The MAST system is a minimal risk investigational device that applies computer-controlled pressure stimuli at precisely controlled intensities for specified durations. The MAST system consists of two touchscreen computers – one for test design/operation and one to capture

participant feedback, and a wireless, hand-held pressure stimulator. Pressure is applied to the participant's thumbnail by a 1 cm² rubber probe driven by a miniature servo-motor. MAST systems have been used in several other clinical studies, including the NIDDK Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. [43–47]

Participants first undergo a MAST familiarization procedure prior to data collection. The purpose of familiarization is to teach participants how to perform the test correctly and to reduce testing anxiety. During familiarization, a series of discrete pressures are delivered in a pattern of ascending intensity levels beginning at 0.5 kgf/cm² and increasing in 0.50 kgf/cm² increments to the participant's non-dominant thumbnail. Each pressure is delivered at a ramp rate of 4 kgf/cm²/second for 5 seconds with an inter-stimulus interval of 20 seconds. The maximal pressure applied is 10 kgf/cm². Immediately after each pressure is released, a prompt appears on the participant-facing computer asking the participant to rate the pain evoked by the preceding pressure using a 0–100 numerical rating scale (NRS; 0 = no pain; 100 = pain as bad as you could imagine). The familiarization procedure ends when participants provide a rating of ≥ 50 on the 0–100 NRS, if they indicate they are unable or unwilling to continue, or after 10 kgf/cm² of pressure is applied. Following task completion, the study coordinator reviews the participant's understanding of the procedure and provides additional guidance as necessary. Data from the familiarization task is not used for analysis.

The MAST Ascending Series test is conducted on the dominant thumbnail immediately following the familiarization procedure. Parameters of the Ascending Series test are identical to the familiarization task with the exception of the stopping criteria. The Ascending Series test is stopped when participants provide a rating of ≥ 80 on the 0–100 NRS, indicate that they are unable or unwilling to continue testing, or after reaching the maximum allowed pressure of 10 kg/cm².

In the MAST Random Series test, a range of tolerable pressures (ranging from 1–4.5 kgf/cm²) are delivered to the dominant thumb and rated, twice each, in pseudo-random sequence following the method of constant stimuli. One of three possible ranges of pressures (identified as A, B, or C) is selected for the Random Series based on each participant's individual tolerance level as determined during the preceding Ascending Series. Participants receive a total of 8–12 pressures depending on the range selected. The MAST Random Series is conducted after auditory sensitivity testing to mitigate the development of peripheral sensitization of thumb tissue from repeated testing. All MAST data are directly uploaded to DCC data servers via SFTP at the completion of testing. The specific data elements that are collected are presented in Supplemental Material 2.

Auditory Sensitivity

Auditory sensitivity is assessed to determine whether individuals with urgency exhibit increased sensitivity to sounds which has been observed in other patient cohorts with known CNS alterations of sensory processing.[48–55] Prior to data collection, hearing screening is performed according to American Speech-Language-Hearing Association guidelines for screening hearing impairments in adults.[56] This involves a brief case history and a 25 dB HL pure-tone screen at 1000, 2000, and 4000 Hz in both ears separately using a calibrated

audiometer. Testing is conducted in a quiet environment using earphones. Participants who fail to respond to either (left or right ear) of the 2000 Hz screening tones are excluded from further testing.

For the Auditory Ascending Series test, participants are asked to listen to a series of audiometer-generated pure tone acoustic stimuli. A total of 6 tones, each 3 seconds in duration, are presented binaurally at ascending intensity levels (40–90 dB, 2000 Hz). After each tone, participants are asked to rate separately the intensity and unpleasantness of the tone on 0–100 NRS (0 = no sound/not unpleasant; 100 = loudest sound imaginable/most unpleasant sound imaginable). If a participant is not able to tolerate or does not wish to hear a tone above a certain level (e.g., 80 dB), the ascending series are stopped and the participant will not be presented with louder tones.

After the ascending series, the Auditory Random Series test begins without a break. Participants are presented with up to 6 tones (40–90 dB, 2000 Hz), three times each, in pseudorandom order according to the method of constant stimuli. If a participant previously indicates that he or she could not tolerate or did not want to hear a tone at or above a certain level (e.g., 80 dB), then that tone and all louder tones will be skipped during the random series. The specific data elements that are collected during auditory testing are presented in Supplemental Material 3.

Quality Control (QC) and Standardization

Data quality assurance, control, and management protocols were developed and executed by the DCC. Prior to study initiation, the DCC administered protocol-specific training and certification sessions for all LURN study personnel. Data entered into the custom web-based database system had built-in data checks for data quality assurance purposes.

Protocol compliance is assessed at regular intervals, and monthly data queries are submitted to each site to ensure accuracy of data acquisition and entry. DCC study monitors visit each site at least once a year to review study documents, monitor compliance, and assess protocol adherence. Regular reports of the data entered into the database are generated to ensure there are no inconsistencies, particularly for repeated data elements. Studies of intra-subject and inter-subject data variability, as well as intra-site and inter-site data variability, is used to further ascertain random or systematic data quality issues.

In order to insure compatible data for multisite analysis of fMRI scans obtained from the different scanner models used by the six clinical centers (see Table 3), standardized neuroimaging protocols and a process of scanner calibration and ongoing quality control was developed and implemented by the Neuroimaging Data Core of the UCLA Center for Neurobiology of Stress and Resilience (CNSR Data Core). Following procedures initially developed for the MAPP Research Network multisite imaging studies,[57] the CNSR Data Core set up specific scanner settings for each scanner type used at the various LURN sites, and instituted procedures for initial evaluation of scans from each site prior to beginning the study. All study scans are uploaded to the CNSR Data Core within 48 hours of data collection and quality assurance (QA) protocols are run on the scans before being archived

for analysis. The CNSR Data Core website portal set up specifically for LURN is used to securely upload scans and was continuously updated with QA feedback for the sites.

Detailed procedures for scanner settings and QA protocols have been previously described. [57, 58] Briefly, site qualification consisted of 1) implementing the proscribed scanner settings for the individual scanner for each of the three scan types; high resolution structural T1 (MP-RAGE), Resting State functional connectivity MRI (RS-fcMRI), and diffusion tensor imaging (DTI), 2) assessing scanner calibration and temporal stability using a physical phantom, and 3) assessing scan quality from human test scans for each scan type.

- The fBIRN agar ball is used as the phantom, and is imaged with a 3-plane localizer.
- The high resolution structural images are acquired with a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence, with repetition time (TR) = 2200 ms, echo time (TE) = 3.26 ms, slice thickness = 1 mm, 176 slices, 256×256 voxel matrices, and 13 mm voxel size. This sequence derives from that developed by The Alzheimer's Disease Neuroimaging Initiative (ADNI).[59] For the GE scanners the T1 was acquired with an SPGR sequence with similar parameters to the MP-RAGE. Images are aligned vertically with the mid-Sagittal plane and horizontally with the AC-PC line.
- The RS-fMRI scans are acquired in 364-slice whole brain volumes, with slice thickness = 4 mm, TR = 2000 ms, TE = 28 ms, and flip angle = 77° . This sequence is based on that developed by the Functional Biomedical Informatics Research Network (fBIRN) for multisite, standardized acquisition across brands and models.[60]
- The diffusion tensor imaging (DTI) sequence is derived from a common q-ball imaging protocol involving 64 directions at equidistant angles on a sphere in q-space. The number of directions (64) were chosen based on a balance between total acquisition time, the need for high angular resolution data for use in probabilistic tractography techniques, and commonly used gradient schemes from MR system manufacturers. The 2mm isotropic resolution and 64 directional encoding scheme is also commonly used in studies involving structural connectivity analysis. The DTI sequence uses a diffusion-weighted single shot spin echo EPI pulse sequence. The 64 directional diffusion vectors validated on the Siemens scanners is used on all scanners. When possible, nine (9) b=0 volumes are acquired for preprocessing methods. Generally, alignment of slices with AC-PC line is used.

The imaging data from the calibration and human test scans are uploaded to the UCLA CNSR Data Core and reviewed for correct scanner settings, calibration, and image quality. Site qualification is performed before study initiation but is also repeated with any upgrades or changes in scanner type at a site. Ongoing QC of incoming scans to the CNSR Data Core consists of checking subject ID consistency and scanner settings in the header of the image file and scan quality in terms of excess movement, head positioning, and presence of artifacts. The QC evaluation is designed to 1) detect and report back to the site the rare

occurrence of a mislabeled, unusable or missing scan for a participant, and 2) flag acquisition errors (such as incorrect scan parameters) and other technical problems (e.g. excess movement) so that investigators who might use these data in the future will have annotated images. Structural MRI human data are assessed visually for subject motion artifacts, poor image contrast, and errors in image prescription. RS-fcMRI phantom data are examined using the fBIRN quality control workflow (BXH/XCEDE tools), which produces a full report including SNR and signal fluctuation to noise ratio (SFNR) along with metrics of signal drift, and spurious fluctuations. RS-fcMRI human data are also assessed for motion, with thresholds of 2mm translation or 2° rotation in any given direction, as well as visual assessment of image quality and presence of signal intensity or extreme image distortion artifacts. DTI phantom and human data are flagged for variations in quantitative metrics, motion artifacts, gradient failures, and geometric distortions. QC findings for each scan are made available on an ongoing basis on the LURN neuroimaging web site and archived with the scan in the CNSR database. Neuroimaging QC (quality control) processing is done centrally, but preprocessing and data analysis will occur at clinical sites based on their specific neuroimaging analytic expertise.

To ensure QST procedural standardization across sites, all study coordinators complete a one-day, in-person training session on QST procedures prior to NIST study protocol initiation. Additional training sessions, protocol reviews, and technical assistance are provided during in-person LURN meetings and as-needed by phone or webinar. A manual of operations outlining the procedures in detail and a dedicated email address/phone number for immediate QST technical assistance is also provided. The MAST device and audiometer undergoes yearly calibration to maintain reliability and consistency across all LURN testing sites. Quality control assessments of QST data is performed routinely by the DCC.

Discussion:

Given the potential roles that the brain and the somatosensory and viscerosensory system might play in processing, interpreting, and modulating normal and abnormal lower urinary tract symptoms (e.g., urinary urgency), it is surprising that there have been few neuroimaging and sensory testing studies.[7–16, 61, 62] The NIST Study brings the following innovations and uniqueness to OAB research by:

1) Examining functional and structural connectivity in normal and abnormal bladder function:

Previous functional MRI BOLD (blood oxygen level dependent) studies have shown that abnormal activation and deactivation of the following brain areas may be associated with UI: the anterior cingulate gyrus, insula, prefrontal cortex, parieto-temporal lobe, thalamus, periaqueductal gray, and pontine micturition center.[7, 8, 12, 61, 62] Although specific brain areas have been described, much less is known about how these regions communicate (i.e., *connectivity*), and how alterations in this connectivity may contribute to the pathophysiology of urinary urgency and/or UI. RS-fcMRI is a neuroimaging modality that can examine how these brain regions connect *functionally* with each other as an integrated neural network (*functional connectivity*). RS-fcMRI is based on the discovery that spontaneous low

frequency (0.1 Hz) BOLD signal fluctuations in functionally related brain areas show strong temporal correlations.[63] RS-fcMRI provides a functional map of related regions of the brain to examine network properties, including between and within sensory, motor, and default mode networks. In contrast to RS-fcMRI, DTI provides a *structural* map to study how specific brains are connected to each other via white matter fiber tracts. Thus, DTI provides *structural connectivity* data to correlate to the functional connectivity data from RS-fcMRI. Finally, the high resolution T1 (MP-RAGE) scan provides *anatomic information* for gray matter volumetric analysis.[64] This study is a critical next step in OAB neuroimaging research, as we leap from imaging individual brain areas (activation/deactivation) to understanding how these brain areas connect both *functionally and structurally* with each other as an integrated network in normal and abnormal bladder function.

2) Using a water ingestion protocol to mimic more physiological bladder filling through natural diuresis:

All published studies except one required that the subjects undergo catheterization, and involved repeated, alternating cycles of rapid bladder filling and withdrawal through a catheter to “provoke” the bladder.[7–15] Unfortunately, this bladder stimulation paradigm is invasive and can sensitize the bladder, urethra, and the pelvic floor during MRI. It can also cause pain and discomfort, and may significantly confound analyses of brain processing related to urinary urgency and UUI. The rapid rates of bladder filling – ranging from 60 cc/min to 400 cc/min in some protocols [7, 14] can trigger non-physiological or supra-physiological sensation of urgency. The feeling provoked during rapid, repetitive, artificial bladder filling by the catheter may not re-create the everyday experience of urinary urgency.

Unlike practically all previous MRI studies on OAB,[7–15] a catheter is not placed inside the bladder during the NIST Study to avoid non-physiological provocation of the bladder, urethra, and the pelvic floor during MRI. Instead, the NIST Study uses a water ingestion protocol to mimic physiological bladder filling through urine production and natural diuresis.

3) Expanding the study to include a large population of both men and women from multiple clinical centers, to compare urgency without UUI, urgency with UUI, and matched controls:

Previous neuroimaging studies of urinary urgency were small, enrolling only 20 patients or less from a single clinical site,[7–13] enrolled mostly women,[7–15] and recruited only patients with urgency incontinence.[7, 8, 10, 12–15] In addition, many studies did not have a control group.[11, 12, 14, 15] The NIST Study is designed to overcome these limitations by being the first study to enroll a large population of both men and women from multiple clinical centers, to compare urgency without UUI, urgency with UUI and matched control participants using both MRI and QST. Another strength is that the NIST Study has developed a protocol that standardizes MRI and QST data acquisition across multiple sites which yields a common dataset on a scale that is unprecedented in OAB research. See Table 4 for a comparison between the MRI studies published to date versus the NIST Study.

4) Quantifying the sensory hypersensitivity of urgency participants using quantitative sensory testing:

QST has been used to characterize sensory function in individuals, and investigate pharmacological efficacy and mechanistic differences between patient subgroups.[41, 65–71] In addition, pre-treatment QST has been shown to predict treatment outcomes for both behavioral and pharmacological interventions.[72–76] Taken together, these studies support our view that mechanistic phenotypes determined by QST may be useful in the development of patient subgroups and personalized treatment algorithms for OAB.[69, 77, 78] More importantly, QST studies will help us understand whether urgency patients with abnormal sensation in the urinary tract might also have global abnormalities in sensory processing. To our knowledge, there is only one small, single institution study that examined QST in OAB. Reynolds et al showed that females with refractory OAB (n=20) exhibited facilitated temporal summation of pain compared to controls, suggesting that central sensitization may be an underlying mechanism contributing to OAB in women.[16] The NIST Study, with over 150 participants with urgency (with and without UUI), is the largest QST study in this population to date.

The use of thumbnail pressure as an evoked stimulus and its validity in the measurement of CNS sensory processing has been discussed extensively.[48, 79–87] The thumb is a neutral body site that is not associated with LUTS, and is remote from the site of primary symptom complaint (the bladder). Thus, findings of increased sensitivity at the thumbnail suggest a CNS-mediated mechanism of global sensory hypersensitivity. Whereas mechanical sensitivity necessarily involves both peripheral and CNS mechanisms, auditory sensitivity is considered a more CNS-mediated test modality. The inclusion of auditory testing improves our ability to detect central mechanisms of sensory amplification across multiple sensory domains.

5) Phenotyping the heterogeneous urgency and/or urgency incontinent population into clinically meaningful subtypes of patients in order to improve patient care and management outcomes:

It is currently unknown whether urinary urgency with and without UUI might represent a true continuum reflecting different degrees of continence control, or if the two entities might have different underlying pathophysiology. The MRI and QST data may help to decipher the differences between urgency with and without UUI. We can determine if the severity of UUI in patients is correlated to alterations in the motor network of the brain that controls pelvic floor function, and in the sensory network that governs visceral sensation.

It is also currently unknown whether there are different subtypes of OAB patients – those with predominant peripheral (e.g., bladder) involvement versus those with “central” phenotype with brain connectivity changes and “global” abnormalities in sensory processing on QST. This distinction may be important since current OAB treatments (e.g., pelvic floor physical therapy, blockade of muscarinic cholinergic and beta-adrenergic receptors in the bladder, botulinum toxin injection into the bladder),[5] have variable rates of success among individuals.[88] It is possible that MRI and QST may be used to identify a distinct phenotype of patients that may respond differentially to specific OAB treatments. This study

will help to sort out the differently associated pathophysiology in the heterogeneous OAB patient population, and from there, lead to more evidence-based categorization and phenotyping of OAB and LUTS patients.

Limitations There are potential limitations of the study. While the MRI and QST findings are suggestive of central mechanisms, it could also suggest a change in brain function or a maladaptive sensory response secondary to peripheral mechanisms. Whether the findings are a sign of inherent brain pathology or the central manifestation of peripheral pathology, or both, cannot be ascertained definitively in this study. In addition, this study can demonstrate associations, but cause and effect cannot be determined. Also, since subjects are not catheterized inside the MRI, we are not able to repeat the bladder filling to obtain BOLD activation patterns, thus there will be no BOLD pattern analyses.

Conclusions

The NIST Study of the LURN is the largest multi-center multi-modal neuroimaging and sensory testing study of its kind to investigate urinary urgency and UI. This study will expand our understanding of the brain-bladder connection in bladder function and bladder control, identify important subgroups or “phenotypes” of urgency patients, and represent a new paradigm of LUTS research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CNS	central nervous system
DCC	data coordinating center
DTI	diffusion tensor imaging
fMRI	functional MRI
LURN	Symptoms of Lower Urinary Tract Dysfunction Research Network
LUTS	lower urinary tract symptoms
MRI	magnetic resonance imaging
NIST	Neuroimaging and Sensory Testing
OAB	overactive bladder syndrome
RS-fcMRI	resting state functional connectivity MRI
QST	quantitative sensory testing
UI	urinary incontinence
UII	urgency urinary incontinence

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Figure 1: Relationship between the NIST Study and other LURN studies

Figure 2: Flow chart for the NIST study visit

Figure 3: Brain MRI scanning sequence (the numbers inside parentheses indicated the approximate time in minutes)

Table 1:

NIST Study eligibility criteria for cases and controls

OAB Cases Eligibility Criteria	
Inclusion criteria	
LURN Observational Cohort Study Criteria	Participants fulfilling the inclusion criteria from the LURN Observational Cohort Study.[18] For example, participants are men or women, 18 years of age and older, who present to LURN physician for evaluation or treatment of their LUTS, and report at least one LUTS on the LUTS Tool.[17]
Urgency Criteria and Sub-classification into with versus without urgency urinary incontinence (UUI)	<p>Participants reporting symptoms of urinary urgency, with or without urgency urinary incontinence (UUI), usually with frequency and nocturia, consistent with the 2002 ICS definition of overactive bladder (OAB).[1] They answer, “sometimes”, “often”, or “always” on question 6 of the LUTS Tool[17] (“<i>During the past month, how often have you had a sudden need to rush to urinate?</i>”). Furthermore, participants are assigned into a subgroup based on UUI status:</p> <ul style="list-style-type: none"> • Urgency with UUI: Participants who answer “sometimes”, “often”, or “always” on question 16b of the LUTS Tool (“<i>How often during the past month... have you leaked urine in connection with a sudden need to rush to urinate?</i>”) are assigned to the subgroup urgency with UUI. • Urgency without UUI: Participants who answer “never” or rarely” on question 16b of the LUTS Tool are assigned to the subgroup urgency without UUI.
Exclusion criteria	
LURN Observational Cohort Study Criteria	Participants fulfilling any exclusion criteria from the LURN Observational Cohort Study are excluded.[18] For example, participants cannot have a history of pelvic malignancy, neurogenic bladder, symptomatic stricture, sling complication, endoscopic surgery in the past 6 months, radiation cystitis, InterStim in place, or Botox in the past 12 months, etc. See the exclusion criteria in reference 18 for full details.
Contraindications to MRI scanning	<p>Participants cannot:</p> <ul style="list-style-type: none"> • Be left-handed, and/or • Be claustrophobic, and/or • Have vision or hearing impairments that would impede completion of study procedures, and/or • Have any metal implants, devices (including InterStim bladder neurostimulators, cardiac pacemakers), or jewelry that would be unsafe in the MRI machine.
Contraindications to QST testing	<p>Participants cannot:</p> <ul style="list-style-type: none"> • Currently, habitually, or had previously (within 12 months) used artificial nails, nailenhancements, or nail extensions that cover any portion of the thumbnail, and/or • Have Meniere’s disease, or use a hearing aid.
Medications	Participants cannot use opioids, including tramadol and sedatives (e.g. benzodiazepines), in the absence of a one-week washout period. Use of over-the-counter and prescribed analgesics (e.g. NSAIDs, acetaminophen, etc.), muscle relaxants, nasal decongestants (e.g., pseudoephedrine, phenylephrine, etc.) is permitted on an as-needed basis, but participants are asked to refrain from taking these medications for a minimum of 24 hours prior to undertaking neuroimaging and QST study procedures.
Other	Participants are asked to refrain from alcohol (24 hours), nicotine (2 hours), and caffeine (6 hours), prior to undertaking neuroimaging and QST study procedures. Participants are asked about these items prior to the start of NIST study procedures to determine compliance. Those who are non-compliant have the relevant items listed as protocol deviation(s).

OAB Cases Eligibility Criteria	
Deferral criteria	
Microscopic hematuria	Participants with microscopic hematuria undergo appropriate evaluation prior to enrollment into the study.
Positive urine culture	Participants with a positive urine culture have to be treated, and have a subsequent negative culture.
Pregnancy	Participants who are currently or were recently (within 6 months) pregnant.
Controls Eligibility Criteria	
Inclusion criteria	
Age	Participants are 18 years of age or older.
Frequency	Participants answering “1–3 times a day” on question 2 of the LUTS Tool (“During a typical day in the past month, how many times did you urinate during waking hours?”).
Nocturia	Participants answering “none” or “1 time a night” on question 3 of the LUTS Tool (“During a typical night in the past month, how many times did you wake up because you needed to urinate?”).
Urgency	Participants answering “never” or “rarely” on question 6 of the LUTS Tool (“During the past month, how often have you had a sudden need to urinate?”).
Urinary incontinence (UI)	Participants answering “never” or “rarely” on question 15 of the LUTS Tool (“During the past month, how often did you leaked urine?”).
Urgency urinary incontinence (UUI)	Participants answering “never” or “rarely” on question 16b of the LUTS Tool (“How often during the past month have you leaked urine in connection with a sudden need to rush to urinate?”).
Other LUTS	Participants score between 0 – 7 on the AUA Symptom Index.[19]
Exclusion criteria	
LURN Observational Cohort Study Criteria	Healthy controls who fulfill any exclusion criteria from the LURN Observational Cohort study are excluded (Cameron et al).[18] Participants who have contraindications to MRI scanning and QST testing are also excluded (see below).
Contraindications to MRI scanning	Healthy controls cannot: <ul style="list-style-type: none"> • Be left-handed, and/or • Be claustrophobic, and/or • Have vision or hearing impairments that would impede completion of study procedures, and/or • Have any metal implants, devices (including InterStim bladder neurostimulators, cardiac pacemakers), or jewelry that would be unsafe in the MRI machine.
Contraindications to QST testing	Healthy controls cannot: <ul style="list-style-type: none"> • Currently, habitually, or have previously (within 12 months) used artificialnails, nail enhancements, or nail extensions that cover any portion of the thumbnail, and/or • Have Meniere’s disease, or use a hearing aid.
OAB diagnosis	Healthy controls cannot have a clinical diagnosis of OAB.
Use of LUTS medications	Healthy controls cannot be currently using medications specifically for LUTS (e.g., anticholinergics, beta-agonists, alpha agonists, 5-alpha- reductases, PDE5-inhibitors,etc.).
High post-void residual volume	Healthy controls cannot have a post-void residual volume of 150 cc or more.
Deferral criteria	
Positive urine culture	Participants with a positive urine dipstick have to be treated, and have a subsequent negative culture.

OAB Cases Eligibility Criteria	
Pregnancy	Participants who are currently or were recently (within 6 months) pregnant.

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Table 2:**NIST Study Self-Reported Questionnaires**

Instrument	Description
<i>Questionnaires specific to the NIST Study that are administrated to participants</i>	
International Consultation on Incontinence Modular Questionnaire - Urinary Incontinence Short Form (ICIQ-UI) [20]	This 3-item instrument assesses the severity and impact of urinary incontinence symptoms
International Consultation on Incontinence Modular Questionnaire – Overactive Bladder (ICIQ-OAB) [22]	This 4-item instrument assesses the severity and impact of overactive bladder symptoms
Urogenital Distress Inventory (UDI-6) [21]	This 6-item instrument assesses the bother of urinary symptoms
Incontinence Impact Questionnaire (IIQ-7) [21]	This 7-item instrument assesses the impact of urinary incontinence on quality of life and daily living
OAB Questionnaire, Short Form (OAB-q) [23]	This 19-item instrument assesses the symptom bother and health-related quality of life impact of overactive bladder symptoms
Poly-Symptomatic and Poly-Syndromic Questionnaire (PSPS-Q) [27]	This 59-item instrument assesses somatic symptom burden
Brief Pain Inventory (BPI) [25]	This instrument assesses pain severity and interference
Hyperacusis Questionnaire (HQ) [24]	This 14-item instrument assesses sensitivity to sound and noise
Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Body Map [26]	This front and back body map contains 45 body sites where participants can check all areas they have experienced pain beyond ordinary pain.
Urgency Catastrophizing Scale (UCS), modified from Pain Catastrophizing Scale [29]	This 8-item instrument assesses ability to cope with urinary urgency symptoms
Complex Medical Symptom Inventory (CMSI) [28]	This 41-item instrument assesses the presence of persistent physical (somatic) symptoms.
<i>Questionnaires from the Observational Cohort Study that are also administrated</i>	
LUTS Tool [17]	This 44-item instrument assesses the severity and bother of a range of 22 lower urinary tract symptoms (LUTS) in men and women
American Urological Association Symptom Index (AUA-SI) [19]	This 7-item instrument assesses the storage and emptying of urinary symptoms in men
The Comprehensive Assessment of Self-Reported Urinary Symptoms (CASUS)	56-item questionnaire currently under development by LURN to capture a comprehensive set of urinary symptoms
Fecal Incontinence Severity Index (FISI) [30]	This 4-item instrument assesses the presence and severity of fecal incontinence
International Index of Erectile Function (IIEF) [31]	This 5-item instrument assesses erectile function in men
Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-revised (PISQ-IR) [32]	This 20-item instrument assesses sexual function in women with pelvic organ prolapse or urinary or fecal incontinence
Pelvic Floor Distress Inventory (PFDI-20) [33]	This 20-item instrument assesses urinary, prolapse, and colorectal function in women
Genitourinary Pain Index (GUPI) [34]	This 9-item instrument assesses genitourinary pain in men and women
Childhood Traumatic Events Scale (CTES) [35]	This 6-item instrument assesses self-reported exposure to childhood traumatic events associated with major upheavals
PROMIS Depression and Anxiety item banks [36]	This 16-item instrument assesses mood, affect, negative self-perceptions, negative social perceptions, fear, anxious feelings
Perceived Stress Scale (PSS) [37]	This 10-item instrument assesses perceived psychological stress
PROMIS Sleep Short Form [38]	This 8-item instrument assesses sleep disturbance
International Physical Activity Questionnaire Short Form (IPAC-SF) [39]	This 9-item instrument assesses four graduated levels of activity
PROMIS Physical Function Item Bank, Mobility Subdomain [40]	This 16-item instrument assesses lower extremity function

PROMIS = Patient-Reported Outcomes Measurement Information System

Table 3:

3T MRI Scanner Models at Each LURN Site

Duke University (GE MR750)
Northwestern University (Siemens Trio)
University of Iowa (GE MR750w)
University of Michigan (GE MR750)
University of Washington (Philips Achieva)
Washington University in St Louis (Siemens Trio) (Siemens Prisma, starting 2/2018)

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Table 4:

Comparison of the NIST Study to previous MRI studies on OAB

Previous MRI studies on OAB	NIST neuroimaging studies
Almost exclusively on women	Men and women (target 1:1 ratio)
Almost exclusively focused on patients with UII and/or detrusor overactivity (DO)	Recruit urgency with UII, and urgency without UII (target 1:1 ratio)
Most studies have small sample size (n < 20)	Large sample size (n>250) permits evaluation of patient subgroups. NIST is the largest study of its kind
Primarily single center studies	Multi-center study across the US, with geographically diverse group of patients
Many studies have no control groups for Comparison	Age and sex matched control group (target cases: control ratio = 2:1)
Participants may be community subjects with OAB symptoms	Participants are clinic patients seeking evaluation and treatment of OAB
Participants were catheterized and filled inside the scanner (invasive, may sensitize the bladder, urethra or pelvic floor, and confound brain signals)	No bladder catheterization
Rapid, repeated, alternating cycles of bladder filling and emptying to elicit BOLD fMRI signals (non-physiologic, does not reproduce clinical urgency)	Bladder is filled by natural diuresis after water consumption.
Most previous studies have used BOLD functional MRI to study activation and deactivation of specific brain regions	Advanced multi-modal techniques (RS-fcMRI, DTI, T1) are used to understand functional connectivity, structural connectivity, and gray matter volume.
Isolated functional MRI studies	Integration with detailed phenotyping data available through the LURN Observational Cohort Study (clinical, questionnaires, and biosample).[18] Comprehensive integration of MRI data with quantitative sensory testing (QST) data to assess CNS roles in urgency.