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CLINICAL ARTICLE

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Differences between brain responses to peroneal electrical transcutaneous neuromodulation and transcutaneous tibial nerve stimulation, two treatments for overactive bladder

Jan Krhut MD, PhD[1,2] | **Jaroslav Tintěra MSc, PhD[3]** | **Michal Rejchrt MD[4]** | **Barbora Skugarevská MD[1,2]** | **Roman Zachoval MD, PhD[5]** | **Peter Zvara MD, PhD[6,7]** | **Bertil F. M. Blok MD, PhD[8]**

[1]Department of Urology, University Hospital, Ostrava, Czech Republic

[2]Department of Surgical Studies, Ostrava University, Ostrava, Czech Republic

[3]Department of Radiodiagnostics and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[4]Department of Urology, 2nd Faculty of Medicine of Charles University and Motol University Hospital, Prague, Czech Republic

[5]Department of Urology, 1st Faculty of Medicine of Charles University and Thomayer Hospital, Prague, Czech Republic

[6]Department of Clinical Research, Biomedical Laboratory and Research Unit of Urology, University of Southern Denmark, Odense, Denmark

[7]Department of Urology, Odense University Hospital, Odense, Denmark

[8]Department of Urology, Erasmus Medical Center, Rotterdam, The Netherlands

Abstract

Objectives: To compare brain responses to peroneal electrical transcutaneous neuromodulation (peroneal eTNM®) and transcutaneous tibial nerve stimulation (TTNS), two methods for treating overactive bladder (OAB), using functional magnetic resonance imaging (fMRI). The present study was not designed to compare their clinical efficacy.

Materials and Methods: This study included 32 healthy adult female volunteers (average age 38.3 years (range 22–73)). Brain MRI using 3 T scanner was performed during three 8-min blocks of alternating sequences. During each 8-min block, the protocol alternated between sham stimulation (30 s) and rest (30 s) for 8 repeats; then peroneal eTNM® stimulation (30 s) and rest (30 s) for 8 repeats; then, TTNS stimulation (30 s) and rest (30 s) for 8 repeats. Statistical analysis was performed at the individual level with a threshold of $p = 0.05$, family-wise error (FWE)-corrected. The resulting individual statistical maps were analyzed in group statistics using a one-sample t-test, $p = 0.05$ threshold, false discovery rate (FDR)-corrected.

Results: During peroneal eTNM®, TTNS, and sham stimulations, we recorded activation in the brainstem, bilateral posterior insula, bilateral precentral gyrus, bilateral postcentral gyrus, left transverse temporal gyrus, and right supramarginal gyrus. During both peroneal eTNM® and TTNS stimulations,

Abbreviations: BCLS, biofeedback closed-loop system; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FWE, family-wise error; LUT, lower urinary tract; OAB, overactive bladder; peroneal eTNM®, peroneal electrical transcutaneous neuromodulation®; PTNS, percutaneous tibial nerve stimulation; ROI, region of interest; TENS, transcutaneous electrical nerve stimulation; TTNS, transcutaneous tibial nerve stimulation.

Peter Zvara and Bertil F. M. Blok are equal effort toward authorship.

Correspondence
Jan Krhut, MD, PhD, Department of Urology, University Hospital, 17. listopadu 1790, 708 52 Ostrava, Czech Republic.
Email: jan.krhut@fno.cz

but not sham stimulations, we recorded activation in the left cerebellum, right transverse temporal gyrus, right middle frontal gyrus, and right inferior frontal gyrus. Exclusively during peroneal eTNM® stimulation, we observed activation in the right cerebellum, right thalamus, bilateral basal ganglia, bilateral cingulate gyrus, right anterior insula, right central operculum, bilateral supplementary motor cortex, bilateral superior temporal gyrus, and left inferior frontal gyrus.

Conclusions: Peroneal eTNM®, but not TTNS, induces the activation of brain structures that were previously implicated in neural control of the of bladder filling and play an important role in the ability to cope with urgency. The therapeutic effect of peroneal eTNM® could be exerted, at least in part, at the supraspinal level of neural control.

KEYWORDS
brain, functional magnetic resonance imaging, mechanism of action, overactive bladder, peroneal electrical transcutaneous neuromodulation (peroneal eTNM®)

1 | INTRODUCTION

Neuromodulation represents the standard third-line treatment for an overactive bladder (OAB).[1] In addition to sacral neuromodulation, which is costly and requires the surgical implantation of a pulse generator, there are several methods available that use stimulation of peripheral nerves in the lower extremities.[2] Among peripheral neuromodulation methods, percutaneous tibial nerve stimulation (PTNS) is supported by most published evidence, however, PTNS requires trained medical staff to introduce a needle electrode, which limits its accessibility.[3] Transcutaneous tibial nerve stimulation (TTNS) aims to deliver the electrical current to the tibial nerve without compromising the skin.[4]

Alternatively, peroneal electrical transcutaneous neuromodulation (peroneal eTNM®) using the URIS® device with biofeedback closed-loop system (BCLS) is a new noninvasive method based on selective stimulation of the peroneal nerve. This method targets the peroneal nerve in the popliteal fossa using specially designed noninvasive electrodes, which allow precise localization of the optimal stimulation point. The stimulation of the peroneal nerve elicits a clearly visible motor response in form of rhythmic feet movement in the transversal plane. The BCLS is attached to the feet of the patient and contains a sensor that detects the motor response elicited by every stimulation impulse. The BCLS does not allow to start the stimulation until the optimal motor response has been achieved. In addition, the BCLS allows for continual adjustment of the stimulation parameters during the stimulation session. This guarantees effective and consistent peroneal nerve stimulation. The principles, efficacy, and safety of peroneal eTNM® in OAB treatment have been recently described.[5]

The mechanism of action of neuromodulation for treating OAB is not fully understood; thus, studies designed to elucidate this mechanism are warranted.[6] Only a single study by Finazzi-Agrò et al. demonstrating brain activation in response to PTNS, have been published to date.[7]

The present study aimed to make a head-to-head comparison of the brain regions activated between peroneal eTNM® and TTNS, based on functional magnetic resonance imaging (fMRI), and to determine whether peroneal eTNM® and TTNS induced responses at the supraspinal level of the central nervous system.

2 | MATERIALS AND METHODS

2.1 | Subjects

The study enrolled healthy adult female volunteers (age > 18 years) that were willing and able to undergo the assessment, according to the study protocol. The exclusion criteria were: the presence of lower urinary tract (LUT) symptoms, urinary tract infection, history of previous malignant disease in the pelvic region, use of medications with potential effects on brain or bladder function, and any condition that would prohibit the individual from undergoing an fMRI.

All subjects provided written informed consent. The study protocol was approved by the Institutional Review

Board of the Institute for Clinical and Experimental Medicine, Prague, Czech Republic (IRB No. A-1925).

2.2 | Study design

Each subject's head was placed into the head coil of the MRI system in the supine position. The feet were placed into a specially designed sham device, which allowed passive feet movements in the mediolateral direction, in the transverse plane, imitating the motor response to electric stimulation of the peroneal nerve. The sham device design and its description is shown in Figure 1. Subsequently, URIS® active electrodes were attached bilaterally over the peroneal nerve in the popliteal fossa, and a neutral electrode was placed on the lower abdomen. Electrodes were connected to the URIS® neuromodulation device (STIMVIA®). To perform TTNS, superficial adhesive electrodes were attached bilaterally, behind the internal malleolus, and another electrode was placed at 10 cm in the cranial direction, according to Amarenco et al.[8] The electrodes were connected to the UROstim2® generator (Schwa-medico GmbH, Ehringshausen, Germany). Both the URIS® and UROstim2® devices were placed outside the magnet room. This setting allowed MRI scanning during three 8-min blocks of alternating sequences. During each 8-min block, the protocol alternated between sham stimulation (30 s) and rest (30 s) for 8 repeats; then peroneal eTNM® stimulation (30 s) and rest (30 s) for 8 repeats; then, TTNS stimulation (30 s) and rest (30 s) for 8 repeats. The study protocol is depicted in Figure 2. All possible measures have been adopted to ensure that both peroneal eTNM® and TTNS were delivered in the optimal manner (experienced medical professional estimated the stimulation points, clearly visible motor response presented during entire experiment, etc.).

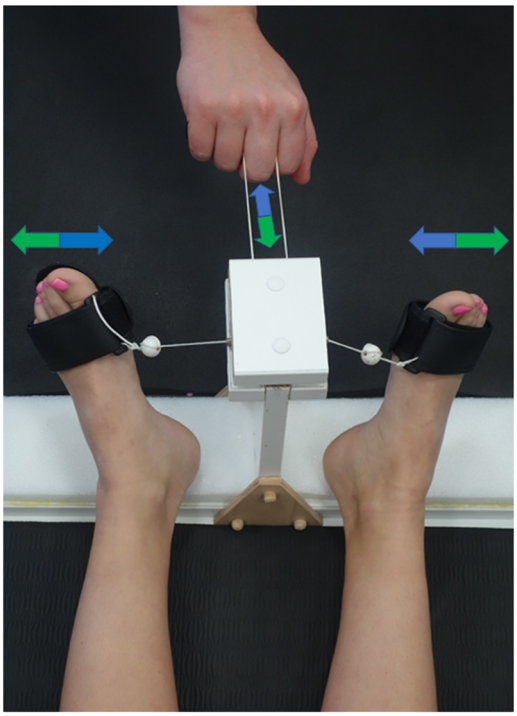

FIGURE 1 Design of the sham device for peroneal eTNM®. Alternating pull and release of the strings on the device mechanically induces passive movement of the feet in the transversal plain, mimicking the typical motor response induced by peroneal eTNM®. (peroneal eTNM®, peroneal electrical transcutaneous neuromodulation).

2.3 | MRI data acquisition

All data were acquired with a 3T MRI scanner (Siemens VIDA 3T) equipped with a 64-channel head coil. The MRI examination protocol consisted of functional and morphological scans, performed using the blood oxygen level-dependent technique (BOLD technique). The fMRI was performed according to the paradigm using 480 dynamics. All technical settings for the MRI sequences are shown in Table 1.

2.4 | Statistical processing

Statistical evaluations were performed with SPM12 software (available at: http://www.fil.ion.ucl.ac.uk/spm). fMRI data pre-processing consisted of motion correction (realignment), slice timing, and smoothing with a Gaussian filter (FWHM = 6 × 6 × 6 mm). Images were normalized to MNI-152 standard-space (http://www.loni.ucla.edu/ICBM).

Statistical analyses on the individual level were performed with a threshold of $p = 0.05$, family wise error (FWE)-corrected for multiple measurements. The resulting individual statistical maps were analyzed in group statistics (random effect) with a one-sample *t*-test, a $p = 0.05$ threshold, and false discovery rate (FDR)-corrected for multiple measurements. A cluster size of at least 10 continuous voxels was used to obtain main effects.

Connectivity evaluations were performed with CONN software (version CONN21.a, http://www.conn-toolbox.org). During the data denoising procedure, a linear regression was performed with the following confounding effects: white matter (5 parameters), CSF (5 parameters), and motion realignment (12 parameters). A band-pass filter (0.008−0.09) was also used for data denoising. In the second level of result analysis, differences in seed-based

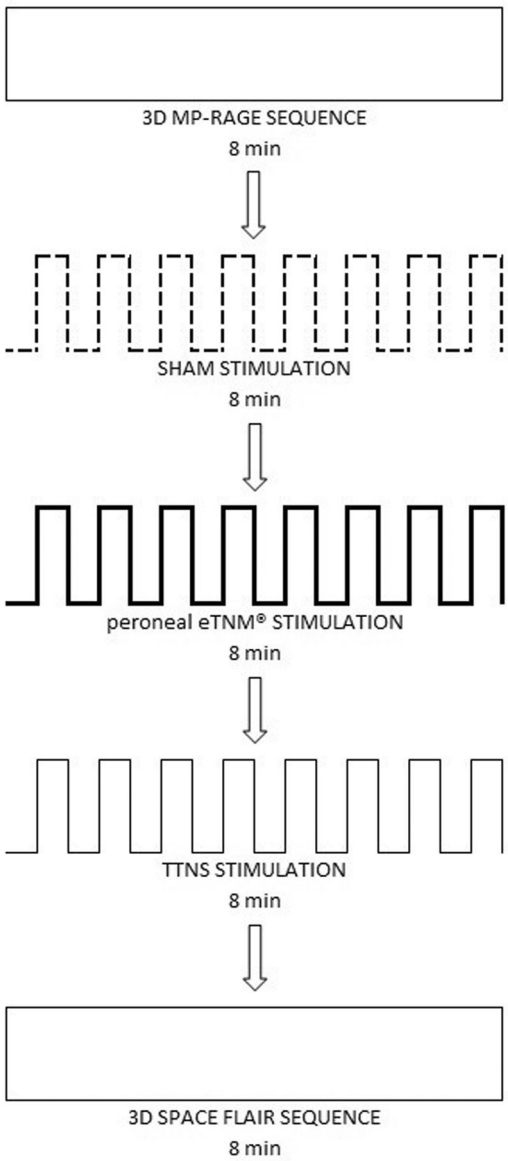

FIGURE 2 Schematic of the study protocol. Each study was initiated with the acquisition of a morphological brain scan with the 3D MP-RAGE sequence. Subsequently, fMRI measurements were acquired during an 8-min block of alternating sequences of 30-s rest and 30-s passive mediolateral movement of the feet, for the sham intervention. This was followed by fMRI measurements acquired during an 8-min block of alternating sequences 30-s rest and 30-s peroneal eTNM® stimulations. Next, the same 8-min block of sequences was performed with TTNS stimulations. The protocol was completed by acquiring T2-weighted morphological images acquired with the SPACE FLAIR sequence. FLAIR, fluid attenuated inversion recovery, fMRI, functional magnetic resonance imaging, MP,RAGE, magnetization prepared rapid gradient-echo, peroneal eTNM®, peroneal electrical transcutaneous neuromodulation; SPACE, sampling perfection with application-optimized contrasts using a different flip angle evolution, TTNS, transcutaneous tibial nerve stimulation.

connectivity between the cingulate gyrus and other brain regions (ROI-to-ROI analysis) were tested. These connectivity differences were studied at the statistical level of an uncorrected $p = 0.05$.

3 | RESULTS

The study included a total of 32 participants. One subject reported an acute episode of anxiety during the fMRI scanning and terminated the examination prematurely. All other subjects underwent the examination according to the protocol. In 8 cases, significant head-motion artefacts rendered the data unanalysable. An additional subject was excluded from the analysis due to artefacts associated with permanent teeth implants. Therefore, 22 subjects were included in the final analysis. The average age was 38.3 years (range 22−73). The motor-threshold stimulation intensity was used in both peroneal eTNM® and TTNS. In peroneal eTNM®, the mean (±SD) stimulation intensities applied were 25.4 ± 6.0 V, on the right leg, and 24.3 ± 7.1 V, on the left leg. In TTNS, the mean stimulation intensities applied were 26.5 ± 6.0 mA, on the right leg, and 25.3 ± 5.9 mA, on the left leg.

3.1 | Topographical analysis of the regions of interest (ROI) activated during stimulation

In the group analysis, with a threshold of $p = 0.05$ (FDR corrected), we observed activation in the brainstem, bilateral posterior insula, bilateral parietal operculum, bilateral precentral gyrus, bilateral postcentral gyrus, left transverse temporal gyrus, and right supramarginal gyrus, during stimulations with peroneal eTNM®, TTNS, and sham protocols. We observed that the left cerebellum, right transverse temporal gyrus, right middle frontal gyrus, and right inferior frontal gyrus were activated during stimulation with both peroneal eTNM® and TTNS, but not with the sham protocol. In addition, we observed activation in the right cerebellum, right thalamus, bilateral basal ganglia (putamen), bilateral cingulate gyrus, right anterior insula, right central operculum, bilateral supplementary motor cortex, bilateral temporal gyrus superior, right angular gyrus, and left inferior frontal gyrus exclusively during stimulation with peroneal eTNM®. None of the brain ROIs were activated exclusively during the stimulation with TTNS. The results are shown in Table 2 and Figure 3.

TABLE 1 MRI technical settings used for data acquisition.

	3D MP-RAGE Sequence	fMRI EPI sequence	3D SPACE FLAIR Sequence
Voxel size (mm^3)	$0.75 \times 0.75 \times 0.75$	3 x 3 x 3	$1.0 \times 1.0 \times 1.0$
Number of slices	224	60	208
Orientation	sagittal	axial	sagittal
TR/TE (ms)	-	1000/30	-
TR/TE/TI (ms)	2400/2.37/1000	-	6000/350/1900
Flip angle	8°	50°	-
Bandwidth (Hz/pixel)	210	2056	770

Abbreviations: EPI, echo-planar imaging; FLAIR, fluid attenuated inversion recovery; fMRI, functional magnetic resonance imaging; MP-RAGE, magnetization prepared rapid gradient-echo; SPACE, sampling perfection with application-optimized contrasts using a different flip angle evolution; TE, echo time; TI- inversion time; TR, repetition time.

3.2 | Quantitative analysis of the ROIs activated during stimulation

We observed significant differences in the numbers of voxels activated in respective regions during peroneal eTNM®, TTNS, and sham stimulations. The most significant differences that favored peroneal eTNM® compared to TTNS or sham (at least twofold differences), were detected in the brainstem, bilateral cerebellum, bilateral basal ganglia (putamen), bilateral insula anterior, bilateral central operculum, bilateral precentral gyrus, bilateral postcentral gyrus, bilateral supplementary motor cortex, bilateral temporal gyrus, bilateral angular gyrus, bilateral supramarginal gyrus, bilateral middle frontal gyrus, and bilateral inferior frontal gyrus. The results are shown in detail in Table 2.

3.3 | Connectivity analysis

Based on the crucial role of the cingulate gyrus in the supraspinal control of LUT function,[9] we performed an analysis of connectivity between regions of interest (ROI to ROI analysis), with the anterior and posterior cingulum as seeds ($p = 0.05$, uncorrected). We observed positive connectivity, expressed as a higher signal correlation between the basal ganglia (caudate nucleus, putamen) and the limbic system (amygdala), during peroneal eTNM® compared to TTNS stimulation. The results are summarized in Figure 4.

4 | DISCUSSION

To our knowledge, this study was the first to make a direct comparison between brain responses to different neuromodulation methods for OAB treatment and a sham protocol. An analysis of the brain areas activated during stimulation revealed significant differences in the number of activated ROI and the sizes of activated voxel clusters.

As expected, peroneal eTNM®, TTNS, and sham stimulations elicited activation in the postcentral and precentral gyri; that is, the cortical regions with primary sensory and motor projections to the lower limbs. In addition, peroneal eTNM® activated other brain structures, such as the brainstem, basal ganglia, anterior insula, cingulate gyrus, supplementary motor cortex, superior frontal gyrus, and inferior frontal gyrus. Importantly, these latter structures were previously described to be involved in supraspinal regulation of LUT function. The brainstem (namely, the periaqueductal gray) is where the afferent neurons that ascend from the sacral spinal cord terminate; therefore, the brainstem plays a pivotal role in the regulation of both urine storage and micturition.[10] The basal ganglia are primary responsible for controlling voluntary motor movements; however, they are also involved in motor learning, executive functions, emotions, and cognition. Several authors have emphasized the role of the basal ganglia in the initiation of micturition and voluntary control of the pelvic floor.[11,12] The insula (particularly the right insula) maps and processes all bladder and other visceral sensations; it is sometimes referred to as the "sensory cortex of the autonomic nervous system".[13] Insula activity increases as the bladder fills and it forms a salient network with the cingulate gyrus and supplementary motor cortex, which generates sensations, such as the desire to void.[14,15] The cingulate gyrus belongs to the limbic system, which is responsible for integrating emotional context with interoception. Accordingly, some authors have suggested that the activation of the cingulate cortex represents the neurophysiological basis

TABLE 2 Brain regions activated during peroneal eTNM®, TTNS, and sham stimulations, evaluated in group analyses.

			Peroneal eTNM®	TTNS	Sham
Brainstem			0.435 (44 vox)	0.389 (12 vox)	0.667 (4 vox)
Cerebellum		R	0.014 (838 vox)		
		L	0.004 (1280 vox)	0.093 (48 vox)	
Thalamus		R	0.599 (15 vox)		
		L			0.212 (30 vox)
Basal ganglia		R	0.033 (256 vox)		
(Putamen)		L	0.026 (285 vox)		
Cingulate gyrus	Middle	R	0.287 (57 vox)		
		L	0.373 (40 vox)		
Insula	Anterior	R	0.022 (306 vox)		
		L	0.049 (214 vox)		0.556 (7 vox)
	Posterior	R	0.305 (53 vox)	0.110 (43 vox)	0.556 (7 vox)
		L	0.204 (82 vox)	0.090 (49 vox)	0.394 (14 vox)
Operculum	Parietal	R	0.011 (394 vox)	0.290 (32 vox)	0.002 (233 vox)
		L	0.007 (449 vox)	0.047 (70 vox)	0.001 (265 vox)
	Central	R	0.048 (304 vox)		
		L	0.040 (334 vox)	0.389 (12 vox)	0.475 (10 vox)
Precentral gyrus		R	0.021 (576 vox)	0.041 (75 vox)	0.005 (194 vox)
		L	0.012 (594 vox)	0.030 (86 vox)	0.002 (239 vox)
Postcentral gyrus		R	0.029 (309 vox)	0.006 (152 vox)	0.023 (114 vox)
		L	0.027 (401 vox)	0.019 (103 vox)	0.015 (134 vox)
Supplementary motor cortex		R	0.031 (265 vox)		
		L	0.033 (257 vox)		
Temporal gyrus	Superior	R	0.460 (28 vox)		
		L	0.309 (63 vox)		
	Transverse	R	0.392 (37 vox)	0.265 (20 vox)	
		L	0.120 (126 vox)	0.157 (33 vox)	0.186 (34 vox)
Angular gyrus		R	0.676 (10 vox)		
		L			
Supramarginal gyrus		R	0.001 (750 vox)	0.005 (158 vox)	0.124 (47 vox)
		L	0.001 (708 vox)		
Frontal gyrus	Superior	R	0.204 (82 vox)		0.067 (69 vox)
		L	0.169 (97 vox)		
	Middle	R	0.236 (120 vox)	0.076 (54 vox)	
		L			
	Inferior	R	0.007 (497 vox)	0.206 (50 vox)	
		L	0.046 (222 vox)		

Note: Values represent uncorrected p-values on the cluster level, with a minimal cluster size of 10 voxels. Smaller values correspond to more significant activation of the brain region. Results were evaluated with a threshold of $p = 0.05$, FDR-corrected. Empty cells represent regions where no activation was recorded at an uncorrected threshold of $p = 0.001$ ($n = 22$).

Abbreviations: FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FWE, family wise error; peroneal eTNM®, peroneal electrical transcutaneous neuromodulation; TTNS, transcutaneous tibial nerve stimulation.

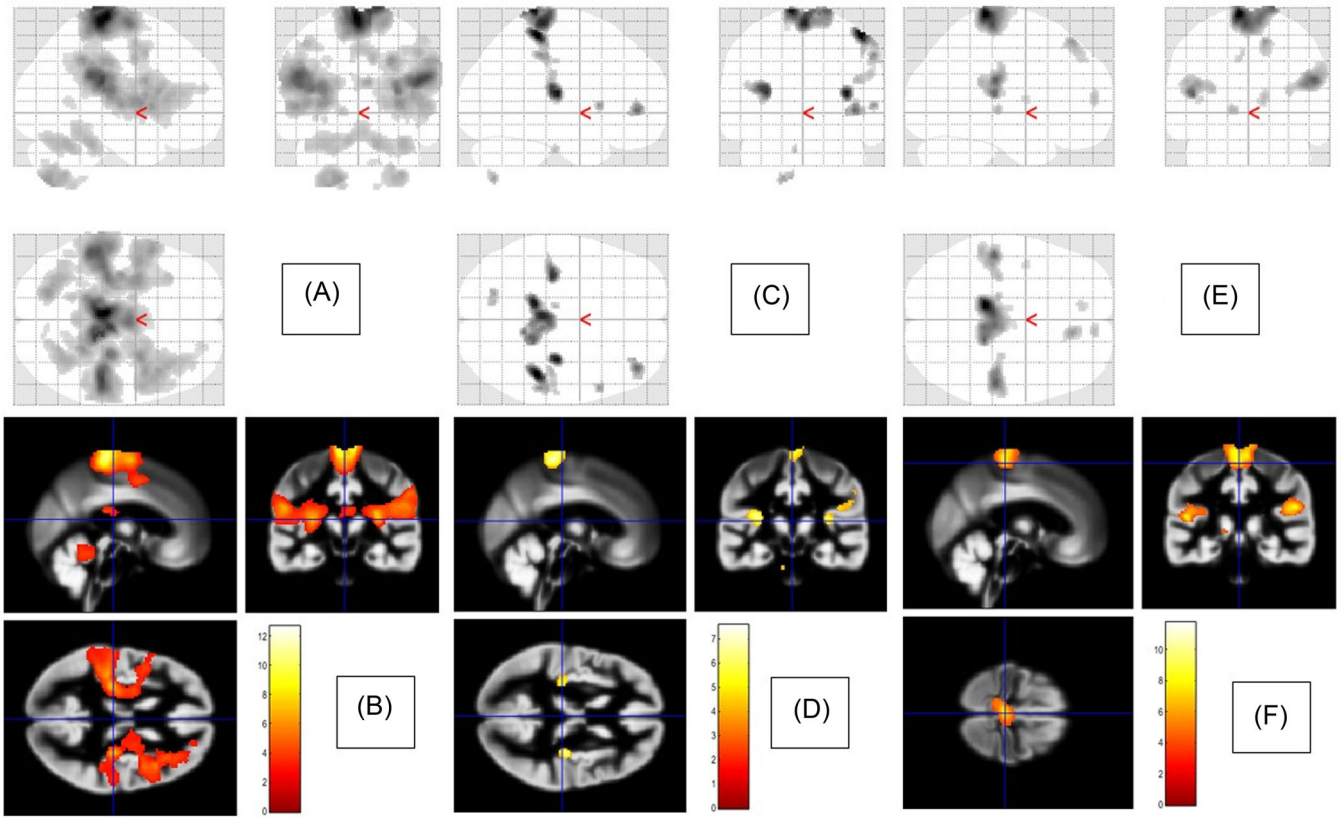

FIGURE 3 fMRI maps from the group analysis ($p = 0.05$, FDR corrected) demonstrate ROIs activated by peroneal eTNM®, TTNS, and sham stimulations. Brain activation in response to the (A, B) peroneal eTNM®, (C, D) TTNS, and (E, F) sham stimulations. fMRI, functional magnetic resonance imaging, peroneal; eTNM®, peroneal electrical transcutaneous neuromodulation; ROI, region of interest; TTNS, transcutaneous tibial nerve stimulation.

of the sensation of urgency.[16] The parietal operculum is involved in sensory, motor, autonomic, and cognitive processing. It is anatomically and functionally closely connected to the insula, and it has been shown to be activated during somatosensory stimulation in humans. Previous studies have shown that the parietal operculum is activated during the initiation of micturition and during the discharge of urine.[17] A solid body of evidence has indicated that the inferior frontal gyrus, the lateral part of the superior frontal gyrus, and the dorsolateral prefrontal cortex are activated during bladder filling. Several fMRI studies have shown that activation of these regions is abnormally weak in patients with urgency incontinence. Those findings suggested that these regions play a role in controlling the storage phase and suppressing the activity of the subordinate spinal and cerebral pathways.[13,18]

Recent studies have shown that most of the brain regions described above comprised part of the central autonomic network that contributes to the maintenance of the balance between sympathetic and parasympathetic activity.[19] This fits well with our current understanding that the physiological function of the LUT requires precise coordination between somatic and autonomous innervation. Our finding of deep brain structures activation during peroneal eTNM® supported the hypothesis that peroneal eTNM® acts, at least in part, at the central level in regulating LUT function.

TTNS activation of these critical brain regions was significantly lower than the activation elicited by peroneal eTNM®. Indeed, often, the activation achieved with TTNS did not differ from that observed during sham stimulation. In addition, the connectivity between brain regions involved in LUT regulation (cingulate gyrus, basal ganglia, and the limbic system) was stronger during peroneal eTNM® stimulation than during TTNS stimulation. This difference could be explained by the fact that TTNS and peroneal eTNM® are based on different principles. Originally, transcutaneous electrical nerve stimulation (TENS) was invented for pain treatment, based on the "gate control theory".[20] This theory suggests that stimulating large-diameter afferent fibers with non-noxious tactile stimulation can inhibit the noxious input of nociceptors by activating inhibitory neurons in the substantia gelatinosa of the dorsal horn of the spinal cord.[21] Therefore,

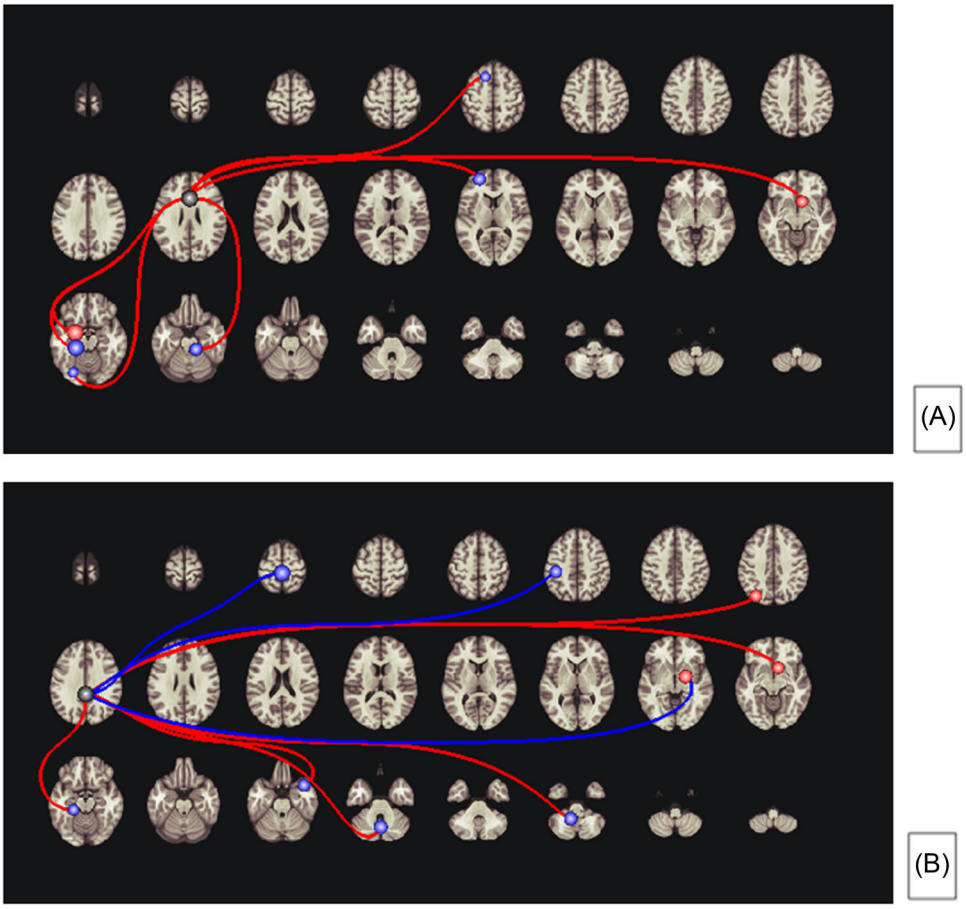

FIGURE 4 Differences in connectivity between peroneal eTNM® and TTNS. Connectivity analyses were performed with (A) the anterior cingulum as a seed and (B) the posterior cingulum as a seed. The ROI-to-ROI connectivity analysis was performed with a threshold of $p = 0.05$, uncorrected. Red lines depict positive connectivity, based on a positive signal correlation (i.e., the ROI was activated when the seed was activated); blue lines depict negative signal connectivity (i.e., the ROI was deactivated when the seed was activated). Red dots mean higher correlation of peroneal eTNM® over TTNS, blue dots mean higher correlation of TTNS over peroneal eTNM®. fMRI, functional magnetic resonance imaging, peroneal; eTNM®, peroneal electrical transcutaneous neuromodulation; ROI, region of interest; TTNS, transcutaneous tibial nerve stimulation.

TENS aims to stimulate a large number of sensory receptors with large surface electrodes placed at the site where pain is felt to prevent nociceptive stimuli from being transmitted to the supraspinal parts of the central nervous system. Later, TENS was adopted for treating OAB and configured as TTNS to eliminate the need for the needle electrode. However, the use of large-area surface electrodes causes a significant spread of the electrical field in tissue and results in poor electrical recruitment of deeper nerves. Furthermore, the lack of standardization of the electrode placement and position may result in inconsistencies in nerve activation and therapeutic effects. Therefore, the motor response to TTNS could be due to direct stimulation of the underlying muscle, rather than nerve stimulation. Despite promising results in clinical trials,[22] real-life data have shown that most patients discontinue TTNS, due to lack of efficacy.[23]

In contrast to TTNS, based on the clearly detectable specific motor response, peroneal eTNM® allows precise detection of the optimal stimulation point. In addition, several other technical features that distinguish peroneal eTNM® from TTNS are described elsewhere.[5] Based on the results of the present study, we propose that highly selective stimulation of the nerve originating from the sacral spinal roots represents a key factor in the therapeutic success of any peripheral neuromodulation method for treating OAB.

However, it is important to acknowledge that the present study was not designed to compare the clinical efficacy of peroneal eTNM® versus TTNS.

Our results are consistent with those obtained in previous fMRI trials that assessed the brain response to suprasensory stimulation with sacral neuromodulation in patients with urgency incontinence.[24] In addition, our hypothesis that the central mechanism of action is

involved in the therapeutic effect was supported by the fact that the effect of peroneal eTNM® may persist for several months. This could be explained by the involvement of learning processes and/or brain plasticity. This learning effect was observed previously in a study on acute versus chronic sacral neuromodulation.[25]

The strengths of the present study included the high number of enrolled subjects, the use of a sham protocol for peroneal eTNM®, and a clearly defined off/on paradigm. In addition, there were several study limitations. First, we did not include a sham protocol for TTNS. Second, the study was performed on healthy subjects, rather than patients with OAB. Additionally, the absence of both subsensory and sensory stimulations in the paradigm prevented a direct comparison between our results and those from previous fMRI studies that applied sacral neuromodulation. We did not implement that paradigm, due to the extreme time demand required; however, we plan to conduct a separate study to assess subsensory and sensory stimulations. Despite these limitations, our study provided novel, valuable insight into the mechanism of action of peroneal eTNM®. Further research should focus on elucidating the complex effects of peripheral neuromodulation on supraspinal regulation in patients with OAB.

5 | CONCLUSIONS

Our study provides evidence that peroneal eTNM®, in contrast to TTNS, induces activation of brain structures that were previously implicated in the neural control of the of bladder filling and play an important role in the ability to cope with urgency. Our data supported the hypothesis that the therapeutic effects of peroneal eTNM® is directed, at least in part, at the supraspinal level of neural control.

AUTHOR CONTRIBUTIONS

Jan Krhut: study concept, study design, data acquisition, interpretation of data, manuscript writing. **Jaroslav Tintěra**: study concept, data acquisition, statistical analysis, interpretation of data, manuscript writing. **Michal Rejchrt**: study concept, data acquisition, manuscript revision; **Barbora Skugarevská**: data acquisition, project administration, manuscript revision. **Roman Zachoval**: study concept, study design, interpretation of data, manuscript writing. **Peter Zvara**: study design, data acquisition, interpretation of data, manuscript writing, supervision. **Bertil F. M. Blok**: study concept, study design, interpretation of data, manuscript revision, supervision.

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CONFLICTS OF INTEREST STATEMENT

J. K. is a consultant for Stimvia. M. R. is the investigator for Stimvia. B. F. M. B. is the member of Scientific Advisory Board of Stimvia. The remauning authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board of the Institute for Clinical and Experimental Medicine, Prague, Czech Republic (IRB No. A-1925). All subjects provided written informed consent.

ORCID

Jan Krhut http://orcid.org/0000-0003-4205-5926
Roman Zachoval http://orcid.org/0000-0003-4222-5497
Bertil F. M. Blok http://orcid.org/0000-0001-9354-7395

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