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Effects of activity dependent plasticity on recovery of bladder and sexual function after human spinal cord injury

Significance:

Approximately 1,275,000 people in the U.S. live with paralysis from spinal cord injury (SCI) [13]. Disabling SCI sequelae include impairments of locomotor, sensory and autonomic functions [1,14]. The U.S. could save an estimated $400 billion on direct and indirect lifetime costs if we can develop therapies to treat SCI. There are currently no available treatments for individuals with chronic SCI. Also, the cost in emotional stress and well-being to the individual and family is demanding.

Bladder Dysfunction in SCI Bladder dysfunction consistently ranks as one of the top disorders drastically affecting quality of life after SCI [1,14]. Urological complications are responsible for most clinical conditions and hospital readmissions [15], and individuals with SCI are eleven times more likely to die from diseases of the urinary system than non-injured individuals. Deficits in urological function after SCI manifest as detrusor hyperreflexia (bladder contractions at low volumes, causing incontinence and smooth muscle hypertrophy), detrusor-sphincter dyssynergia (uncoordinated bladder and external urethral sphincter contractions, causing inefficient emptying and smooth muscle hypertrophy), decreased compliance (unable to store urine under appropriately low pressures) and loss of continence, requiring lifelong management, maintenance, and health care visits **[16]**. Current therapies to improve efficiency of bladder voiding, management and continence after SCI include catheterization, pharmacologic and surgical interventions, functional electrical stimulation, and urethral stents**[17,18]**. Frequent daily catheterization can induce scarring, stricture formation, cystitis and frequent urinary tract infections due to introduction of bacteria into the urethra **[19]**. Pharmacological agents alter internal urethral sphincter tone (α blockers) or relax the detrusor muscle (anticholinergics increase bladder compliance and decrease pressure) but do not treat voluntary voiding. These drugs have side effects like dry mouth and constipation further complicating the issue of fluid restriction to control timely urine evacuation**[17,20]**. Surgeries to reduce high bladder pressures and chronic urinary incontinence include urinary diversion and lower urinary tract reconstruction **[18,21,22]**. Surgery to implant neural control devices to artificially influence voiding circuitry often requires ablation of intact neural tracts. This would not be the case for spinal cord epidural stimulation.

Bowel Dysfunction in SCI A new SCI survey related to bowel (not yet published; data presented by Dr. Bruno Gallo Santacruz of Coloplast at the Neilsen Foundation workshop on Bowel and Bladder Function, March 2017 [23]) indicates 78% consider bowel equal to urinary, 56% hospitalized at least once with bowel problems in past 12 months (68% were emergency admissions – patient report), and there is a link between bowel and other problems (urinary and psychological - 51% with urinary; 31% UTi; 33% depression; 33% anxiety - self-report). Commonly reported secondary complications in bowel function after SCI include: constipation [24-27], fecal incontinence [27,28], fecal impaction [28], diarrhea [2], and difficulty with evacuation [29]. Experiencing disrupted bowel function has been shown to lower quality of life (QOL) for individuals after SCI, not only by being a significant source of morbidity, but also by the life limiting effect of incontinence and fecal accidents which impede participation in many activities of daily life [3,29-31]. The inability to sense and control bowel function makes it necessary to schedule ones' day around bowel programs. Also, many people with SCI experience significant difficulty with defecation and sometimes require between 1-2 hours for completion of their bowel care program [2]. This often leads many SCI individuals to conduct their programs only every other day [32] and may increase the risk of constipation, fecal impaction, colonic and rectal distension, and bouts of autonomic dysreflexia. Investigations of bowel dysfunction after SCI have reported a wide range of incidence. An early 1954 study by Pollock and Finkelman [33] asked patients about bowel complications immediately after injury and found the incidence of bowel complications to be between 28-72% of patients, based on level of injury and primary symptom being fecal retention. A more recent study [2] found that 95% of the people in their study required at least one method (e.g. laxatives, manual digital stimulation) to initiate defecation which is indicative of dysfunction, making it clear that an overwhelming proportion may experience bowel dysfunction post-SCI that requires some intervention. One physiological clinical assessment tool for bowel is anorectal manometry (ARM), which measures contractile waves produced by the smooth muscle as well as recording intra-colonic pressure. Using ARM one can determine the patterns of activity in the colon, resting and contractile pressures of the colon and sphincters, and integrity of the recto-anal inhibitory reflex (inhibition of internal anal sphincter tone to rectal distension). One study found a significant reduction in the motility index and mean amplitude of

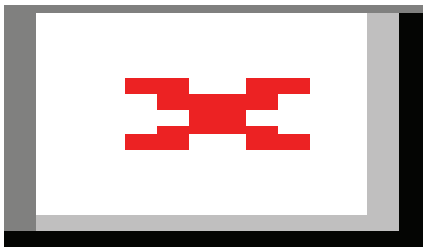
contractions after SCI [34]. Although some ARM studies find that colonic motility measures (amplitude and velocity of peristaltic waves) are reduced after SCI [35], others have found either no resting state difference in colonic motility [36] or increased colonic motility after SCI [37,38]. These differences can be explained by differences in measurement methods and the location of manometric probe placement [39]. It is difficult to rectify findings of increased colonic activity with the clinical presentation of constipation after SCI. Furthermore, after upper motor neuron lesions the unimpeded parasympathetic projections should cause an overall increase in colonic motility but studies more often report reduced motility. It has been noted that even with increased myoelectric activity in the colon, the consequence of that activity may be segmental motility rather than propulsive [40]. If the data from these studies are taken together, there is clearly a dysfunction in colonic motility that is leading to the complications seen in the clinic. Overall, the literature supports that colonic transit is reduced and propulsive reflexes are impaired after SCI. These dynamics lead to a higher likelihood of morbidity and mortality.

Cardiovascular Dysfunction in SCI Cardiovascular complications [41,42] associated with autonomic dysregulation [43,44] are listed as the leading causes of morbidity and mortality in patients with chronic SCI [45-47]. However, there is no clinical standard of care that has been established for individuals with these abnormalities [48]. SCI-induced autonomic dysreflexia (AD) [49], a life-threatening sudden increase in arterial blood pressure that occurring multiple times a day [50], is elicited by either noxious (e.g., pain) and innocuous stimuli (e.g., bladder filling) from below the level of injury [9]. If poorly managed, AD can result in disastrous consequences and even death [51,52]. Urodynamic investigation is the gold standard to assess neurogenic lower urinary tract dysfunction in patients with SCI [53,54], but it may induce AD [55,56]. Our previous work showed that autonomically-mediated cardiovascular deficits can be ameliorated by using activity-based rehabilitative strategies and scES, specifically configured to normalize arterial blood pressure in individuals with SCI-induced cardiovascular deficits [11,57,58]. These studies demonstrate that tonic scES at the lumbar level in individuals with SCI lead to dramatic positive changes in the cardiovascular functional state. Importantly, after 80 sessions of scES stimulation specifically configured to normalize the arterial blood pressure, three SCI individuals with severe autonomic dysfunction have been able to sustain improved autonomic regulation even in the absence of scES during testing [12]. Therefore, our groups recent data strongly suggest that specifically configured scES at the lumbar level can be used therapeutically as part of bladder/bowel management to attenuate associated AD.

Neuromodulation to improve Bladder and Bowel Electrical stimulation of various nerves including the dorsal nerve of the penis (DNP; sensory branch of the pudendal nerve which innervates the urethra in both rats and humans [71-73]) has been used to inhibit and activate bladder reflexes of animals [74-77]. Electrical stimulation has also been designed for therapeutic use with both idiopathic and neurogenic bladder disorders including sacral neuromodulation for SCI [78-83]. Surgery to implant the neural control devices to artificially influence voiding circuitry often require ablation of intact neural tracts, leading to the devastating loss of sexual and bowel function. In recent studies, scES has been shown as an effective alternative less invasive approach for both bladder and bowel which mechanistically may involve indirect activation of the same reflex circuitries [68,84]. Our lab has demonstrated in an animal study funded by Medtronic which we published in 2013 that direct activation of the pudendal reflex circuitry increases storage capacity [85]. Specifically, we found that DNP stimulation increased the voiding cycle during filling at relatively low amplitudes and frequencies, with a lasting after-effect of two minutes on average post-stimulation. This finding is consistent with clinical neuromodulation studies showing that conditional and continuous DNP stimulation significantly increases bladder capacity [86]. The finding is also consistent with a case report by Dr. Graham Creasey who is a consultant on our studies demonstrating suppression of bladder contraction with DNP stimulation (25 Hz frequency) both during in lab cystometry and with at home use [87]. Our stimulus parameters to evoke the response are also consistent with animal studies in other labs showing low frequency DNP stimulation inhibits bladder contractions [74,76,88]. Note that a recent study by Grill and colleagues (2014) has shown that bladder inhibition by pudendal stimulation may occur in part via a spinal GABAergic mechanism [89]. Stimulation of DNP afferents in cats has also been shown to promote bladder contractions. In multiple studies, stimulation frequencies in the 20-40 Hz range evoked bladder contractions, but even lower frequencies (10 Hz) could promote contractions, which was hypothesized to be related to stimulation of multiple pudendal branches and/or afferent fiber diameters [74,90,91].

Note that pudendal afferent discharges with similar ranges of frequencies have been shown to be related to rate of fluid flow along the urethra [92]. In our current ongoing bladder mapping study funded by NIH SPARC, we have used scES to maintain continence (see typical example from one of ten animals in Figure 1 below).

Figure 1. Representative cystometrogram (CMG) and external urethral sphincter (EUS) EMG record during fill/void cycles in a complete spinally transected (T9) female rat. There is suppression of voiding during scES (black bars on "Stim" line) while maintaining low bladder pressure (green) and EUS EMG activity (filtered to remove stimulus artifact) during scES. Note larger void volume (0.612 ml) post-scES. Inter-contraction intervals are 72 sec between contraction 1 and 2, 165 between 2 and 3 (due to scES), and 86 sec between 3 and 4. The scES effects are frequency and intensity dependent (heat maps for data analysis – not shown - are being generated for publication later this year).



Therapeutic treatments for bowel dysfunction have included approaches such as electrical stimulation, which aim to modulate these reflex pathways. Defecation is organized into two phases, storage and evacuation, which are controlled by reflexes involving the spinal cord, enteric nervous system, and brainstem. Sacral nerve stimulation has been shown to improve bowel function by facilitating fecal retention in those with flaccid anal sphincter musculature [93]. In contrast, the Finetech-Brindley system, acting on the anterior sacral roots, has shown improvements in bowel motility in individuals with SCI [94]. Although the clinical indication for this device is to target bladder function, due to an overlap in innervation, stimulation also promotes peristalsis in the distal colon and the rectum, leading to reductions in transit time and increased frequency of defecation. However, a limitation with this device and its application for bowel function is that it is also associated with simultaneous anal sphincter contraction during stimulation, blocking direct emptying. Implantation of this device is also complicated by the fact that it is accompanied by an irreversible posterior rhizotomy, abolishing reflex micturition, defecation, and ejaculation [95]. While each approach does have limitations, they appear to be effective in some individuals for at least one phase of defecation. Our group is currently mapping with scES for bowel function in a rodent SCI model using anorectal manometry and external anal sphincter EMG as the outcome measures. scES may be an effective alternative to enhance motility and propulsion, appropriate storage and timely emptying, thereby enhancing coordinated bowel activity.

Vasoactive Peptides Together, noradrenaline, renin, and atrial natriuretic peptide (ANP) are several key vasoactive hormones that have potential to serve as biomarkers for improved urinary function along with autonomic dysreflexia risk factors. Both noradrenaline and renin promote vasoconstriction and subsequent increased blood pressure through different pathways. Noradrenaline is released upon mental and physiological stress, including bladder and bowel distention [96,97]. Following an increase in blood volume/pressure, ANP is released from the heart to promote an increase in excretion of sodium through urine, and in turn increasing urine volume and bladder distention [98]. Bladder distention has been shown to correlate with increased blood pressure [99]. After SCI, plasma noradrenaline levels and the urinary excretion of noradrenaline are significantly lower in tetraplegic men that able-bodied persons [100] but levels are increased corresponding to increased blood pressure from stimuli such as bladder distention [101,102]. Thus, measurement of noradrenaline is viewed as a reliable index of prevailing sympathetic nervous activity [102]. For renin, baseline levels have been shown to be above normal and to rise more rapidly and to a greater extent upon head-up tilt relative to able-bodied test subjects, supporting the view that renal baroreceptors are important in the control of renin release [103]. Note

that renin is crucial for activation of the renin-angiotensin-aldosterone system, which is activated upon decreased sodium levels detected in the kidney. Renin also plays a direct role in the activation of vasopressin, which causes vasoconstriction (increased blood pressure) and increase in urine output. There is also a decrease in vasopressin after SCI in both clinical [104], and animal studies [105], suggesting that these three specific vasoactive hormones play an important role in autonomic dysreflexia after SCI, specifically in connection with bladder and bowel distention.

Progress Report for Renewal

General Overview of Previous R01. Two cohorts of individuals who sustained a SCI included 3 groups of 10 subjects (30 in total; target of 8 per group re power analysis with 2 for potential loss of data/withdrawal from study). Participants were evaluated before and after receiving either a standardized locomotor training (LT) program, stand only program, or upper extremity (arm crank) exercise program that is provided clinically at Frazier Rehab Institute within the NeuroRecovery Network (NRN) (***Aims 1 and 2***). The second cohort included 10 subjects evaluated before and after receiving scES in combination with various forms of activity-based training that was provided by our research team (n=10; goal of two per year) (***Aim 3***). For Aims 1 and 2 studies, experiments were completed on 29 subjects (one arm crank withdrew due to non-compliance). For Aim 3, experiments have been completed on 10 subjects. Thus, after five years, our enrollment is complete. The data is currently being analyzed from the Year 5 participants (Aim 3 still awaiting one-year follow-up for two persons). Thus, the following report includes a very brief overview of the findings from our two publications to date (PLOS One and Scientific Reports) [10,68] and data from more recent poster presentations (including the American Spinal Injury Association April 2019 meeting), comparing the three forms of activity-based training (LT vs stand vs upper extremity; n of 24 of 30) and summarizing the scES findings to date. Completion of data analysis and preparation of two additional manuscripts is underway in our current extension year.

Previous Specific Aim 1 Accomplishments: A total of 8 subjects (5 males; 3 females) who sustained a SCI (AIS A-D) received 80 daily sessions of LT on a treadmill using body-weight support (one hour per session) or LT plus stand (weight bearing without stepping) training (one hour of each per day, separated by at least 3 hours). Four usual care (non-trained; regular at-home routine) research participants were also enrolled in this study and had the same assessments collected twice, at least 3 months apart. Filling cystometry documented significant increases in bladder capacity, voiding efficiency and detrusor contraction time as well as significant decreases in voiding pressure post-LT training relative to baseline. International data set questionnaires revealed a decrease in the frequency of nocturia and urinary incontinence for several of the research participants. No significant improvement was found for usual care research participants. These results were published January 2018 in PLOS One journal [10]. Although based on a small sample size, these pilot trial results suggest a) that an appropriate level of sensory information provided to the spinal cord, generated through task-specific stepping, can positively benefit the neural circuitries controlling lower urinary tract functions; and b) individual variability in the numerous bladder measures needs to be considered. Both neural and hormonal systems are being explored as possible mechanisms underlying these improvements. The other activity-based training groups were done to determine whether the urologic LT benefits could have been derived just with weight-bearing (standing group) or with exercise in general (non-weight bearing upper extremity group). The urologic LT benefits were not found with just weight-bearing alone (standing group) or with exercise in general (non-weight bearing upper extremity group), although there was an overall trend given the variability in the upper extremity group toward improvements in both bladder capacity and pressure with exercise. A comparison between these groups is provided in Figure 2.

Previous Specific Aim 2 Accomplishments: International data set questionnaires revealed that the SCI research participants exhibited marked deficits in sexual function, low levels of sexual satisfaction, and profound bowel dysfunction upon entering the study. Note that modest ongoing engagement in sexual activity around the time of the study limited questionnaire data to element domains regarding primarily overall satisfaction and desire. After step or step plus stand training, a significant decrease in time required for defecation and a significant increase in sexual desire was found post-training. These results were also published in PLOS One journal [10]. The data for the stand and arm crank groups to date are in the process of being evaluated. Interpretation of the data is awaiting analysis of the data from the last few participants.

Previous Specific Aim 3 Accomplishments: A Medtronic Specify 5-6-5 (16-electrode array) epidural device at vertebral level T11-L1 over spinal cord segments L1 to S1 along midline was used for scES. A summary of the findings for bladder function is provided in Figure 3. Activity based therapies in combination with scES resulted in improvements in bladder outcomes. These modest effects were from scES configurations targeting other functions (stand, step, voluntary movement, arterial blood pressure). Initial testing of scES specifically targeting the neural circuitry for bladder function (lower lumbosacral regions with electrodes at the bottom of the scES array) improved overall voiding efficiency values [68]. Current bladder mapping studies are going to allow for the optimization of stimulation parameters to enhance both the storage and voiding phases of micturition. For this renewal, additional scES mapping goals include ability to modulate both CV and bladder parameters simultaneously to minimize AD and bladder pressure associated with over-distention, thereby extending time between catheterizations, thus improving flexibility in daily activities and ultimately quality of life.

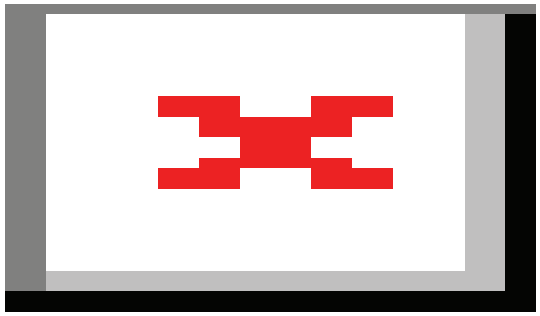


Figure 2. A comparison of pre- and post-training effects on bladder function between the three activity-based training groups of study participants. (A) Whereas capacity increased significantly with locomotor training (LT), standing (weight-bearing) alone had the opposite effect (small but significant decrease) and was significantly different in terms of % change relative to LT. Upper extremity training approached significance with a trend toward improvement in capacity. (B) The maximum intravesical pressure during filling was significantly reduced post-training for only the LT group, although the upper extremity group was approaching significance. (C) Voiding efficiency was not different across the three activity-based training groups.

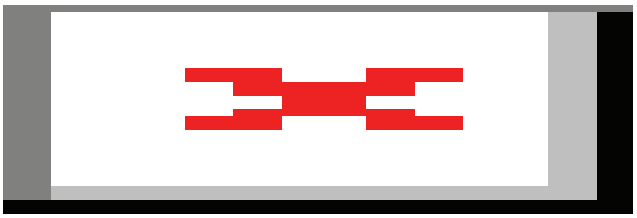


Figure 3. Effects of scES in combination with task-specific training on bladder outcomes. *Note: scES was not used during cystometry.* A) Bladder capacity (volume voided or leaked + residual volume) in the LT group was assessed prior to scES implant surgery (pre-training), post-implant post-LT training with Step-scES (80 sessions) and at the 1yr follow-up point (Stand-scES). Note participant A60 has not reached the 1yr time point. LT combined with scES increased capacity for 4/5 participants compared to pre-training values. B) Bladder capacity in the cardiovascular (CV) group was assessed prior to CV training, post implant post-CV-scES (80 sessions), post-voluntary motor (VM)-scES, and post stand-scES training (80 sessions). All participants had increased bladder capacity compared to pre-training values with each task-specific intervention in this group. C) Maximum detrusor pressure (MDP) values for both the training groups are provided at pre- and post-training time points following epidural implant surgery. Activity-based training in combination with scES decreases both mean and median MDP values post-training towards normative ranges (<40 cmH_2O[5]) in the LT group (n=5) (Median: 65 cmH_2O vs 24 cmH_2O; Mean:56.4 ± 35.7cmH_2O vs 28 ± 18.2 cmH_2O). Although median and mean MDP values decrease post-CV-scES training (n=3), they do not fall within normal limits. Although there are many key important findings from the first R01 that need follow-up (including those related to polyuria and sexual dysfunction), there are 3 critical areas that we have prioritized for our subsequent studies. The first relates to modest effects of scES optimized for step, stand, voluntary movement and cardiovascular function on urogenital function and thus the need to target the bladder circuitries directly (re our initial data published in Scientific Reports [68]). Thus, scES that specifically targets the bladder network is being pursued for bladder pressure as part of Aims 2 and 3 and we are currently mapping for storage and voiding functions as part of an NIH SPARC-funded initiative in both humans and in a pre-clinical rodent model in parallel (no overlap with current proposal). The second major crucial pursuit, which has not been well studied, relates to the very unexpected finding that AD triggered with bladder filling is such a key limiting factor for capacity (plus our questionnaires documented how many participants use the sensations as an indicator of time for toileting, which is a very unsafe practice and a major health concern). The third key aspect relates to a very understudied area of SCI, bowel dysfunction. Our findings from bowel questionnaires indicate a high incidence of AD-related symptoms and thus the need to control the triggering of AD during evacuation. The current study is well positioned to address all these issues. The information gained regarding how multiple systems interact with one another will have an immediate impact on the field.

Innovation:
Examining inter-system interactions and their functional impact is highly innovative as the tendency is to remain within functional silos which is not how the body works in daily living. Our approach to AD and the assessment of urinary biomarkers is novel and innovative. The control of multiple systems simultaneously with a single neuromodulation device is also quite unique and highly innovative. The information generated from SA1 is expected to have an immediate impact on the field in terms of shedding light on the frequency and potential detrimental effects of recurring AD on the SCI population with respect to daily triggers from bladder and bowel. Long-range, SA2 and 3 of this study will provide strong preliminary evidence for the therapeutic benefits of scES as a single neuromodulatory intersystem device capable of regulating multiple interacting bodily functions simultaneously and maintaining homeostasis that will benefit overall health, lower long-term health-care costs, and improve quality of life. Our innovative approach and novel application of this Medtronic Specify 5-6-5 (16-electrode array) epidural device will allow us to determine specific types of scES needed for maintaining low pressure during bladder filling and bowel evacuation and CV regulation, which will lay the groundwork for expedient translation of this promising technique to larger numbers of individuals with SCI who currently have few effective treatment options. Thus, the current proposed study will increase our understanding of human lumbosacral spinal networks and guide the use of innovative therapeutic strategies that would be immediately available to not just to improve motor output during standing and walking but to ameliorate autonomic dysregulation and thus improve bladder and bowel function and thus quality of life in individuals after SCI. Importantly, the discovery-driven insights of how scES affects autonomic functions not only will lead to imminent treatments for those suffering with SCI but may influence the treatment of other neurological disorders such as multiple sclerosis, Parkinson's, and stroke, and stimulate investigations on other systems such as pulmonary dysfunctions.

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Approach:

a. Study Design

Specific Aim 1 (SA1; n=60): The purpose of this aim is to systematically measure symptomatic indices of autonomic nervous system activation and corresponding CV changes in persons with SCI's during bladder filling and bowel stimulation. Inclusion criteria are male and female adults, AIS A to D, and presence of neurogenic bladder and bowel dysfunction. Exclusion criteria is Botox injections of the bladder and/or bladder augmentation surgery and/or colostomy. The first assessments for SA1 will be done in a controlled lab setting and include a total of 60 participants (large number to account for likely variability amongst the SCI population). Two testing sessions per participant will occur, one involving bladder filling (cystometry - CMG; 90-minute session) and the other bowel distention (anorectal manometry - ARM; 45-minute session). Data will be collected using our acquisition software system (see example for bladder in Figure 4 and further details of symptom entry for AD in Figure 5 below). The second part of SA1 will be done on a minimum of 20 of the 60 participants who demonstrate evidence of AD (20 for bladder; 20 for bowel – same individual can participate in both) and use intermittent catheterization as their method of emptying. Up to eight non-consecutive 24-hour at-home periods over a months' time per participant will be done for bladder and bowel using a mobile application program (APP) for data entry (iUFlow voiding diary APP; PoopTrack APP) and a wearable non-invasive CV monitoring system for physiological recordings of blood pressure and heart rate (details in Methods below). Participants who qualify will be recruited soon after the completion of the first part until the enrollment numbers are met for the second part. Note that a participant with elevated blood pressure to both the bladder and bowel can be recruited to undergo at home monitoring for both (thus, Part 2 of Aim 1 could have a range of 20 up to 40 participants by the end of the study).

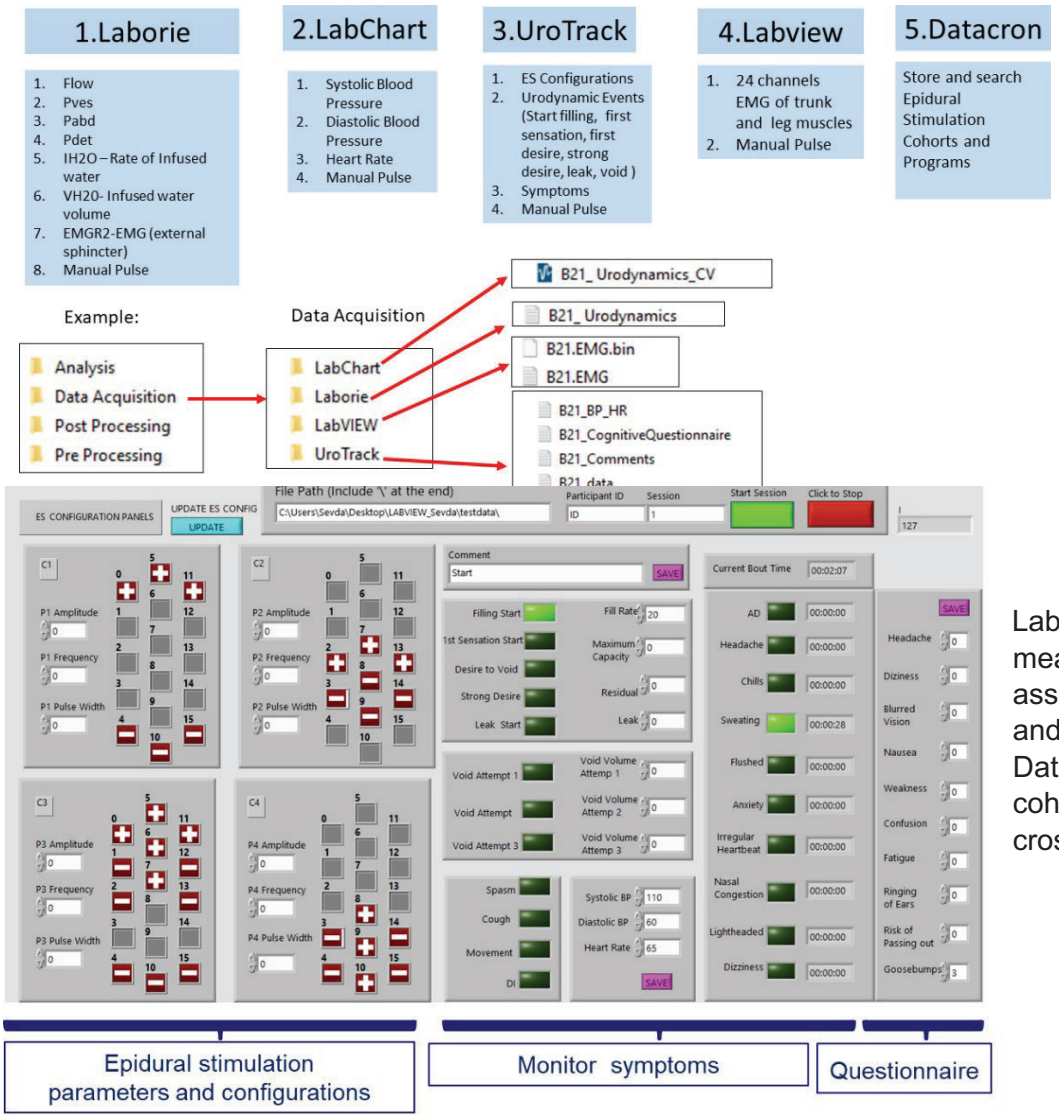

Figure 4: Data system demonstrating simultaneous acquisition of intersystem parameters. The integrated programs include Laborie (shown for bladder – e.g. #4 P det - detrusor pressure; same system used for anorectal manometry), LabChart (for cardiovascular parameters), UroTrack (entry of autonomic dysreflexia related symptoms, bladder or bowel sensations, scES configuration if applicable), Labview (EMG muscle activation measured in parallel – routine assessment during our bladder and bowel evaluations) and Datacron (storage of scES cohorts for database searches cross studies).

Figure 5: Urotrack program used in our Human Bladder and Bowel Core Lab demonstrating simultaneous acquisition of intersystem parameters. For example, under Monitor Symptoms, if a Participant reports onset of a headache at 324 cc fill volume during cystometry, the green button next to headache will be clicked and automatically time stamped and aligned with values acquired in the Laborie software for bladder pressure and the volume (324 cc in this case). CV parameters (systolic, diastolic, heart rate) will also be recorded simultaneously (see lower middle panel). Questionnaire involves symptom ratings of severity on a 1 to 10 ordinal scale, where 1 is very mild and 10 is intolerable.

Anticipated Results: Rapid blood pressure elevations with discernible AD symptoms are expected in the lab portion of SA1 with the at-home portion demonstrating occurrences multiple times a day in association with the timing of bladder catheterization and bowel program. Based upon fascinating preliminary data, occurrences of AD are expected to be much more common for bladder than bowel, and more common in those with lesions T5 and above. Preliminary data from CMG and ARM assessments for ongoing clinical trials by our group include data from 23 research participants (70% male; 30% female) with neurological level of injury ranging from C2 to T2. AIS evaluations indicated that 74% of this group were A's and 26% B's. In total, 91.3% had AD during bladder filling of whom 62% used intermittent catheterization as their method of emptying (remaining 38% had indwelling suprapubic catheters). Surprisingly, only 26.1% had AD triggered by balloon inflation in the rectum during ARM assessments. It is possible that this type of activation is an under-estimate as it does not replicate distention created by stool, which emphasizes the importance of the at-home measurements that are proposed for the second part of SA1. In addition, vasoactive hormones are expected to differ from those having regular daily occurrences of AD relative to those who do not have daily re-occurring AD symptoms. For example, after SCI, plasma and urinary levels of norepinephrine are known to be low whereas renin high [106], resulting in low resting systolic and diastolic arterial pressures. Preliminary feasibility data for measurement of urinary norepinephrine and renin in 12 SCI research participants (selected at random; all AIS A & B's with lesions T5 and above) with samples obtained during a screening urodynamics assessment indicate low urine levels of norepinephrine in all 12 (Abnova NE ELISA kit with published normative range of 58.6-260 ng/ml) and high urinary renin in 7 of 12 (58.3%) based upon RnDSystems normal sample mean value of 60.4 pg/ml with a range from non-detectable to 96.7 pg/ml (5 of 12 within this range in our group tested).

Potential Problems and Pitfalls: Overall, based upon our prior experience and expertise in the areas of bladder and bowel, we do not anticipate any major problems with SA1. Noteworthy is that given our preliminary data showing less frequent occurrence of AD triggered by bowel, recruitment of participants having AD to both bladder and bowel for at-home assessments in the second part of the aim may prove challenging. However, as stated in the previous section, most have AD to bladder and it is possible that ARM procedures do not mimic stimulation (air filled balloon versus solid stool) in the same way. Moving forward and after consultation with Laborie representatives, we are switching to water-filled versus air-filled balloon distension. Even if this does not make a difference in terms of triggering AD for bowel in the lab setting, the at-home bowel portion will likely still provide informative results for translation. Also, the at-home portion will be limited to those using intermittent catheterization as their method of emptying. This criterion is necessary as indwelling catheters are continuously draining and AD only gets triggered if there is an occasional issue with the catheter (may kink, for example). One further potential problem is the use of urine (easy to obtain regular samples) versus plasma for detecting changes in vasoactive hormones. Although we have demonstrated feasibility in humans (NE, renin) and rats (NE, atrial natriuretic peptides [105]), if we encounter detection problems, we will collect plasma during in-lab assessments pre/post CMG and ARM (routine at Frazier Rehab as all human study participants have plasma samples drawn – part of screening standard operating procedure).

b. Methods.

Diaries: A voiding diary with frequency/volume of each void and/or catheterization will be generated throughout the study by using the iUFlow App. The number of voids, voided volume, and distribution between daytime and night-time will be obtained. In addition, urine samples, obtained when the bladder is emptied prior to filling cystometry (Aim 1) or prior to lab testing with scES (Aim 2) will be tested for the presence of blood,

urobilinogen, glucose, ketones, bilirubin, protein, nitrites, leukocytes, pH, and specific gravity using Multistix Pro 10LS reagent strips for urinalysis (Siemens) and a Clinitek Status+ Urine Chemistry Analyzer (Siemens). For bowel function, the Pooptrack APP diary will be used. The APP documents frequency, time to complete bowel program, and stool consistency and color. The stool section is based upon a 7-point scale derived from the Bristol Stool Chart [108], which is used to monitor alterations in intestinal functioning.

Urodynamics/Cystometry: Urodynamic study will include an initial measurement of the urinary flow (uroflow: voided volume, maximum flow rate, time to maximum flow rate and total voiding time). This will be followed by cystometry evaluation using standard procedures [109-111] per International Urodynamic Data Set (measuring bladder pressure during filling, possible uninhibited bladder contraction and maximum cystometric capacity), with determination of the leak point pressure and post-void residual volume when voiding is possible at the end of the study when a second uroflow can be obtained. Details can be found in our two published articles [10,68]. As with all our studies, blood pressure and heart rate are monitored continuously in all subjects during cystometry, and the volume of water and bladder pressure will be recorded, including identification of uninhibited non-voiding bladder contractions. Detrusor-sphincter dyssynergia will be evaluated and classified according to the Blaivas classification [112,113].

Anorectal Manometry (ARM): The Aquarius® LT system by Laborie Medical Technologies (Williston, VT, USA) will be used to provide a comprehensive assessment of pressure activity in the rectum and anal sphincter region together with an assessment of rectal sensation, rectoanal reflexes and rectal compliance [114,115]. In our center, we have successfully conducted the ARM procedure in more than 30 participants this year, which has helped us develop a more comprehensive picture of anorectal dysfunction after SCI. Procedurally, with the participant is in the left lateral decubitus position, a small, flexible tube, about the size of a thermometer, with a balloon at the end is inserted into the rectum. The participant is asked to squeeze, relax, and push at various time points during the assessment while internal anal sphincter pressure is measured in 4-quadrants. During the assessment, the small balloon attached to the catheter is inflated in the rectum to assess normal reflex pathways. Anal sphincter electromyography (EMG), evaluates the nerve supply to the anal muscle while the participant is at rest, and during squeeze and push maneuvers. The anal sphincter muscle electrical activity is recorded and confirms the proper muscle contractions during squeezing and muscle relaxation during pushing. A measurement of the time it takes to expel the balloon from the rectum is also conducted. During the ARM assessment, continuous beat-to-beat blood pressure will be recorded via the Finapres Medical Systems unit.

Common Data Elements - International SCI Data Set Questionnaires: A private room will be used to complete the questionnaires. The International Lower Urinary Tract Function and Urodynamic Basic Spinal Cord Injury Data Sets [109,116] will be used to assess bladder function as previously described[10]. The International SCI Bowel Function Basic Data Set (Version 2.0) [117] incorporates the Neurogenic Bowel Score (shown to be a valid measure of bowel dysfunction in those with SCI [118]) and collects data on 16 items, including defecation method and bowel-care procedures, average time required for defecation, frequency of defecation, uneasiness, headache or perspiration during defecation, digital stimulation or evacuation of the anorectum, frequency of fecal incontinence, flatus incontinence, and abdominal pain.

Blood Pressure Monitoring: Continuous arterial blood pressure may be acquired during Urodynamics from a finger cuff placed around the left middle or index finger or thumb (Portapres-2; Finapres Medical Systems). The left hand will be placed in an arm sling and kept at the level of the heart throughout the study. Manual arterial

blood pressure measurements will be taken periodically with a digital blood pressure measurement device for calibration purposes. A three-lead ECG (ML132, AD Instruments) may also be placed for ECG monitoring.

Urinary Biomarkers: Urine samples will be obtained using a sterile 12 French straight catheter that is inserted through the urethra for cystometry. The bladder is always emptied prior to filling for cystometry recordings, so once the volume is measured, urine samples will be placed in sterile storage vials and stored at 4C for less than 3 hours. Procedures will follow established methods used by us and multiple groups. Briefly, samples will be centrifuged (3,000 rpm for 10 minutes) and 1 ml supernatant aliquoted into 1.5 ml tubes, with some used to determine creatinine concentration. Creatinine levels will be measured using a Siemens Clinitek Status+ analyzer and Siemens Multistix Pro 10LS testing strips for urinalysis. In addition to creatinine, urine samples will be tested for the presence of blood, urobilinogen, glucose, ketones, bilirubin, protein, nitrites, leukocytes, pH, and specific gravity. The supernatant aliquots will be frozen at -80 C for later processing. Urinary levels of vasoactive hormones, including noradrenaline, renin, vasopressin and atrial natriuretic peptide will be determined on thawed samples using the Emax ImmunoAssay System with specific ELISA kit per manufacturer instructions [105].

We may record audio during these tests for analysis purposes. Due to the intimate nature of some tests, embedded signatures within the study consent(s) will acknowledge and confirm use of audio recordings.

Statistical plan:
Sample size calculation and Power Analysis: Preliminary data on 23 participants who completed both urodynamics and anorectal manometry (ARM) indicated most (21/23; 91.3%) experienced AD during cystometry and 26% during ARM. In aim 1, to characterize and document AD associated with bladder filling and bowel stimulation in SCI, a large enough sample size needs to be enrolled to represent all the different variabilities of SCI and also large enough to provide enough power to detect meaningful differences for the different hypotheses (refer back to Aims). Based on our aim to characterize and document AD associated with bladder filling and bowel stimulation in SCI, we need to enroll a sample size large enough to represent all the different variabilities of SCI (especially level of injury which will be the focus of some hypotheses) and also large enough to provide enough power to detect meaningful differences for hypothesis 1.1, 1.2 and 1.5. Based on a published online report (https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%20-%202018.pdf), individuals with tetraplegia (more likely to correspond to injuries above T5) make up about 60% of the SCI

population. Power analysis reveals a sample size of 20 participants per level group (above and below T5) is needed to have 80% to detect a Cohen's h effect size of 1.2 (classified as very large [119,120] corresponding to a 40% difference in proportions of AD) using a 2-sided Chi-square test with a significance level of 0.05. Given that the 20 participants make up about 40% of the population (proportion of injuries below T5), we need at least 50 participants in total. To account for potential loss of data (due to loss to follow-up or other reasons), we will enroll 20% more participants. Thus, a sample size of 60 will be needed for first part of SA1. The sample size of 20 participants T5 and above will also provide over 80% power to detect meaningful results for the at home portion of SA1

Statistical analysis: We will analyze the outcomes using the McNemar test for dependent binary variables (Hypotheses 1.1 and 3.2), the Chi-square test for independent binary data (Hypothesis 1.2), the 1-sample test (Hypothesis 1.4), the paired t-test for dependent continuous variables (Hypothesis 3.1) and the Pearson correlation (Hypothesis 3.3). If the tests assumptions are not satisfied, we will use non-parametric equivalents. If the sample is heterogenous in characteristics or the groups are statistically different in characteristics (for aims where comparisons are performed), multivariable regressions models will be used for independent outcomes and multivariable regression mixed models for dependent outcomes.

Timeline and Deliverables: See **Section 2.7** of Study Record Sections per new NIH guidelines (after 1/25/19).

Data Sharing

This study shares matching assessment procedures with IRB#'s 07.0224, 17.0204, 14.0062, 16.0179, and 17.1024. A complete waiver will be utilized for the sharing of data among these studies collected from matching assessments. Participant demographics, specifically those requested by the National Institute of Health sponsor, will be collected for this study using the IRBs listed in the complete waiver.
Our program is a highly collaborative center addressing the myriad of consequences of those with spinal cord injury and by integrating findings among faculty we have been able to understand many mechanisms that would not otherwise be possible. In addition, due to the unique nature of the epidural stimulation implant, all research participants have chosen to keep the stimulator after the study has been completed, so we follow research participants for many years (to date one individual has been followed for a decade). In some cases, the valuable utilization of data across studies is recognized long after the initial study. The complete waiver would be used to gain access to de-identified data from previous studies.
The spinal cord injury field is interested in the long-term effects of neuromodulation on neuromuscular function, health and quality of life and as additional studies become funded, participants may choose to enroll, and so we have strategically utilized full waivers as these studies emerge. The longitudinal data we can acquire in our cores, as in this Neurophysiology Core, and across studies has been of tremendous value both scientifically and clinically. The assessment procedures used to acquire the data accessed via the complete waiver, will match the data assessment procedures and complement the specific aims in this study.

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