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Potts B A[1], Degoski D J[2], Brooks J M[2], Peterson A C[1], Nelson D E[3], Brink T[3], Fraser M O[4]
1. *Duke University Medical Center,* ***2.*** *Institute for Medical Research,* ***3.*** *Medtronic, Inc.,* ***4.*** *Duke University and Durham Veterans Affairs Medical Centers*

DIFFERENTIAL RESPONSIVENESS TO SACRAL NEUROSTIMULATION ACROSS THE BLADDER FILLING CYCLE IN RODENTS: LATER-PHASE IS MORE EFFECTIVE FOR INCREASING BLADDER CAPACITY THAN EARLIER-PHASE STIMULATION

Hypothesis / aims of study
Sacral neurostimulation (SNS) has most commonly been used as a continuous treatment for urge incontinence, but preclinical and clinical evidence suggest that non-continuous or discrete stimulation periods may also be efficacious. We utilized our rat model to investigate whether continuous SNS is required for increasing bladder capacity or if SNS temporally targeted to specific phases of the bladder filling cycle (e.g. immediately post−void, mid-bladder fill, or immediately prior to a void event) show similar responses.

Study design, materials and methods
Urethane anesthetized female Sprague−Dawley rats (n=24) were implanted with jugular and transvesical bladder catheters. The L6/S1 nerve trunks were isolated bilaterally and two fine wire electrodes were placed on each exposed nerve. Electrodes were electrically insulated with parafilm and mineral oil. The wounds were closed with suture.

Bladder catheters were connected to infusion pumps and pressure transducers via stopcocks. True bladder capacity (TBC) was determined using stable single−fill cystometrograms following control continuous cystometry (0.1 ml/min) and prior to every stimulation period. In an initial experimental series, we tested the responses to SNS durations that were calculated to cover the initial 25%, 50%, 75%, and 100% of the control filling cycle duration (n=10). For this test, all stimulations were initiated at the start of bladder filling. In a second series of experiments, we measured responses to SNS over 25% or 50% of the bladder fill cycle, but initiated SNS to coincide with 0, 25, 50 or 75% of the control filling cycle (for the 25% duration) or beginning at 0 or 50% of the control filling cycle (for the 50% duration). For this test the 25% fills were randomly delivered. Data were analysed using the Friedman Test and Dunn's Multiple Comparisons Test.

Results
In the first set of experiments, which tested the duration of SNS initiated at fill onset, we observed significant increases in TBC only when SNS was applied for 75% or 100% of the fill cycle duration (30 and 35% increases over controls, resp., $p<0.05$). For the second set of experiments that tested the timing of equal durations (25% and 50%) across fill cycle phases, we observed significant increases in TBC only to SNS delivered beginning at 75% of the control filling cycle duration (for the 25% duration) and beginning at 50% the control filling cycle duration (for the 50% duration; 32 and 43%, resp., $p<0.001$). Pre−SNS baseline control values did not change in any systematic fashion in either series.

Interpretation of results
These data demonstrate that bladder filling phases measured from the onset of bladder filling or fill-state can significantly impact the responsiveness to SNS in rodents. Stimulation timed to occur within the latter phases of bladder filling (e.g. the final 25 or 50% of the bladder fill cycle) appear most important for increasing bladder capacity.

Concluding message
A clinical strategy taking advantage of this principle may improve battery life and reduce frequency of reoperation for battery replacement. The results also suggest important physiological differences among the different phases of bladder filling that should be further explored. Temporal or physiological targeting of therapies to these most sensitive phases of bladder filling may allow improved efficacy or reduced side effects for therapies.

Disclosures
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