Brain Targets in Patients with Bladder Emptying Difficulties

NCT03574610

Document Date: January 24, 2020

Research Strategy: Supraspinal Targets in Neurogenic Voiding Dysfunction

1. SIGNIFICANCE

Voiding dysfunction (VD) is a morbid and costly urological condition characterized by intermittent, fluctuating, or absent flow of urine.[1] VD may lead to incomplete bladder emptying or urinary retention, urinary tract infections, sepsis, bladder or kidney stones, and permanent renal failure and can be present in patients with or without neurologic disorders.[2]

- *Currently the only available therapies for VD include indwelling bladder catheters or intermittent selfcatheterizations.*

Catheterization is a burden, in general, and even more so in neuropathic patients, in whom lower extremity spasms, compromised hand dexterity, or visual disturbances, may be present. The cost and morbid side effects (hematuria, pain, trauma, strictures, and infections), associated with catheterizations, urge us to look into alternate ***therapeutic targets for VD, possibly beyond the bladder, such as the brain*** (where bladder an urethral control centers are located).

The human lower urinary tract has two functions: storage and voiding. This study will concentrate on supraspinal (brain) areas controlling the delicate and complex neural circulatory (the "switch") from storage of urine to initiation of voiding. Normal voluntary voiding is controlled by suprapontine centers in the brain, allowing the pontine micturition center to trigger (switch on) the voiding reflex. VD occurs if the detrusor muscle cannot maintain effective contractions (e.g., *detrusor underactivity*), if the urethra fails to relax and lower urethral resistance, or if there is failure in synchronizing these actions leading to detrusor sphincter dyssynergia (DSD) in subset of neuropathic patients.[3,4] ***Almost all patients with DSD are dependent on catheterization and are at much higher risk for autonomic dysreflexia, recurrent urinary tract infections, and renal insufficiency.***[2]

Animal models have conventionally been used to study neural control of the bladder. However, animals differ from humans in numerous ways (e.g. social behavior). Critical distinctions exist between voluntary voiding (humans) and more instinctive bladder emptying (animals), when all the social, emotional, and mechanical criteria for voiding are considered. ***The conscious human intention to void, or not to void, highlights the need for human research, rather than exclusive reliance on animal data, in brain control over bladder.***

With the evolution of neuroimaging tools and resources, such as functional magnetic resonance imaging (fMRI), we have begun to gain additional insight into brain control over bladder function in *healthy* individuals. ***Yet, our understanding of supraspinal centers and their role in initiating or modulating voiding continues to be rudimentary in patients with neurogenic*** *(e.g. Multiple Sclerosis [MS] or Stroke)* ***or nonneurogenic voiding dysfunction*** *(e.g. underactive bladder or Fowler's syndrome)***.**

- The ***overall objective*** of my proposed study is to characterize and modulate specific supraspinal regions during the "switch over" of urine storage to voiding in MS patients with VD to improve voiding.

- Supraspinal involvement in VD in humans (especially in neuropathic patients) have not been investigated, and our proposed study will be the *seminal research* in the field.

- The findings from my proposed study may lay the foundation to study other etiologies of VD such as Underactive Bladder or detrusor underactivity, stroke, or Parkinson's disease, all of significant interest to National Institute of Diabetes and Digestive and Kidney Diseases.

2. INNOVATION

Investigation of brain control over the bladder in *healthy* individuals through the use of functional neuroimaging shows that the initial afferent sensory input comes from the bladder during "bladder fullness or the strong desire to void". Next, the forebrain determines the person's social circumstances and whether to proceed with voiding

or not. Once it is socially acceptable to void, centers in the brain and spinal cord coordinate and initiate urethral sphincter/pelvic floor relaxation, followed by a sustained detrusor contraction.[5] Specifically, the pontine micturition center (PMC) signals the bladder to begin the voiding phase when the sensations from the bladder are transmitted to the periaqueductal gray (PAG) and higher brain centers.[5-7] Previous positron emission topography studies in *healthy* individuals have demonstrated activation of the right dorsomedial pontine tegmentum, PAG, hypothalamus, and the right inferior frontal gyrus at the time of voiding.[8,9] ***Neuroimaging may augment the diagnosis of VD and aid in therapeutic planning in certain etiologies of VD.***[10-12]

- Combining urodynamic studies (UDS) with functional magnetic resonance imaging (fMRI) is technically challenging, but necessary, in order to elucidate simultaneous brain-bladder activities. We have established and refined our simultaneous platform in healthy individuals and neuropathic patients.

- Despite the challenges, our fMRI/UDS platform evaluates the entire bladder cycle, including the ***voiding phase.*** This is the ***strength*** and ***novelty*** of our protocol as, in contrast to other neuroimaging studies, individuals in our study void or attempt to void while in the MRI scanner during the UDS.

- In this proposal, we have taken ***the next step to move beyond the exploratory phase*** of identifying supraspinal targets involved in VD, into *targeted cortical stimulation of these regions (another testament to the novelty of our project).*

- Our investigative brain targets will also include areas of ***urethral activity***, which is innovative and not traditionally studied.

Our fMRI/UDS platform: UDS provides valuable information on bladder pressures and urethral sphincter function especially in patients with neurogenic VD.[13-15] Over the past four years, we have established a concurrent fMRI/UDS platform in healthy controls[16] and in MS patients[17,18] and evaluated the entire bladder cycle in realtime in over fifty individuals, specifically *when patients void or attempt to void in the fMRI scanner while UDS is being performed.* ***Our platform outperforms other neuroimaging studies, wherein voiding is not studied.***

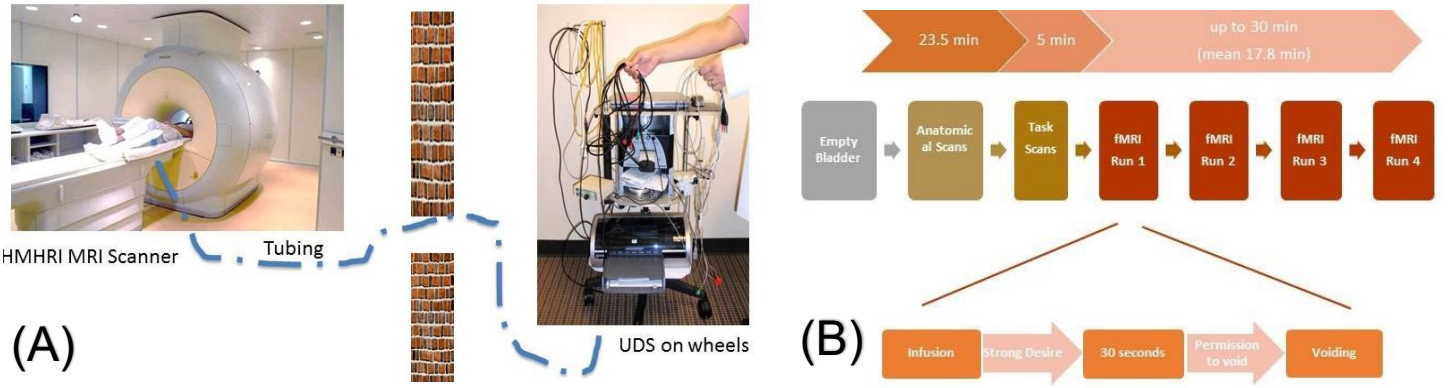


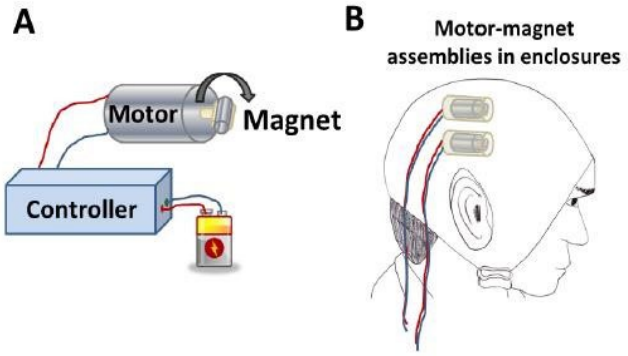
Figure 1. A. Our concurrent UDS and fMRI set up where MRI-compatible bladder and rectal catheters are passed through a small opening in the wall between the control room and the scanner room (Philips Ingenia 3.0T full body scanner with a standard 12-channel head coil). B. Our combined fMRI and UDS testing protocol.

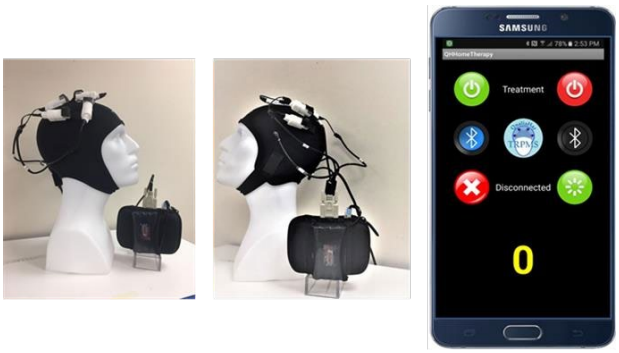
Transcranial Magnetic Stimulation (TMS) and Transcranial Rotating Permanent Magnet Stimulator (TRPMS): Currently, the only neuromodulation modalities available for bladder target the peripheral nerves, including the Sacral Neuromodulator, the Posterior Tibial Nerve Stimulator, and the intradetrusor injection of neurotoxin OnabotulinumtoxinA. Further, they mainly target the storage phase (urinary urgency and incontinence). ***As part of my K12 proposal I have focused on identifying supraspinal changes following onabotulinumtoxinA injection in the bladder using our fMRI/UDS platform in MS patients***.[19] While others have evaluated the brain changes following sacral neuromodulator use for overactive bladder patients.[20,21]

- ***However, to date, there has been no central (brain) neuromodulation for bladder and specifically for the voiding phase.*** It has become prudent to look beyond the bladder in managing neurogenic bladder VD and fMRI/UDS identified supraspinal regions and our proposal offer some hope for potential therapeutic targets.

TMS is a non-invasive centrally acting electromagnetic neuromodulator that is held over the scalp and delivers a rapidly pulsed magnetic field to the cortex to activate neurons, within a limited area, without requiring anesthesia or causing any significant side effects. TMS and repetitive TMS (rTMS) are substantially safe and are widely used for brain mapping and/or to modulate cortical excitability.[22,23] Two small studies have demonstrated the feasibility and efficacy of rTMS in patients with MS (n=10), and Parkinson's disease (n=8) with bladder symptoms. Their findings suggest that TMS improves both the storage and voiding phase, and reduces postvoid residuals of the urine, while appropriately increasing the detrusor pressure at the time of voiding.[24,25] *Interestingly, in three MS patients with DSD, following rTMS, the abnormally high detrusor pressures at the time of voiding were decreased to a more appropriate level, possibly implying the restoration of synergistic voiding with coordinated relaxation of urethral sphincter and the pelvic floor.*[24] In a more recent study, fifty-eight children (ages from 6 to 14) with nocturnal enuresis were randomly assigned to receive anticholinergic medication (oxybutynin), TMS, or placebo TMS. Authors reported improvements in bladder capacity, voiding scores, and enuresis events, seven months following TMS use.[26]

Limitations of TMS and ***Innovation in our proposal****:* Commercialized TMS devices use large coils that restrict their portability and can only be applied to one location of the cortex. ***However, brain control during voiding appears to be dependent on multiple regions and their connectivity including the urethral regions, requiring a transcranial modulator that could safely stimulate/inhibit multiple areas at the same time.*** The neurophysiology and





neuromodulation laboratory at our institution has developed a non-invasive, portable, and *multifocal* brain magnetic modulator, called[27,28] Transcranial Rotating Permanent Magnet Stimulator (TRPMS).

- TRPMS uses small, high field strength permanent magnets rapidly spun by miniature electric motors. It is therefore wearable and portable, and capable of multifocal stimulation.[27] TRPMS will selectively ***induce, modulate, or suppress*** neuronal activity, and also ***modulate the strengths of the functional connections between two or more cerebral cortical areas when they are stimulated simultaneously***, depending on the strength, frequency and pattern of stimulation.[29]

Figure 2. TRPMS cap with microstimulators placed on sites corresponding to left primary motor, right lateral premotor, and right supplementary motor cortex. The smartphone image shows the Android app used to operate the device.

The current prototype operates on a 9 – 12 V battery and can be triggered by a smartphone or tablet app, thereby allowing it to be *potentially used for stimulation treatment at home in the future*.

Flexibility of TRPMS applications: Earlier studies involving repeated stimulation of the left inferior frontal gyrus pars triangularis (IFG) has shown that TRPMS stimulation of this part of Broca's area during encoding of words facilitates word memory. In contrast, chronic repeated stimulation of this area at rest in the absence of word memorization disrupts it.[30] A preliminary open label study done in one chronic ischemic stroke (CIS) patient prior to the start of an ongoing randomized double blind sham treatment-controlled trial, has revealed the following restorative changes: after 2 two-week sessions of treatment, *movement-related fMRI* showed increasing levels

of neural activation of the stimulated intact cortex surrounding the lesion. Marked quantitative improvements were seen in grip strength, lower extremity motor function, and sensation measures on the affected side, as well as gait speed. These changes persisted at the 3-month follow-up time point after two other two-week treatment sessions.[31] Other unpublished studies in healthy adults have shown modulatory effects on perception of body ownership, numerical ability, motor skill learning and functional connectivity of cortical areas.[29]

- ***Therapeutic effects of multifocal TRPMS are currently being studied in pilot clinical trials on developmental stuttering, CIS, and type 1 myotonic dystrophy at our institution.***[32]

Safety profile of TRPMS: Repeated cerebral cortical stimulation with this device is well tolerated with no reported serious adverse events in more than 200 adult human subjects, including patients with chronic ischemic stroke, amyotrophic lateral sclerosis, type 1 myotonic dystrophy, and developmental stuttering in our institution. Electroencephalic recordings in 45 subjects have demonstrated that repeated TRPMS stimulation does not induce seizures or epileptiform changes.

- ***TRPMS has been determined to be a Non-Significant Risk device by the Food and Drug Administration.*** Please see attachments under appendix for this proposal.

Regions of Interest (ROI) from the literature: Earlier neuroimaging studies have identified brain regions directly involved in initiating or continuing voiding in ***healthy*** individuals. These regions include: Precentral Gyrus, Supplementary Motor Area, Dorsolateral Prefrontal Lobe, Inferior Frontal Gyrus (IFG), Cingulate Gyrus, Insula, Hypothalamus, PAG, and Pons (PMC).[8,9,16,33] Although, PAG and PMC are the more apparent regions involved in initiation of voiding and could serve as potential targets for intervention, they are deep and inaccessible with our current technological modalities. Besides, these regions are responsible for other core vital functions such as regulating circulation and breathing wherein modulation would not be safe.

- On the other hand, ***we propose that if we shift our focus to modulate areas of the brain that are more cortically accessible and amendable to modulation, such as areas responsible for urethral sphincter relaxation, we may indirectly improve voiding.*** Table 1 summarizes the currently available cortical brain regions involved in voiding as potential ROIs in healthy, MS and non-neurogenic VD.

MNI	BA	HA	Area	Neuroimaging	Task	Reference
Healthy						
52, 24, 12	45/44	Right	IFG	PET	Voiding	Blok 1998[8]
63, 18, 18	44/45	Right	IFG	fMRI	Initiation of voiding	Mehnert 2015[34]
40, 35, 6	46	Right	IFG	fMRI	Initiation of voiding	**Khavari 2014[16]**
8, -8, 62	6	Right	Medial frontal gyrus	fMRI	PF contraction	Zhang 2005[35]
6, -18, 57 3, -18, 57	6	Right	Medial frontal gyrus	PET	PF contraction	Kuhtz-buschbeck 2005[36]
2, 2, 62	6	Right	Superior frontal gyrus	fMRI	PF contraction	Kuhtz-buschbeck 2011[37]
48, 4, 10	6	Right	IFG	PET	**Voiding (urethral)**	Nour 2000[38]
-44, 1, 28	6	Left	Precentral gyrus	fMRI	Initiation of voiding	**Khavari 2014[16]**
2, -32, 66	4	Right	Superiomedial precentral	PET	Voiding	Blok/Holstege 1997[8,9]
-6, -26, 74	4	Left	Superiomedial precentral	PET	Voiding	Blok/Holstege 1997[8,9]
Non-neurogenic voiding dysfunction						
54, -4, 6	6	Right	Precentral	fMRI	**Urethra**	Fowler 2010[39]
Neurogenic voiding dysfunction (MS)						
-39, 34, 5	45	Left	IFG	fMRI	Initiation of voiding	**Khavari 2017[17]**
38, 33, 6	45	Right	IFG	fMRI	Voiding	**Khavari 2017[17]**

Table 1: MNI: Montreal Neurological Institute coordinates; BA: Brodmann Areas; HA: Hemisphere; PF: Pelvic Floor

In a small group of women with urinary retention, due to urethral sphincter dysfunction, *peripheral nerve* neuromodulation modified the activity of the right postcentral gyrus, precentral/temporal, and inferior temporal regions.[10,39] fMRI studies report that medial prefrontal cortex and supplementary motor areas are the main cortical regions involved in pelvic floor contraction[36,37,40], and could be used to phenotype responders versus non-responders to biofeedback assisted pelvic floor physical therapy in overactive bladder patients.[41]

- Aims 1 and 2 of this proposal characterize specific brain regions that are activated during voiding in MS and these regions ***will be added to the current data (table 1) to individualize the targets used in aim 3 for multi-site transcranial modulation.***

3. APPROACH

Preliminary Data over the past four years

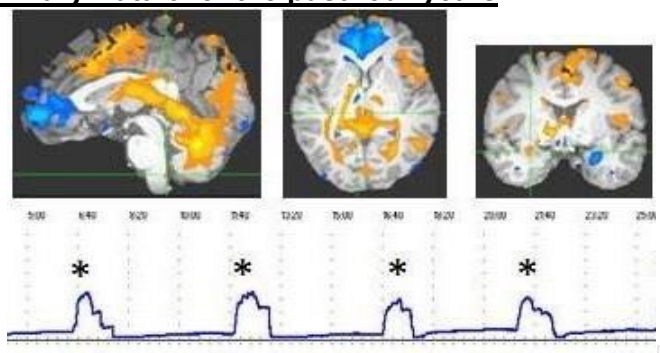


Figure 3. Average fMRI activation maps with concurrent UDS tracings. Asterisk denote "initiation of voiding" in the event-related analysis of the fMRI data in HC.

Healthy Controls (HC): Our established fMRI/UDS platform demonstrated activation of brain regions of cerebellum, thalamus, caudate, lentiform nucleus, *supplementary motor area, postcentral gyrus, left superior frontal gyrus*, anterior and posterior cingulate gyrus and insula, as well as other brain structures such as the pons at the time of "initiation of voiding" HC, figure 3.[16] We also have established an algorithm for visualization and evaluation of neuroimaging data with a three-dimensional augmented reality (AR) device in HC during repetitive voiding.[42] The network under investigation was found to consist of two large sub-networks, one in the frontal lobe and one that connected sensory regions with deeper brain structures, including the PMC. This data will serve as our HC for this proposal.

MS patients: We have evaluated twenty-seven MS patients with neurogenic lower urinary tract dysfunction using our established fMRI/UDS platform.[16] Our analyses described, for the first time, brain regions activated at initiation of voiding in female MS patients (Figure 4).[17]

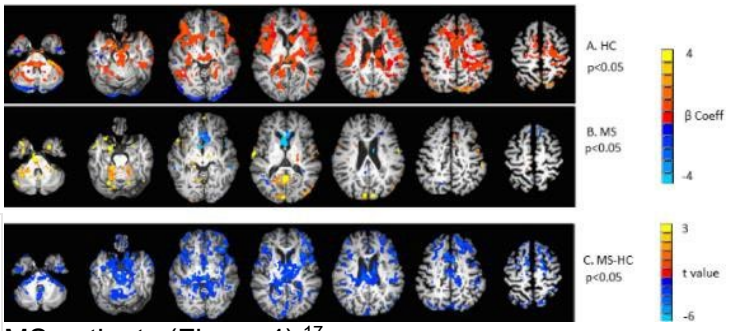
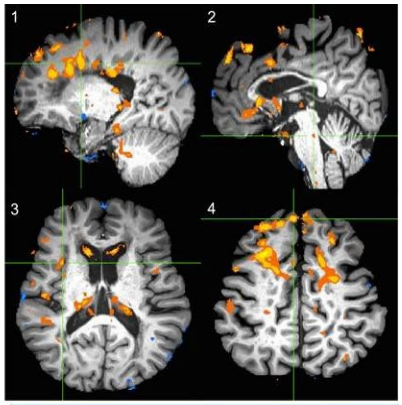


Figure 4. BOLD signals at initiation of voiding. A, HCs B, MS showing higher signals in regions with warmer colors. C, subtraction image between MS and HCs.

MS patients with DSD: Our data on a subgroup analysis of MS patients with DSD (n=4), showed statistically significant greater activation in the right middle frontal gyrus, right medial frontal gyrus, right cingulate gyrus, right caudate nucleus, and brainstem at "initiation of voiding".[17]

Changes in brain following intradetrusor injection of OnabotulinumtoxinA (IDBTX-A): fMRI/UDS results from our recent study examining the impact of IDBTX-A in MS with urinary urgency (N=12) demonstrated that activation increased in specific brain regions associated with the sensation and process of urinary urgency six weeks post therapy (Figure 5). This is the first study of its kind to evaluate the possible sensory effects of IDBTX-A in humans. These preliminary results have been submitted to the 2018 national Urology and Neurourology meeting.

A



B

ROI	R	P	I	p value
Right Cingulate Body	17	4	39	0.0012
Left Posterior Cingulate	-7	-37	22	0.02
Left Anterior Cingulate	-3	24	8	0.0015
Right Prefrontal Cortex	3	51	46	0.0015
Insula	32	12	14	0.0138
Pons Micturition Center	3	-29	-28	0.05
Left Cerebellum	-31	-63	-62	0.001
Left Fusiform Gyrus	-40	-3	-28	0.065
Left Lentiform Nucleus	-17	6	-9	0.026
Right Lentiform Nucleus	18	2	-9	0.026

Figure 5. A. subtraction BOLD activation maps of post minus pre IDBTX-A for the ROIs in sagittal (1 and 2) and horizontal (w and 4) images. 1) Right Cingulate 2) Pons 3) Insula 4) Right Prefrontal Cortex; B. ROI coordinates using MNI and RPI coordinates, and the p values.

OBJECTIVES/ SPECIFIC AIMS/ HYPOTHESES

A priori selected grey matter Regions of Interest for aim 1: Based on our preliminary data and the summary of literature outlined in table 1, we propose the following *a priori* selected ROIs for the ***cortical and deep grey matter and nuclei for aim 1***: Inferior frontal and precental gyrus, thalamus, PAG, and pons. ***A priori selected white matter tracts (WMT) for aim 2:*** Since MS lesions affect the white matter mainly, it is prudent to evaluate the WMT involved in bladder function in this patient population. Two WMTs are particularly important in proper function of the bladder: Anterior thalamic radiation (ATR) and Superior longitudinal fasciculus (SLF)[43,44].

Clinical and UDS data will be used to categorize female MS patients with stable disease into two groups. The standardization of terminology by the International Continence Society does not provide clear definition for VD,[45,46] however we propose the following based on expert opinion. Group 1: MS patients with VD (patients who perform self-catheterization or have a postvoid residual of urine ≥ 20%Maximum Cystometric Capacity); and Group 2: MS patients without VD (patients who void spontaneously and their postvoid residual of urine < 40%% Maximum Cystometric Capacity). Patients in Group 1 will be further subdivided into patients with DSD (Group 1a) versus without DSD (Group 1b). DSD is defined as increased EMG activity ≥ 20% during detrusor contraction (voiding) in the absence of valsalva maneuvers on UDS.[47,48]

We ***hypothesize*** that female MS patients with VD have a distinct pattern of brain activation and connectivity at "initiation of voiding" and targeted cortical modulation may be feasible and lead to improved voiding.

Specific Aim 1: *Activation patterns of the grey matter ROIs are different among female MS subjects with VD, specifically those with DSD.* We will determine the distinct activation patterns by:

a) Assessing Blood Oxygen Level Dependent (BOLD) signal and functional connectivity (FC) patterns in the ROI's at "initiation of voiding" in Groups 1a, 1b, and 2.
b) Comparing BOLD signals and FC patterns in Group 1 versus 2, and specifically Group 1a versus 1b.

Specific Aim 2: *Damage to preselected WMT in female MS patients provides an independent predictive measure for VD.* We will use diffusion tensor imaging and our established algorithm of measurement[42] to:

a) Measure fractional anisotropy (FA) and mean diffusivity (MD) of the ATR and SLF in Groups 1a, 1b, and 2.
b) Assess whether damage to SLF or ATR are associated with voiding dysfunction in our patient population.

Specific Aim 3: *Targeted cortical stimulation in Group 1 causes changes in ROI (identified during specific aim1) that better recapitulate the activation patterns in group 2 or HCs by:*

a) Assessing BOLD and FC activation in the ROIs following individualized TRPMS in patients in Group 1.
b) Evaluating voiding improvement via UDS and validated questionnaires following TRPMS.

c) Identifying baseline clinical/UDS or neuroimaging factors that could predict response to TRPMS.
d) Evaluating EMG changes in the pelvic floor following TRPMS.

EXPERIMENTAL PLAN AND FEASIBILITY

We have completed and recently published a well-powered study, on twenty-seven female MS patients, that evaluated brain response to bladder filling during the bladder *storage phase*.[17] Aims 1 and 2 are retrospective analysis of the *voiding phase* from our extensive and meticulously collected neuroimaging raw data available to us from our prior completed cohort. Aim 3 is a small, pilot feasibility study (n=8).

Study duration: Based on our experience, we anticipate that one year will allow appropriate time for data analysis for Aims 1 and 2. An additional (concurrent) 1-2 years will allow for appropriate patient recruitment, performance of the protocols, and data evaluation for Aim 3.

Endpoints

Primary Endpoint

a) BOLD signal intensity and FC pattern in *a priori selected* ROIs at "initiation of voiding" in MS patients.
b) BOLD and FC pattern changes following TRPMS.

Secondary Endpoints

a) FA and MD of ATR and SLF white matter tracts in Groups 1 and 2.
b) Clinical scores: UDS parameters, urinary symptom scores, surveys at baseline and following TRPMS.
c) BOLD signal characteristics and FC patterns in ROIs in patients with versus without DSD.

Selection and Recruitment of the Subject

Inclusions: Adult female patients with clinically stable MS [Expanded Disability Status Score (EDSS) ≤6.5], with bladder symptoms ≥3 months, will be screened. Patients will be considered to have VD if they have an increased Postvoid Residual (≥ 20% Maximum Cystometric Capacity) or abnormally slow and /or incomplete micturation based on abnormally slow urine flow rates. Patients who perform self-catheterization will be included in the VD category as well.

Patients with active UTI can be treated and subsequently screened for the trial.

Regarding patients with DSD: Appropriately placed and traced perineal surface electrodes used for EMG recordings can be used to determine presence or absence of DSD.[50] There is no clear cutoff or consensus for the amount of EMG activity change during the voiding phase. We will use increased EMG activity by 20% during detrusor contraction (voiding), in the absence of valsalva maneuvers, to determine DSD.[51]

Exclusions: Men, anatomical bladder outlet obstruction (anti-incontinence procedures, urethral strictures, or advanced pelvic organ prolapse). Severe debilitating MS, history of seizures, pregnancy or planning to become pregnant, contraindications to MRI, history of augmentation cystoplasty, presence of other neurological disorders besides MS.

Relevant biological variables (sex): At this point, males are excluded from our evaluation to avoid potential confounding factors by common bladder outlet pathologies secondary to benign or malignant prostatic pathology, primary bladder neck obstruction, and urethral strictures (all common in men). In addition posture during urination (lying flat in the scanner versus sitting or standing) appears to affect voiding and this difference is more noticeable in males versus females, especially when bladder symptoms are present.[52-54] Due to these differences between sexes and the possibility of them being confounding factors at this point we are excluding males.

Subject recruitment: Our Neurourology Clinic where I serve as the clinical director, has three fulltime fellowship trained urologists and is a referral center in Houston. My mentor and chairman Dr. Boone is a nationally recognized clinician in this field. Eligible patients for our study will be screened and recruited from our clinic.

Description of interventions

Subject Evaluations: Each patient will undergo a detailed history and physical examination with the following assessments: Demographic Form, American Urological Association Symptom Score (AUASS), Neurogenic

Bladder Symptom Score (NBSS)[55], MRI Safety Screening Questionnaire, Hospital Anxiety and Depression Scale[56], and Expanded Disability Status Scale[57]. AUASS and NBSS both include questions regarding the voiding phase and are validated in neurogenic patients. Postvoid residual urine, urinalysis, urine culture, and pregnancy (if applicable) will be assessed prior to the MRI scan. A clinical UDS will be performed within 10 years prior to the neuroimaging scan. Consent will be signed during the first visit. High density Eelectromyography (EMG) will be performed at the beginning of the first and the last sessions of TRPMS treatment however this is an optional testing and patients can refuse to participate in the EMG testing Patients from Group 1 who participate in the TRPMS will undergo a repeat fMRI scanning following the completion of the therapy. In addition their symptoms will be assessed with repeat UDS and validated questionnaires.
After their post TRPMS Intervention Fmri visit, subjects will return to the clinic to complete 4 months (+/- 1 month) and 12 months (+/-1 month) follow up visits. At these follow-up visits, they will completing validated questionnaires, uroflow testing and PVR scan.

Simultaneous UDS/fMRI: Double lumen 7 French MRI-compatible catheters are placed in the bladder and rectum. Either 3T or 7 T full body MRI scanner with standard 12 channel head coil is used. Instructions to communicate using right hand signals representing “strong desire to void” and “voiding” are given. In order to keep our noise-to-signal ratio low, all stimulators including any extra visual stimuli and the UDS machine are removed from the MRI room. Filling and voiding cycles are repeated up to 4 times in each patient. If the patient is unable to void, then the bladder will be drained passively.

Transcranial Rotating Permanent Magnet Stimulator (Aim 3 only): We will use the data obtained in Aim 1 to further identify superficial cortical targets for intervention in each patient with voiding dysfunction and we will construct an individualized therapeutic cap to deliver repeated 100 – 500 ms stimuli at 0.02 Hz for 40 min each week day for 2 weeks (based on our preliminary TRPMS data in other neurological disorders)[27,29]. As discussed in the Innovation section of this proposal, TRPMS is safe, precisely programmable, inexpensive, and can modulate ***multiple areas*** of the brain at the same time, making it an ideal modality for our proposal.

Data Collection and Statistical Analysis

Three-dimensional structural images are obtained from a T1-weighted sequence; (sagittal direction, 0.7 in-plane resolution) as well as functional images collected with simultaneous UDS (axial echo-planar, TR = 3,000ms, 4.0mm slice thickness, 3.38mm in-plane resolution). AFNI software will be used for analysis. Structural and functional images will be registered and motion-corrected. Patients with rapid motion (> 4.5mm) will be excluded from analysis. Voxel activation will be identified at “initiation of voiding” which is signaled by patient’s right hand. Significant differentially-activated voxels will be identified under the generalized linear model. Group level analysis will be performed by transforming data into Talairach space, and significantly activated/deactivated voxels will be identified using a Student’s T-test or a non-parametric test if indicated. We will use SPSS (v19.0) to perform statistical analysis of clinical data (i.e. demographic, UDS data). FC analysis will be performed using CONN, a functional connectivity toolbox for MATLAB[58], Version 15a, which utilizes the statistical parametric mapping MATLAB toolbox. fMRI images acquired during the voiding task together with their corresponding anatomical datasets will be processed using the default- Montreal Neurological Institute (MNI) preprocessing option to enable group analysis in MNI space. A region-based connectivity analysis will be performed for each patient group based on ROIs. FC will be quantified by T-values for a p-value < 0.05 (two-sided, FDR-corrected). Diffusion Tensor Imaging (DTI) images will be acquired (32 directions, one B0 image) using the standard MRI pulse sequence available on the Siemens 3Tesla or 7 Tesla MRI scanner. The software packages TackVis (version 0.6.0.1) and the Diffusion Toolkit (version 0.6.3, trackvis.org) will be used to calculate and extract selected white matter tracts of interest. This software also enables calculating FA and MD values for the segmented WMTs.

Power Analysis: fMRI studies suggest that approximately 12 subjects are required to achieve 80% power at the single voxel level for typical activations, while accounting for intra-and inter-subject variability.[59] Most fMRI studies, evaluating bladder function have included 8-12 subjects.[60] For this proposed study, we account for 10% exclusions due to movement artifact and anticipate 13 patients for groups 1 and 2, with total of N=26.

(Recruitment and scanning is already completed for Aims 1 and 2, data analysis is pending funding). Aim 3 is a small pilot feasibility study and we propose N=8.

Limitations of the study and alternative strategies: The primary strength of this study is the simultaneous neuroimaging and UDS platform which includes the voiding or attempt to void phase. However, limitations do exist: voiding dysfunction is heterogeneous and dynamic and variations within studies may exist. Our patient population represents only a subset of a larger and more complex group and may have inter and intra-subject variability. Although patients with MS are generally accustomed to UDS and MRIs, combined UDS/fMRI may create anxiety and non-physiologic state. Furthermore, voiding supine may pose a challenge to many individuals who can void spontaneously while seated. The repetition of the filling and voiding task four times is an attempt to provide a high enough level of signal to evaluate the fMRI data. This provides a rich dataset that can be analyzed to infer information about the brain at initiation of voiding. Additionally, by preselecting our ROIs and WMTs we increase our specificity; however we may miss other important brain centers/pathways.

Direct comparisons between the current TRPMS prototype that we plan to use and a commercially used conventional TMS coil show that the maximum voltage induced in an inductor by the former (12 - 30 V/m) is about 6% of the maximum machine output of the latter (200 - 500 V/m). Although this lower voltage has added advantages of portability, multi-site stimulation capability, and significantly lower side effects such as heat, seizure activity, or headaches, it may raise a concern of not being strong enough to have an effect in our patients. Alternatively we may add to the stimulated targets or consider selecting only one region and use the commercially available TMS for our next trial.

TRANSITION PLAN AND FUTURE DIRECTIONS

Etiology of voiding dysfunction (neurogenic and non-neurogenic) remains unknown. Currently, we are not aware of any study that has evaluated supraspinal centers involved in voiding in MS patients with VD. This project seeks to improve our ability to understand brain control of the bladder, suggest new diagnostic methods, and provide a crucial step in improving the treatment for the morbid and intractable condition of VD. Following the completion of this proposal we would be able to:

- Apply our findings to patients with ***non-neurogenic voiding dysfunction***, such as patients with Fowler's syndrome, where the data concerning the etiology and effective treatments are scarce.[61] Concerning etiology, some investigators believe this is a result of learned behavior in response to pain or injury, such as UTI or trauma. Others theorize that the dyssynergic sphincter exists, and is due to habitual contraction of the pelvic floor (external sphincter) that results in reflexive abnormal muscle contractions. The use of our unique fMRI/UDS platform to target the voiding phase, and the results from this study, will provide an excellent preliminary data to evaluate patients with non-neurogenic voiding dysfunction.
- Apply our findings to patients with ***Underactive Bladder (UAB) or detrusor underactivity***. The National Institute on Aging and the National Institute of Diabetes and Digestive and Kidney Diseases have invited applications to investigate the etiology and consequences of UAB in older persons to identify better diagnosis, evaluation, and treatment options. ***We believe the results of our proposed study could lay the foundation to study supraspinal control in UAB, and potentially create avenues for translational clinical trials.***
- Evaluate effects of individualized TRPMS as a potential therapy for VD in neurogenic or non-neurogenic patients. This new understanding of the cortical regions of the brain related to voiding and how they can be modulated might shift clinical attention from the bladder to more cerebral control, possibly creating further avenues for intervention. Data obtained in this study will provide the scientific rationale for subsequent multicenter, efficacy-based clinical trials and could potentially transform VD.

ETHICAL CONSIDERATIONS AND RESOURCE SHARING PLAN

A similar version of this trial is already approved by our Institutional Review Board and is ongoing as part of my K12 (KURe Program). All subjects will be properly counseled and consented before enrolling in this study. Our informed consent states that participation is completely voluntary and patients can withdraw at any point and this will not affect their relationship with the physician and their treatment course. All staff members involved in the collection of data and handling of patients will have proper privileges and training by our Research Institute and

MRI Core. Before proceeding with fMRI testing, patients will be asked to remove all clothing and items containing metal. All materials used during the fMRI/UDS scans are MRI compatible. Pregnancy tests and urinalysis will exclude patients who are pregnant or have a UTI. No minor or vulnerable individuals will be recruited for the study. If an adverse effect occurs, the principal investigator and appropriate authorities will be informed and proper actions will be taken based on Good Clinical Practice.

Our research sharing plan includes:

- All data and resources developed within the scope of this proposal will be made available to the scientific community. This includes publications (through PubMed Central and/or publication in open-access journals) and raw data if applicable. Our trial will be registered at http://clinicaltrials.gov/.
- Houston Methodist Hospital and Research Institute are committed to the open and timely dissemination of research outcomes. We recognize that promising new methods, technologies, and scientific insights may arise during the course of our research. We are aware of and agree to abide by the principles for sharing research resources as recommended by National Institute of Health (NIH). We will follow NIH recommendations on ***Rigor and Reproducibility***.
- The data generated in this grant will be presented at national and international conferences, including NIH-sponsored meetings and specifically American Urology Association, Society of Urodynamics, Female Pelvic Medicine and Urogenital reconstruction, and International Continence Society. In addition, over the past three years I have presented my work at the annual Urology Program Directors' meeting by NIDDK and I will continue to do so.
- The data and results will be published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the ***digital archive PubMed Central***. The format or presentation of final research data shall be determined at the time such data is generated and in accordance with generally accepted scientific standards. Final progress reports will include information detailing the steps towards implementation of additional data-sharing plans. These manuscripts will be deposited into ***NIH Manuscript Submission system*** as required by the public access policies of NIH funding.
- Any unique research resources generated from this project, as available, will be freely distributed upon request to qualified academic investigators for non-commercial research through Methodist's Material Transfer Agreement
- BBRAIN working group is an international working group focusing on Brain-Bladder connection and includes experts in the field such as Derek Griffiths, Bertil Blok, and Ulrich Mehnert. BBRAIN meets annually and my results have been presented and will continue to be presented within this focused research group. BBRAIN is considering creating a secure international platform for future collaborative and multicenter data analysis studies of which I will be a part.