



Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN)

**Neuroimaging and Sensory Testing Study Protocol
Project 1B**

Manual of Operations

Version 4.0

Based on Protocol Version 8.0



Current Version: December 6, 2016

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1. Preparation for Study Implementation

- Print recruitment materials (post after IRB approval)
- Purchase Maico MA41 Audiometer
 - For purchasing information, technical support, and calibration services - go to e3 *Diagnostics* (<http://www.e3diagnostics.com>) and search for your local audiometer supplier (for technical specifications, see Appendix A).
- Purchase or confirm availability of other study materials:
 - Copy of the Manual of Operations (MOO)
 - Scripts to read to participants for neuroimaging, Multimodal Automated Sensory Testing (MAST) testing, and auditory testing
 - Watch or clock
 - Timer (for neuroimaging)
 - Stopwatch (for audiometry)
 - Gloves
 - Urine Dipsticks
 - Pregnancy tests (for women)
 - A beaker to measure water volume
 - Urinal (for men) or a toilet hat (for women)

-Purchase from your hospital material service. Examples of the items are below:

	Item#: 1032	COLLECTOR, SPECIMEN TOILET HAT
	Price: \$0.31	Manuf#: 02072 Manuf: MEDEGEN MEDICAL PRODUCTS
	Stock: S	Packing: 100EA/CA U of M: EA Conversion: 100
		Location: B-07-01-02 LATEX FREE Category: PERS
		LT Days: 1 On LUM: Y
	Item#: 2044	URINAL, MALE W/ COVER PLASTIC DISP
	Price: \$0.355	Manuf#: H140D-01 Manuf: MEDEGEN MEDICAL PRODUCTS
	Stock: S	Packing: 50EA/CA U of M: EA Conversion: 50
		Location: A-02-01-02 LATEX FREE Category: PERS
		LT Days: 1 On LUM: Y

- Hospital gown
- Pull-ups of various sizes
- Bottled water (12 oz.) or cups for 350mL of water
- Possible source for \$.99/bottle - Kim Rheinecker

3820 Packard Rd., Suite 240

Ann Arbor, MI 48108

office: 734-922-8003

fax: 734-662-3532

email: krheinecker@theimagegroup.net

- Another source of bottled water is the grocery store (12oz. bottled water) in bulk.
- Paper copies of questionnaires
 - ICIQ-UI
 - ICIQ-OAB
 - UDI-6
 - IIQ-7
 - OAB-q
 - PSPS-Q
 - BPI
 - Hyperacusis questionnaire
 - MAPP-2 Body Map
 - Urgency Catastrophizing Scale
 - CSMI
- Part 1 and Part 2 instruction sheets for the auditory testing (See Appendices B and C)
- Paper copies of Case Report Forms (CRFs) to record patient-reported data during the MRI procedures
 - Neuroimaging CRF (Appendix D)
 - Pressure pain sensitivity CRF (Appendix E)
 - Auditory sensitivity CRF (Appendix F)
- Confirm audiometer settings doing the Initial Device Set-Up, as described in Section 6.1.2 of the MOO.
- Coordinate with MAPP colleague about the location and availability of the MAST System.
 - It should include the MAST handpiece, two laptops, assorted cables, and operation manual.
 - Discuss with MAPP colleague how you will coordinate subject testing between the two studies (i.e. shared Outlook Calendar, etc.).
- Practice pressure pain sensitivity testing –
 - MAST familiarization
 - MAST Ascending Series

- Break (could practice the auditory testing during this time, as described in the study protocol)
- MAST Randomized Series
- If you encounter problems, need technical assistance, repairs, or calibration, email the MAST Help Desk at MASTHelpDesk@umich.edu
- Upload practice pressure pain sensitivity data to the data coordinating center (DCC) (see Section 5.13).
- Practice auditory testing
 - Hearing screening
 - Auditory ascending series
 - Auditory randomized series
- Print consent forms
- Arrange subject payment procedures

2. Screening & Enrollment Procedures

See Appendix G for training slides and additional information.

2.1. Patient Groups (Urgency with or without Urinary Incontinence):

- Participants in the “Urgency without urgency incontinence” group and the “Urgency with urgency incontinence” group will be recruited from participants of the Lower Urinary Tract Dysfunction Research (LURN) Observational Cohort Study. Participants will be recruited from outside the Observational Cohort Study once this study is closed to enrollment (See Appendix H for recruitment materials).
- Participants who are eligible and willing to participate will be screened for eligibility and willingness to participate in the LURN Neuroimaging & Sensory Testing Study.
- Participants who decline to provide biospecimen for the Observational Cohort Study (op-out) will still be able to participate in the Neuroimaging & Sensory Testing Study if otherwise eligible. Participants who are not part of the Observational Cohort Study will also have the option of opting out of providing biospecimens.
- For participants who are also part of the Observational Cohort Study, it is preferable that neuroimaging and sensory testing be performed on the same day of the Observational Cohort Study baseline visit when the biological specimens and detailed questionnaire data are collected. This same-day-visit allows the strongest possible correlation between the different data sets (urologic and non-urologic symptoms, psychosocial measures, biomarkers, imaging, sensory testing) without large temporal gaps between them.
- Screening for eligibility should ideally occur prior to the Observational Cohort Study baseline visit, so that the study coordinator can potentially schedule patients to complete the Observational Cohort Study and Neuroimaging & Sensory Testing Study on the same day (the ideal situation).

- If scheduling conflict does not permit a same day visit when the biological specimens and detailed questionnaire data are collected, neuroimaging and sensory testing should be performed within four weeks of that visit (prior to or after).
- The lower urinary tract symptoms (LUTS) **LUTS Tool – 1 month version** and LUTS Scoring Algorithm will be used to screen patients for the Neuroimaging and Sensory Testing Study. (See Appendices I and J)
- The Observational Cohort screening form and the **Neuroimaging & Sensory Testing Study Eligibility eCRF** (screening log in LURNLink on Census Page) will be completed by the study coordinator, and informed consent will be obtained. (See Appendix K)
- The Observational Cohort Study will recruit participants for 12 months, while the Neuroimaging & Sensory Testing Study will recruit participants for 24 months or longer. Identical procedures (same eligibility fulfilled, same baseline questionnaires) will be implemented in the later part of the study, however these Neuroimaging & Sensory Testing Study participants will not formally be part of the Observational Cohort Study cohort and they will not be followed longitudinally to 12 months.
- The inclusion and exclusion criteria for the two urgency groups are as followed:

Urgency subjects:

Inclusion criteria:

ALL of the following criteria have to be fulfilled to be eligible:

- a. Enrollment in the LURN Observational Cohort Study. (*Exception: can continue to enroll after the Observational Cohort Study has closed as long as participants would have been eligible for the Observational Cohort Study and agree to the same baseline procedures*).
- b. Symptoms of urinary urgency, with or without urgency incontinence, usually with frequency and nocturia, consistent with the 2002 ICS definition of overactive bladder (OAB).¹
- c. Answered “sometimes”, “often”, or “always” on question 6 of **LUTS Tool – 1 month version** (“During the past month, how often have you had a sudden need to rush to urinate?”). Participants who answered “never” or “rarely” are not eligible since they are not deemed to have significant urgency symptoms. Participants will be assigned into two subgroups using the following:

For assignment into the sub-group “Urgency with urgency incontinence”:

- d. Answered “sometimes”, “often”, or “always” on question 16b of the **LUTS Tool – 1 month version** (“How often in the past month have you... Leaked urine in connection with a sudden need to rush to urinate?”).

For assignment into the sub-group “Urgency without urgency incontinence”:

- e. Answered “never” or “rarely” on question 16b of the **LUTS Tool – 1 month version** (“How often in the past month have you... Leaked urine in connection with a sudden need to rush to urinate?”).

Deferral criteria: See the deferral criteria for the Observational Cohort Study.

- a. Microscopic hematuria.
 - Patient must undergo appropriate evaluation.

- b. Positive urine culture.
 - Patient needs to be treated and have a subsequent negative culture before he or she is eligible.
- c. Recent (within 6 months) pregnancy.
- d. Current sexually transmitted infection (STI).
 - Patient needs to be treated and have a subsequent negative test before he or she is eligible. This refers to acute, treatable STIs such as gonorrhea or chlamydia. It does not refer to chronic infections such as HPV or HSV.

Exclusion criteria:

- a. See exclusion criteria in the Observational Cohort Protocol. In addition,
- b. Answered “never” or “rarely” on question 6 of **LUTS Tool – 1 month version** (“During the past month, how often have you had a sudden need to rush to urinate?”).
- c. Inability to schedule a neuroimaging and quantitative sensory testing (QST) visit within four weeks (before or after) of the LURN Observational Cohort Study visit where questionnaire data are collected.
- d. Any contraindication to MRI scanning, including:*
 - 1) Left-handed individuals.
 - 2) Participant has central nervous system (CNS) diseases, including structural brain abnormalities (e.g., neoplasms, subarachnoid cysts), cerebrovascular disease, ongoing infectious disease (e.g., abscess), history of other neurological disease, including stroke, peripheral neuropathy, or seizure disorders.
 - 3) Participant has claustrophobia. Potential participants will be questioned about possible discomfort being in an enclosed space (e.g., MRI scanner). Those who report such problems will be excluded.
 - 4) Participant has vision or hearing impairments that would impede completion of study procedures.
 - 5) Participant has any metal implants, devices, or jewelry that would be unsafe in the MRI, or meets any other exclusionary criteria as specified by the MRI Screening form. Presence of InterStim bladder neurostimulator (whether or not it is functioning or whether it is turned on or off) is a contraindication to MRI.
- e. Any contraindication to QST sensory testing, including:*
 - 6) Current, habitual, or previous use (within the last 6 months) of artificial nails, nails enhancements, or nail extensions that cover any portion of the thumbnail. Exceptions, including brief and/or occasional use, may be permissible at the discretion of the study team.
 - 7) Menière’s disease or the use of a hearing aid in either ear.
- f. Use of opioids, including tramadol, and sedatives including benzodiazepines, in the absence of a 1-week washout period for those participants undergoing neuroimaging and QST. If the participant is non-compliant with the 1-week washout, he/she will be EXCLUDED from the study and do NOT proceed with testing. Examples of opioids: morphine, methadone, buprenorphine, hydrocodone, oxycodone, hydromorphone, heroin, codeine, tramadol. Common trade names might include: Tylenol #3, Oxycontin, Percocet, Fentanyl, Vicodin, Percodan, Demerol, Ultram. Examples of benzodiazepines:

alprazolam, clonazepam, diazepam, lorazepam, midazolam, temazepam. Common trade names might include: Xanax, Valium, Klonopin, Ativan, Versed, Restoril.

- g. Participants are permitted to use the following medications on an as-needed basis: over-the-counter or prescribed analgesics (NSAIDs, acetaminophen), muscle relaxants (cyclobenzaprine, carisoprodol, Flexeril, Soma, Baclofen), nasal decongestants (pseudoephedrine, phenylephrine); however, participants will be asked to refrain from taking these medications for a minimum of 24 hours prior to their QST and neuroimaging study visit. In addition, participants will be asked to refrain from the following prior to QST and neuroimaging visits: alcohol (24 hrs.), nicotine (2 hrs.), and caffeine (6 hrs.). A compliance check will be conducted at the start of the visit to determine if participants followed these instructions and to record instances of non-compliance. If the participant is non-compliant to these instructions, he/she can still PROCEED with the testing; however, record this protocol deviation(s) on the CRF.

Table 1: Deviations and Exclusions

Protocol deviation:	Absolute exclusion:
<p>Participants used over-the-counter or prescribed analgesics (NSAIDs, acetaminophen), muscle relaxants, nasal decongestants (pseudoephedrine, phenylephrine) within 24 hrs. prior to testing.</p> <p>Participants consumed alcohol (24 hrs.), nicotine (2 hrs.), or caffeine (6 hrs.) within the defined time period prior to testing.</p>	<p>Participants unable to do the 1-week washout of opioids (including tramadol) or sedatives (including benzodiazepines).</p>
<p>Action: Record the protocol deviation on the CRF, but OK to PROCEED with testing.</p>	<p>Action: EXCLUDE from the study. Do NOT proceed with testing.</p>

***Note:** Contraindications to either MRI or QST will preclude any study participation since it is expected that participants will undergo both neuroimaging and sensory testing.

The overall recruitment goals are noted in Table 1. The DCC will be monitoring the recruitment progress in each of the cells. The three patient groups are expected to be age-matched to each other and this will be monitored by the DCC.

Table 2: Recruitment Table

N=252	Urgency with urgency incontinence	Urgency without urgency incontinence	Controls (without urgency or other LUTS)
Male	42	42	42
Female	42	42	42

2.2. Screening & Enrollment Procedures for Controls

Control Group (Without urgency and other LUTS):

- Since the LURN Observational Cohort Study will not be recruiting controls, a separate mechanism will be used to recruit for the Control Group. Each LURN site will have the discretion to utilize the recruitment strategies that work best for them as long as the following eligibility criteria are fulfilled for the Control Group.
- Controls will be individuals without urinary urgency or other LUTS. Controls should have no urinary frequency (<8 voids/day), nocturia (0-1 void/night), urgency, or any urinary incontinence, including urgency incontinence, as assessed by the **LUTS Tool – 1 month version**; in addition they must have only minimal to mild LUTS (AUA-SI <8) as assessed by the **AUA Symptom Index (AUA-SI)**.
- The **LUTS Tool – 1 month version, LUTS Scoring Algorithm** (See Appendices I & J) and the AUA-SI (Appendix L) will be needed for screening purposes.
 - In order to screen prior to consent, sites may choose to ask similar questions to those relevant questions found in the LUTS Tool and AUA-SI to get a rough assessment of eligibility before approaching for consent. For an example of a local screening script, see Appendix M.
- The **Neuroimaging & Sensory Testing Study Eligibility eCRF** will be completed by the study coordinator and an informed consent will be obtained.
- The inclusion and exclusion criteria for the Control Group are as follows:

Inclusion criteria:

ALL of the following criteria have to be fulfilled to be eligible as a control:

- a. 18 years of age or older, and
- b. Answered “1 to 3 times a day” or “4 to 7 times a day” on question 2 of the **LUTS Tool – 1 month version** (“During a typical day in the past month, how many times did you urinate during waking hours?”), and
- c. Answered “none” or “1 time a night” on question 3 of the **LUTS Tool – 1 month version** (“During a typical night in the past month, how many times did you wake up because you needed to urinate?”), and

- d. Answered “never” or “rarely” on question 6 of the **LUTS Tool – 1 month version** (“During the past month, how often have you had a sudden need to rush to urinate?”), and
- e. Answered “never” or “rarely” on question 15 of the **LUTS Tool – 1 month version** (“During the past month, how often did you leak urine?”), and
- f. Answered “never” or “rarely” on question 16b of the **LUTS Tool – 1 month version** (“How often in the past month have you... Leaked urine in connection with a sudden need to rush to urinate?”), and
- g. **AUA Symptom Index** (7-item) scores of 0 to 7 (i.e. mild LUTS for the past month).

Deferral criteria: See the deferral criteria for the Observational Cohort Study.

- a. Positive urine culture.
 - A urine dipstick will be performed. If positive for nitrite on the urine dipstick, recruitment is deferred and the subject is recommended to undergo a urine culture with their physician. Subject may be recruited if the urine culture result is negative. Subject with positive urine culture needs to be treated and have a subsequent negative culture before he or she is eligible.
- b. Recent (within 6 months) pregnancy.
- c. Current sexually transmitted infection.
 - Patient needs to be treated and have a subsequent negative test before he or she is eligible. This refers to acute, treatable STIs such as gonorrhea or chlamydia. It does not refer to chronic infections such as HPV or HSV.

Exclusion criteria:

- a. See exclusion criteria in the Observational Cohort Protocol.
- b. A clinical diagnosis of overactive bladder (OAB).
- c. Currently using medications specifically for LUTS (e.g. anti-cholinergics, beta-agonists, alpha-agonists, 5-alpha-reductase inhibitors, PDE5-inhibitors for urinary problems).
- d. A post-void residual volume of 150 CC or more. This will be determined via patient report. If the patient responds affirmatively to the question, “Have you ever been told by a doctor that you retain urine in your bladder right after you urinate?”, s/he will be excluded from the study.
- e. Contraindications to MRI scanning, as described in the *MRI exclusion criteria* above.
- f. Contraindications to QST sensory testing, as described in the *QST exclusion criteria* above.
 - The same baseline LURN Observational Cohort Study questionnaires will be answered by control subjects preferably on the day of neuroimaging and sensory testing (or if not feasible, within 4 weeks prior to or after imaging and sensory testing).

2.3. The Day(s) Prior to the Neuroimaging & Sensory Testing Visit

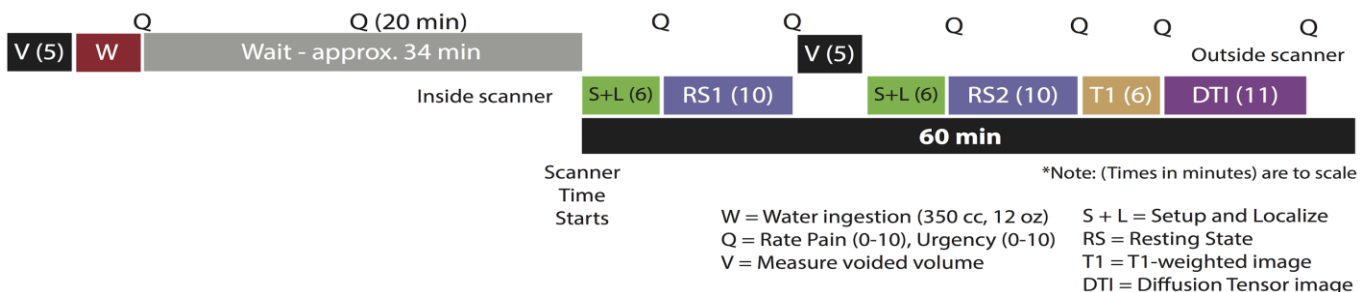
- Call the participants the day(s) before their neuroimaging and sensory testing visit to confirm the visit and remind them of the following: (See Appendices N (Phone Script) and O (Participant Instructions & Worksheets)).

- Avoid consuming products containing caffeine within 6 hours of the testing. The same is true for the consumption of alcohol (24 hrs.) and nicotine (2 hrs.).
- Avoid over-the-counter analgesics (NSAIDs, acetaminophen), muscle relaxants, nasal decongestants (pseudoephedrine, phenylephrine) for 24 hours before the testing.
- If the participant uses opioids, including tramadol, and sedatives including benzodiazepines, he/she should already have initiated the 1-week washout. If the participant is non-compliant with the 1-week washout, he/she is EXCLUDED from the study and do NOT proceed with testing.
- In terms of fluid volumes, participants should drink the amount of fluid they would normally drink, and should not be dehydrated prior to the imaging session.
- To facilitate voiding on the day of testing, remind the participant to refrain from urination immediately prior to checking-in on the day of testing.
- Participants should not bring metal or jewelry to the testing (e.g. metal necklace, earrings, wedding ring). They should dress comfortably to the testing.

3. Neuroimaging Procedures

- For each participant, the MRI scan should be performed **PRIOR TO** sensory testing (thumbnail pressure pain sensitivity testing, auditory testing) on the same day. If, for some unforeseen circumstances the order of the testing needs to be reversed (QST first, then neuroimaging), the testing can still proceed. However, the study coordinator will note this on the “Protocol deviation” section.
- The scanner time should be blocked out for up to 90 minutes. The scanner time usually does not start until the participant is lying inside the MRI. The time in the waiting room should not count. Even though the black shaded block is about 54 minutes, we need to have flexibility, for example, if the second voiding V(5) takes longer. The bladder filling and voiding protocols will be as follows:

Figure 1:



To do this test you will need:

- Copy of the manual (i.e., scripts to read to participants)
 - Watch or clock
 - Timer
 - Gloves
 - 350 CC of water
 - A beaker to measure water volume
 - Urinal (for men) or a toilet hat (for women)
 - Urine Dipsticks
 - Urine Pregnancy Tests
 - Hospital gown
 - Pull-ups (diapers) of various sizes
 - Paper questionnaires
 - **Neuroimaging CRF** (Appendix D) to record the data (data can be recorded on paper and transferred to LURNLink later, or recorded directly into LURNLink).
- About an hour and 20 minutes prior to the scheduled MRI block time, bring the participant to a waiting room close to the MRI scanner. The waiting room should be close to a bathroom (if possible).
 - Double check your site's specific MRI-specific exclusion criteria (e.g. no pacemaker, Interstim neurostimulator). Make sure there is no metal on the participant.
 - You (or the technician) might ask, "Do you have any of the following items in your body? Dental implants, false teeth/retainers, braces, etc.?"
 - Double check the dietary and medication restrictions: No over-the-counter analgesics (NSAIDs, acetaminophen), muscle relaxants, nasal decongestants (pseudoephedrine, phenylephrine), or alcohol for 24 hrs., no caffeine containing products for 6 hrs., and no nicotine for 2 hrs. Record any protocol deviations on the CRF.
 - If the participant uses opioids, including tramadol, or sedatives including benzodiazepines, and he/she is non-compliant with the 1-week washout, he/she will be EXCLUDED from the study and do NOT proceed with testing.
 - The participant will be asked to complete the following questionnaires for the next 20 minutes. If the participant is not able to finish the entire package, he/she can complete them after voiding or after all the scans have been completed, and prior to QST testing. Note that the subject can complete the surveys at any time during the visit as long as it occurs prior to the QST testing. These questionnaires will be administered on paper, and will be entered into LURNLink by the study coordinator later. The questionnaires will include:

- (1) **ICIQ-UI** (urinary incontinence),²
- (2) **ICIQ-OAB** (overactive bladder),³
- (3) **UDI-6** (urinary distress inventory),⁴
- (4) **IIQ-7** (incontinence impact questionnaire),⁴
- (5) **OAB-q** short form,⁵
- (6) **PSPS-Q** (symptom burden questionnaire),⁶
- (7) **BPI** (brief pain inventory),⁷
- (8) **Hyperacusis** questionnaire,⁸
- (9) **MAPP-2 Body Map**,
- (10) **Urgency catastrophizing scale** (from the pain catastrophizing scale),⁹
- (11) **CMSI** (complex medical symptom inventory).¹⁰

After the participant has completed the surveys, review the PSPS-Q (symptom burden questionnaire) questions 56-59. If the subject has answered “Yes” in the “Last Month” column to any of these or “Yes” to these questions in the “Before Age 30” column AND the subject is less than 30 years old, refer the subject for psychological intervention according to the guidelines at your site.

General Deviations

1. **Was the order of testing for the day reversed (QST and Audiometry was done before imaging)?**
 - No
 - Yes

2. **Did the participant consume over-the-counter analgesics (NSAIDs, acetaminophen), muscle relaxants, nasal decongestants (pseudoephedrine, phenylephrine) within 24 hours prior to testing?**
 - No
 - Yes
 - Unknown

3. **Did the participant consume alcohol within 24 hours prior to testing?**
 - No
 - Yes
 - Unknown

4. **Did the participant consume caffeine within 6 hours prior to testing?**
 - No
 - Yes
 - Unknown

5. Did the participant use nicotine within 2 hours prior to testing?

- No
- Yes
- Unknown

Read the following script to the participant (Appendix D): ***“Now we’ll start the MRI scan task. Your participation will help us understand how the brain responds to bladder discomfort and fullness. We will ask you to empty your bladder and drink 12 ounces of water. Then we will have you relax and answer a few questionnaires before the scans. You will undergo 4 scans, each about 10-15 minutes long. For the scans you will be asked to lie on your back in the scanner. During the scans just relax and keep your eyes closed. Don’t think about anything in particular, but do not go to sleep. Be sure to keep your head still during the scans, because moving in the scanner causes blurry, unusable images. You’ll know when the scan is happening because the MRI will be making a series of loud banging noises. We will fit you with earplugs to block out the sound. We would like to image your brain when your bladder is as full as possible. You may experience increased urgency or urge to urinate, but we hope that this will help us to better understand your bladder condition. In between scans there is an intercom, where we can speak with you and you can let us know how you are doing. During the scans there is an emergency button you can press that tells us to stop the scan. Do you have any questions?”***

1. Date of MRI Scan: _____

Read the following script to the participant: ***“We want to make sure you have an empty bladder before we start the task, so please try to urinate. If nothing empties from your bladder that is okay. If you are able to urinate, we want to measure the volume you void. To do this we will use a specimen collection (hat, for females / urinal for males). If you cannot urinate, please let us know.”***

- Go to the bathroom close to the waiting room.
- For females, lift the toilet ring, where the participant will sit, and place the hat on the toilet. Lower the toilet ring to hold the hat in place and then ask the participant to empty the bladder into the hat in their privacy (the coordinator leaves the toilet).
- For males, give the participant a specimen collection urinal, and ask the participant to empty the bladder into the urinal in their privacy (the coordinator leaves the toilet).
- Record the time of day (H:M) when the participant is done voiding. Collect urine sample and measure the voided urine volume in the hat (for females) or in the urinal (for males) in CC and record the value.
- Ask participants to put on hospital gown (optional) keeping undergarments on, and if needed, a protective pull up or diaper (e.g., urgency incontinence patients). Participants can also wear gown bottoms or loose-fitting pants to increase privacy. This step can occur any time prior to the MRI scan.

2. **First void completed?**
 - **No (If No, please explain: _____)**
 - **Yes**
3. **First void time (H:M): _____ am / pm**
4. **First Void Volume (cc): _____**
5. **Results of Pregnancy test:**
 - **Negative**
 - **Positive**
 - **Not done (Reason: _____)**

- Some sites require a urine pregnancy test on the day of neuroimaging. For those sites, after you have measured the first void volume (above), use some of the urine for the pregnancy test. For controls who have not yet had a urine dipstick test, perform the dipstick test. If positive for nitrites, defer (see Deferral Criteria).

6. **Result of urine dipstick test (for controls):**
 - **Negative**
 - **Positive**
 - **Not done (Reason: _____)**

- About 40 minutes prior to the start of the imaging session, provide a water bottle to the participant and instruct the participant to try to finish the water inside the bottle in 5 minutes. The bottle contains 350 CC of water. A beaker may be used to measure the water volume.
- Record the drinking start time, drinking end time, and volume of water drank in CC.

7. **Water ingestion completed?**
 - **No (If No, please explain: _____)**
 - **Yes**
8. **Water drink start time (H:M): _____ am / pm**
9. **Water drink end time (H:M): _____ am / pm**
10. **Volume of ingested water (cc): _____**

- Explain the rating of bladder urgency and bladder pain (show page demonstrating scales). Read the following script to the participant: ***“Several times during the session we will ask you to rate your bladder pain and your urgency to urinate. Urgency is different from normal bladder feelings. For urgency, we mean the sudden, compelling desire to pass urine which is difficult to defer, or a sudden feeling that you need to pass urine and if you don’t you may have an accident. Please rate urgency from 0 (no urgency) to 10 (worst urgency imaginable). In addition, we will also ask you to rate your bladder pain. Bladder pain refers to pain, pressure, or discomfort in the general area of the bladder in the midline below your belly button. Please rate the bladder pain from 0 (no pain) to 10 (worst pain*”**

imaginable). Please be careful and don't mix them up. We will ask you about the bladder pain 0 to 10 first, then urgency 0 to 10 next, for several times inside the scanner."

- Immediately after water ingestion, ask the participant to rate their urgency and pain. Set the timer to zero (0) minutes.
 11. **0-min Post-ingestion procedure completed? (Directions and Pain/Urgency scales)**
 - No (If No, please explain: _____)
 - Yes
 12. **0-min Post-ingestion Time (H:M): _____ am / pm**
 13. **0-min Post-ingestion Pain (0-10): _____**
 14. **0-min Post-ingestion Urgency (0-10): _____**

- Reassure the participant that they won't be in the scanner for very long with a full bladder: ***"You will only be in the scanner for about 15 minutes at most with a full bladder. After that, you will be taken out of the scanner to urinate, and then return to the scanner for some additional scans with your bladder empty. Although it's important to stay in the scanner as long as possible, you are in control of these scans, and if you are certain that you can't hold your urine any longer, squeeze the emergency button and we will immediately remove you from the scanner."***
- The participant will be asked to wait for 20 minutes. If the participant did not complete all questionnaires earlier (prior to voiding), he/she can complete them now, or wait until after all the scans have been completed, and prior to QST testing.
- At the 20 minute mark (look at the timer), ask the participant to rate their urgency and pain, and record the time:
 15. **20-min Post-ingestion procedures completed?**
 - No (If No, please explain: _____)
 - Yes
 16. **20-min Post-ingestion Time (H:M): _____ am / pm**
 17. **20-min Post-ingestion Pain (0-10): _____**
 18. **20-min Post-ingestion Urgency (0-10): _____**

Ask subject if they feel they can hold off urination for the next 30 min. If not, then proceed with setting up for scan immediately.

- At the 24 minute mark (look at the timer):
Direct the participant towards the scanner room and have the MRI tech begin positioning the participant in the scanner.

Remind the technician that it is important that the subject not listen to music while in the scanner.

- At the 34 minute mark (look at the timer):
 - (1) Have MRI technician perform **Localizer Scan (S+L)**.
 - (2) Ask the participant to rate their urgency and pain, and record the time:
- 19. **Pre-RS1 procedures completed?**
 - No (If No, please explain: _____)
 - Yes
- 20. **Pre-RS1 Time (H:M): _____ am / pm**
- 21. **Pre-RS1 Pain (0-10): _____**
- 22. **Pre-RS1 Urgency (0-10): _____**
- Instruct the participant: ***“This first scan is 10 minutes. Rest with your eyes closed but do NOT go to sleep. Please keep your head as still as possible.”***
- Have MRI technician perform **Resting State 1 Scan (RS1)**.
- After the RS1 scan, ask the participant to rate the urgency and pain while he/she is still in the scanner and record the time:
 - 23. **Post-RS1 Time (H:M): _____ am / pm**
 - 24. **Post-RS1 Pain (0-10): _____**
 - 25. **Post-RS1 Urgency (0-10): _____**
 - 26. **Post-RS1: Did the participant go to sleep?**
 - No
 - Yes
 - Unknown (Comments: _____)
 - 27. **Post-RS1: RS1 imaging data acquisition successful?**
 - No (If No, please explain: _____)
 - Yes
- Have MRI technician remove the participant from the scanner, and instruct the participant to try to void, using the same instruction as above for the urine collection (hat for females, urinal for males). Give sufficient time to void; it is OK if this takes more than 5 minutes. Record the time and voided volume.
 - 28. **Post-RS1 Void Completed?**
 - No (If No, please explain: _____)
 - Yes
 - 29. **Post-RS1 Void Time (H:M): _____ am / pm**

30. **Post-RS1 Void Volume (cc):** _____
- Have MRI technician position the participant back in the scanner.
 - Have MRI technician perform **Localizer Scan (S+L)**.
 - Ask the participant to rate the urgency and pain and record the time:
31. **Pre-RS2 procedures completed?**
- **No (If No, please explain:** _____)
 - **Yes**
32. **Pre-RS2 Time (H:M):** _____ **am / pm**
33. **Pre-RS2 Pain (0-10):** _____
34. **Pre-RS2 Urgency (0-10):** _____
- Instruct the participant: ***“This next scan is 10 minutes. Rest with your eyes closed but do NOT go to sleep. Please keep your head as still as possible.”***
 - Have MRI technician perform **Resting State 2 Scan (RS2)**.
 - Ask the participant to rate the urgency and pain and record the time:
35. **Post-RS2 Time (H:M):** _____ **am / pm**
36. **Post-RS2 Pain (0-10):** _____
37. **Post-RS2 Urgency (0-10):** _____
38. **Post-RS2: Did the participant go to sleep?**
- **No**
 - **Yes**
 - **Unknown (Comments:** _____)
39. **Post-RS2: RS2 imaging data acquisition successful?**
- **No (If No, please explain:** _____)
 - **Yes**
- Instruct the participant: ***“This next scan will be about 6 minutes. Please keep your head as still as possible.”***
 - Have MRI technician perform **T1 Scan**.
 - Ask the participant to rate the urgency and pain and record the time:
40. **Post-T1 procedures completed? (pain and urgency)**
- **No (If No, please explain:** _____)
 - **Yes**
41. **Post-T1 Time (H:M):** _____ **am / pm**

- 42. **Post-T1 Pain (0-10):**
- 43. **Post-T1 Urgency (0-10):**
- 44. **Post-T1: T1 imaging data acquisition successful?**
 - No (If No, please explain: _____)**
 - Yes**

- Instruct the participant: ***“During the next scan, the table will vibrate- this is normal. This scan will be about 11 minutes. Please keep your head as still as possible.”***
- Have MRI technician perform **DTI Scan**.
- Ask the participant to rate the urgency and pain and record the time:

- 45. **Post-DTI procedures completed? (pain and urgency)**
 - No (If No, please explain: _____)**
 - Yes**

46. **Post-DTI Time (H:M):** am / pm

47. **Post-DTI Pain (0-10):**

48. **Post-DTI Urgency (0-10):**

- 49. **Post-DTI: DTI imaging data acquisition successful?**
 - No (If No, please explain: _____)**
 - Yes**

Scan Deviations

- 1. **Did the subject remain continent inside the scanner for the entire imaging sequence?**
 - No**
 - Yes**
 - Unknown**
- 1a. **If No, at what point was the subject incontinent? Check all that apply:**
 - First S+L**
 - RS1**
 - Second S+L**
 - RS2**
 - T1**
 - DTI**

2. Did the participant need to void after water ingestion prior to RS1, leading to RS1 not being completed?

- No
- Yes
- Unknown

3. Did the participant need to void in the middle of RS1, leading to RS1 not being completed?

- No
- Yes
- Unknown

4. Participant needed to void mid-RS2, T1, or DT and returned to MRI.

- No
- Yes
- Unknown

5. Participant terminated scan and did not return to MRI.

- No
- Yes
- Unknown

5a. Scan in progress during termination:

- First localizer scan (S+L)
- Resting state 1 scan (RS1)
- Second localizer scan (S+L)
- Resting state 2 scan (RS2)
- T1
- DTI

6. Termination reason:

- Anxiety/Claustrophobia
- Too high of void frequency
- Refused to continue
- Other (*ex. problem with scanner; timeline delayed*)

How to Handle Protocol Deviations

- If the participant is certain he/she has to void **prior to entering the MRI** for the first Localizer Scan (S+L) then allow the participant to void and begin with the second Localizer Scan (S+L), then Resting State 2 (RS2), T1 and lastly DTI. **Do not repeat the water ingestion. Do not perform RS1 (skip).**
- If a participant terminates (asks for the MRI to stop) due to the need to void:
 - **During the first Localizer Scan (S+L)** - allow the participant to exit the scanner, void, and return for the second Localizer Scan (S+L), Resting State 2 (RS2), T1, and DTI scans. **Do not repeat the water ingestion. Do not perform RS1 (skip).**

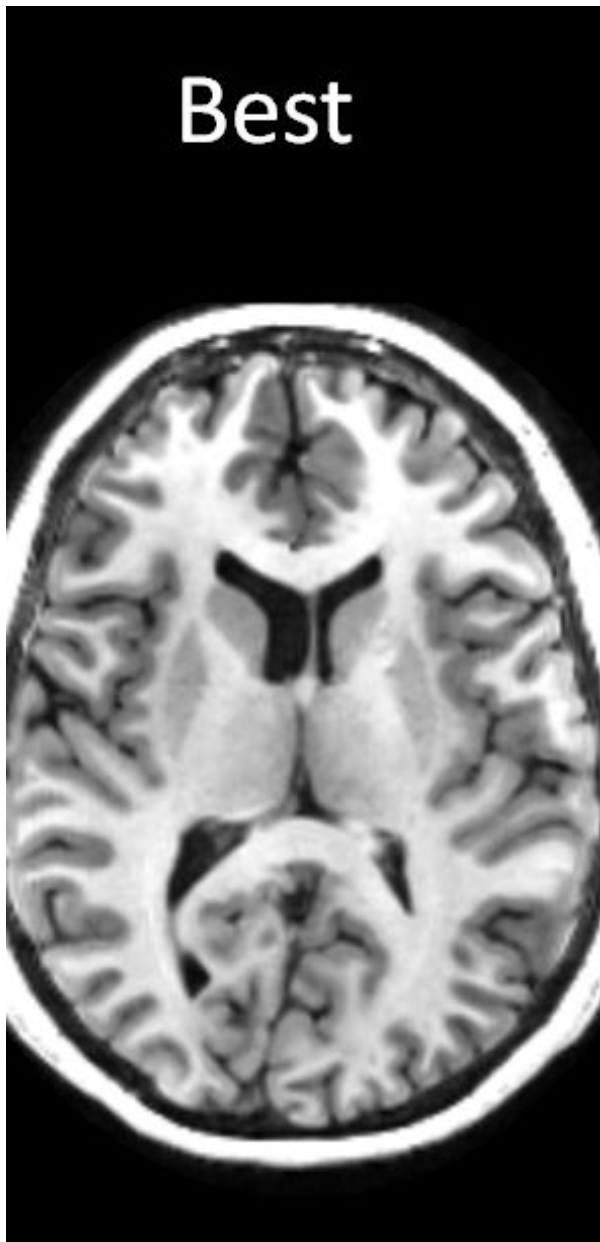
- **In the middle of Resting State 1 scan (RS1)** - allow the participant to exit the scanner, void, and return for the second Localizer scan (S+L), Resting State 2 (RS2), T1, and DTI scans. **Do not repeat the water ingestion. Do not repeat RS1.**
- **During the second Localizer Scan (S+L)** - allow the participant to exit the scanner, void, and **repeat the second Localizer Scan (S+L)**. Then proceed with Resting State 2 (RS2), T1, and DTI scans.
- **During the second Resting State Scan (RS2)** - allow the participant to exit the scanner, void, and **repeat the second Localizer Scan (S+L) and the second Resting State Scan (RS2)**. Then proceed with T1 and DTI scans.
- **During the T1 scan** - allow the participant to exit the scanner, void, and **repeat the second Localizer Scan (S+L) and the T1 scan**. Then proceed with DTI scans.
- **During the DTI scan** - allow the participant to exit the scanner, void, and **repeat the second Localizer Scan (S+L) and the DTI scan**.

3.1. Abnormal MRI Findings

There is a remote possibility that the fMRI will show an abnormal incidental finding either at the time it is performed or during a later review. If the incidental finding is noted at the time of the fMRI, the site's research staff will refer the subject for clinical follow-up. If the incidental finding is noted during a later review, then the central reading site (LURN Central Imaging Repository) will contact the clinical site and inform them of the results and the subject's study ID. The research staff will then refer the subject for follow-up clinical care. All interactions regarding incidental findings will be documented up through the referral step. It will be the subject's responsibility to access further clinical care once incidental results and clinical referral information are provided.

3.1.1. Evaluation of the T1 Scan

- After the DTI scan is completed the subject may exit the scanner and void if necessary. The MRI technician should examine the T1 scan to determine if the quality is sufficient for the study. If it is not, the subject should return to the scanner for a repeat of the T1 scan.





The MRI technician should look for sharp/clear margins between the gray and white matter and also between the deep gray nuclei and the surrounding WM (basal ganglia+thalamus). Motion is often seen as the ring artifacts that are marked with the yellow arrows, and these artifacts can obscure the GM/WM border.

3.2. Neuroimaging: Coordination of Data Transfer, De-Identification and Entry

- The LURN Central Imaging Repository (LCIR) will be responsible for data transfer arrangements with each of the participating LURN sites on the MRI raw data.
- Data on eligibility (e.g. LUTS Tool, AUA-SI, the Neuroimaging & Sensory Testing Study Eligibility Form), data on the specific questionnaires (e.g. ICIQ-UI, ICIQ-OAB), and the urgency ratings during the scans (questions above) will be entered into the DCC LURNLink system after the scan has been completed.
- After the scanning has been completed, the site study coordinator will contact the LCIR to anticipate MRI raw data transfer.

- Many research MRI units automatically strip protected health information (PHI) from the files. You should request this for LURN if it is not currently policy. The MRI tech can do this easily.
- Data are transferred to the LCIR by the MRI tech or your site's "imaging person" using a secure upload portal. It can also be configured to upload automatically. Additional de-identification occurs at the LCIR as a backup measure.
- Once the raw data has been transferred successfully to the LCIR, the LCIR will notify the DCC that data have been uploaded successfully. The DCC will cross-check that all associated LURNLink data have been entered successfully. Incomplete data should be rectified by the site study coordinator promptly.
- If the LCIR has not received any MRI raw data within 7 days of completion of the scan, LCIR will contact the site study coordinator to resolve the data transfer.
- Contact for LURN Central Imaging Repository :
 - Cathy Liu – cliu@ucla.edu
 - Bruce Naliboff - naliboff@ucla.edu
- Contact for DCC: LURN-Monitoring@ArborResearch.org
- The LCIR will do quality control (QC) checks on the uploaded data. The LCIR will contact the site study coordinator and the DCC if the scan fails the QC check. The LCIR will rectify the quality issue with the site study coordinator promptly.
- The DCC will keep track of demographics data (sex, age of scanned participants) and update the enrollment table for LURN sites (see **Table 1**).

3.3. Neuroimaging: Phantom Protocol

- Initial calibration for the LURN Imaging protocol will be conducted using both a physical phantom and a human subject. The initial calibration will be conducted via the MAPP study, since the same equipment and testing routine will be utilized in both studies.
- The phantom will be the fBIRN agar ball phantom. The phantom will be imaged with the 3-plane localizer, T1-weighted MP-RAGE, resting state fMRI, and diffusion imaging from the LURN imaging protocol. The human test subject will be scanned using the entire LURN imaging protocol except that the prior water ingestion will not be performed (starting with the second S+L Localization, then RS2, T1 and DTI). The agar phantom and the human subject exam should be completed within one week of each other. All imaging data for these two calibration scans will be uploaded to the central imaging repository. The scans will be reviewed for image quality and scan parameters by the LCIR. The sites will notified if they passed the site qualification or if changes need to be made to the protocol and qualification scans reacquired.
- After the initial site qualification scan, the fBIRN phantom will be scanned on a yearly basis to assess scanner stability. It will be the responsibility of the DCC to notify sites when the calibration scan is required. The DCC will also monitor the timeliness of data uploads to the LCIR. Scanner stability will be assessed and issues concerning scanner stability will be sent to the sites in a timely manner.

4. Sensory Testing Overview

Order of Sensory Testing Procedures at all sites

- (1) MAST Familiarization (L thumb) – Section 5.1.4
- (2) MAST Ascending Series (R thumb) – Section 5.1.5
- (3) Short break (3-5 min)
- (4) Hearing Screening (L and R ear separately) – Section 6.1.5
- (5) Auditory Ascending Series (L and R ears together) – Section 6.1.6
- (6) Auditory Randomized Series (L and R ears together) – Section 6.1.6
- (7) Short break (3-5 min)
- (8) MAST Randomized Series (R thumb) – Section 5.1.6

5. Pressure Pain Sensitivity Assessment Procedure

5.1. Multimodal Automated Sensory Testing (MAST) System

Figure 1: MAST System



- Pressure pain sensitivity will be assessed using the MAST System. The MAST is a non-significant-risk investigational device that applies computer-controlled pressure stimuli to the thumbnail bed. The MAST system consists of two laptop computers: 1) a Server computer: used by the research coordinator to design and manage each test, and 2) a Client computer: used by the participant to enter pain ratings. The system also includes thumbnail pressure stimulator, the “handpiece”. The handpiece is a pistol-grip-style device

manufactured in cast urethane with a slot into which the participant inserts his or her thumb. Pressure is applied to the participant's thumbnail by a 1 cm² rubber probe. The probe is attached to a cylindrical transducer driven by a miniature servo-motor. A dynamic, closed-looped control system uses digital load-cells to measure the exact pressures applied to the thumb, and self-adjusts motor output to the resistance of the thumb and any movement to ensure accurate and repeatable force delivery. The MAST System incorporates a series of redundant mechanical, electrical, and software safety features to prevent patient injury in the event of user error or device failure.

- Detailed instructions on how to set up the MAST System, as well as, a description of safety features and risks, can be found in the *MAST Operation Manual* (Appendix P).
- Requests for MAST technical assistance, repairs, and calibration should be sent to MastHelpDesk@umich.edu.
- Note: The LURN Network will be sharing MAST equipment with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) MAPP Research Network. It is the responsibility of LURN research staff to develop and coordinate an equipment sharing plan with the MAPP staff at their site. The DCC will provide contact information for the MAPP coordinator at each site.

5.1.1. Preparing Before the Participant Arrives

- To do this test you will need:
 - Script to read to participants
 - MAST System (includes MAST handpiece, two laptops, assorted cables, operation manual)
 - Pressure Pain Sensitivity CRF (datasheet)
 - Sensory testing restriction checklist
 - A quiet room to perform test
- Ensure MAST handpiece and laptops are fully charged.
- Turn on all MAST System components and connect the computers (see MAST Operation Manual). The password for both computers is, "mast" in lower case letters (minus the quotation marks).
- Connect the MAST handpiece to the "Right Thumb Device" side of the Device Configuration window (see MAST Operation Manual, Appendix P).
- Confirm that the MAST System is working by applying a test pressure (0.25 kg is sufficient) from the Device Configuration window. You can use either your thumb or the supplied plastic test phantom (a 10cc syringe provided in the case) for this test. The "State" information bar will indicate "OK" if the pressure was administered correctly.
- Enter your participant demographic information into the MAST server: Participant ID, Site ID, and RC ID (your initials) are required.

- When entering demographic information, it is not necessary to complete all fields. Do not enter DOB to avoid PHI issues. Use the notes box to record unusual circumstances.
- Use the “LURN MAST Server” app located on the desktop (not MAPP). It was pre-configured to upload data to the LURN DCC. The DCC will need to grant permission to your specific site to gain access to their servers. To do this, they will need the IP address of the MAST computer after it’s connected to the internet at your site. The MAST Help Desk can help you figure out your IP address if you don’t know how. You may also need the help of your IT department to determine the range of IP addresses at your site.

5.1.2. MAST Computer Information

- Microsoft Updates has been disabled on these computers. A firewall and basic virus protection is enabled but these computers should not be used for risky web surfing. Limit browsing to university email clients and LURN website.
- Computers should be preconfigured with your correct time zone. Change the time zone if it is wrong. It’s important for record keeping that the computers show an accurate time.
- Computer hard drives will automatically defrag on Mondays at 4 PM or at next start-up if the computer is not turned on at that time. Defragmentation should not interfere with MAST testing. No other computer maintenance should be required for some time. However, contact the MAST Help Desk if you notice the computer is running poorly.
- Automatic power saving options, including screen savers, sleep/hibernate, turning off the monitor, etc. have been disabled so as to not interfere with testing. However, that means that computers should be powered down or manually put to sleep if not used for extended periods to avoid draining the battery unnecessarily.
- A folder on the desktop labeled *LURN Random Signals* includes all the random algorithms you will need for the Random Test.
- Although it is unlikely you will experience many problems, the simplest troubleshooting strategy that you should try first, like all computers, is restarting, namely: the MAST handpiece (turn off and then on), the MAST server and/or client software, and/or the computers themselves. Usually in that order. Also follow the instructions in the manual closely until you are comfortable with the operation of the equipment. Afterwards, there are many shortcuts that people use to decrease set up time. Once you are familiar, it should take less than a minute to set up the system.

5.1.3. MAST Familiarization Procedure (Non-dominant Left Thumb)

- Participants will undergo a familiarization procedure prior to the actual test. The purpose of familiarization is: 1) to teach participants how to perform the task correctly, 2) reduce test anxiety, and 3) to acclimate participants to the sensations (pressures, sounds, etc.) experienced during the task.
- Pressures are to be applied to the non-dominant (left) thumb during the familiarization procedure, and to the dominant (right) thumb for the actual Ascending Test.
- You will read the following instructions to the participant (Appendix Q): ***“In a few moments, I will conduct a test to measure your sensitivity to pressure using this device [show MAST***

handpiece]. ***We will start with a practice test before conducting the actual test so that you can become comfortable with this procedure.***

During testing, various pressures will be applied to your thumbnail for 5 seconds. After each pressure is released from your thumbnail, you will be asked to rate how painful it felt using a rating scale with numbers 0 through 100. This scale is shown here on this computer screen [show Client computer]. A zero (0) means ‘no pain’ and a one hundred (100) means ‘pain as bad as you could imagine.’ To indicate your rating, you will use this pen or your finger to press the location on the scale that best describes the intensity of your pain. If you prefer, you may use these arrows at the bottom of the screen to adjust your rating up or down. Once you have selected your rating, press the green confirm button in the lower right corner of the screen. Keep in mind that there is no right or wrong response, and you can use any number from 0 to 100, not just multiples of ten. Some pressures may be painful while others may not. Remember, if it just feels like pressure but not pain, rate (0) zero. If any pressure is too painful and you cannot tolerate it, let me know and I can release it immediately. You can also release the pressure yourself by pressing the ‘STOP’ button on your screen. You can also let me know if you feel your thumb is not in the correct position and needs to be adjusted. During testing, sit in a comfortable position and try to relax. This test usually takes 5 to 7 minutes to complete. Do you have any questions?’

- Rotate the screen of the client computer so that the participant only has access to the screen and not the keyboard. The stylus is much nicer on these computers and the screen also responds to finger touch.
- Next, demonstrate how to properly hold MAST handpiece, and assist the participant in doing so. The participant will hold the handpiece like a joystick while placing his or her thumb into the opening in the device, with their thumbnail positioned beneath the rubber tip. Place the wrist strap over the subject’s wrist. The plunger tip should contact the center of the thumbnail bed. It is recommended to perform a test pressure on you in the presence of the participant to demonstrate proper thumb positioning and device handling.
 - A thumb wedge was also included. Use this if a patient has a particularly thin or crooked thumb and the device is not extending far enough down to provide the correct pressure. Email us for assistance on its use.
- Instruct participant to keep his/her hand relaxed and to rest his/her thumb on the bottom surface of the thumb hole. They should never push the thumb upwards against the rubber tip during testing as this can interfere with pressure measurement.
- Ensure that the participant is seated comfortably with the hand, forearm and elbow resting on a table. You may need to place a towel or pad underneath his/her arm, particularly around the elbow, to improve comfort.
- Instruct participant to not stand the handpiece upright after the test is completed. It is top heavy and will fall over. After testing, he/she should gently place handpiece down on its side.
- One or two light “test” pressures will be applied to the participant’s thumbnail in advance of the familiarization procedure in order to ensure proper thumb positioning. To apply test pressures, navigate:

- Server Computer → Menu → Device Configuration
- Set force to 0.2 kg; set duration to 2 seconds (if not already selected).
- Click the green check mark to apply the pressure.
- The rubber tipped plunger in the MAST handpiece will lower to apply the pressure to the participant's thumbnail. The rubber tip should fall directly in the center of the thumbnail and not on the cuticle or the tip of the nail.
- Once the participant's thumbnail is in the proper position, the familiarization procedure will be conducted. It is ok to speak to the participant during the familiarization test to ensure he/she understands the procedure and scale, and to answer questions as needed. However, avoid non-task related conversation.
- To perform the familiarization test, navigate to:
 - Server computer → Testing Algorithms → Discrete Stimuli
 - Select "LURN ASC" from the menu of saved tests and click the green check mark to load the test.
 - This test consists of a series of ascending pressures beginning at 0.50 kg/cm² and increasing in 0.50 kg/cm² increments. Each pressure is delivered for 5 seconds. After the pressure is released, a prompt will appear on the Client computer to rate the pain evoked by the preceding pressure using a 0-100 rating scale. Ratings will be entered directly into the Client computer.
 - Start the test by selecting the "Play" button on the main screen on the server.
 - You will manually stop the test by pressing the "Pause" or "End Test" button at the first occurrence of one of three following possible stop criteria:
 - Participant provides a rating ≥ 50 on the 0-100 scale, or
 - Participant asks you to stop the test and indicates that they are unable or unwilling to continue, or
 - After 10 kg/cm² of pressure has been applied.
- If a participant requests a pressure to be released prematurely, ask them whether they want to continue testing or end the test at that time.
- It is recommended that participant ratings after each stimulus are recorded on the CRF in real time (i.e., during the actual test). This provides a backup of the data in the event of catastrophic equipment failure (e.g., hard drive crash) during testing and it also helps to maintain focus on the test procedure.
- After test completion, review the participant's understanding of the procedure and provide additional guidance as necessary. This is particularly important if he/she rated very low pressures (e.g., 0.5 kg/cm²) as painful or rated the highest pressure that they could tolerate < 70/100. This *could* indicate poor understanding of the rating scale or user error when entering responses. It's often useful to monitor test progress in real time and address these issues immediately when they occur. If you suspect that the participant doesn't understand the scale,

explain that ratings less than 30 are typically thought of as mild pain, ratings of 40-60 as moderate pain, and ratings over 70 as intense or severe pain.

5.1.4. MAST Ascending Series (Dominant – Right Thumb)

- Following the familiarization procedure, you will conduct the MAST Ascending Series Test on the participant's dominant thumb.
- Read the following instructions (Appendix Q): ***“We are almost ready to begin the actual test. This test will be conducted on your right thumb instead of your left thumb but all other aspects of this test will be the same as the one we just completed. Before we start, I will again give a test pressure to make sure your thumb is in the right location. Remember, some pressures may be painful while others may not. If it just feels like pressure but not pain, rate (0) zero. If any pressure is intolerable, let me know and I will release it immediately. Once the test begins, try to relax and remain focused on the task until it is completed. Any questions?”***
- Apply 1-2 test pressures from the Device Configuration window to ensure proper thumb placement in the device.
- To perform the Ascending Series: hit the “Reset” button and then the “Play” button on the MAST Server. Note: You do not need to reselect the “LURN ASC” testing algorithm if you conduct the Ascending Series directly after the familiarization procedure.
- This test consists of a series of ascending pressures beginning at 0.50 kg/cm² and increasing in 0.50 kg/cm² increments. Each pressure is delivered for 5 seconds. After the pressure is released, a prompt will appear on the Client computer to rate the pain evoked by the preceding pressure using a 0-100 rating scale. Ratings will be entered directly into the Client computer.
- Although you don't have an active role in performing this test, you should closely monitor test progress from the Server computer so as to ensure accurate data collection and equipment function. Any unusual circumstances that cannot be corrected should be recorded in the Notes section of the MAST software or on the CRF (Appendix E).
- You will manually stop the test by pressing the “Pause” or “End Test” button in the MAST software at the first occurrence of one of three following possible stop criteria:
 - Participant provides a **rating ≥ 80** on the 0-100 scale, or
 - Participant asks you to stop the test and indicates that they are unable or unwilling to continue, or
 - After 10 kg/cm² of pressure has been applied.
- Save data locally (i.e., on MAST computer) by clicking the “End Test” button in the MAST software, navigating to the folder in which the file should be saved, and then clicking the “Save” button.
- Upload data file to the LURN DCC server by following the prompts initiated after saving the data locally. SFTP Username, Password, and IP address for the DCC have already been entered into the computer prior to shipment.

- Open the saved .csv data file on the MAST Server to determine the participant's pressure pain tolerance level. The pressure pain tolerance is the most intense pressure (in kg/cm²) that the participant tolerated in the Ascending Series. In other words, it's the last pressure that was delivered before testing stopped. Record this value on the CRF.

5.1.5. MAST Randomized Series (Dominant – Right Thumb)

- The MAST Randomized Series test will be conducted on the dominant thumb after the Ascending Series.
- To provide participants an adequate amount of time to rest their dominant thumbs after the Ascending Series and reduce tissue sensitization, we will conduct the Randomized Series after the Auditory Sensitivity Assessment (see Section 4). This should provide at least 15 minutes of rest between pressure tests on the right thumb.
- Determine which series of randomized pressures is appropriate for the participant using his/her tolerance level from the Ascending Series as a guide:
 - **Series A: Tolerance ≥ 5 kg/cm²**
 - 2.5, 1.5, 4.5, 2, 1, 3.5, 1, 2.5, 3.5, 1.5, 2, 4.5 kg/cm²
 - **Series B: Tolerance 4 - 4.5 kg/cm²**
 - 2.5, 1.5, 2, 1, 3.5, 1, 2.5, 3.5, 1.5, 2 kg/cm²
 - **Series C: Tolerance ≤ 3.5 kg/cm²**
 - 2.5, 1.5, 2, 1, 1, 2.5, 1.5, 2 kg/cm²
- This method allows us to tailor the Randomized Test to the pressure sensitivity limits of each participant and it should prevent participants from receiving pressures that they cannot tolerate. Based on previous data in urological patients, we expect that 73% participants will fall into Series A, 18% in Series B, and 9% in Series C.
- In this test, 4-6 pressure levels will be delivered in (pseudo) randomized order. This order will be the same for every participant at every site across the LURN network.
- Read the following instructions (Appendix Q): ***For the next test, various pressures will again be applied to your right thumbnail. None of the pressures are going to be more or less intense than the previous test. You will be using the same 0-100 rating scale as you did in the earlier pressure test. A zero (0) means 'no pain' and a one hundred (100) means 'pain as bad as you could imagine.' This test will last about 5 minutes. Do you have any questions before we get started?***

To initiate the Randomized Series:

- Locate the "Load/Save Signal" buttons in the upper left corner of the MAST Server main screen.
- Click the icon of a folder with an arrow.

- Navigate to the appropriate folder and test file depending on the participant's sensitivity group (e.g., LURN Random Signals -> LURN Random A_right.cvs) located on your computer and click "Open" to load the file.
- Click the "Reset" button and then the "Play" button to start the test.
- Note: If you turned off the computer or closed the MAST software since completing the Ascending Test, you will first need to reload the Ascending Test before selecting and loading the random test.
- As with the Ascending Series, it is recommended to record participant responses on the CRF during testing.
- After the last stimulus in the series is delivered, save the data locally (i.e., on the MAST computer) by clicking the "End Test" button in the MAST software, navigating to the folder in which the file should be saved, and then clicking "Save".
- Upload data file to the LURN DCC server by following the prompts initiated after saving the data locally.
- MAST pressure testing is complete.

6. Auditory Sensitivity Assessment Procedure

6.1.1. Maico MA41 Audiometer

- The Maico MA41 is a portable air, bone, speech audiometer.
- Each LURN site is required to purchase and oversee the maintenance of this device. Maintenance consists of yearly calibration checks.
- For purchasing information, technical support, and calibration services - go to e3 *Diagnostics* (<http://www.e3diagnostics.com>) and search for your local audiometer supplier.

6.1.2. Initial Device Set-Up (**done only once after device arrival**)

1. Plug in the device and turn it on using the switch on the back right.
2. Click on "Menu" button on right of screen to enter settings. You will use the dial **A** to scroll through the options and button **B** (pictured below) to select options.
 - Frequency settings:
 1. Set default to ON.
 2. Set standard frequencies to 1000, 2000, and 4000 Hz by deselecting frequencies that will not be used (1000 is standard and is not listed; so you should see dots by 2000 and 4000 only).
 - Level:
 1. Set default to ON.

2. Open “Set Default Levels” tab. Set default for tone to 25 dB. This way, it will automatically go to 25dB (level used in initial screening) when machine is booted. Press “OK” button on left of screen to exit.
- Signal:
 1. Presenter duration should be changed to 3 seconds. Click the “User Defined” tab, and use dial to set to 3 seconds. Press the “S” (i.e., save) button on top right or left of device to save.

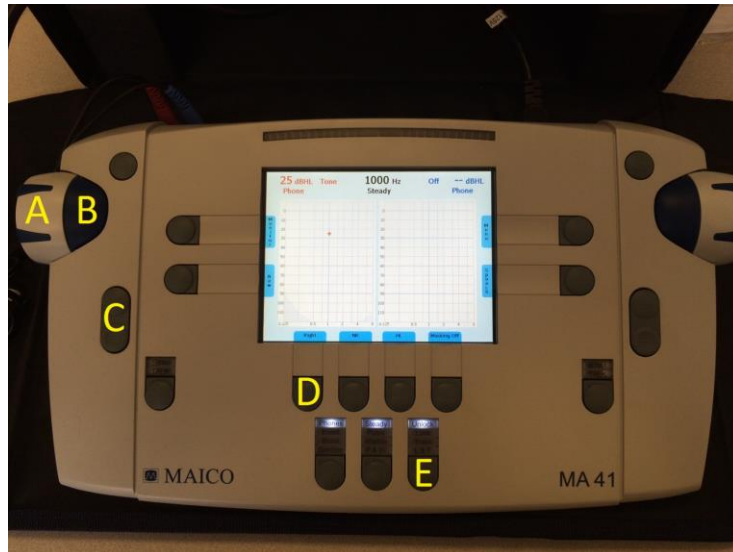
6.1.3. Preparing Before Participant Arrives

- To do this test you will need:
 - Script to read to participants (see Appendix R)
 - Timer (stopwatch, phone or computer timer, etc.)
 - MA41 carrying case (includes MA41, power cord, and headphones)
 - Part 1 and Part 2 Instruction sheets (see Appendices B and C)
 - Auditory Sensitivity CRF (datasheet, Appendix F)
 - A quiet room to perform test

6.1.4. Preparing the MA41 for Testing

1. Fold open the MA41 carrying case. Do not remove the MA41 from the carrying case.
2. Plug in the device and turn it on using the switch on the back right.
3. The headphones should be plugged in on the back left in the two jacks labeled “Phone”. Match the colors.
4. You will manipulate the following labeled buttons at some point during testing:
 - **(A)** Turning this dial towards you will increase the intensity of the tone, and turning it away from you will decrease tone intensity, in steps of 5 dB. When the device is turned on initially it should automatically be set at 25 dB - the intensity to be used during the hearing screening.
 - **(B)** This button will be used to present sounds to the participant when it is pressed. The device is programmed to present sounds for 3 seconds - the duration to be used during all procedures.
 - **(C)** Pressing the up (down) arrow will increase (decrease) the frequency of the sound. You will test three frequencies (1000, 2000, and 4000 Hz) in the Hearing Screening Test and one frequency (2000 Hz) in the Auditory Stimulation Tests.
 - **(D)** Pressing this button will control which ear receives the tone (right, left, or both). For the Hearing Screening it should initially be set to “Right”, and you should see a red crosshair on the screen.

- **(E)** This button will be used to lock in the right and left ear's programming during the Auditory Sensitivity Test. During the Hearing Screening it can be left on "Unlock", since you are testing the right and left ears separately. During the Auditory Sensitivity Test it should be set to "L & T", meaning lock and track. The two buttons to the left of button **E** will not need to be changed. They should stay on "Phones" and "Steady".



5. Position the participant in a chair 1-2 m away from the apparatus, and ensure that he or she will not be able to see the testing screen or the movements of the experimenter during testing. This can be accomplished either by having the participant face away from the experimenter, or by using the MA41 carrying case as a screen.

6.1.5. Hearing Screening

1. Tell the participant: ***"Your job in this first task is to raise your hand when you hear a tone. We will play several sounds, some in your right and others in your left ear."***
2. Instruct the participant to put the headphones on, saying ***"Red goes on your right ear"***, and make sure that the participant has the earphones on correctly.
3. Double check that the device is set to deliver a 25 dB, 1000 Hz tone to the right ear.
4. Place the "Part 1" Instruction sheet (Appendix B, shown below) in view of the participant as a reminder of the instructions.

PART 1.

Raise your hand when you hear a tone.

5. Press AND HOLD button **B** to deliver the first sound. You will be able to tell that the sound is being delivered by observing the "STIM" button (just to the right of button **C**; see right) light up. When this light is on, a sound is being presented; when it's off, no sound is being presented. The device is pre-programmed to present a tone for no more than 3 seconds. Holding the button longer than 3 seconds (e.g. 4 or 5 seconds) will not continue to play



the sound (it automatically stops after 3 seconds with the light); just make sure you hold the button long enough (i.e. until the full 3 seconds have elapsed and the light is off) so that the sound plays for the full 3 seconds. This is particularly important in the second procedure.

6. If the participant raises a hand to indicate the sound has been heard, check “Response” on your data sheet. If the participant does not respond, check “No Response” to indicate this.
7. Repeat steps 5 and 6 at 2000 and 4000 Hz, pausing for **5-10 seconds** between each tone. (Please begin a timer the moment the last tone is given, and wait at least 5 seconds before delivering the next sound. You may use a stopwatch, phone or computer timer, etc.) To increase the frequency (Hz) of the tone in each subsequent trial, press the “+” on button **C**. Make sure that the screen displays the correct frequency and dB (25) before each presentation.
8. Next you will repeat steps 5-7 on the left ear. Press button **D** to switch the sounds to the left ear. The crosshair and the numbers on the screen will be blue. Use the opposite (right) side **B** button to deliver left ear sounds.
9. Have the participant remove the headphones and prepare for the Auditory Sensitivity Test.
10. **Participants who fail to respond to any of the 2000 Hz (left or right) screening tones should be excluded from further auditory testing.** Participants who fail to respond to 1000 Hz or 4000 Hz can PROCEED with the auditory testing, provided they have passed both the left and right 2000 Hz screening tones. Record this information on the CRF.

Protocol deviation:	Absolute exclusion:
Failed 1000 Hz or 4000 Hz screening tone(s)	Failed 2000 Hz screening tone(s)
Action: Record the results on the CRF, but OK to PROCEED with auditory testing.	Action: EXCLUDE from the study. Do NOT proceed with auditory testing.

6.1.6. Audiology Sensitivity Test (Ascending and Randomized Series)

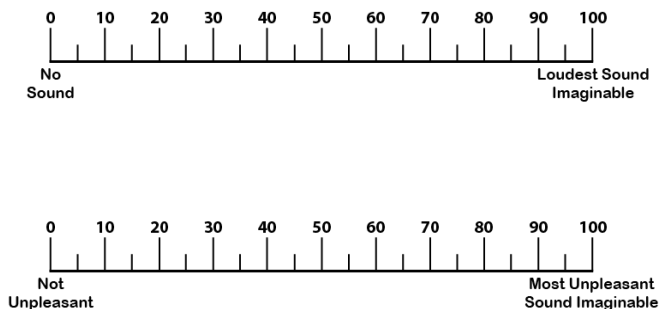
1. Press button **D** again to set the audiometer to “Both”. Now there should be two crosshairs on the screen, one for the right ear (red side) and another for the left ear (blue side). It is important that the left and right signals are set to the same intensity. Check that they both read the same dB. They should initialize to the same level here, but if they don’t (e.g. one is 35 dB and the other is 25 dB) rotate dial **A** (or the right dial for the right graph) so that the two numbers match.
2. Now press button **E** until “L & T” (meaning lock and track) is highlighted. This makes it so that you only need to press the left button **B** (or the right, if you prefer) to play sounds to both ears

and you only need to rotate the left dial **A** (or the right, if you prefer) for you to change the intensity.

- Use the “+” and “-” sides of button **C** to position the crosshairs on 2000 Hz, the frequency that will be used on every trial in this test.
- Instruct the participant on what she or he will do in this task. ***“I will put these two scales on the table in front of you [show Part 2 Instruction sheet], and you will use them to rate the intensity and unpleasantness of different tones. Each tone will be several seconds duration. After each tone, I would like you to first call out a number that describes how loud you perceived the sound to be. This will be on a scale from 0 to 100, where 0 means “no sound” and 100 means “the loudest sound imaginable”. Next, you should call out a second number that describes how unpleasant you perceived the sound to be. This will be done using the second scale which also ranges from 0 to 100, where 0 means “not unpleasant” and 100 means “the most unpleasant sound imaginable”. [When describing these scales, point to the relevant portions of the instruction sheet.] A few seconds after you give me the two ratings, I will play the next sound. While some of the sounds may be loud, they are all at a safe level at the short durations we will be playing them. If, however, you find a sound to be louder than you’re willing to tolerate, let me know and I will not present any sound that is louder than that again. Do you have any questions about these procedures?”***
- Place the “Part 2” Instruction sheet (Appendix C, shown below) in view of the participant as a

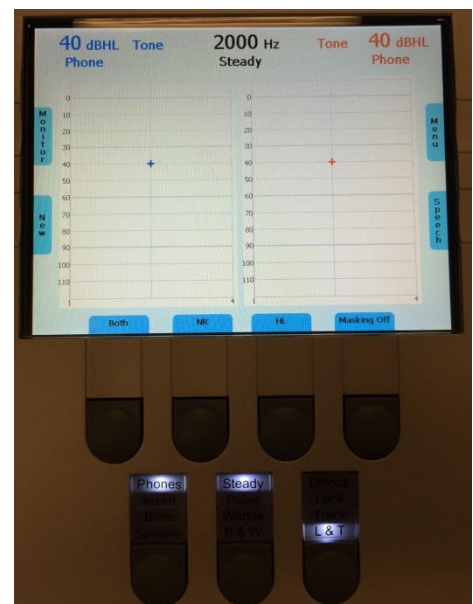
PART 2.

After you hear a tone you will say TWO ratings out loud.



reminder of the instructions.

- First you will present an ascending series of tones. **Start with 40 dB**, setting this intensity using dial **A**. Things should look like this (right). Note: It’s ok if the red and blue are on opposite sides as depicted, as long as they both show the same number (40 dBHL here).
- Present the tone for **three (3) seconds** (remember to hold button **B** until the light goes off), wait for the participant’s ratings, and record them in the appropriate row on the CRF. If the participant has not given a response after a couple seconds, ask ***“Intensity?”*** [wait for rating to




be provided] and “**Unpleasantness?**” at your discretion. As more trials are repeated, you probably will not need to prompt the participant any longer.

8. Next, continue testing by presenting the 50, 60, 70, 80, and 90 dB tones in ascending order following the same procedure as above. Tones should be separated by **5-10 seconds**. (Please begin a timer the moment the last tone is given, and wait at least 5 seconds before delivering the next sound. You may use a stopwatch, phone or computer timer, etc.).
9. **Note:** If a participant cannot tolerate or does not wish to hear a sound above a certain level (e.g., 80 dB), stop the Ascending Series and do not present the louder tones. Go through the datasheet with the randomized dB values and cross out the objectionable intensity level and those that are louder. Skip over those values as you progress through the Randomized Series.
10. Present each intensity (change between trials using dial **A**) and record the responses. After the Ascending Series, go right into the Randomized Series without a break or additional instructions. Continue with this process for the 18 random stimuli (LURN Randomized Sequence: 50, 80, 60, 40, 70, 90, 60, 70, 80, 40, 90, 50, 60, 40, 50, 70, 90, 80 dB). If a participant cannot tolerate a certain level (e.g., 80 dB), skip only the higher dB tone (e.g., all the 90 dB) in the Randomized Series, but continue the rest of the tones, and record this modification on the CRF (write “SKIP” for that particular tone on the CRF).
11. Tell the participant that he or she can remove the headphones. Auditory testing is complete.
12. Proceed with the MAST Randomized Series (see Section 4.1.5).

7. Neuroimaging Data Uploading Procedures


7.1. The LURN Data Upload Portal

1. Go to the UCLA CNS Data Portal site (www.painrepository.org) and click on the LURN logo or the ‘Log in’ link under the LURN logo.
2. The LURN site is a secured site that can only be accessed by



Welcome to the UCLA CNS Data Core Portal

This new portal is now the access point for multiple brain imaging initiatives housed at the UCLA Oppenheimer Center for Neurobiology of Stress (CNS). All are aimed at the characterization of brain signatures associated with chronic pain and related disorders, understanding underlying mechanisms, and identifying novel treatment targets. These include the NCCIH/NIDA funded PAIN Repositories (Standardized and Archived), the NINDK MAPP Neuroimaging Network, NIH SCOR Network and the Network of direct UCLA CNS Collaborators. All initiatives are independent of each other and can only be accessed by users authorized for a particular initiative. If you are part of one or more of these groups, you can log into the relevant sites using the icon links below. To learn more about the UCLA CNS, please visit our Center's website at uclacns.org.

 Neuroimaging data from multiple pain conditions open to members of the pain research community	 NIH MAPP Research Network neuroimaging datasets accessible to MAPP investigators	 NIH LURN neuroimaging datasets accessible to LURN investigators
 Center for Neurobiology of Stress datasets accessible to CNS investigators	 NIH Specialized Centers of Research collaborative studies accessible to SCOR investigators	 IBSOS website accessible to IBSOS Members

registered users. You will be prompted to log in if you have not already done so.

7.2. Request User Account for the LURN Site

1. Click on the 'Register' link under the LURN logo on the UCLA CNS Data Core Portal site.
2. Complete and submit the form
3. For security reasons, a member of the UCLA CNS Data Core personnel will review the request before an account is created.
4. Requestor will receive their username and password via email. The email will come from UCLA CNS Data Core.

The following sections reference the top menu bar of the LURN site.



7.3. Uploading Data

1. On the LURN site, click on 'Upload Data' in the top menu bar
2. Instructions for naming and uploading files are outlined on the page. They are:
 - a. Each tarball or zip file* should contain the scans from ONE scan session from ONE subject. One complete scan session includes one structural, one DTI and two resting state scans.
 - b. Use the following naming convention for each file:
 - c. L[2 digit site ID]-[4 digit LURN LINK subject ID].tar/zip/.tar.gz.

Examples: L02-1010.tar, L02-1010.zip**

**** Site Designations:**

Duke University: 01

Washington University, St Louis: 02

Northwestern University: 03

University of Michigan: 05

University of Washington: 06

University of Iowa: 07

3. Report any anomalies and issues with the scan session in the text box provided under Step 1 (e.g. 'DTI was not run due to equipment failure.')

Step 1: Report Anomalies/Issues for This Scan Session

If there are are no anomalies or issues to report, leave **BLANK**.

Maximum characters: 255. You have characters left.

4. Click on the orange 'Select File' button and select the zipped file that was created for the subject.
5. Click on the green 'Upload File' to upload the file.

Step 2: Upload Image File

Select File

Upload File

6. A confirmation notice will be displayed on the page once the file has been successfully uploaded.

L01-1111.tar was successfully uploaded.

7. You may then begin to upload additional files. You do not need to refresh the page. Both the text box field and the file name field will be blanked out once the previous upload is successfully completed.
8. Email confirmation of upload will be sent to the user who uploaded the scan(s), other site designated personnel, UCLA CNS Data Core personnel, and selected personnel at the DCC
9. If an error occurs at any stage of the upload process or if there are any questions, email the UCLA CNS Data Core team at Support@PainRepository.org

7.3.1. * Compressing Scans for Upload

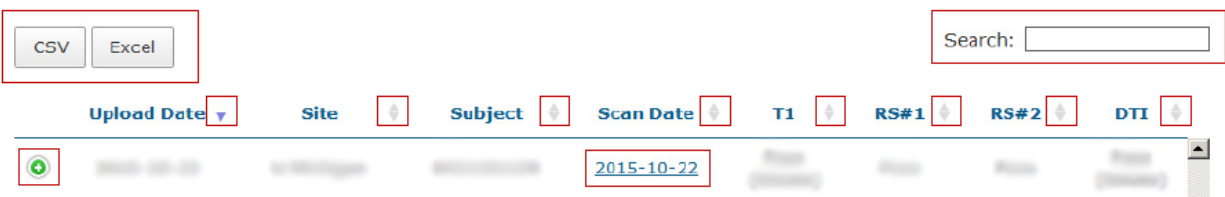
All current operating systems have built-in compression tools.

- Windows: Select a folder or groups of files, right-click, select Send To → Compressed (zipped) folder.
- Mac OS: Select a folder or group of files, right-click, select Compress <file name or # of items>.
- Linux, Mac OS, & other Unix-based systems also provide the command-line tar utility.

7.4. LURN Scan Reporting

1. To see the current status of all uploaded scans, click on 'Data' in the top menu bar of the LURN site.
2. By default, the list of scans is sorted in descending order by Upload Date. You may change this by clicking on the up-down arrows next to the header of each column.
3. To filter the list, use the search box at the top right corner of the list.
4. Scans that were uploaded with notes will be marked with a green plus sign at the left of each row. Click on the icon to expand the row to read the note.
5. You may also download the report by clicking on either the CSV or Excel button.
6. The acceptable scanning parameter used for determining the QC status of each scan can be viewed on the 'LURN QC Parameters' page located under the Data tab in the top menu bar. There is also a link to this page above the search box on the Data page.
7. To get QC details and metrics of a scan session, click on the session date for that session.

[View the acceptable LURN QC Parameters](#)



8. Below the list is a legend explaining the meaning of each QC value:

Legend	
Pass =	No issues detected.
Pass (Issues) =	Some issues detected but likely will not impact analysis. Click on scan date to see details.
Flagged =	Scan has failed to meet one or more parameters. Usability for analysis should be evaluated on an individual basis. Email sent to site.
Unusable =	Scan is likely unusable for any type of analysis but will be archived in the LURN repository. Email sent to site with recommendation to rescan.
No QC =	Scan has not been QC'd yet.
Under QC =	Scan undergoing QC but has not been finalized.
Blank Cell =	No scan.

7.5. LURN Site Qualification

To complete the site qualification process, each site must submit a complete scan session that meets all QC criteria AND a pdf file of the scanner parameters used.

1. For LURN Site Qualification instructions, click on 'Manuals' in the top menu bar of the LURN site. The manual may also be downloaded as a pdf.
2. To upload site qualification scans, click on 'Site Qualification' in the top menu bar and follow the instructions on the page. They are:
 - a. Each tarball or zip file should contain the scans, ONE scan session from ONE subject.
 - b. Use the following naming convention: L[2 digit site ID]-[4 digit subject ID].tar/zip/.tar.gz.

Use the following naming convention for 6 digit Subject ID:

- Phantoms: "FP" followed by any two numbers you wish to use, e.g. FP01
- Human Subjects: "HS" followed by any two numbers you wish to use to identify the subject, e.g. HS01

Examples: [L02-HS01.tar](#), [L02-FPS01.zip](#)

3. Click on the orange 'Select File' button and select the zipped file that was created for the subject.
4. Click on the green 'Upload File' to upload the file.

5. To upload a pdf file of the scanner parameter used, use the 'Scan Parameters File' upload tool below the 'Image File' upload tool.

Scanner Parameters File

6. The Image File and Scanner Parameters File upload tools act independently of each other. A confirmation notice will be displayed for each file that has been successfully uploaded.
7. Email confirmation of upload(s) will be sent to the user who uploaded the scan(s), UCLA CNS Data Core personnel, and selected personnel at the DCC.

Please make certain to use the same scanner that was used to site qualify. If you foresee the possibility of using a different scanner at your site, each of those scanners must be qualified before running a subject on it.

If your scanner undergoes a software upgrade, please let us know as soon as possible so we can work with your scanner personnel to re-qualify the scanner before running your next subject.

8. Site Qualification Status

The site qualification status of each site is located on the 'Site Qualification Status' page under the 'Site Qualification' tab in the top menu bar. The current scanner settings at each site can be found as a pdf file on this page.

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