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Noninvasive Brain Stimulation in the Treatment of Functional Urological and Pelvic Floor Disorders: A scoping review

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Abstract

Functional pelvic floor disorders (PFD) such as bowel and bladder dysfunctions can be challenging to manage with our current therapeutic modalities. Recently, noninvasive brain stimulation has emerged as a novel strategy for noninvasive pelvic floor management. Here, we assessed the current state of research on this topic. A scoping review was conducted with Pubmed, Web of Science, Embase, in conjunction with clinicaltrials.gov, encompassing all manuscripts published without past time limit up until June 30th, 2022. Of the 880 abstracts identified in a blind selection by two reviewers, 14 publications with an evidence level of 1 or 2 (Oxford scale) were eligible and included in this review. Review articles, case reports (<5 patients), letters, and protocol studies were excluded. PFDs were described as either pelvic pain or lower urinary tracts symptoms (LUTS) with repeated Transcranial Magnetic Stimulation (rTMS) as the most common treatment modality. Despite heterogeneous therapeutic protocols, significant improvements were observed such as reduction in post-void residual of urine, increased bladder capacity, improved voiding flow paraments, and decreased chronic pelvic, and bladder pain. No appreciable adverse effects were noted. However, low sample populations allowed only provisional conclusions. Noninvasive transcranial neurostimulation for LUTS and pelvic pain is emerging as an effective tool for clinicians to utilize in the future. Further investigation is needed to elucidate the full significance of the indicated outcomes.

Keywords

transcranial magnetic stimulation; transcranial direct current stimulation; pelvic floor disorder; urination disorder; pelvic pain

1. Introduction

Brain transcranial stimulation is a technique that uses neuronal membrane depolarization to initiate action potentials to modulate their excitability. This depolarization can be induced by an electric or magnetic stimulus. This principle was first described in 1994 by Rossini et al.

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[1]. When subjected to external perturbations, the neural network reorganizes and interacts with each other in different ways, this mechanism is the basis of cortical plasticity.

Repetitive pulses for several minutes with a magnetic or electric field applied to the brain cortex can induce network change, with more long-lasting effects. Early approaches with electrical high voltage have been supplanted by two more comfortable and painless techniques, transcranial magnetic stimulation (TMS) in 1985 by Barker et al. [2] and transcranial direct current stimulation (tDCS) by Nitsche and Paulus, in 2000 [3].

Therapeutic applications can be achieved by stimulation or inhibition of a given cortical network. With neuronavigation and noninvasive stimulation technology advancement in the last twenty years, stimulation targeting more specific brain regions has become feasible (Figure 1). Research in brain behavior, psychiatric disorders, depression, and neurogenic pain were then developed.

Although repetitive TMS (rTMS) has been around for decades, only recently has it become a fundamental therapy for depression, yielding great results. Not only has it received clearance for clinical use by the Food and Drug Administration (FDA) in the United States, but it has also become a recommended application for depression by the International Federation of Clinical Neurophysiology (IFCN) [4]. Moreover, recent research on neuropathic and non-neuropathic pain, as shown in a review by Lefaucheur et al. [5], has demonstrated a consistent painkiller effect of this noninvasive therapy. Therefore, establishing rTMS as a novel multidimensional therapeutic option for various pathologies that are difficult to treat.

The time has come to extend the scope of noninvasive neurostimulation to a new field: functional pelvic floor disorders. Lower urinary tract symptoms (LUTS), pelvic pain, or bowel issues are possible applications for this therapy. The principle of cortical neuromodulation comes directly from the application of electrical currents to peripheral nerves [4]. Peripheral neuromodulation is a well-established therapy, commonly utilized to improve LUTS and pain. It makes sense to try brain stimulation where peripheral neurostimulation has shown effectiveness.

A recent review by Ruiz et al. [6] underlines the applicability of rTMS in Multiple Sclerosis (MS) for spasticity, manual dexterity, gait, and memory. They highlight its promising application in urology for LUTS. However, due to the heterogeneity of stimulation strategies and protocol design, it is difficult to know whether noninvasive transcranial stimulation could indeed be beneficial in this indication.

Here, we performed a scoping review of the current literature to identify the current use of noninvasive transcranial stimulation for functional urological and pelvic floor disorders.

2. Materials and Methods

A scoping review of the literature and ongoing clinical trials was conducted using Pubmed, Web of Science, Embase, and ClinicalTrial.gov, including all articles published in the subject matter until June 30th, 2022. The PRISMA's guidelines [7] were applied, to match

good practice recommendations for a literature review. A formula with keywords and MESH terms was used to identify articles and can be found in supplementary materials.

Only articles in English or French were included, the software Covidence® was utilized as a screening method to do a blind selection by two different reviewers. As part of the inclusion criteria, only abstracts or titles that included noninvasive transcranial therapy and pelvic floor or urinary disorders in human adult individuals were included. Review articles, case reports (<5 patients), letters, and protocol studies were excluded. Results from the literature search and selected articles are shown in the PRISMA flow chart in figure 2.

Full articles were retrieved for inclusion in the final selection and references from said articles were searched for applicable supplementary publications. Next, we reviewed the abstracts and full articles, and classified them using the updated Oxford Level of Evidence [8], identifying methodological quality, design and bias.

Pelvic floor disorders were described according to the nature of the devices and the protocols used for delivery of the stimuli. Then, analysis of the effectiveness of treatment was made by individualizing the two possible indications (LUTS or pelvic pain), taking into account the number of patients in the studies.

3. Results

Utilizing our research strategy, we identified 14 articles, with a prospective, non-randomized, randomized, controlled, open, and double-blind design. Oxford level of evidence utilized was 1 or 2. Details of our results are summarized in Table 1.

The average number of patients included in the studies is 10. Men and/or women were enrolled. Patients included had the followings diseases: MS, Parkinson's Disease (PD), Spinal cord injury (SCI), refractory pelvic pain, urologic pelvic pain syndrome (UCPPS), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), CPPS and endometriosis.

The pelvic floor disorders retrieved exclusively pelvic pain, which was evaluated with various scales and questionnaires. LUTS were widely explored in different dimensions like urodynamics (UDS), scales, questionnaires, electromyography (EMG), functional magnetic resonance imaging (fMRI), and ultrasound (US).

4. Discussion

Noninvasive stimulation is produced by two main techniques, magnetic fields (TMS, Transcranial Rotating Permanent Magnet Stimulator-TRPMS) and electric current (tDCS). LUTS was studied in 5 articles [9-13], pelvic pain for the 8 others [14-21] and 1 [22] both of them.

rTMS was the most common technique used by authors in 10 publications, including the first study by Centonze et al.[9] in 2007. The Magstim Company (UK) provided the first device for medical use in the field of depression and then pain. For both LUT and pelvic pain, 9 of the authors used the Magstim 200, Magstim Rapid2, or Bistim2 (Figure 1B). Only

the Pinot-Monange et al. [17] study used the MagProX100 (Magventure Tonika Elektronic, Denmark) device. During treatment the stimulator was connected to the figure-of-eight coil and was held over the head with the handle pointing backward, to elicit a “motor hotspot”. The dominant hemisphere or both sides when possible was targeted [19].

The area near Cz-vertex in the 10-20 System to elicit the “soleus muscle hotspot” was the cortex target in four LUTS treatment studies. For pelvic and LUT pain, the C3 and/or C4 area corresponding to the M1 (primary cortex motor) was chosen by 5 authors. This area elicits the first interosseous hand muscle and the pelvic floor area. Only Yani et al. [18] tested the supplementary motor area (SMA) for pelvic pain.

The therapeutic protocol varied from one study to another. For LUTS treatment, the frequency varied from 1 to 5Hz, 900 to 1000 stimuli with 65 to 120% MSO/RMT. For pelvic pain treatment, the frequency varied from 10 to 20Hz, 1500 to 2000 stimuli, and 80 to 110% resting motor threshold (RMT) with an average of 20 minutes of treatment. However, Calabro et al. [20] preferred to use 5Hz and 110% active motor threshold (AMT) over RMT, for the need of the study that couples rTMS with recorded focal muscle vibration. To go further, Yani et al. tested two types of stimuli: 10hz and 1Hz therapy, by applying the principle that cortex areas inhibition and stimulation are frequency dependent.

tDCS is an alternative noninvasive treatment that uses direct electrical currents to stimulate the same specific brain areas. Two electrodes are placed over the head to modulate cortical activity. Only 2 studies explored this modality with a specially developed battery-driven, constant current stimulator (Schneider Electronic, Germany). They used a 1 or 2mA current, to stimulate the M1 for 20min therapy. A third study used 2 devices (Active Dose Company, Thailand) to stimulate simultaneously the M1 and the dorsolateral prefrontal cortex, with a 0,3mA intensity for each area.

The most recent study, a pilot experiment from Khavari et al. represents the next step of the stimulation protocols. The paradigm investigated in this study was based on the concept that cortex areas involved in LUT function are numerous so modulations must be multiple and simultaneous, with both stimulation and inhibition targets.

They used a custom made TRPMS device, able to produce multiple focal magnetic fields at the same time. Areas targeted for LUTS therapy were F3, F4, C3, C4, and Cz, 3 areas were inhibited and 2 were stimulated for a total of 40 min of treatment.

Therapeutic protocols were delivered once a day, five consecutive days for 10 studies. Others varied from one unique session to 10 consecutive ones. One or two weeks was the most common duration. Assessment of measurement tools for primary and secondary outcomes followed a very heterogenous design, depending on the various study designs.

4.1 LUTS therapeutic effects

Over the six studies exploring noninvasive stimulation with magnetic fields (rTMS or TRPMS), 3 are about MS, 2 for SCI, and 1 for PD patients.

The patient's symptoms were overactive bladder, with or without urethral sphincter dyssynergia, or underactive bladder. They had significant improvements with TMS. Post void reduction decrease for 3 authors with 2 Pdet-Qmax positive association. Bladder capacity increased for 2 and decreased for 1. Patients felt subjectively better during the voiding phase, according to results obtained by multiple validated questionnaires.

The International Prostate Symptom Score and the first sensation of bladder filling were greater for PD patients as reported by Brusa et al. [10].

Vasquez et al. [11] explored eliciting modulation of the pudendo-anal reflex (PAR) in response to rTMS with EMG in SCI patients, results were analyzed for its basic science findings. The therapy displayed a significant facilitating effect on the PAR, which confirm a real motor effect in the theoretical LUT area.

These results are limited and the last recommendations on TMS therapy, highlight the lack of evidence on LUT treatment [5]. All study populations were small (N≤13), except for Vasquez et al., and more power is essential to asses a clinical effect. However, all of these data converged and showed a real effect on various populations of patients.

4.2 Pelvic Pain therapeutic effects

The rTMS and tDCS studies were tested in 7 complex pelvic pain studies. All patients had medical and surgical treatment failure with a diagnosis of refractory pelvic pain for bladder pain syndrome/interstitial cystitis or UCPPS which include CP and CPPS. Kang et al. [15] studied neuropathic pain in SCI patients, while Pinot-Monange et al. tested rTMS for endometriosis.

A significant decrease in pain was present in eight articles with analogic or numeric pain scales (visual analogue scale -VAS- numeric rating scale). Bladder pain index showed an improvement for two of the studies. Country and disease-specific scales for various dimensions of pelvic pain (Functionnal Pelvic Pain Syndrom, Neuropathic Pain Syndrom Inventory, McGill, National Institute of Health Chronic Prostatitis Symptom Index, Oswestry Disability Index) were also effective to ensure the efficacy of rTMS and tDCS.

In addition, two studies looked for the mechanism of action underneath analgesic therapy. Simis et al. [16] utilized magnetic resonance spectroscopy (MRS) to explore the central neural network and its activity with tDCS. They found a positive correlation between thalamus and pelvic pain levels. MRS positive and negative correlations between primary cortex motor and VAS-level Pelvic pain patients were also discovered. In a more physiopathological study design with an EMG and fMRI protocol, Yani et al. confirmed a bond between the SMA and pelvic floor pain.

Refractory pain is difficult to manage, patients are constantly suffering and the therapeutic options available often fail, emphasizing the importance of the analgesic effect of noninvasive stimulation demonstrated by Rossini et al. [4]. Applications for pelvic pain are a logical way for the field of rTMS to continue to grow, as can be seen from the increase in publications over the last decade. In a multidisciplinary approach, this new therapeutic offers new hope for patients. However, more studies are needed to move in this direction.

4.3 Duration of effects

The lasting effect of noninvasive brain stimulation on treating PFDs is variable and relies on many different parameters. One of the most relevant to compare is the total number of days of stimulation provided. The range of effect duration when stimulation occurred for five consecutive days was about one to four weeks. In contrast, when patients were treated for two weeks, the effects lasted about one to four months as shown by multiple site stimulation delivered via TRPMS by Khavari et al. The effects of tDCS and rTMS appear similar in the absence of a comparative study.

4.4 Safety of use

Ten studies had safety evaluations in their protocols. None found any serious adverse effects using the different devices. Headaches were rare and only reported in 5 to 10% of cases. With the stimulation parameters set up by the studies described in this review, side effects were demonstrated to be very low compared to safety recommendations for rTMS[23]. Additionally, although tDCS has been used extensively in experimental research and side effects are low, there is a lack of data about safety in symptomatic patient protocols [24].

4.5 Limitations

Our study protocol is limited by the lack of assessment of the risk of bias and of certainty, as recommended by the PRISMA checklist. With an average number of 10 patients included in studies (except for the El Habayashi study, which enrolled 40 subjects), the statistical differences reported here for various clinical and paraclinical parameters are to be considered as exploratory data from pilot studies. Although the design of the studies is Oxford Level 1 or 2, with prospective controlled trials, these results should only be considered as validating preliminary effects of noninvasive stimulation in the indication of pelvic floor disorders. In addition, only 5 out of 14 studies are blinded and placebo-controlled. Therefore, the short duration of stimulation does not rule out a potential placebo effect.

5. Conclusions

Transcranial noninvasive brain stimulation has become a feasible therapy for LUT and pelvic pain treatment in the near future, and the evidence of its effectiveness is numerous. Although, thorough knowledge of cortical control will be required to better target and stimulate/modulate areas of interest. As even if the areas of interest are identified, the intricate neural control and interaction between different areas remain ill-defined. The modulation of one, or even several areas at the same time playing a role on LUT opens a door to incredible possibilities, still largely unknown. Further studies, with larger participant numbers, are absolutely necessary to validate the extent, intensity and duration of these therapeutic effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list

PFD	pelvic floor disorders
LUTS	lower urinary tracts symptoms
rTMS	repeated Transcranial Magnetic Stimulation
tDCS	transcranial direct current stimulation
FDA	Food and Drug Administration
IFCN	International Federation of Clinical Neurophysiology
MS	multiple sclerosis
PD	Parkinson's disease
SCI	spinal cord injury
UCPPS	urologic pelvic pain syndrome
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
UDS	urodynamics
fMRI	functional magnetic resonance imaging
US	ultrasound
TRPMS	Transcranial Rotating Permanent Magnet Stimulator
SMA	supplementary motor area
RMT	resting motor threshold
AMT	active motor threshold
PAR	pudendo-anal reflex
VAS	visual analogue scale
MRS	magnetic resonance spectroscopy

References

1. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994 Aug;91(2):79–92. [PubMed: 7519144]
2. Barker AT, Jalinous R, Freeston IL. NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX. The Lancet. 1985 May 11;325(8437):1106–7.
3. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000 Sep 15;527 Pt 3:633–9. [PubMed: 10990547]
4. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015 Jun;126(6):1071–107. [PubMed: 25797650]
5. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014 Nov;125(11):2150–206. [PubMed: 25034472]
6. León Ruiz M, Sospedra M, Arce Arce S, Tejeiro-Martínez J, Benito-León J. Current evidence on the potential therapeutic applications of transcranial magnetic stimulation in multiple sclerosis: a systematic review of the literature. Neurol Engl Ed. 2022 Apr;37(3):199–215.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.
8. Marx RG, Wilson SM, Swiontkowski MF. Updating the Assignment of Levels of Evidence. J Bone Jt Surg. 2015 Jan 7;97(1):1–2.
9. Centonze D, Petta F, Versace V, Rossi S, Torelli F, Prosperetti C, et al. Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. Mult Scler J. 2007 Mar;13(2):269–71.
10. Brusa L, Agrò EF, Petta F, Sciobica F, Torriero S, Lo Gerfo E, et al. Effects of inhibitory rTMS on bladder function in Parkinson's disease patients. Mov Disord. 2009;24(3):445–7. [PubMed: 19133657]
11. Vasquez N, Balasubramaniam V, Kuppuswamy A, Knight S, Susser J, Gall A, et al. The interaction of cortico-spinal pathways and sacral sphincter reflexes in subjects with incomplete spinal cord injury: A pilot study. Neurourol Urodyn. 2015;34(4):349–55. [PubMed: 25867009]
12. El-Habashy H, Nada MM, Maher EA, Shamloul R, Maged M, Abdelazim MS. The effect of cortical versus sacral repetitive magnetic stimulation on lower urinary tract dysfunction in patients with multiple sclerosis. Acta Neurol Belg. 2020 Feb;120(1):141–7. [PubMed: 31828602]
13. Khavari R, Tran K, Helekar SA, Shi Z, Karmonik C, Rajab H, et al. Noninvasive, Individualized Cortical Modulation Using Transcranial Rotating Permanent Magnet Stimulator for Voiding Dysfunction in Women with Multiple Sclerosis: A Pilot Trial. J Urol. 2022 Mar;207(3):657–68. [PubMed: 34694911]
14. Fenton BW, Palmieri PA, Boggio P, Fanning J, Fregni F. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. Brain Stimulat. 2009 Apr;2(2):103–7.
15. Kang BS, Shin HI, Bang MS. Effect of Repetitive Transcranial Magnetic Stimulation Over the Hand Motor Cortical Area on Central Pain After Spinal Cord Injury. Arch Phys Med Rehabil. 2009 Oct;90(10):1766–71. [PubMed: 19801069]
16. Simis M, Reidler JS, Duarte Macea D, Moreno Duarte I, Wang X, Lenkinski R, et al. Investigation of Central Nervous System Dysfunction in Chronic Pelvic Pain Using Magnetic Resonance Spectroscopy and Noninvasive Brain Stimulation. Pain Pract. 2015 Jun;15(5):423–32. [PubMed: 24799153]
17. Pinot-Monange A, Moisset X, Chauvet P, Gremeau AS, Comptour A, Canis M, et al. Repetitive Transcranial Magnetic Stimulation Therapy (rTMS) for Endometriosis Patients with Refractory Pelvic Chronic Pain: A Pilot Study. J Clin Med. 2019 Apr 13;8(4):508. [PubMed: 31013910]

18. Yani MS, Fenske SJ, Rodriguez LV, Kutch JJ. Motor cortical neuromodulation of pelvic floor muscle tone: Potential implications for the treatment of urologic conditions. Neurourol Urodyn. 2019 Aug;38(6):1517–23. [PubMed: 31044482]

19. Jussi N, Anu H, Marjo S, Teemu J, Esa R, Antti K. Repetitive Transcranial Magnetic Stimulation for Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective Pilot Study. Int Neurourol J. 2020 Jun 30;24(2):144–9. [PubMed: 32615676]

20. Calabrò RS, Billeri L, Porcari B, Pignolo L, Naro A. When Two Is Better Than One: A Pilot Study on Transcranial Magnetic Stimulation Plus Muscle Vibration in Treating Chronic Pelvic Pain in Women. Brain Sci. 2022 Mar 15;12(3):396. [PubMed: 35326352]

21. Divandari N, Manshadi FD, Shokouhi N, Vakili M, Jaberzadeh S. Effect of one session of tDCS on the severity of pain in women with chronic pelvic pain. J Bodyw Mov Ther. 2019 Jul;23(3):678–82. [PubMed: 31563388]

22. Cervigni M, Onesti E, Ceccanti M, Gori MC, Tartaglia G, Campagna G, et al. Repetitive transcranial magnetic stimulation for chronic neuropathic pain in patients with bladder pain syndrome/interstitial cystitis. Neurourol Urodyn. 2018;37(8):2678–87. [PubMed: 29797500]

23. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 Dec;120(12):2008–39. [PubMed: 19833552]

24. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. Brain Stimulat. 2012 Jul;5(3):175–95.

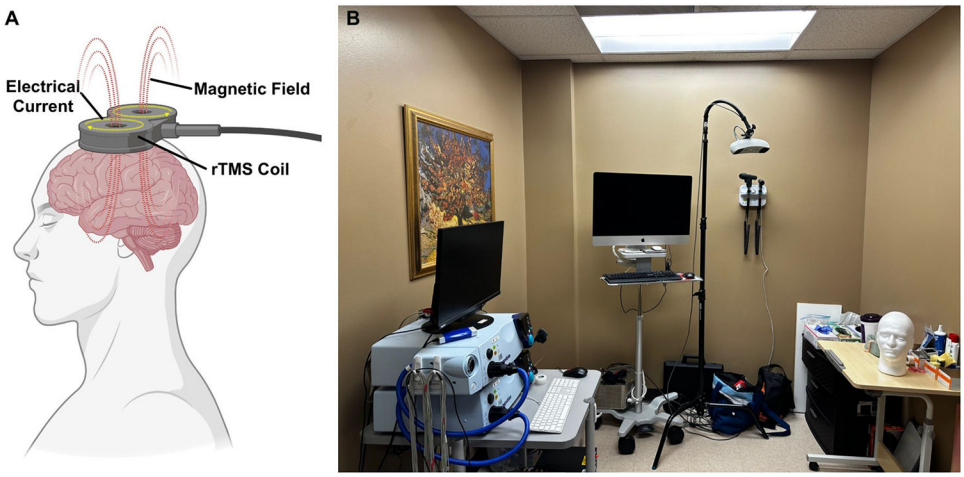

Figure 1.

Noninvasive neuronavigated stimulation. A) Repetitive transcranial magnetic stimulation (rTMS) is a form of noninvasive stimulation that allows for targeted inhibition and excitation of cortical networks (created with BioRender.com). B) Magstim BiStim2 TMS system used along with Brainsight neuronavigation for accurate targeted neuromodulation.

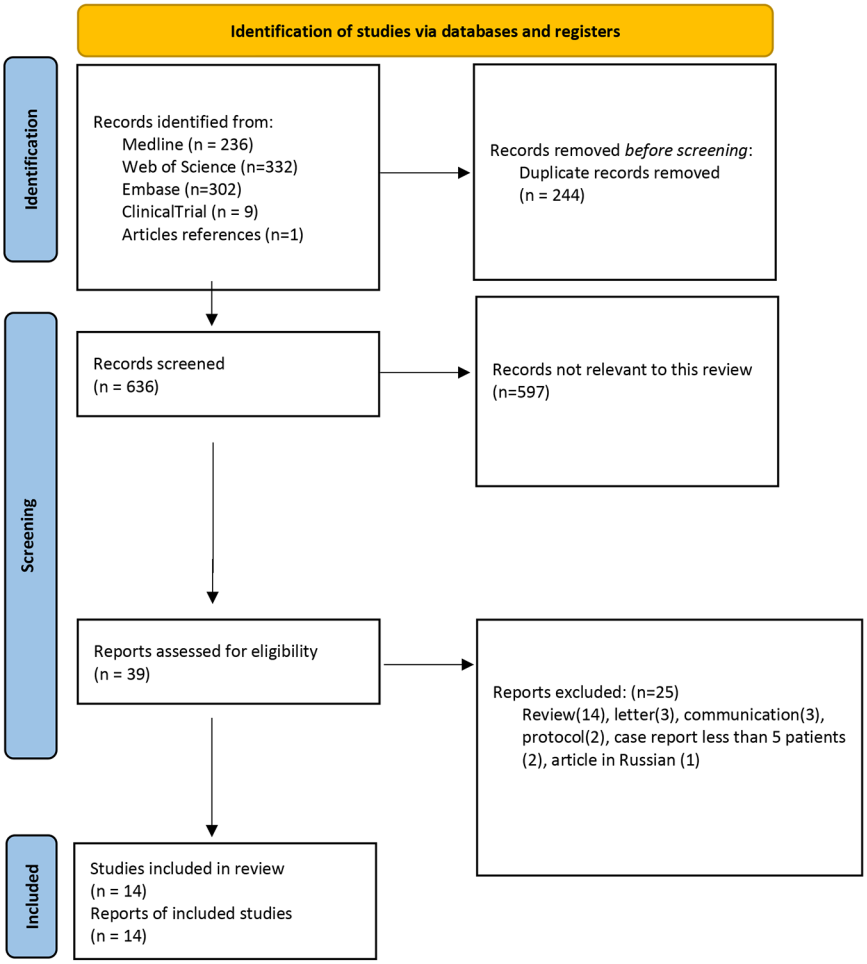

Figure 2.
Flowchart for the selection and inclusion process

Table 1.

Noninvasive stimulation designs and protocols

	Author	Year	Institution, Country (1st Author)	Study design	LE	N	Age	Sex	Population	Disorder inclusion
1	Centonze	2007	Clinica Neurologica, Universita di Roma Tor Vergata, Roma, Italy	single center, prospective, open, non-controlled	2	10	43	H+F	MS	LUTS: DO, DO/DSD, DU + lower limb spasticity
2	Brusa	2009	Clinica Neurologica, Universita di Roma Tor Vergata, Roma, Italy	single center, prospective, open, non-controlled	2	8	65	H+F	PD	LUTS: DO
3	Fenton	2009	Summa Health System Department of Obstetrics and Gynecology, Akron, USA	single center, prospective, double blind, randomized, 2 arms, cross over, pilot	1	7	38	F	Refractory chronic pelvic pain	IC, IBS and myofascial pain syndrome
4	Kang	2009	Bundang Hospital, Seoul National University College of Medecine, South Corea	single center, prospective, simple blind, randomized, 2 arms, cross over	1	11	55	H+F	SCI	Chronic neuropathic pelvic pain
5	Simis	2015	Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, USA	single center, prospective, simple blind, randomized, 2 arms, controlled	1	9	35	H+F	Refractory chronic pelvic pain	Treatment resistant painful symptom
6	Vasquez	2015	Royal National Orthopaedic Hospital, Stanmore, United Kingdom	single center, prospective, open, controlled	2	26	54	M	SCI and healthy (n=3)	LUTS: DO/DSD and positive pudendal anal reflex
7	Cervigni	2018	University Hospital Foundation A. Gemelli, Rome, Italy	single center, prospective, double blind, randomized, 2 arms, cross over, pilot	1	13	52	F	BPS/IC + neuropathic resistant pain	LUTS / pain
8	Divandari	2019	Shahid Beheshti University, Tehran, Iran	single center, prospective, simple blind, randomized, 2 arms, cross over	1	16	35	F	CPPS	Chronic pelvic pain
9	Pinot-Monange	2019	Centre Hospitalier Universitaire, Clermont-Ferrand, France	single center, prospective, open, non-controlled, pilot	2	12	38	F	Endometriosis	Treatment resistant painful symptom
10	Yani	2019	University of southern California, Los Angeles, USA	single center, prospective open, non-controlled	2	6	55	H+F	UCPPS	Chronic pelvic pain
11	EL-Habashi	2020	Faculty of Medicine, Cairo University, Egypt	single center, prospective, open randomized, 4 arms, controlled	1	40	34	H+F	MS	LUTS, Group A: detrusor overactivity, Group B: detrusor underactivity
12	Jussi	2020	Tampere University Hospital, Tampere, Finland	single center, prospective, open, non-controlled	2	7	54	H	CP/CPPS	Treatment resistant painful symptom
13	Calabro	2022	Centro Neurolesi Bonino Pulejo, Messina, Italy	single center, prospective, open, non-controlled	2	7	42	F	CPPS	Treatment resistant painful symptom
14	Khavari	2022	Houston Methodist Hospital, Houston, USA	single center, prospective, open, non-controlled	2	10	53	F	MS	LUTS: VD

	Device	Area of stimulation 10-20 system	Stimulation specifications	Stimulation protocol	Stimulator tool
1	rTMS	Cz-vertez, dominant spastic leg motor hotspot (soleus muscle)	5Hz, for 16 min, 1000 stimuli, 20 train of 50 stimuli in 10s, interval 40s, 100% RMT	once a day, five consecutive days over two weeks	MagStim Rapid (Magstim Company, UK)
2	rTMS	Cz-vertex, leg motor hotspot	1Hz, 900 stimuli, 65% MSO, bellow RMT	once a day, five consecutive days over two weeks	MagStim Rapid (Magstim Company, UK)

3	tDCS	primary cortex motor (C3 or C4), dominant hemisphere, midline pelvic pain	1mA for 20min	once a day, real or sham tDCS for two days, two-week in-between	Specially developed current stimulator (Schneider electronic, Germany)
4	rTMS	right M1 cortex (C3), left first dorsal interosseous hand hotspot	10Hz rTMS, 20 trains in 5s, 80% RMT	once a day, real or sham rTMS for five consecutive days, 12 weeks in-between	MagStim 200 (Magstim Company, UK)
5	tDCS	primary motor cortex (C3 or C4) contralateral of more painful or began side	2mA for 20min	once a day, real or sham tDCS for ten consecutives days	Specially developed current stimulator (Schneider electronic, Germany)
6	rTMS	Cz-vertex (anal reflex region)	80% MSO	10 times repetitions on 5 occasions, healthy control without stimulation	MagStim 200 (Magstim Company, UK)
7	rTMS	M1 motor cortex area (pelvic region)	20Hz, 20min, 30 trains of 50 stimuli, 110% RMT	once a day, real or sham rTMS, for five consecives days, 2 weeks with 3-week washout in-between and 6 weeks between the two treatment	MagStim Rapid2 (Magstim Company, UK)
8	tDCS	simultaneous C3 and F3: left (dominant) M1 and dorsolateral prefrontal cortex	0.3mA each for 20min	one session, real or sham tDCS, 1-week inbetween	X2 Active Dose Company, Thailand
9	rTMS	left M1 (C4) primary motor cortex, right first interosseous hand	10Hz, 1500 stimuli, 80% RMT	once a day, five consecutive days over one weeks	MagPro X100 (Magventure Tonika Elektronic, Denmark)
10	rTMS	supplementary motor area (SMA) for pelvic floor muscle (X: −2, Y: −16, Z: 68 in MNI system)	10Hz or 1Hz, 2000 stimuli, 80% RMT	one session, high or low frequency rTMS, 1-week inbetween	MagStim Rapid2 (Magstim Company, UK)
11	rTMS	Cz-vertez cerebral cortex motor area (leg area motor hotspot)	5Hz, 1000 stimuli, 75% to 120% RMT	A1 and B1 Groups: once a day, five consecutive days over two week, A2 and B2 Groups: control with 5Hz sacral root neuromodulation s	MagStim Rapid (Magstim Company, UK)
12	rTMS	both left and right M1 motor cortex (pelvic area), left hand thenar muscles	10Hz, 20 min, 1500 stimuli 110% RMT	once a day, five consecutive days over one weeks	MagStim Rapid2 (Magstim Company, UK)
13	rTMS-FMV	rTMS: motor hot spot first dorsal interosseous right hand - FMV: perineum, suprapubic, and sacrococcygeal	5Hz, 10min, 50 stimuli, 10s, 500 stimuli 110% AMT - 150Hz, 30min	once a day, five consecutive days over three weeks	MagStim Bistim2 (Magstim Company, UK) - Vibraplus (@-Circle, Italy)
14	TRPMS	individualization treatment for: F3, F4, C3, C4, Cz	Inhibition: 10min, 100ms stimuli train, 5s; Stimulation: idem for 40min	once a day, five consecutive days over two weeks	TRPMS: custom device developed at Houston Methodist Hospital

	Measurement tool	**Protocol measure**	**Urological and pelvic significative results**	**Duration**	**Adverse effects**
1	Clinical (subjective), UDS	one to 5 days before & 3 days after	PVR reduction, Pdet-Qmax for DU increase, subjective improvement of the voiding phase	3 days	no serious adverse effects
2	IPSS, UDS	before & after, 1 (UDS+IPSS), 2 and 4 weeks (IPSS)	IPSS score reduction, BC and FSBF increase	2 weeks	no serious adverse effects
3	VAS, ICSI	before and during two weeks after	VAS pelvic pain decrease	1 week	0.8%, not significant
4	Average Pain NRS, Worst Pain NRS, BPI score	24h before and 1, 3, 5, 7 weeks after	Worst Pain NRS decrease	1 week	-

5	MRS, VAS, von Frey monofilament	before and 10 days after	Increase sensory and pain thresholds, MRS changes in 3 cortex areas	10 days	no serious adverse effects
6	pudendal nerve stimulation and anal sphincter EMG detection	immediately after	facilitate eliciting dorsal penile nerve stimulation	-	-
7	VAS, FPPS, NPSI, MPQ, OABq, O'Leary-Saint Questionnaire, bladder ultrasound and diary	before and after the 2 weeks, after 3 weeks washout	VAS, FPPS overall reduction. FPPS, NPSI, Mc Gill questionnaire, OABq within-subject reduction	3 weeks	no serious adverse effects
8	VAS, Oswestry Disability Index	before and after each two seances	decreases VAS pain severity and improves disability status	1 hour	no serious adverse effects
9	Physical examination, VAS, EPH-30, BPI	28 days before, one, 8 and 28 day after	BPI improvement at 8 and 28 days after	28 days	no serious adverse effects
10	Pelvic floor EMG, functional MRI	EMG during rTMS, fMRI before and 20 min after	change in pelvic floor resting EMG and SMA fMRI area	-	-
11	UDS, bladder ultrasound	before and during first week after	BC decrease, Pdet-Qmax increase in all groups. Urine flow rate increase for Group B. PVR reduction in all groups except A2	1 week	-
12	NIH-CPSI, NRS, DAN-PSS-1, drug consumption	before and after, 1, 4, 8, and 12 weeks	Decrease NRS, NIH-CPSI, drug usage and symptoms duration	8 weeks	no serious adverse effects
13	VAS, BPI	before and after 7, 30 days	overall and intra individual VAS and BPI reduction	30 days	no serious adverse effects
14	UDS-fMRI, EDSS, AUASS, NBSS, UDI-6, IIQ-7, uroflow, PVR, 2 days bladder diary	2 times before and after 2 weeks, 4 and 12 months	increase activation in fMRI regions involved a voiding, PVR/BC decrease, improvement of bladder emptying in UDI-6, AUASS, NBSS	four months	no serious adverse effects

AUASS: American urology association symptom score, BC : bladder capacity, BPI : brief pain inventory, BPI: brief pain inventory, BPS/IC: blader pain syndrom, intersitial cystitis, CP/CPPS : chronic prostatitis/chronic pelvic pain syndrome, DAN-PSS-1: Danish Prostatic Symptom Score, DCS: transcranial direct stimulation, DO : detrusor overactivity, DSD : detrusor-sphincteria dyssynergia, DU : detrusor underactivity, EDSS: expanded disability status score, EPH 30: Endometriosis Health Profile Questionnaire, FMV: focal muscle vibration, FPPS: fumctionnal pelvic pain syndrom, FSBF : first sensation of bladder filling, IBS ; irritable bowel syndrom, IC : interstitial cystitis, ICSI : interstitial cystitis symptom index, IIQ-7: incontinence impact questionnaire, IPSS : International Prostate Symptom Scale, LE : level of evidence, LUT : low urinary tract symptom, MNI system: Montreal Neurological system, MPQ: Mc Gill Pain Questionnaire, MRS : magnetic resonance spectroscopy, MS : multiple slerosis, MSO : maximum stimulator output, NBSS: neurogenic bladder symptom score, NIH-CPSI : National Institute of Health Chronic Prostatitis Symptom Index, NPSI: Neuropathic Pain Syndrom Inventory, NRS : numeric rating scale, OABq: Overactive Bladder Questionnaire, PD : parkinson desease, Pdet-Qmax: pressure detrusor at maximal urinary flow, PVR : post void residual, RMT : resting motor threshold, SCI : spinal cord injury, TMS: transcranial magnetic therapy, TRPMS: transcranial rotating permanent magnet stimulator, UCPPS: urologic pelvic pain syndrom, UDI-6: urogenital distress inventory, UDS : urodynamics, VAS : visual analogic scale, VD: voiding dysfonction