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Lower urinary tract sensory assessments in patients with neurogenic lower urinary tract dysfunction undergoing sacral neuromodulation

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ABSTRACT

Objective: To evaluate the feasibility and outcomes of lower urinary tract electrical sensory assessment (LUTESA) in patients with neurogenic lower urinary tract dysfunction (NLUTD) undergoing sacral neuromodulation (SNM).
Methods: Sensory evoked potentials (SEPs), current perception (CPT) and pain (PT) thresholds were assessed using repetitive electrical stimulation at four different LUT locations in 46 patients (24 female) with refractory NLUTD before and after SNM testing. Group comparisons were performed between patients with predominant storage and those with predominant voiding symptoms, with additional analysis based on clinical response to SNM (responders: ≥50 % improvement in urological symptoms).
Results: SEP analysis revealed a prominent N1 component, with largest amplitudes for bladder dome stimulation. Descriptive analyses revealed differences between patients with voiding and storage symptoms for CPTs, PTs and SEPs. Pre/post SNM there were some changes in the N1 topography and in the transition phase (following the N1 component). SNM responders exhibited lower sensory thresholds and more distinct classical SEP waveforms already at baseline, than non-responders.
Conclusions: LUTESA is feasible with elicitable SEPs pre/post SNM and differential manifestations for type of NLUTD. Further research on the predictive value of LUTESA for SNM success is warranted.
Significance: LUTESA is feasible in patients with NLUTD and may help to better characterize patients for tailored treatment options.

1. Introduction

Sacral neuromodulation (SNM) is an established treatment for urinary and bowel symptoms (Assmann et al., 2022; Goldman et al., 2018; van Kerrebroeck et al., 2007; Siegel et al., 2016) with increasing evidence in patients with neurogenic lower urinary tract dysfunction (NLUTD) (Averbeck et al., 2020; Kessler et al., 2010; Liechti et al., 2022; van Ophoven et al., 2021; Peters et al., 2013; Sun and Song, 2024). SNM is normally performed in two phases. During the initial test phase, tined leads are typically placed into the sacral foramina S3 or S4, and optimal stimulation parameters are determined. If sufficient symptom improvement is achieved (i.e., the patient qualifies as an "SNM responder"), a second phase follows in which a pulse generator is implanted for permanent stimulation (van Kerrebroeck et al., 2007; Kessler et al., 2007a; Spinelli et al., 2003; Wöllner et al., 2012).

The mechanism of action of SNM is incompletely understood. Human and animal studies suggest that SNM involves the modulation of spinal cord reflexes and brain networks through peripheral afferent nerve

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pathways (Janssen et al., 2017; De Wachter et al., 2020; Zhang et al., 2013). A supraspinal involvement is also supported by a study investigating cortical sensory evoked potentials (SEPs) following sacral root stimulation in patients with neurogenic and idiopathic bladder dysfunction (Braun et al., 2002). These potentials showed maximum activity over the sensory cortex, even in patients who did not perceive the electrical stimulation. Another study in women with overactive bladder symptoms (OAB) found a decrease in regional brain activity during urgency after successful SNM (Weissbart et al., 2018). This small study reported differential effects between SNM responders (increased brain activity in insula and thalamus) and non-responders, indicating a therapeutic response. Different cortical activation patterns were reported in acute versus chronic SNM for urgency urinary incontinence suggesting a supraspinal mechanism in lower urinary tract (LUT) control (Blok et al., 2006). Further evidence of changes in afferent signal processing was demonstrated by the increased LUT current perception thresholds (LUTCPTs) at various stimulation frequencies after SNM in female patients with OAB (Wenzler et al., 2015). SNM also affected bladder sensitivity, with reduced current perception thresholds (CPTs) during stimulation compared to the SNM off situation (Wyndaele et al., 2000). Investigating a full bladder situation in patients with voiding symptoms, Dasgupta and colleagues found no significant brainstem activity but enhanced limbic cortical activity. SNM restored a normal pattern of midbrain and cortical activity (Dasgupta et al., 2005). Further research is needed to better understand the role of supraspinal involvement, and how SNM induces alterations in afferent signaling. Currently, there is no clinically established objective and reliable assessment tool for evaluating the function and integrity of human bladder and urethral afferent nerves. Lower urinary tract electrical sensory assessments (LUTESA), in particular LUT sensory evoked potentials (LUTSEPs) and LUTCPTs, may be useful correlates for SNM and to investigate changes in relation to NLUTD. Several studies have demonstrated the feasibility of recording SEPs from the LUT during electrical stimulation in both healthy subjects and patients (Badr et al., 1982; van der Lely et al., 2022, 2019b; Sarica et al., 1996). For good reliability, constant measurement conditions are important, e.g. bladder pre-fill and stimulation electrode placement (Knüpfer et al., 2017; van der Lely et al., 2019b). The cortical LUTSEP components described so far (typically recorded from the vertex referenced to a frontal electrode, Cz-Fz) include a prominent negative peak (N1) flanked by two smaller positive peaks (P1 and P2). In healthy subjects, the N1 emerges as the most robust and reliable LUTSEP component in Cz-Fz recordings and regarding map strength (Gänzer et al., 1991; Gregorini et al., 2013; van der Lely et al., 2020). LUTSEPs (latencies and amplitudes) were reported to differ among stimulation locations (Gerstenberg et al., 1991; Gregorini et al., 2015, 2013; Knüpfer et al., 2018; Sarica et al., 1986), whereby amplitudes rather consistently decreased from bladder to distal urethral locations (Gregorini et al., 2015, 2013; Knüpfer et al., 2018). In comparison to healthy subjects or non-neurogenic LUT dysfunction, LUTSEPs seem to be diminished and prolonged in neurological patients with LUT dysfunction (Badr et al., 1984; Sarica et al., 1996; Schmid et al., 2004). These patients generally also present with increased LUTCPTs compared to healthy individuals (van der Lely et al., 2022). Increased LUTCPTs were also found after pelvic surgery (Abernethy et al., 2014; Davis et al., 2012; John et al., 2000; Kessler et al., 2007b).

Taking all this into account, SNM may affect bladder sensitivity in different ways depending on the type of LUT dysfunction, and may actually "normalize" aberrant sensitivity toward healthy control levels. It has been hypothesized that patients with urinary urgency typically present with increased bladder sensitivity (lower CPTs), meaning they experience the urge to urinate at lower bladder volumes compared to individuals without OAB (Lee et al., 2010). For patients with voiding symptoms, however, it is less clear how bladder sensation is affected and cannot be generalized. It remains uncertain whether these patients have diminished bladder sensation or an inability to effectively sense bladder fullness.

After SNM, altered bladder sensation is plausible with corresponding effects on SEPs. For the LUT-related pudendal nerve, a significant decrease in pudendal SEP latency and amplitude was found after SNM (Malaguti et al., 2003). This shows that SNM can modify cortical sensory afferent information and highlights the role of SEPs in assessing treatment response in patients with NLUTD, although, so far, no studies have assessed LUTSEPs in patients undergoing a neuromodulative treatment.

The aim of this study was to evaluate the feasibility and outcomes of LUTESA in patients with NLUTD undergoing SNM testing. To this end, LUTESA was investigated for its feasibility in patients with NLUTD, as well as its potential to differentiate subtypes of NLUTD and to assess changes and clinical relevance before and after the SNM test phase. Assuming that SNM is enhancing LUT function by modulating aberrant afferent sensory signals transmitted to the brain, we hypothesized that successful SNM would lead to alterations in CPT, PT and SEP outcome patterns, shifting them towards those observed in healthy controls. Under the assumption that patients suffering from urinary urgency/incontinence, in contrast to voiding difficulties, exhibit heightened bladder sensitivity, as indicated by diminished CPTs and PTs, we hypothesized that SNM may go in line with decreased bladder sensitivity. In contrast, we expected diminished or abolished sensation in patients with urinary voiding symptoms and decreased CPTs and PTs (increased bladder sensitivity) after successful SNM. Regarding LUTSEPs, we hypothesized that SNM will change amplitudes rather than latencies. The dimension of change was expected to reflect the degree of clinical success.

2. Methods

This neurophysiology project (comprising feasibility and outcomes of LUTESA pre and post SNM test phase, Fig. 1) was embedded in an investigator-initiated randomised, sham-controlled, double-blind, multicentre clinical trial (RCT, ClinicalTrials.gov, NCT02165774); investigating the efficacy of SNM in NLUTD (Liechti et al., 2022). During the screening for the SNM RCT, patients were asked for an additional participation in a side-project comprising complementary neurophysiology assessments at the main study centre. The corresponding neurophysiology protocol was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to inclusion.

2.1. Participants

Symptomatic patients with refractory NLUTD (i.e., URGENCY: urgency frequency syndrome or urgency incontinence; RETENTION: chronic urinary retention; or the combination (COMBINED) of urgency frequency syndrome or urgency incontinence, and chronic urinary retention) willing to be enrolled in an SNM RCT with additional neurophysiology assessments were screened for enrolment. Further inclusion and exclusion criteria (e.g., pregnancy or breast feeding, etc.) as well as other details on the SNM study design are summarized in the corresponding protocol and main RCT paper (Knüpfer et al., 2014; Liechti et al., 2022).

2.2. Sacral neuromodulation

Patients underwent bilateral tined lead implantation as part of the SNM trial. During a test phase of at least three weeks, SNM was tested regarding optimal stimulation frequency (min: 5 Hz, max: 120 Hz), and lead configuration typically using a pulse width of 210 μs and starting with a frequency of 15 Hz. These parameters were reprogrammed to achieve best possible urological outcome. According to our study protocol, the test phase was considered successful if the bladder diary outcomes (for example, number of voids and/or number of leakages, post void residual) improved by at least 50 % compared to baseline values (Knüpfer et al., 2014; Liechti et al., 2022). If this criterion was

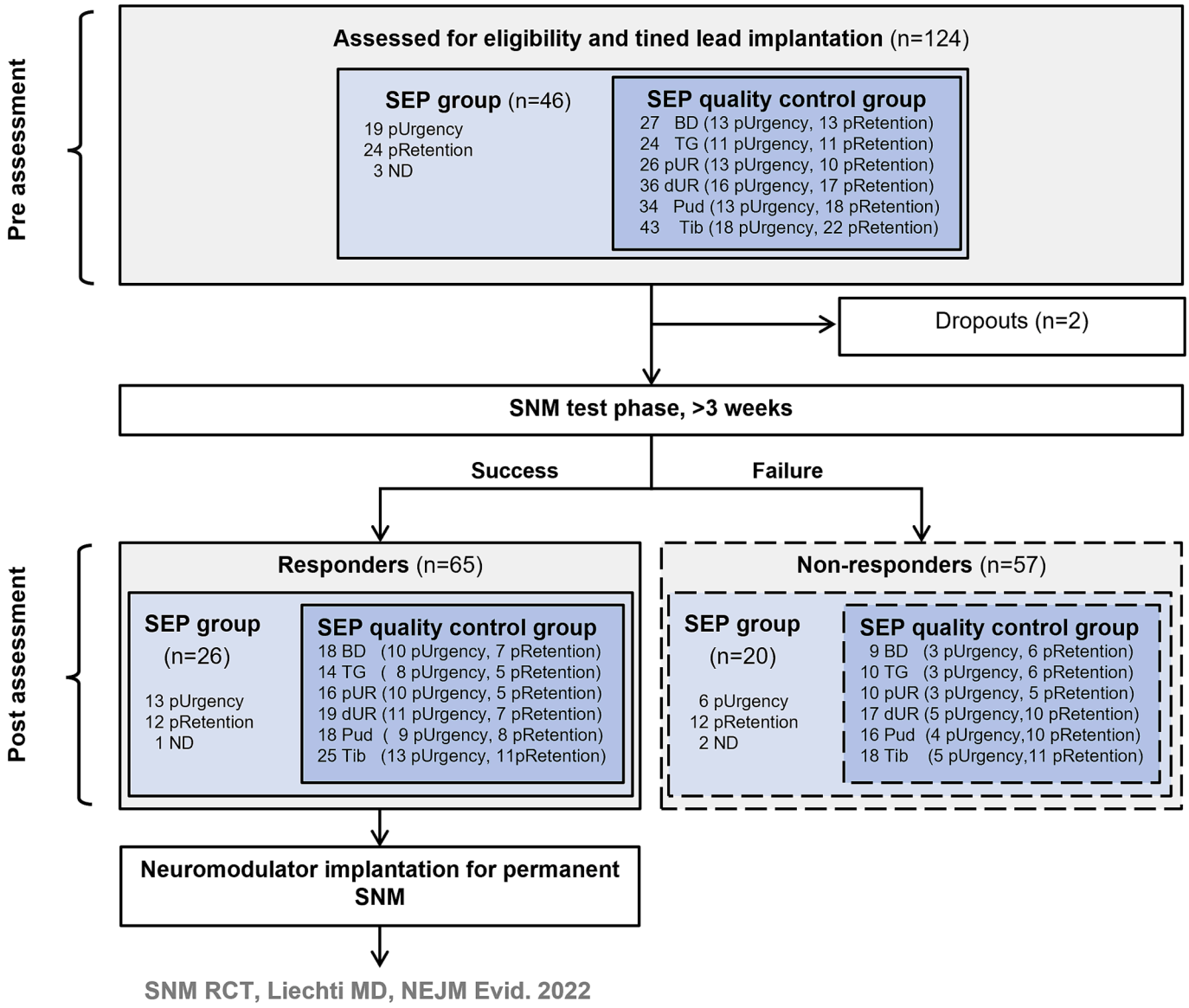

Fig. 1. Patient flow for the screening of the sacral neuromodulation (SNM) RCT (grey boxes) considering different patient subgroups: 46 patients underwent neurophysiology assessments (light blue boxes) before and after SNM test phase. Patients providing measurements fulfilling additional quality criteria (optimal catheter placement, good odd/even sensory evoked potential (SEP) replication, quotient of stimulation intensity to current perception threshold (CPT) greater than one, no transurethral resection of the prostate) are additionally listed for the respective stimulation locations of the SEP quality control group (darker blue boxes). After the SNM test phase, patients were further grouped into responders (demonstrating clinical SNM success, i.e. > 50 % improvement in key bladder diary parameters) and non-responders (depicted as hatched). BD, bladder dome; TG, trigone; pUR, proximal urethra; dUR, distal urethra; Pud, pudendal; Tib, tibial nerve; pRetention, predominant chronic urinary retention; pUrgency, predominant urgency frequency syndrome or urgency incontinence; ND, not definable, both features (chronic urinary retention and urgency frequency syndrome and/or urgency incontinence) equally pronounced. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

met, the patient was considered as "responder" and the neuromodulator was implanted for permanent stimulation.

2.3. Procedures for sensory afferent assessments

Electrical stimulation was used to assess sensory afferent information from different locations in the LUT as well as from the pudendal (Pud), and tibial (Tib) nerves. Prior to any LUT procedures, urinary tract infection (UTI) and pregnancy were excluded based on a urine dipstick analysis (Combur-Test) and a pregnancy test. For the neurophysiology assessments, subjects were placed in a comfortable supine position in a quiet room. For each LUTSEP assessment, the bladder was prefilled with 60 mL of contrast medium (Ultravist 150TM, Bayer AG, Switzerland) at body temperature (37 °C). Stimulation electrodes (catheter) were positioned using a custom-made 8-F transurethral catheter under fluoroscopic control according to previously defined protocols (Gregorini et al., 2015, 2013; Knüpfer et al., 2017). To minimize potential bladder/urethral irritation resulting from frequent catheter movement the protocol followed a consistent sequence of stimulation locations starting from the bladder dome (BD) and gradually moving caudally via the trigone (TG) and proximal (pUR) to the distal urethra (dUR). Biphasic square wave stimuli were applied using a frequency of 0.5 Hz and pulse width of 1 ms. For the following stimulations of the tibial and pudendal nerve, a stimulation frequency of 3 Hz and 0.2 ms pulse width was used (Gregorini et al., 2013; Knüpfer et al., 2017).

For the SEP recordings investigated here, the SNM stimulator was switched off and switched on again after the last SEP assessment. Each stimulation cycle started with the assessment of the CPT using the

methods of limits (Yarnitsky, 1997). During the pain assessment (except for tibial stimulations), the patients indicated when the stimulation was getting painful using a Numerical Rating Scale (NRS) ranging from 0 to 10 (0 = "no pain" and 10 = "worst pain imaginable") (Haefeli and Elfering, 2006). After PT assessment, the stimulation intensity was individually adapted to the highest tolerable level for each stimulation cycle, aiming at an intensity of 2–3 times CPT, but also staying below the pain threshold. Tibial nerve stimulation was performed above motor threshold. A minimum of 200 stimuli were applied per stimulation location using a neurophysiological stimulator (Dantec Keypoint Focus, Neurolite AG, Belp, Switzerland) capable of delivering a stimulation intensity of up to 100 mA. After every stimulation cycle, the bladder was emptied and the patients were asked about the perceived intensity of pain (NRS 0–10) during the preceding stimulation.

2.4. Sensory evoked potential recordings

The electroencephalogram was recorded using 64 Ag/AgCl surface electrodes mounted on a cap-based extended international 10–20 montage (Klem et al., 1999), with Fz as the recording reference, F1 as ground. Electrode impedances were kept below 20kΩ by using abrasive electrolyte gel. The signals were continuously recorded using BrainAmp amplifiers and BrainVision Recorder (Brain Products, Gilching, Germany), digitized at a sampling frequency of 5000 Hz and analogue-filtered between 0.016 and 1000 Hz. Detailed information about the electrode montage, multichannel processing and general procedure can be found in van der Lely et al. (van der Lely et al., 2020).

2.5. Data processing and analysis

For data preprocessing and analysis BrainVision Analyzer2 (Version: 2.2; Brainproducts GmbH, Munich, Germany) was used. For the following analysis steps, EEG data was down sampled to 2000 Hz, and transformed to average reference. A bandpass (0.5–70 Hz) filter and 50 Hz Notch filter were utilized. After ocular correction (Gratton et al., 1983), automatic artefact rejection (± 100 μV) excluding remaining eye artefacts, muscle artefacts and technical artefacts was performed. From the continuous data, segments ranging from 100 ms before the stimulus to 600 ms after the stimulus, respectively from −100 ms to 320 ms for Pud and Tib SEPs, were extracted. Artifact-free segments were then averaged. For single-channel analyses and peak detection with marker setting, Cz-Fz (LUT) and Cz'-Fz (Tib and Pud) differences were calculated for SEP evaluation, respectively. Cz' was located 2 cm posterior to the Cz position which is the clinical standard position to enhance the recording of somatosensory responses.

2.5.1. Subgroup definition and marker setting for SEP quality control group (QC)

To better assess the validity of the data, supplementary analyses were performed using only data from a separately defined subgroup fulfilling strict data quality criteria (QC): in the odd/even alignment of an averaged potential, the curves had to replicate regarding SEP shapes. Concerning the catheter placement (only for BD, TG, and pUR), a radiograph image taken before the stimulation was used to confirm that both stimulation electrodes were visible and correctly positioned as outlined in van der Lely et al. (Gregorini et al., 2013; van der Lely et al., 2019a) with comparable placement across visits. For the dUR location, the correct catheter placement was visually verified during the measurement (no radiograph images recorded). Another criterion required that the quotient of stimulation intensity to CPT was greater than 1, excluding measurements under insufficient stimulation and patients without sensation for the respective stimulation. Lastly, patients who previously had transurethral resection of the prostate were excluded from the QC group of TG and pUR locations, as this could influence catheter placement and afferent signalling pathways. A patient was only considered for the QC group, if all criteria mentioned above were fulfilled for both visits.

For each measurement of this subgroup (both visits and each location), markers were set on the Cz-Fz and Cz'-Fz channels for the N1 (LUT) and P40/N50 (Pud/Tib) components, respectively, (van der Lely et al., 2020). For marker-based analyses, the following criteria had to be fulfilled for each stimulation location: the presence of an identifiable N1 component (local minima) for LUTSEPs, and P40 and N50 for Pud and Tib SEPs, respectively, for both visits.

Based on these markers, peak latencies, and peak-to-peak amplitudes (P40N50) were calculated. The response rate was calculated as the percentage of recordings that resulted in a stable SEP with existing N1 or P40, and N50 marker setting, respectively, and was determined for each stimulation location and visit.

2.5.2. Time windows for topographical analyses

For the topographical analysis of LUTSEPs, time windows around the expected N1 component were defined following an approach based on the inflection points of the global field power (GFP, a measure of map strength) (van der Lely et al., 2020). Mean values were investigated for two specific N1 time windows:

1) 87–123 ms – using the most powerful map area (between the GFP inflection points) based on the data from patients with NLUTD assessed here
2) 85–154 ms – an alternative time window based on the GFP from healthy subjects (van der Lely et al., 2020).

2.6. Statistical methods

Statistical analyses were performed using RStudio (Version 2023.03.0, Boston, MA, U.S.A.) and Randomization Graphical User interface (RAGU, for multichannel event-related electroencephalography data) (Koenig et al., 2011; Koenig and Melie-García, 2010). Alpha level was set at 0.05 for statistical analyses.

For categorical variables, counts and percentages were reported. Normal distribution of the data was tested using Shapiro–Wilk test and by visual inspection of histogram and qq-plots. For demographics, SEP latencies and amplitudes, median and range (interquartile range), were calculated for continuous variables. Sensory thresholds, SEP trajectories and the presence of components (Tib and Pud SEPs: P40, N50; LUTSEPs: N1) were analyzed on group level and for SEP data stratified by stimulation location. Considering the expected differences in baseline and differential changes in sensation between NLUTD groups over the SNM test phase (i.e. interaction) the primary analyses were stratified for the underlying **predominant type of NLUTD**. Therefore, patients were reallocated from the original three (URGENCY, RETENTION, COMBINED) into two study groups according to the underlying predominant type of NLUTD (predominant URGENCY [pUrgency], predominant RETENTION [pRetention]) as assessed by an expert consultant urologist.

To assess sensory threshold variables (CPT and PT) over SNM test phase (visit – pre/post SNM), as well as the effects of type of NLUTD and clinical success of SNM (responders vs. non-responders), multivariable linear mixed-effects models (LMM) were fitted from the lme4 package in R (Bates et al., 2015).

In these models, CPT and PT were the dependent variables, while visit, type of NLUTD (pUrgency, pRetention) and stimulation location (BD, TG, pUR, dUR) were included as fixed effects. An interaction between type of NLUTD and visit was included to account for hypothesized differential changes in the NLUTD groups during the SNM test phase. Age and sex were included as potential confounders regarding the main relationship of interest (Coolen et al., 2022; Gregorini et al., 2015; Jairam et al., 2022; Knüpfer et al., 2018). Subject was included as a random effect on intercept to account for the repeated measure structure of the data. Both CPT and PT had right skewed distributions and were accordingly transformed with a natural logarithm in the models. In situations where 100 mA stimulation intensity (the maximum

stimulation capacity of the device) was insufficient to assess a sensory threshold, a value of 101 mA was allocated for the respective threshold analysis. Models were run separately for the LUT stimulations as well as for the pudendal and tibial stimulation. In addition, stimulation intensity and relative stimulation intensity were assessed and analysed in an LMM to account for their potential influence on the results.

Post-hoc pairwise comparisons of estimated marginal means (emmeans) were conducted using the emmeans package (Lenth, 2023) to derive meaningful predictions of CPT and PT outcomes from the multivariable models and to explore statistically significant fixed effects further. Specifically, post-hoc tests were performed with the Tukey method used for p-value adjustment to control for multiple comparisons. The Kenward-Roger method was utilized to provide more accurate degrees of freedom in these comparisons. All data was available for the predictor variables in the model, and missing outcome data was handled by the LMM under the assumption of missing at random. Sensitivity analysis was run including the following multivariable regression analyses: i) restricted to patients with CPT and PT values $\leq$ 100 mA (the maximum stimulation capacity of the device) to evaluate the robustness of the model results, particularly regarding potentially "not applicable" cases; ii) LUT CPT and PT analyses including clinical success (identified as a potential collider, and therefore not included in the main multivariable model); iii) LUT CPT and PT analyses stratified by type of NLUTD to evaluate model overfitting and stability concerns; and iv) LUT CPT and PT analyses stratified by clinical success again to evaluate overfitting and stability concerns.

For the analysis of scalp field data (topographies) the same methods as in van der Lely et al. (van der Lely et al., 2020) were used regarding time-wise topographical analysis of variance (TANOVA – independent of map strength) and global field power (GFP – the parametric assessment of reference-independent map strength as a function of time) analysis. Topographical distribution and map strength were analysed for defined N1 time windows (see section 2.5.2) and compared between conditions (within-subject factor pre/post SNM test phase and stimulation location and between-subject factor clinical success [responder/ non-responder] or predominant NLUTD type [pUrgency/pRetention]) as well as interactions for type of NLUTD and clinical success. Paired t-tests were used to evaluate pre/post SNM test phase differences, while unpaired t-tests were conducted to assess the significance between NLUTD type as well as clinical success groups. The results were visualized as t-maps, with colour gradients adjusted to group sizes. In these t-maps, the initial colour gradient represents a trend toward significance, and the subsequent gradient indicates statistical significance ($p < 0.05$).

3. Results

Out of 124 patients (47 URGENCY, 38 RETENTION, 39 COMBINED) screened for the SNM RCT, 47 patients (15 URGENCY, 17 RETENTION, 15 COMBINED) were consented to undergo additional neurophysiology measurements. One subject had to be excluded from the analyses due to missing values for multiple LUT locations and data quality issues. Table 1 presents the baseline characteristics of the different SEP study groups. There were no significant group differences regarding age, height and sex.

All subjects tolerated the LUTESA procedures well and completed the pre and post SNM measurements. Regarding predominant NLUTD group allocation, there were 19 pUrgency, 24 pRetention and three patients (from COMBINED group) with no predominant NLUTD (excluded from respective analyses). After the SNM test phase, patients were further grouped into responders (demonstrating clinical SNM success, i.e. > 50 % improvement in key bladder diary parameters) and non-responders. Patient flow and study groups are shown in Fig. 1. Due to the small number of patients in the pUrgency group that were SNM non-responders (n = 6), statistical comparisons and modelling considering clinical success was not performed in the urgency group due to reliability concerns. For pRetention, the groups were more balanced allowing statistical comparisons of responders (n = 12) versus non-responders (n = 12).

3.1. Sensory thresholds

Descriptive analyses for CPTs and PTs (Fig. 2a,b) revealed elevated thresholds for patients with pRetention in comparison to those observed in the pUrgency group. Additional stratification for clinical success can

Table 1
Demographic and clinical baseline characteristics.

			Predominant type of NLUTD				Clinical success			
Characteristics	all		**Urgency**		**Retention**		**Responder**		**Non-responder**	
Patients — No. (%)	46	*(100)*	19	*(41)*	24	*(52)*	26	*(57)*	20	*(43)*
Female — No. (%)	24	*(52)*	14	*(74)*	8	*(33)*	20	*(77)*	4	*(20)*
Male — No. (%)	22	(48)	5	*(26)*	16	(67)	6	(23)	16	(80)
Age [years] – median (IQR)	56	*(20)*	58	*(21)*	46	*(21)*	56	*(18)*	52	*(21)*
Height [cm] — median (IQR)	170	*(11)*	170	*(10)*	173	*(13)*	168	*(11)*	175	*(8)*
NLUTD type — No. (%)										
predominant Urgency	19	*(41)*	19	*(100)*	–		13	*(68)*	6	*(32)*
predominant Retention	24	*(52)*	–		24	*(100)*	12	*(50)*	12	*(50)*
no predominance	3	*(7)*	–		–		1	*(33)*	2	*(67)*
Bladder emptying method — No. (%)										
Spontaneous voiding	17	*(36)*	17	*(100)*	–		12	*(71)*	5	*(29)*
Intermittent self-catheterization	26	*(57)*	2	*(9)*	21	*(91)*	13	*(50)*	13	*(50)*
Indwelling catheter	3	*(7)*	–		3	*(100)*	1	*(33)*	2	*(67)*
Neurological disease — No. (%)										
Spinal cord injury	15	*(33)*	4	*(31)*	9	*(69)*	3	*(20)*	12	*(80)**
Herniated disc	10	*(22)*	4	*(40)*	6	*(60)*	9	*(90)*	1	*(10)**
Post-surgical pelvic nerve injury	7	*(15)*	2	*(29)*	5	*(71)*	6	*(86)*	1	*(14)**
Parkinson's disease	2	*(4)*	2	*(100)*	–		–		2	*(100)*
Multiple sclerosis	4	*(9)*	–		4	*(100)*	2	*(50)*	2	*(50)*
Diabetic neuropathy	2	*(4)*	2	*(100)*	–		1	*(50)*	1	*(50)*
Myelomeningocele	1	*(2)*	1	*(100)*	–		1	*(100)*	–	
Guillain-Barré syndrome	1	*(2)*	1	*(100)*	–		1	*(100)*	–	
Stroke	1	*(2)*	1	*(100)*	–		–		1	*(100)*
Other neurological disease	3	*(7)*	2	*(100)*	–		3	*(100)*	–	

Group characteristics stratified by type of neurogenic lower urinary tract dysfunction (NLUTD) and clinical success. Statistical analyses were performed within type of NLUTD and clinical success subgroup. Statistically significant differences ($p < 0.05$) are indicated by *. Pearson's Chi-squared test was used for sex, the Wilcoxon rank-sum test for age and height, and Fisher's exact test for bladder emptying method and neurological disease.

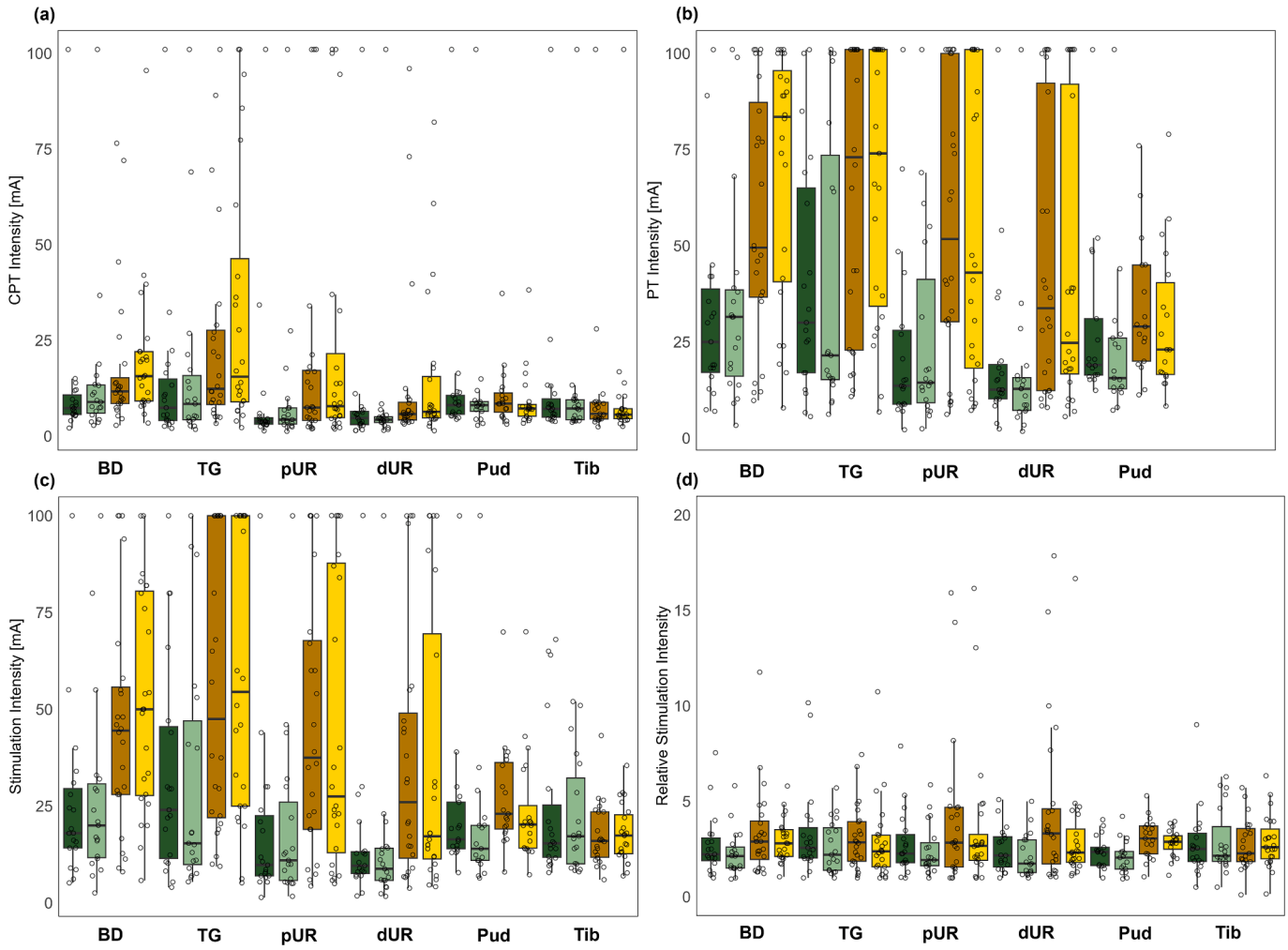

Fig. 2. Boxplots depicting (a) current perception threshold (CPT), (b) pain threshold (PT) before, (c) stimulation intensity, and (d) relative stimulation intensity before (dark green & brown) and after (light green & yellow) the sacral neuromodulation test phase, stratified by stimulation location and type of neurogenic lower urinary tract dysfunction (NLUTD): green (light & dark) for patients with predominant urgency NLUTD (n = 19) and yellow/brown for predominant retention NLUTD (n = 24). The box-whisker plots represent lower whisker/upper whisker (maximum 1.5 x interquartile range), 25th percentile / 75th percentile, and median values. Individual subject data points are indicated by single dots. BD, bladder dome; TG, trigone; pUR, proximal urethra; dUR, distal urethra; Pud, pudendal nerve; Tib, tibial nerve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be seen in supplementary material (Fig. S1).

Using multivariable models, including type of NLUTD, age, sex, visit, and LUT location as factors revealed significant effects for stimulation location and **type of NLUTD** (Table 2 & Supplementary Table S1, S2). Thresholds were generally higher and more variable in the pRetention group compared to pUrgency group across visits and stimulation locations (Fig. 2 & Table 2). This difference was already present at baseline (Fig. 2). Regarding **stimulation location**, bladder stimulations revealed generally higher values compared to urethral stimulations for CPT and PT (Table 2). Also, stratified multivariable analyses for type of NLUTD, clinical success or visit revealed consistent significant effects for location (Supplementary Table S3 & S4). There was no significant interaction between stimulation location and type of NLUTD (CPT: coefficient: 0.57; p = 0.75; PT: coefficient: 0.70; p = 0.41).

Over SNM test phase (pre vs. post), there were no relevant changes in sensory thresholds nor interactions with type of NLUTD or clinical success (Supplementary Table S1, S3, S4). Only a small albeit significant increase was found for CPT (Table 2 and Supplementary Table S1). The stratified analysis of SNM clinical success showed that this was driven by non-responders (Supplementary Table S4). Stratified analyses for type of NLUTD (Supplementary Table S3) or stimulation location revealed no significant changes over time.

When considering **clinical success** of the SNM test phase in the models, significantly lower CPTs and PTs were found for responders compared to non-responders (Supplementary Table S1), which was also true already at baseline and for pRetention patients only (Supplementary Fig. S1b,d & Table S1). Also, stratified analyses for stimulation location revealed significant differences between responders and non-responders for TG, pUR, and dUR. For these locations, responders showed lower electrical stimulation response thresholds than non-responders. In the clinical success stratified model (Supplementary Table S4), responders show no change in CPT pre/post SNM test phase. This is in contrast to non-responders showing slightly increased CPT after SNM test phase.

Sensitivity analysis considering only values $\leq$ 100 mA for CPT and PT, revealed consistent results as presented above, except for the absence of the visit effect in the CPT analysis. No sex differences were found for any of the LUT models.

For **pudendal** stimulation, no significant effects were observed for the CPT (LMM: Type NLUTD p = 0.55, visit p = 0.10, age p = 0.28, sex p = 0.21; Fig. 2a & Supplementary Fig. S1), but PT decreased over SNM test phase (p = 0.01, emmean, lower & upper confidence interval: pre SNM: 27.7 mA, 22.6 mA, 34.0 mA; post SNM: 22.2 mA, 18.1 mA, 27.1 mA; Fig. 2b). For **tibial** stimulation, only sex differences were found to

Table 2
Multivariable linear mixed effect models to identify factors associated with (a) current perception threshold (CPT) and (b) pain threshold (PT) – for the overall population n = 46.

CPT overall model	Coefficient	2.5 % CI	97.5 % CI	p value		Emmean	2.5 % CI	97.5 % CI
(Intercept)	2.06	0.95	3.18	0.00	***			
pUrgency	ref					6.65	4.40	10.07
pRetention	0.54	−0.03	1.12	0.05	*	11.92	8.32	17.09
pre SNM	ref					8.37	6.42	10.92
post SNM	0.08	−0.10	0.27	0.38		9.47	7.26	12.36
Bladder dome	ref					11.22	8.49	14.83
Trigone	0.09	−0.09	0.26	0.32		12.26	9.27	16.21
distal urethra	−0.60	−0.59	−0.24	0.00	***	7.40	5.60	9.78
proximal urethra	−0.42	−0.77	−0.42	0.00	***	6.18	4.68	8.17
Age	0.01	−0.02	0.02	0.95		7.01	6.07	8.09
Male	ref					9.02	6.07	13.40
Female	−0.02	−0.57	0.52	0.93		8.80	6.09	12.70
pNLUTD*pre/post SNM	0.08	−0.17	0.33	0.53				
pUrg- pre SNM						6.38	4.18	9.75
pUrg- post SNM						6.94	4.54	10.59
pRet- pre SNM						10.98	7.60	15.88
pRet- post SNM						12.94	8.95	18.71
PT overall model	**Coefficient**	**2.5 % CI**	**97.5 % CI**	**p value**		**Emmean**	**2.5 % CI**	**97.5 % CI**
(Intercept)	3.16	2.22	4.15	0.00	***			
pUrgency	ref					20.15	14.08	28.84
pRetention	0.74	0.21	1.21	0.00	***	42.27	30.94	57.75
pre SNM	ref					29.51	23.42	37.18
post SNM	−0.02	−0.23	0.12	0.54		28.86	22.91	36.37
Bladder dome	ref					36.10	28.28	46.08
Trigone	0.06	−0.10	0.22	0.45		38.44	30.10	49.08
proximal urethra	−0.33	−0.50	−0.17	0.00	***	25.86	20.26	33.01
distal urethra	−0.58	−0.74	−0.42	0.00	***	20.22	15.84	25.82
Age	0.00	−0.01	0.02	0.81		29.18	23.32	36.53
Male	ref					30.20	21.44	42.55
Female	−0.07	−0.54	0.40	0.78		28.20	20.52	38.76
pNLUTD*pre/post SNM	0.06	−0.17	0.29	0.59				
pUrg- pre SNM						20.70	14.33	29.91
pUrg- post SNM						19.61	13.58	28.34
pRet- pre SNM						42.06	30.53	57.96
pRet- post SNM						42.48	30.82	58.55

Coefficients are depicted in mA and back transformed from the used ln model transformation. Estimated marginal means (Emmeans) represent model predictions for the expected value of current perception threshold (CPT) or pain threshold (PT) for the respective covariate. CI, confidence interval; pUrgency, predominant urgency neurogenic lower urinary tract dysfunction (NLUTD); pRetention, predominant retention NLUTD; *Indicates statistical significance $P < 0.05$, ** for $p < 0.01$, *** for $p < 0.001$.

be significant in all LMMs ($p \leq 0.01$), showing generally lower CPTs for females compared to males (emmean, lower & upper confidence interval: female 5.6 mA, 4.1 mA, 7.5 mA; male 10.5 mA, 7.5 mA, 14.5 mA).

3.2. Single-channel sensory evoked potentials

In our cohort of patients with NLUTD, LUTSEPs were detectable from different locations with characteristic albeit diminished and narrower components compared to previously described ones in healthy subjects. The stimulation in the LUT evoked cortical potentials with a prominent N1 component appearing around 100 ms in the Cz-Fz channel (Fig. 3 and Supplementary Fig. S2). The following positivity was rather late (around 300 ms) for a "P2 component". This late positivity as well as the N1 components replicated between visits. **Depending on the stimulation location**, an early positivity around 200 ms (more prominent in pUrgency and distal locations) was detected right after the N1 followed by another positivity around 300 ms (more prominent in pRetention). Largest N1 amplitudes were found for BD stimulation. There were no obvious **changes in N1 component between visits**, but rather in the subsequent transition phase (TP) (Fig. 3 and Supplementary Fig. S2).

Different types of NLUTD presented with characteristic waveforms among stimulation locations, which differed mostly in time course after N1 (Fig. 3). There seemed to be a transition phase with additional peak (s) between N1 and the later positivity around 300 ms.

In the pUrgency group, the N1 was visually more pronounced in the distal LUT locations. On a descriptive level, there were some changes in the TP trajectory over the test phase, most pronounced in the BD stimulation and responder group (Fig. 3b, Supplementary Fig. S2b). **In the pRetention group** (Fig. 3c), it was noticeable that the N1 component was most pronounced for BD stimulation in contrast to TG or urethral stimulation. Furthermore, there was an additional pudendal SEP at the dUR location. The N1 seemed to be rather weak and delayed in non-responders compared to responders, especially at the more distal LUT locations (Supplementary Fig. S2e&f).

Considering waveforms with respect to clinical success of SNM testing, **clinical non-responders seemed to deviate from responders**, with a more W-shaped curve from N1 to late positivity (Fig. 3d-e, Supplementary Figs. S2). This was most pronounced for TG, pUR and dUR stimulation locations with a W-shaped curve before and after SNM.

For the Tib and Pud SEPs, P40 and N50 components known from healthy individuals were found at the patient group level (Fig. 3, Supplementary Fig. S2). For the stratification for type of NLUTD, the SEPs showed all prescribed components, whereby the late components were more pronounced compared to the early ones and most prominent for Pud stimulation in the pRetention group. Over the SNM test phase, the early components and waveforms remained quite constant. Purely descriptively there may be some differential changes after SNM in the long latency components of Pud SEPs, subsequent to the N85 component, mostly in pUrgency and responders.

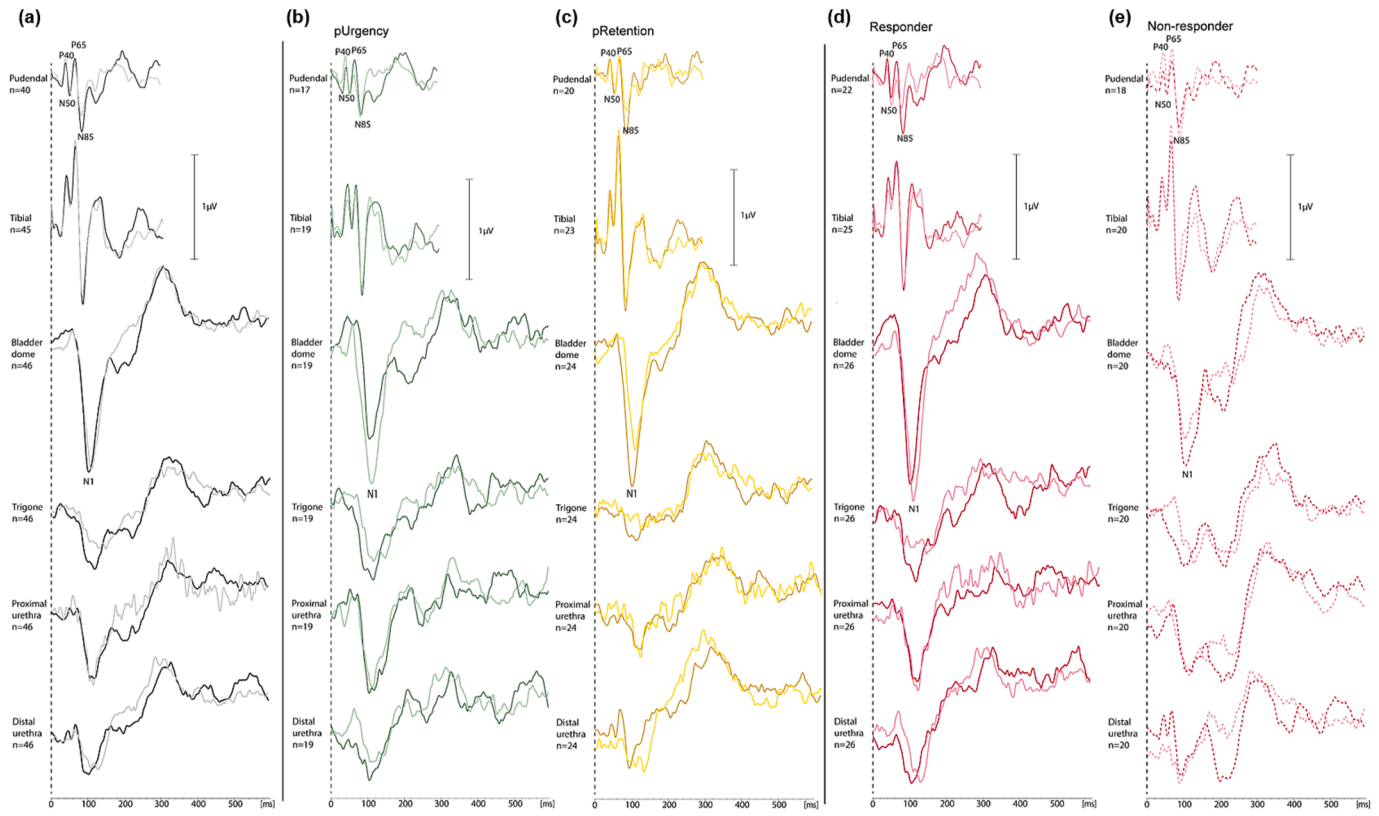

Fig. 3. Group averaged sensory evoked potentials for (a) the overall population: pre (dark colours) and post (light colours) sacral neuromodulation (SNM) test phase stratified by stimulation location and type of neurogenic lower urinary tract dysfunction (NLUTD) as well as clinical success. (b) predominant urgency (green), (c) predominant retention (yellow), (d) SNM test phase responders (red), (e) SNM test phase non-responders (red – hatched lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Topographical representation of sensory evoked potentials

Topographical analyses of the N1 component stratified for type of NLUTD, clinical success and stimulation location are shown in Fig. 4 for pre and post SNM test phase using the time window from 87–123 ms. Topographically the N1 presented as a centro-parietal negativity. Statistical analyses (RAGU) using factors location, visit, and type of NLUTD with corresponding interactions in Tanova and GFP (map strength) revealed significant differences between **LUT stimulation locations** (Tanova: p = 0.00, exp. variance = 7.2 %; GFP: p = 0.00, exp. variance = 8.5 %). The map strength was strongest for BD (GFP BD: 0.62, dUR: 0.55, pUR: 0.50; TG: 0.45; Fig. 4, Supplementary Fig. S3), driven by the pRetention group, also when using a slightly wider N1 window (85–154 ms; GFP BD: 0.50, dUR: 0.45, pUR: 0.40; TG: 0.35; Supplementary Fig. S4). **Over the test phase**, there was a significant change in N1 topography over all locations (Tanova: p = 0.03, exp. variance = 7.5 %); also, for TG and pUR, when tested separately (Fig. 4)**.** The topography before the SNM test phase was more centralised compared to the topography

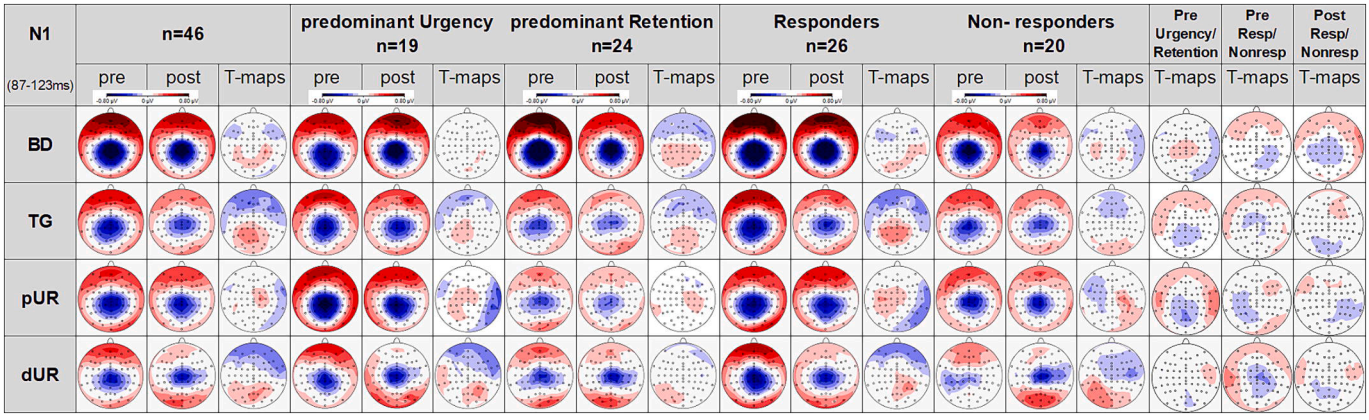

Fig. 4. Topographical maps and t-maps of the group averaged N1 component stratified per stimulation location for neurogenic lower urinary tract dysfunction (NLUTD) type and clinical success using a time window according to the global field power (GFP) inflection points of healthy controls (87–123 ms). T-values of the second colour grade indicate statistical significance. The last columns display t-maps illustrating the differences between the urgency and retention groups pre sacral neuromodulation (SNM) test phase as well as between responders and non-responders pre and post SNM test phase. BD, bladder dome; TG, trigone; pUR, proximal urethra; dUR, distal urethra.

after the SNM test phase (more parietal), whereby no significant change in map strength (GFP) could be observed.

Regarding **type of NLUTD**, some location-specific differences between pUrgency and pRetention group were indicated for the N1 component using t-tests (BD & pUR, see corresponding t-maps in Fig. 4 and Supplementary Fig. S4), and there was a statistical trend (Tanova: p = 0.08, exp. variance = 3.09 %, GFP: p = 0.058, exp. variance = 3.4 %) for the interaction between stimulation location and type of NLUTD. In **pRetention,** the N1 component was more pronounced in BD compared to TG, pUR and dUR.

Considering clinical **success after SNM test phase**, no significant difference between SNM responders and non-responders were found for N1 (Tanova: p = 0.17, exp. variance = 3.5 %; GFP: p = 0.16, exp. variance = 4.4 %; Fig. 4, Supplementary Fig. S5) also not when stratified for LUT location. On a purely descriptive level, it is noticeable that in responders, the N1 peak exhibited consistent topography across SNM test phase, with only a slight decentralization observed in the distribution, while the non-responders showed no consistent changes over the SNM test phase in the locations (BD and TG: centralisation over SNM test phase, pUR and dUR: decentralisation). However, there was no significant interaction between success and location (Tanova: p = 0.72, exp. variance = 1.2 %, GFP: p = 0.42, exp. variance = 1.8 %), also not for baseline assessments (Tanova: p = 0.76, exp. variance = 1.5 %, GFP: p = 0.91, exp. variance = 0.5 %).

3.4. Subgroup and marker-based analyses

In the SEP QC subgroup (BD n = 27, TG n = 24, pUR n = 26, dUR n = 36, Pud n = 34, Tib n = 43), the recorded sensory thresholds (CPT and PT) revealed similar results as the whole group (n = 46). The median latencies for N1, P40, and N50 based on the individually set markers for Cz-Fz (LUTSEPs) and Cz'-Fz (Tib & Pud) recordings were analysed (Table 3 and 4).

The LMM calculated for each LUT stimulation location showed no latency change for most LUT locations, except for significant N1 latency differences in TG for the NLUTD type (p = 0.02, emmean, lower & upper confidence interval: pUrgency: 124 ms, 98 ms, 150 ms; pRetention: 175 ms, 147 ms, 203 ms).

For Tib and Pud P40 latency, the LMMs revealed no significant changes over SNM test phase. For pudendal N50 latency, significant differences were found between responders and non-responders (p = 0.05, emmean, lower & upper confidence interval: responder: 59 ms, 55 ms, 63 ms; non-responders: 53 ms, 50 ms, 57 ms). For Tib stimulation, type of NLUTD revealed significant changes (p = 0.04, emmean, lower & upper confidence interval: pUrgency: 58 ms, 56 ms, 61 ms; pRetention: 55 ms, 53 ms, 57 ms). Regarding P40N50 amplitudes, lower amplitudes were observed after SNM test phase (Pud only a trend, Tib: p = 0.02 emmean, lower & upper confidence interval: pre SNM: 1.2 mA, 0.9 mA, 1.5 mA; post SNM: 1.0 mA, 0.7 mA, 1.3 mA).

Response rates of 58 – 89 % were found for the N1 component (Table 3) which were close to those of the clinically established Tib and Pud SEPs (>82–88 %; Table 4).

Supplementary topographical and map strength analysis of the SEP QC groups per location showed comparable results, for the most part the results of the large groups could be confirmed, and only for BD topography the changes over SNM test phase in the smaller group did not reach significance.

Table 3
Response rates and median latencies pre/post sacral neuromodulation test phase in the sensory evoked potential quality control group for the N1 lower urinary tract SEP component.

	BD, n = 27		TG, n = 24		pUR, n = 26		dUR, n = 36	
	pre	post	pre	post	pre	post	pre	post
Response rate – No. (%)	24 (89)	21 (78)	21 (88)	14 (58)	18 (69)	22 (85)	27 (75)	24 (67)
Latency – ms (IQR)	108 (28)	115 (20)	131 (55)	140 (43)	134 (63)	125 (45)	117 (53)	133 (40)

IQR, interquartile range; BD, bladder dome; TG, trigone; pUR, proximal urethra; dUR, distal urethra.

Table 4
Response rates, median latencies and peak-to-peak amplitudes pre/post sacral neuromodulation test phase in the sensory evoked potential quality control group for the P40 and N50 pudendal (Pud) and tibial (Tib) SEP components.

	Pud, n = 34		Tib, n = 43	
	pre	post	pre	post
P40				
Response rate – No. (%)	28 (82)	30 (88)	37 (86)	37 (86)
Latency – ms (IQR)	43 (6)	44 (7)	47 (6)	47 (8)
N50				
Response rate – No. (%)	28 (82)	30 (88)	37 (86)	37 (86)
Latency – ms (IQR)	54 (5)	55 (7)	56 (7)	55 (7)
P40N50				
Amplitude – μV (IQR)	0.7 (0.8)	0.5 (0.6)	1.1 (0.9)	0.9 (0.9)

IQR, interquartile range.

4. Discussion

This study demonstrates the feasibility of LUTESA, showing that afferent sensory information can be consistently assessed from different locations in the LUT in this highly selected but heterogeneous group of SNM candidates with various neurological conditions, manifestations and degrees of sensory-motor and NLUTD. The group mean LUTSEPs showed that all components described in healthy individuals (Gregorini et al., 2015; Knüpfer et al., 2018; van der Lely et al., 2020; Van Der Lely et al., 2016), were generally present in all stimulation locations and over visits, although obviously diminished in amplitude. Furthermore, this study represents the first application of LUTSEPs using a standardized protocol (van der Lely et al., 2019b) involving four stimulation locations, performed both pre and post the SNM test phase in patients with NLUTD. Given the underlying neurological impairments, it was uncertain whether patients would tolerate the procedure or yield interpretable signals, highlighting the significance of these findings. Notably, the LUTSEPs revealed a newly described transition peak in our patient population pre and post SNM. In the group average, the N1 was typically followed by a transition phase peaking in a positivity around 300 ms, which was rather late for the positivity around 200 ms (P2) known from LUTSEP studies in healthy subjects (van der Lely et al., 2020). Analogous to studies with healthy subjects (Knüpfer et al., 2017), all LUTESA outcomes investigated here showed a clear dependence on the stimulation location with BD leading to highest electrical thresholds, largest SEP amplitudes, and N1 map strength compared to other locations. One possible explanation for this could be the lower density and potentially uneven distribution of sensory afferents in the bladder (Gabella and Davis, 1998). Regarding scalp distribution of LUTSEPs, it is known from previous publications that a decrease in map strength can be observed in healthy subjects across locations (BD > pUR > dUR) (van der Lely et al., 2020). This is in line with our findings here and might indicate differences in innervation and processing of the nerve fibres among LUT locations.

In line with our hypothesis, patients with predominant retention showed consistently higher CPTs and PTs than those with predominant urgency-frequency problems, also when controlling for other factors, such as age, sex, visit, and SNM success. This would be in line with a loss of bladder sensation as the main reason for voiding symptoms. For N1, RAGU and descriptive analyses of the SEP curve revealed no significant effect for type of NLUTD in explaining the variance. Rather, it suggested some differences during the transition phase, which includes the P2 component, and some stimulation location-specific differences between

different types of NLUTD. LUTESA was useful to better characterise LUT location-specific deficits in patients with predominant storage problems in contrast to those with predominant voiding problems. However, there were no relevant changes in established LUTESA outcomes over the SNM test phase, apart from some topographical changes in the N1 component. Taking the clinical success of the SNM testing into account, there were consistent differences in electrical thresholds between SNM responders and non-responders, already before SNM. They also seem to differ in the timing and waveform of the LUTSEP, although only descriptively assessed for the Cz-Fz channel here. Our results also indicated some LUTSEP changes after the SNM test phase; however, they need to be confirmed in larger, blinded studies using longer periods of SNM better tailored to answer this research question.

4.1. Lower urinary tract electrical sensory assessment to differentiate types of neurogenic lower urinary tract dysfunction

Regarding bladder sensation, significantly higher CPTs and PTs could be shown in patients with pRetention compared to those with pUrgency. The findings of increased bladder sensation in patients with urgency symptoms is in line with the general knowledge about the types of NLUTD. Regarding bladder sensitivity, the average CPT of 16 mA for bladder locations indicates that the pRetention patients measured had reduced bladder sensitivity compared to pUrgency and mostly also compared to healthy individuals from previous studies (Kiesswetter, 1977; Knüpfer et al., 2017; Reitz et al., 2003; Wyndaele, 1991).

On a descriptive level, there seemed to be location-specific differences in the LUTSEP waveform for the Cz-Fz channel characteristic for the respective type of NLUTD. Over all subjects, the N1 component was present among all stimulation locations with largest amplitudes for BD stimulation and pUrgency. Location-specific differences in N1 were statistically confirmed using topographical RAGU analyses. The P2 component appeared less consistent, with some NLUTD-specific early and late manifestations in a longer transition phase following the N1 component. Furthermore, did the pRetention group at the dUR location show an additional pudendal SEP. This phenomenon may be related to the fact that a high stimulation intensity was used at this location. The presence of this additional pudendal EP could suggest that the increased stimulation intensity at dUR may enhance or reveal additional neural responses that are not evident at lower stimulation intensities. Generally, across all stimulation locations and visits, the relative stimulation intensity was CPT* 2.4 (median, IQR: 1.7, 3.5) which corresponds to sufficient stimulation according to the literature (Supplementary Table S2) (Knüpfer et al., 2017; Sarica et al., 1986).

A trend toward a more prominent P2 peak component was observed in the pRetention group. In contrast, the pUrgency group appears to exhibit either a delayed P2 peak or a double peak waveform that coincides with the transition peak, regardless of SNM success. In pRetention patients, the P2 component was well-developed across all stimulation locations, with a visually stronger presence in non-responders compared to responders.

SEP QC subgroup analyses revealed similar results for LUTESA as the overall group analysis, with some showing trends rather than significant differences, probably due to the smaller sample size.

4.2. Lower urinary tract electrical sensory assessment pre and post sacral neuromodulation testing

There were no gross differences pre/post SNM test phase considering previously established LUTESA outcomes (CPT, PT, SEP component N1). While there was a subtle change in N1 topography over SNM test phase, PT was only selectively decreased during pudendal and urethral stimulation, irrespective of type of NLUTD.

The purely topographical changes of the LUT N1 component over SNM and the appearance of a transition peak around 150–250 ms in the Cz-Fz channel, that seemed to be more prominent in responders than non-responders, point towards first modulatory changes at the beginning of permanent SNM treatment suggesting shifts in how sensory information from the LUT is processed. Such functional reorganization may happen due to neuroplasticity. Regarding bladder sensitivity, our hypothesis regarding differential CPT changes for the pUrgency and pRetention NLUTD types was not supported by our results. The pUrgency group showed no significant change in CPTs throughout the SNM test phase, regardless of their SNM success. For the retention group, there was only a decrease in PTs over SNM testing which would be in line with our hypothesis.

Overall, LUTCPTs increased slightly over SNM test phase when taking clinical success (50 % responders in pRetention and up to 70 % responders in pUrgency of the patients) into account. Given that this change was minimal without differential effects for NLUTD type and driven by the SNM non-responders, this was nothing of clinical significance.

Furthermore, the effect disappeared when CPT values above 100 mA were excluded from the analysis. We would also expect a change in bladder sensitivity to correspond with a change in the PT. A significant visit effect for PT was only found for dUR, however, showing a decrease over SNM testing. Previous studies have reported on the test–retest reliability of CPT, indicating that it should be stable over time (Knüpfer et al., 2017; van der Lely et al., 2022). Our data cannot clearly confirm or deny a group-specific visit effect, due to the small and highly heterogeneous sample size which limits our ability to draw definitive conclusions.

In terms of the evoked potentials, significant changes in the topography (Tanova), but not in map strength, were found for the prominent N1 component over the SNM test phase. The N1 topography changed from a more centralized topography before SNM to a less centralized one after SNM testing. These changes might indicate cortical reorganization as reported in previous imaging SNM studies (Blok et al., 2006; Braun et al., 2002). Contrary to this literature, a decrease in activity after the SNM test phase could not be demonstrated in our study using GFP analysis.

For the SEP QC group and the marker-based analyses, no differences in latencies and amplitudes pre/post SNM testing could be shown for LUT assessments. However, Pud (trend only) and tibial SEPs revealed some reduction over SNM test phase, in the P40N50 amplitudes, which may be due to some modulatory effect. Considering the entire SEP waveform, an increased positivity in the transition phase around 100 ms may be noted after SNM test phase, most prominent in the pUrgency group. This would be in line with a study that found increased P80 and P100 amplitudes after tibial nerve stimulation treatment in patients with overactive bladder (Finazzi-Agrò et al., 2009).

4.3. Relation of lower urinary tract electrical sensory assessment and clinical outcome after sacral neuromodulation testing

It is notable that two-thirds of the pUrgency were responders to the SNM test phase, whereas the success rate in pRetention groups was around 50 %. The lower success rate of SNM in neurogenic patients with voiding dysfunction has been described previously (Arlen et al., 2011; Minardi and Muzzonigro, 2012) as well as the assumption that there may be different mechanisms of action for the respective type of NLUTD (De Wachter et al., 2020).

There were consistent differences in electrical thresholds between SNM responders and non-responders in the overall model as well as for TG and urethral stimulation locations already before SNM. It is important to note that the success of SNM could not be statistically evaluated at the level of NLUTD type due to the small sample size of non-responders in the pUrgency (only 6 patients). SNM responders showed lower PTs compared to the non-responders, also in the pRetention group. The elevated electrical sensitivity observed in the SNM responders is an interesting finding, potentially offering valuable insights into the mechanisms underlying SNM therapy. It may be indicative of a

more reactive or better sensory processing from the LUT. A lower severity of injury and a greater number of spared nerve fibres in responders, may contribute to the positive response to the treatment. Understanding these characteristics could help refine the criteria for predicting successful outcomes in SNM therapy and further distinguish the responder group from non-responders. Additionally, this finding could guide the development of personalized treatment strategies, where patients with similar sensory profiles might be more likely to benefit from SNM. Descriptive analysis of the graphs indicates that the pRetention group exhibits increased variability in CPT and PT values following SNM, whereas the pUrgency generally shows lower values with less variability. This suggests that while the overall sensitivity did not significantly differ, there seems to be differences in variability and trends between the NLUTD groups that could provide insights into their responses to SNM. However, further research is needed to explore the clinical implications of this observation and to determine whether bladder sensation could serve as a prognostic indicator for SNM success across larger patient populations.

Considering the Cz-Fz channel, SEP waveform looked different between responders and non-responders already before SNM. The newly described transition phase between N1 and P2 showed a more pronounced second negativity in non-responders. However, the clear definition or importance of this phase remains unclear. Although it is plausible that there is more variability among our patient groups for the P2 component, there may also be an additional peak which has not been described in healthy subjects yet. One publication from 1991 associated an extra peak in healthy subjects with discomfort during stimulation and the activation of structures with faster-conducting fibres (Gerstenberg et al., 1991). Since there is no difference in stimulation intensity between responders and non-responders in this study, this extra component cannot simply be explained by this factor. Additionally, this component does not change over the test phase but remains constant, suggesting that it might potentially be used as a predictor for the success of the SNM test phase.

In pRetention, the N1 peak is less pronounced for distal bladder locations in SNM non-responders compared to responders pre and post SNM. While it is not yet clear whether the prominence of the N1 peak could serve as a predictive factor for SNM success in patients with pRetention, this observation may warrant further investigation. Future studies should explore this feature in greater detail to assess its potential role in predicting SNM outcomes. Furthermore, in pRetention patients, the P2 component was visually stronger in non-responders compared to responders. Conversely, the pUrgency group demonstrates a prominent early central positivity, particularly at BD, which becomes more pronounced in responders following SNM. In non-responders, this positivity seems to be broader and even distributed over several peaks.

In terms of SEP marker analysis, only N50 latency of Pud stimulation showed significant differences between responders and non-responders. Further investigation of later components is needed to see if there are any modulating or even predictive outcomes of SNM success.

4.4. Limitations

One major limitation of this study is the rather small patient population with heterogeneous neurological conditions and urological dysfunction willing to undergo extra neurophysiology assessments. This study was not powered specifically for any research question related to LUTESA as this study was part of the screening phase of a bigger SNM RCT. As there might be different pathophysiological mechanisms underlying the same type of NLUTD, even within the urgency and retention groups, the mechanism for SNM success might vary according to the individual neuro-urological situation. Given the small sample size, especially in the pUrgency non-responder subgroup (6 in contrast to 13 responders), it was not possible to fully disentangle potential SNM responder effects from NLUTD group effects.

The LUTESA outcomes presented here, however, are very interesting for the field and informing future studies. While there seems to be some potential of predictive value regarding the success or failure of an SNM test phase, our results do not allow for conclusions about the actual treatment effect of SNM.

Our limited sample size carries a higher risk of statistical overfitting; hence, the results must be interpreted with caution and need to be replicated in larger studies. Regarding the robustness of our results, it was reassuring that exploratory analysis in our QC subgroup, which was selected based on more stringent data quality criteria, revealed similar results as in the overall group ($n = 46$). Another limitation is the rather short and variable duration of the test phase. It is plausible that longer-lasting SNM treatment would be needed for meaningful modulations in LUTESA outcomes.

5. Conclusions

The present study confirmed the feasibility of LUTESA in patients with clinically significant neuro-urological problems and revealed meaningful differences in electrical thresholds between patients with predominant voiding and those with predominant storage symptoms. Neurophysiology assessments pre/post SNM, showed only minor alterations in N1 topographies. With respect to clinical success of SNM, responders and non-responders differed significantly, already pre SNM, and the LUTSEP waveforms exhibited differences (descriptive nature) between these two groups.

Lower urinary tract electrical sensory assessment has great potential as a diagnostic tool and for investigating SNM-induced neuroplasticity in the sensorimotor system. It provides quantitative data for monitoring treatment response, assessing therapeutic outcomes and informing clinical decision-making. Whether such assessments may also be useful to predict SNM success, as indicated by our results, needs further investigations. Larger, more neuro-urologically homogeneous study groups, also investigating specific and more permanent SNM effects (short- and long-term follow-ups) using blinded and randomized study designs are required. Further research on the predictive value of LUTESA for SNM success is highly warranted.

Author contributions

Stephanie C. Knüpfer, Thomas M. Kessler and Martina D. Liechti contributed to the conception and design of the study. Data collection, and measurements were performed by Stéphanie van der Lely, Stephanie C. Knüpfer, Lorenz Leitner, Ulrich Mehnert, Jure Tornic, Thomas M. Kessler and Martina D. Liechti. Stephanie A. Stalder, Stéphanie van der Lely, Stephanie C. Knüpfer, Collene E. Anderson, Ulrich Mehnert, Carl M. Zipser, Thomas M. Kessler and Martina D. Liechti contributed to the analysis of the data and the interpretation of the results. Stephanie A. Stalder, Stéphanie van der Lely and Martina D. Liechti drafted the first version of the manuscript. All authors have contributed to data interpretation and critical review and revision of the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.2111003.

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