Study Protocol

Investigation of Brain Mechanisms Involved in Urgency Urinary Incontinence

University of Pittsburgh STUDY19090167

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Overview

The brain plays a vital role in the continence mechanism. Understanding the bladder control system and its failure is key to identifying novel therapeutic targets to complement and improve efficacy of current therapy. Using Trospium, an anticholinergic medication for urinary incontinence which does not cross the blood brain barrier, and placebo, in a crossover study will allow identification of 'responders' and 'nonresponders' to each intervention, categorized by reduction in number of leakage episodes after treatment. These groups of participants will form the basis of quantitative and qualitative evaluation of brain structure and function to build on the working model of the brain's role in the continence mechanism.

Scientific Background

Prevalent, morbid, and costly (≤$83 billion/year), urgency urinary incontinence (UUI) is a major problem, especially for older adults. It also impairs quality of life, social interaction, and independence; contributes to functional decline; and increases risk for falls, hip fractures, UTIs, urosepsis, anxiety, depression, and institutionalization. Although usually ascribed to bladder spasms, UUI's cause is unknown and bladder targeted therapy remains inadequate. Yet, because the brain controls the bladder, UUI must reflect causal changes in the brain, inadequate brain response to urinary tract dysfunction, or inadequate viscerosensory feedback. Thus we were excited by our recent discovery that success and failure of a behavioral approach (biofeedback, BFB) correlates with different brain activity signatures, which may represent disease phenotypes as well as mechanisms of therapy. To confirm this bladder control model, we must further probe the brain control system. The proposed study used a bladder-targeted drug (trospium) to address response to an intervention that does not affect brain function. Specifically, those who respond to the drug will allow investigation of mechanism(s) that mediate drug response. Likewise, response to therapy versus placebo will allow understanding of how the brain responds to bladder mediated therapy. Our overall goal is to better understand the brain's role in incontinence, primarily by better characterizing the brain mechanisms involved in response to drug or placebo therapy. Regardless of whether the brain's role is causal or secondary (owing to inability to suppress bladder dysfunction), such knowledge will identify brain targets to suppress or augment, which in turn could transform current therapy. The study will provide the first-ever data on brain mechanisms involved in UUI response to a drug. Regardless of results, it will contribute substantially to current understanding of UUI and continence.

Study Objectives

The primary objective of this study is to use an anticholinergic incontinence drug as a probe to further understand the role of the brain in the continence mechanism by interrogating responders and non

responders to the drug and placebo. Thus, the primary outcome of this study is evaluation of response to drug/placebo categorized by reduction in number of incontinence episodes. Such categorization of participants will allow synthesis of complex structural and functional brain MRI data to further understanding of the brain's role in the continence mechanism.

Study Design & Methods

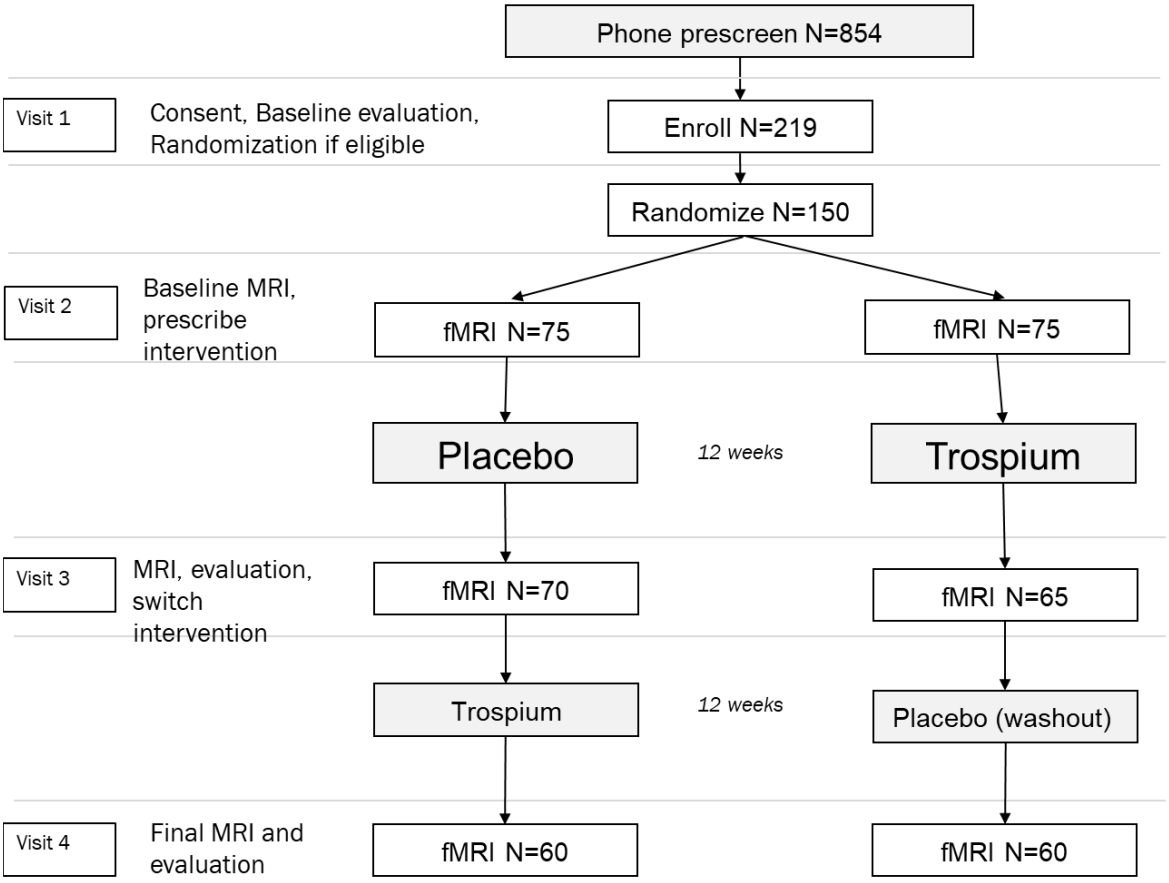

Figure 1, study design and flow

Study Procedures:

Screening

Screening procedures include: a) telephone interview and b) Visit 1 to study research suite - Continence Research Unit at UPMC Montefiore Hospital. If the subject is interested and qualifies, then the other visits are scheduled.

Telephone Interview

Use IRB approved telephone script to determine eligibility (5-20mins; study nurse/coordinator)

Visit 1a

1 hour; study nurse; telephone

1. Obtain informed consent and document.
2. Questionnaires:
    - Basic demographics

- Current incontinence
- Incontinence history
- ICIQ
- Obstetrics
- Daily routine
- Medical and surgical history
- MRI screen

Visit 1b

1 hour; study nurse; continence research unit MUH NE547

1. Recap consent and sign document.
2. Questionnaires:
    - Sensation of urge
    - PHQ-9
    - Beck SF-36
    - MoCA (paper)
3. Uroflow and dip (at appropriate bladder fullness)
    - Measure flow rate and volume of normal void
    - Test for infection (leukocytes/nitrites) using a dipstick
    - Post-void residual measurement by ultrasound
4. Urinalysis (conditional): If the dip procedure indicates or suggests infection, a catheterized specimen will be sent for urinalysis and culture. If positive, participant will be advised to see PCP for treatment.
5. Physical examination: Height, weight, blood pressure.
6. Voiding diary to complete at home: 3 day voiding diary and one day pad diary
7. Randomization

Visit 2

Pre-intervention (about 3-4 hours)

1. Uroflow
2. Measure flow rate and volume of normal void
3. Test for infection (leukocytes/nitrites) using a dipstick
4. Post-void residual measurement by ultrasound
5. Transfer to MRI scan room
6. Catheters inserted per urethra and connected to Laborie Goby UDS system
7. Structural scans (20 mins)
8. Functional MRI scans with coordinated bladder filling on empty bladder x2 (ePrime; 5 minutes)*
9. Fill bladder until button signal *
10. Functional MRI scans with coordinated bladder filling on full bladder x2 (ePrime;5 minutes)*
11. Withdraw catheters
12. Empty bladder into specimen pan (measure)
13. Post void residual ultrasound

14. Give participant intervention assigned at randomization (blinded: Trospium (60 mg extended release) or placebo daily)
15. End of visit

* If participant signals that she is uncomfortable we will pause, or stop the whole procedure if necessary.
Unanticipated disease: If the above procedure suggests a serious disease (e.g., brain tumor or brain abnormality), the subject will be informed and permission asked to inform either the appropriate physician or refer the subject back to her private physician. The subject may withdraw or be withdrawn from the study.

Phone check in 4 and 8 weeks post visit 2

Check for side effects, AEs, adherence. Bladder pad diary for visit 3.

Visit 3

12 weeks post visit 2 (about 3-4 hours)

1. Redcap Questionnaires:
    - Current incontinence
    - Daily routine
    - Sensation of urge
    - PHQ-9
2. Pill count
3. As visit 2.

Visit 4

12 weeks post visit 3 (about 3-4 hours)

1. Redcap Questionnaires:
    - Current incontinence
    - Daily routine
    - Sensation of urge
    - PHQ-9
2. Pill count
3. As visit 2, but without further intervention/bladder diary.

Eligibility Criteria

Inclusion criteria:

1. 60+ years old
2. Has UUI or urge-predominant mixed incontinence at least 5 times/ week for > 3 months despite treatment for reversible causes

Exclusion criteria:

1. conditions/medications contraindicating trospium
2. If currently taking anticholinergic medications (participant must refrain from anticholinergic medications for 4 weeks prior enrollment in order to be eligible)
3. Impaired mobility or cognition sufficient to preclude following study procedures; MoCA test score <24/30; a clinically-apparent neurological

condition
4. Prolapse beyond the hymen
5. Interstitial cystitis
6. Spinal cord injury
7. History of pelvic radiation or advanced uterine/bladder cancer
8. Urethral obstruction (uroflow); PVR >200 ml
9. Medical instability
10. Prior UUI treatment with onabotulinum toxin or sacral neuromodulation (SNM) within 3 years. SNM must be removed.
11. Drug interaction or expected medication change during the study
13. Conditions requiring IV antibacterial prophylaxis
14. New incontinence treatment < 3 months prior to enrollment
15. Fecal incontinence, and symptomatic colitis/IBS
16. Contraindications to MRI.
17. Severe CKD with eGFR < 30

Statistical Considerations

This is a mechanistic study designed to use the study drug as a probe, rather than evaluate its efficacy, to understand the brain's role in bladder control. We present the primary outcome of response to drug/placebo as a cross-over drug study which allows evaluation of the study drug in a clinical population. The synthesis of the groups of responders and non-responders to drug or placebo is crucial to allow in depth analysis of changes in brain structure and function which will provide insight into how the brain controls the bladder. However, such analysis is necessarily qualitative, complex and challenging to convey in a context-free numerical format.

Power and design

Power estimation for cluster-level tests of significance of activations and deactivations is complex, but our own experience and published approximations[105,106] suggest that subgroups of 20 are adequate in simple situations. For complex studies an approximation can be based on the mean T-value in the *a priori* ROI, calculated for each subject and compared pre- and post-therapy. Applying this simplified approach, we base our sample size justification on ours and others' preliminary studies of between-subject standard deviations and response/ retention rates, and on ability to detect statistical significance with 80% power in 2-tailed tests with α=0.05. We conservatively assume a drug response rate of 77% (based on our fesoterodine study, since this response metric is not reported for trospium) and 64% for placebo.[107] The design in Fig. 6 will provide us with 70+65=135 three month periods from individuals on drug with an assumed 104 responders and 31 non-responders. (A more realistic placebo response in this population[108] (~50%) will reduce the required sample.)

Study outcomes

Primary outcome: Responder(yes/no)

We fitted a generalized estimating equations model to whether a participant had at least a 50% improvement (yes/no) as the dependent variable; a binomial distribution and a logit link function; randomized arm, time period and their interaction as fixed effects of interest; and an exchangeable working correlation structure.

Secondary Outcomes

The secondary outcomes of this study involves qualitative evaluation of whole brain functional and structural MRI variables to synthesize of a model of compensation, mediation and function of the lower urinary tract in older women with UUI as follows:

MRI analysis

1. Functional MRI analysis: Single-subject functional images are pre-processed in a standard way using Statistical Parametric Mapping (SPM12) to correct for head movement (realignment) and normalize images to a standard brain (ICBM152). Response to bladder filling is determined from the paired signal contrast, representing infusion minus subsequent withdrawal, allowing for the delayed hemodynamic response to neural activity. A negative value represents relative deactivation. First-level statistical analysis is performed for a given measurement block, and at each voxel, the value of Student's *t* is calculated for four paired signal contrasts (infusion – subsequent withdrawal), thus reducing the many whole-brain scans to one 3-dimensional map of t-values. Each t-value represents activity in a voxel of size 2.3mm^3 (~10,000 per brain). Using a mixed-effects approach, these first-level t-values are input into a series of second-level (group) tests to examine the significance of within-group and between-group differences, corresponding to our *a priori* hypotheses. Voxel-wise calculations are performed using a threshold (typically False Discovery Rate (FDR) of 0.05 for multiple comparison correction), suppressing regions with <20 contiguous activated voxels. Hypothesis-testing analyses will be targeted at clusters within the ROIs specified *a priori* (see Fig. 2) using a small-volume correction. Clusters in each of the ROIs that display significant BOLD signal changes will be identified by a t-test (FDR 0.05) and a cluster extent threshold of 20 voxels. The individual BOLD signal change in each ROI will be described by the first eigenvariate of the adjusted contrast (adjusted for mean and covariates) in the cluster. At a later hypothesis-generating stage, we shall search for trends to significance in additional brain regions, based on uncorrected probability values (e.g. $p < 0.01$ or 0.001) in accordance with common practice.

2. Approach to Hypotheses 1-3:

Employing SPM12, we will test these hypotheses by using response to intervention as a probe to gain insight into neural mechanisms, rather than as a way to assess therapy efficacy. We will split the participants as a primary outcome into those who respond (>50% reduction in UI episodes) and don't respond to trospium/placebo and those in the withdrawal group (who may lose or retain treatment effect). We will fit a series of second-level models using SPM's multiple regression procedure with pre- to post-treatment change in t-value (= activation level) as the dependent variable, and participant group as the factor of interest. We will test each model in the appropriate predetermined ROI.

3. Hypothesis 4: *White matter connectivity using DSI:* DSI data will be collected using a 20-min, 271-direction sequence using a twice-refocused spin-echo EPI sequence and multiple *q* values (TR = 4250 ms, TE = 150 ms, voxel size = 2.4 X 2.4 X 2.4 mm, FoV = 230 X 230 mm, b-max = 4,000 s/mm^2), motion and eddy current corrected, and reconstructed using DSI Studio software and a Q-space diffeomorphic reconstruction (QSDR) approach[96]. Tractography will be performed in individuals using a seed-based approach. **STwm tractography:** the seed is a fornix ROI dilated to the mid-point of the head of the caudate encompassing the STwm and terminal vein[97]. **MFB tractography:** select fibers that course through the mid-brain tegmentum towards BST/PVN. Measures of structural integrity (generalized fractional anisotropy, GFA, and normalized quantitative anisotropy NQA), which describe the diffusion of water molecules around neuronal compartments (e.g., myelin, neurofilaments and microtubules) will be extracted from each individual.[98] Larger values can be interpreted as greater structural integrity. NQA is superior to DTI-derived FA; it is less sensitive to partial volume effects of crossing fibers and free water and provides better tractography resolution and fewer false fibers than FA-aided tractography[99]. These measures provide mechanistic indices of demyelination (i.e., increased diffusion *across* the axon) and/or axonal degeneration (e.g., reflecting decreased diffusion along the *length* of the axon due to debris).[100,101]

Functional connectivity (Resting State and gPPI): Resting state connectivity analysis and dual regression will be performed using SPM12 standard pre-processing. Using white matter and cerebrospinal fluid tissue components, and motion artifacts identified using wavelet de-spiking methods as nuisance

covariates, the residual time series will be extracted from each voxel and a band-pass filter (0.008-0.1 Hz) will be applied. Each ROI (mPFC, Insula, dACC/SMA, BST) will be applied as a mask on the resulting maps. Using principal components analysis, the time series data will be combined to extract a single eigenvariate for each ROI for each subject. The correlation between the eigenvariates for each ROI to ROI pair will be calculated to determine connectivity between the two regions for full and empty bladders focusing on ROIs and networks (default mode [DMN], anterior salience [ASN], executive control [ECN]). Assessing differences between full and empty bladder at rest with respect to UUI severity and treatment response will allow us to better understand whether control mechanisms behave differently with steady-state viscerosensory signals or only in the case of urgency stressors as during the infusion-withdrawal task. Generalized psycho-physiological interaction (gPPI) analysis of connectivity[78] during the infusion/withdrawal task will be performed to assess functional connectivity; this may, in light of white matter connectivity differences, allow us to more accurately hypothesize sites of damage and alternate pathways.