

Improving Sacral Neuromodulation for Lower Urinary Tract and Bowel Dysfunction

Citation for published version (APA):

Douven, P. G. H. (2022). *Improving Sacral Neuromodulation for Lower Urinary Tract and Bowel Dysfunction: A Translational and Multidisciplinary Approach*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20220614pd>

Document status and date:

Published: 01/01/2022

DOI:

[10.26481/dis.20220614pd](https://doi.org/10.26481/dis.20220614pd)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Impact Paragraph

Appendix

Appendix

Lower urinary tract and bowel dysfunction (i.e. urinary incontinence, voiding dysfunction, faecal incontinence and constipation) is a significant burden for patients that become housebound with often desolation as a consequence. Sacral neuromodulation (SNM) can be a good therapy for these patients to reduce symptoms and return into society. Success rates for SNM in lower urinary tract and bowel dysfunction usually range from 50-80% for up to five years after implantation and are dependent on inter-individual variety and indication. Nevertheless, this leaves 20-50% of patients with no or a suboptimal treatment outcome. In addition, loss of efficacy is noted in 75-88% of patients overtime and only 40-75% of patients completely recover and achieve complete continence. Over the years, small hardware changes in SNM technology occurred, which resulted in a decrease in the occurrence of side effects. Interestingly, and important in view of the studies performed in this thesis, SNM stimulation parameters used for the treatment of lower urinary tract or bowel dysfunction have not changed significantly over time. In this thesis, we aimed to further facilitate SNM research by establishing two animal models of lower urinary tract dysfunction (LUTD) and faecal incontinence (FI) as well as gain more insights into alternative SNM stimulation paradigms.

In order to study the efficacy and underlying mechanisms of action of lower urinary tract and bowel dysfunction and SNM, good, reproducible preclinical animal models are required. To this end, we established two animal models for lower urinary tract dysfunction (LUTD) and faecal incontinence (FI), respectively. To our knowledge, we were the first to measure bladder volume in awake rats by means of ultrasound imaging for a period of 4 weeks in an animal model of LUTD. Additionally, using an animal model of FI (the vaginal distention or VD model), we showed for the first time that these animals develop FI as measured by defecation behaviour. These advancements in two commonly adopted models for LUTD and FI will now allow for studies to be conducted in order to better understand the mechanisms underlying LUTD and FI. By gaining more insight into the mechanisms that underlie LUTD and FI, new targets for intervention can be explored and developed in future research. Furthermore, by developing adequate, reproducible animal models for LUTD and FI, the effect and

mechanisms of action of pharmacological and neuromodulatory therapies such as SNM can not only be properly tested, but also implemented into the clinic.

Based on two literature reviews (one preclinical and one clinical review), we observed that the parameter space of SNM (“settings of the stimulation”) were hardly explored, especially in the clinical setting (e.g. only frequencies lower than 50 Hz were used). Nevertheless, first preclinical studies have shown that the implementation of high frequency protocols for SNM might benefit voiding dysfunction in preclinical animal models. In contrast, adjacent neuromodulation fields such as neuromodulation studies in the field of pain more often deploy such novel stimulation waveforms, which bear the potential to benefit patients that are refractory to conventional therapies. As the use of bursting paradigms has provided compelling results in refractory pain patients, we performed a pilot study using SNM with Burst patterns at different interburst frequencies in patients with LUTD. Under general anaesthesia, we found that Burst SNM, but not conventional SNM (Con-SNM), increased bladder pressure, especially at lower Burst SNM frequencies. Additionally, also urethral pressure was higher with Burst SNM as compared to Con-SNM. These results suggest that at least some differences exist in terms of fundamental responses to the Burst SNM waveforms as compared to Con-SNM, which may provide a platform for future studies on Burst SNM in order to optimize clinical outcomes. In the end, the results of this academic thesis will aid in improving SNM therapy for lower urinary tract and bowel dysfunction in patients and better understand its underlying mechanisms of action. New SNM stimulation paradigms developed using the here described models may allow for more disease specific and personalized therapies in patients.