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Repetitive transcranial magnetic stimulation for chronic neuropathic pain in patients with bladder pain syndrome/interstitial cystitis

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Aims: To evaluate the efficacy, safety, and tolerability of repetitive Transcranial Magnetic Stimulation (rTMS) associated with standard drug therapies for neuropathic pain that does not respond to pharmacological treatment alone in patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC). Secondary goals were to assess the effects of rTMS on Lower Urinary Tract Symptoms (LUTS) and Quality of Life (QOL).

Methods: Fifteen patients with BPS/IC were enrolled in this randomized, double-blind, sham stimulation-controlled, crossover study. Patients were treated for 2 weeks with either real-rTMS (for five consecutive days in 20-min sessions) or sham-rTMS (for five consecutive days in 20-min sessions). After a 6-week washout period, the patients who had previously undergone real-rTMS underwent sham-rTMS, and vice versa. Patients were rated at each visit by means of questionnaires on pain, urinary disturbances, depression, and QOL.

Results: The statistical analysis revealed significant effects of real-rTMS, when compared with sham-rTMS, on pain (in the VAS, Functional Neuropathic Pelvic Pain, Neuropathic Pain Symptom Inventory, McGill questionnaire, and Central Sensitization Inventory), urinary LUTS (in the Overactive Bladder Questionnaire score, bladder emptying, and daily urinary frequency), and QOL (in the subscores of the SF-36 related to physical pain and to emotional status). No serious adverse events were reported during the study.

Conclusions: The results of this study show that rTMS applied with an H-coil over the M1 in the area corresponding to the pelvic region in patients with BPS/IC appears to improve chronic pelvic pain (CPP) and associated urinary disorders.

KEYWORDS
bladder pain syndrome, chronic pain, neuropathic pain, rTMS, transcranial magnetic stimulation

Mauro Cervigni and Emanuela Onesti contributed equally to this study.

1 | INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a rare disease that is characterized by filling-related bladder pain in the suprapubic pelvic and perineal region, that is accompanied by other symptoms such as urinary urgency, frequency, and nocturia, though without proven urinary tract infections or other urological disorders, and that lasts more than 6 months.[1,2] BPS/IC is the cause of pain in more than 30% of women with chronic pelvic pain (CPP). CPP is associated with gastrointestinal involvement in 37% of patients, with gynecological diseases in 20%, and with musculoskeletal disorders in 13%.[3] Other disorders such as irritable bowel syndrome, fibromyalgia, migraine, temporomandibular joint syndrome, and chronic fatigue syndrome are often associated with BPS/IC and all fall within the definition of central sensitization syndrome (CSS).[4–6]

Pain is the main symptom of BPS/IC: it is neuropathic and perceived as violent pressure or a stabbing pain in the suprapubic region causing a persistent discomfort that increases with bladder filling. It tends to spread out to the inguinal, perineal, vaginal, rectal, and lumbo-sacral regions. The pain is often alleviated by bladder emptying but then suddenly reappears.[7–10] The pain is worsened by ingestion of various foods and drinks and is often associated with painful sexual intercourse (in women during penetration, in men during ejaculation), so much so that it may prevent it.[10]

No single therapy for BPS/IC currently exists, though a multidisciplinary approach associated with dietary changes is strongly recommended.[11,12] To date, the most common approach to neuropathic pain is the use of tricyclic antidepressants, pregabalin, gabapentin, opioids, duloxetine, topical lidocaine, and capsaicin patches.[13] Neurostimulation of the sacral or tibial nerves may be offered as fourth-line treatment on account of the ability of such stimulation to modulate the somatic afferent activity of the bladder, thereby interfering with the abnormal activity of the C-fibers.[1,14–18] Central sensitization (CS) has been shown to be responsible for maintaining pain in patients with BPS.[19] It is based on the enhancement of the functional status of circuits in nociceptive pathways through an increase in membrane excitability and synaptic efficacy or a reduction in inhibition.[20]

Transcranial Magnetic Stimulation (TMS) is a non-invasive and painless neurophysiological technique that induces a transient electrical current in the cortical surface below the coil and depolarizes the underlying cortical neurons in both locally and functionally correlated regions involved in pain processing, thereby modifying their excitability.[21–28] A number of rTMS-controlled studies have been conducted on patients with spinal cord injuries, post-ictal central pain, type II painful regional syndrome (CPSP), trigeminal nerve lesions and peripheral nerves, phantom pain, fibromyalgia, and non-neuropathic pain (migraine, low back pain, visceral pain, and postoperative pain).[29]

However, no study has yet investigated rTMS as a treatment option for chronic neuropathic pain in BPS/IC. In the present study, we investigated whether using rTMS delivered by H-coil to modulate excitability over the primary motor cortex (M1) improves neuropathic pain in patients with BPS. We also evaluated the possible beneficial effects of this treatment on urinary disorders commonly present in such patients. The primary aim of our study was to evaluate the efficacy, safety, and tolerability of rTMS in patients with BPS/IC associated with standard drug therapies for pain that does not respond to pharmacological treatment alone. The secondary aim was to evaluate the effects of rTMS on lower urinary tract symptoms (LUTS) in both the filling and voiding phases as well as on quality of life (QOL).

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomized, double-blind, sham stimulation-controlled, crossover study. It was performed at the Rare Neuromuscular Diseases Center at Sapienza University of Rome in collaboration with the Interstitial Cystitis Referral Center at the A. Gemelli University Hospital of Rome Foundation, Italy.

Upon enrollment, the patients were randomized into two groups according to a 1:1 ratio: a first group of patients received the rTMS-real treatment followed, after a 6-week washout period, by rTMS-sham treatment (Real-Sham Group, Group I); the second group received the same treatments in an inverted order (Sham-Real Group, Group II) (Figure 1). The patients' clinical conditions were evaluated before the start of each session and at the end of each session. The following tests were performed at each evaluation: clinical examination, questionnaires on pain (VAS for pain, the Functional Pelvic Pain Syndrome—FPPS, the Neuropathic Pain Symptom Inventory—NPSI, the McGill Pain Questionnaire—MPQ), on urinary disturbances (Overactive Bladder Questionnaire—OABq, the O'Leary-Saint Questionnaire, and a bladder ultrasound for the study of bladder residue), on depression (Beck Depression Inventory—BDI) and on QOL (36-Item Short Form Health Survey—SF-36). The Minnesota Multiphasic Personality Inventory (MMPI) and Douleur Neuropathique 4 (DN4) were also performed at the initial screening examination to assess any personality disorders and neuropathic pain, respectively. A thorough clinical work-up, including a urodynamic evaluation according to ESSIC criteria, was carried out before enrollment in the study and at the end of the two treatment periods.

According to the double crossover study design, the patients' clinical conditions were evaluated before the first

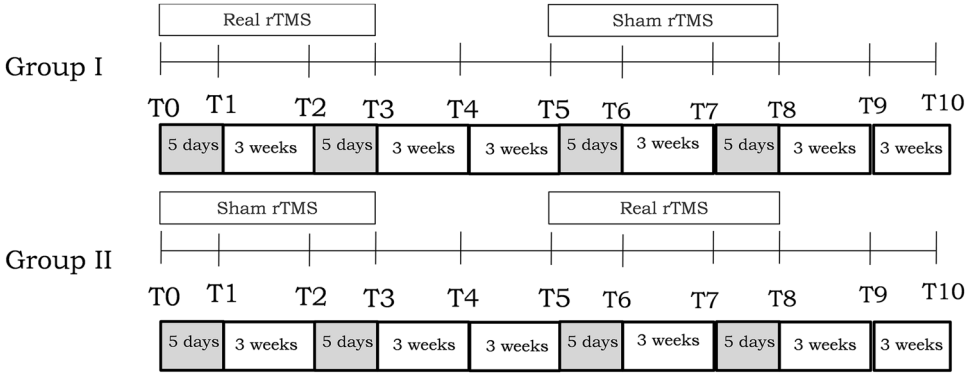

FIGURE 1 Study design. (T0) Clinical assessment and randomization; begin real or sham repetitive transcranial magnetic stimulation (rTMS) session; (T1) last day first week of first session treatment; clinical assessment; (T2) clinical assessment, first day second week of first session treatment; (T3) last day second week of fist session treatment; clinical assessment; (T4) clinical assessment; (T5) clinical assessment, begin first week of second session of real or sham treatment; (T6) last day first week of second session treatment; clinical assessment; (T7) clinical assessment, first day second week of second session treatment; (T8) last day second week of second session treatment; clinical assessment; (T9) clinical assessment; (T10) clinical assessment

week of treatment began (T0), at the end of the first week of treatment (T1) and at the start (T2), and at end (T3) of the second week of treatment. Patients were evaluated again after a 3-week wash-out period (T4). After a further 3 weeks of wash-out, patients started the alternative rTMS treatment. Primary outcome variables were assessed once again before and at the end of the 2 weeks of treatment (T5-T6 for the first week, and T7-T8 for the second week). Three (T9) and 6 (T10) weeks after the end of the last treatment session, two new clinical evaluations were performed (Figure 1).

Neither the physicians who administered the tests nor the patients were aware of which type of rTMS treatment was being used (double-blind study).

2.2 | Patients

Fifteen patients with BPS/IC and neuropathic pain resistant to common treatments were enrolled. The diagnosis of BPS/IC was made according to ESSIC criteria.[2] The diagnosis of neuropathic pain was confirmed by means of the DN4 scale. The Central Sensitization Inventory (CSI) was also evaluated. The pain was considered to be resistant to standard therapies when it persisted for more than 6 weeks despite treatment and if associated with a score of 40 or more at the VAS despite an adequate duration and dosage of pharmacological therapy. The dosage of the symptomatic treatments taken by the patients had to be stable for at least 4 weeks prior to enrollment in the study. Exclusion criteria for rTMS included a history of epilepsy, drug-resistant migraine, cardiac pacemakers, neurostimulators, and surgical clips or medical pumps. Patients whose MMPI was significantly altered at the screening visit were also excluded.

2.3 | Repetitive magnetic transcranial stimulation (rTMS)

The rTMS was performed using a Magstim Rapid2 stimulator (Magstim, Whitland, UK). The Brainsway H-coil (Brainsway, Jerusalem, Israel) was used to perform deep stimulation. The H-coil was placed on the patient's head over the M1 so as to achieve stimulation to a depth of 3 cm below the motor cortex in an area corresponding to the pelvic region, which is located deep in the medial longitudinal fissure.

Active rTMS sessions consisted of 30 consecutive trains of 50 stimuli delivered at 20 Hz at 110% of the resting motor threshold (RMT) calculated on the anterior tibial muscle, separated by intertrain intervals lasting 30 s. The RMT for each patient was obtained by stimulating the leg motor area with the stimulation intensity needed to evoke a motor response with an amplitude greater than 50 μV in at least 50% of the resting stimuli in the anterior tibial muscle.[28] A higher threshold was chosen to ensure that the deepest region corresponding to pelvic musculatures was reached.[30]

Sham stimulation was performed using a different coil placed in the same helmet encasing the active rTMS coil that produces an acoustic artefact and facial muscle activation similar to that produced by the active coil but that induces a negligible electric field.[31,32]

2.4 | Clinical evaluations

The CSI consists of a self-administered questionnaire developed to evaluate symptoms typically present in CS; the higher the number of sensitization patterns involved, the more severe the sensitization.[33]

2.4.1 | For pain

VAS for pain[34]; FPPS, which allows functional impairment induced by pelvic pain to be quantified. Eight functional domains are included, each of which is assigned a score ranging from 0 to 4, with the highest score indicating a major functional impairment[35]; MPQ, which allows pain to be evaluated as a three-dimensional experience: sensory, emotional-affective and evaluative[36]; the NPSI, a self-administered questionnaire that allows different aspects of neuropathic pain to be evaluated.[37]

2.4.2 | For quality of life

SF-36, a valid and reproducible questionnaire that focuses on the patient's state of health.[38]

2.4.3 | For depression

BDI, which is designed to measure behavioral manifestations of depression.[39]

2.4.4 | For urinary disturbances

OABq, a tool that assesses urological symptoms associated with QOL[40]; O'Leary Sant Questionaire, which evaluates aspects of urgency and urinary frequency, nicturia and pelvic pain, and consists of two indices each containing four questions. The higher the score, the greater the severity.[41,42]

A bladder ultrasound scan (Menfis Biomedica) was performed to measure post-void residual urine.

Patients were then asked to fill out a clinical diary for the entire duration of the study, before and after each treatment session with rTMS. They were required to record any episodes of urgency, incontinence, nicturiA, and urinary frequency on a daily basis together with their perception of pain intensity and the number of medical drugs taken.

2.5 | Statistical analysis

The data for all the subjects who fulfilled the inclusion/exclusion criteria and completed the two experimental sessions were included in the statistical analysis. The descriptive statistical analysis (mean, standard deviation) was applied to describe the demographic characteristics of the sample.

Mann-Whitney *U* or Fisher's exact test (for continuous and dichotomous variables, respectively) were used to check that the two groups were well balanced. Repeated measures analyses of variance (ANOVA) was used to determine any effect of rTMS on the different parameters and differences between the various time points and baseline.

In particular, when Mauchly's sphericity test was significant, sphericity was violated and Greenhouse-Geisser correction was adopted; when Mauchly's sphericity test was not significant, sphericity was assumed. A within-subject simple contrast test was used to determine differences between the various time points and baseline values for each parameter. *P* values equal to or less than 0.05 were considered as significant. In order to exclude a sequence effect, the two groups (real-sham vs sham-real) were considered as the between-subject factor in the ANOVA.

Data were analyzed by an external statistician, who was unaware of the clinical procedure adopted, using the Statistical Package for Social Sciences, version 22.0 (SPSS, Chicago, IL).

3 | RESULTS

Two patients discontinued the study prematurely owing to an exacerbation of the pathology during the screening phase, with active Hunner's ulcers in the cystoscopic examination in one patient and concomitant infectious-based cystitis in the other patient. Thirteen subjects completed the study and were included in the statistical analysis. The patients' clinical characteristics upon enrollment in the study are shown in Table 1. The high BDI score indicates a significant level of deflection of the tone of mood. Ten patients had other diseases typical of CSS in addition to BPS.

Seven patients first received the rTMS-real treatment (Group I) and the remaining six first received the rTMS-sham treatment (Group II). No significant demographic or clinical differences were observed between the two groups at the baseline ($P > 0.05$). The results for both the real and sham phases are shown together in the figures because no difference associated with the treatment order was detected.

3.1 | Effect on pain

In the Real Stimulation Phase, a significant overall reduction emerged for the *VAS* ($F[5,45] = 5200$, $P = 0.001$); the within-subject simple contrast revealed a significant reduction in the VAS at T2 ($P = 0.026$), T3 ($P = 0.018$), T4 ($P = 0.002$), and T5 ($P = 0.021$) compared with T0 (Figure 2). A significant overall reduction in the *FPPS* score was also observed in the Real Stimulation Phase ($F[5,50] = 2544$, $P = 0.040$); the within-subject simple contrast revealed a significant reduction in the FPPS at T1 ($P = 0.044$), T2 ($P = 0.007$), T3 ($P = 0.017$), and T4 ($P = 0.011$) compared with T0. As regards the *NPSI* score, although no significant overall reduction was observed in the *Q4 subscale* score (duration of spontaneous pain) in the Real Stimulation Phase, the within-subject simple contrast did reveal a significant reduction in the

TABLE 1 Demographic and clinical data of the 13 patients with BPS/IC at baseline

Characteristics	Mean (±SD)
Gender (F/M)	13/0
Age	52.6 (±12.6)
Disease duration (ys)	19.1 (±9.4)
Delay in diagnosis	10.4 (±8.7)
DN4	5.3 (±1.0)
Central sensitization scale	82.1 (±23.0)
VAS for pain	79.1 (±13.2)
NPSI (tot)	0.05 (±0.02)
McGill questionnaire (tot)	17.6 (±4.3)
OABq	18.8 (±7.0)
FPPS	14.7 (±7.4)
O'Leary saint questionnaire	28.8 (±4.6)
BDI	19.3 (±13.0)
Residual bladder volume	187.3 (±29.2)
Daily number of voluntary urinations (from patient's clinical diary)	11.0 (±4.6)
Nycturia (number of episodes according to patient's clinical diary)	3.6 (±1.5)
Urinary urgency (from patient's clinical diary) (1 = all days)	0.8 (±0.3)
Perceived pain (from patient's clinical diary)	6.6 (±1.7)
Number of days taking drugs for pain (from patient's clinical diary) (1 = all days)	0.3 (±0.3)

score at T1 (0.033) and T2 (0.042) compared with T0; no significant overall reduction was observed in the *Q8-Q9-Q10 subscale* score (intensity of provoked pain) in the Real Stimulation Phase, but the within-subject simple contrast did reveal a significant reduction in the score at T2 (0.040) compared with T0. As regards the *McGill questionnaire,* no significant overall effect was observed in the Real Stimulation Phase, whereas the within-subject simple contrast revealed a significant reduction at T1 ($P = 0.013$) and T4 ($P = 0.037$) compared with T0. As regards the *affective subscale,* no significant overall effect was observed in the Real Stimulation Phase although the within-subject simple contrast did detect a significant effect at T3 ($P = 0.00042$) compared with T0; as regards the *mixed subscale*, no significant overall effect was observed in the Real Stimulation Phase although the within-subject simple contrast revealed a significant effect at T2 ($P = 0.006$) compared with T0, and an effect approaching significance at T4 (0.052) and T5 (0.053) compared with T0.

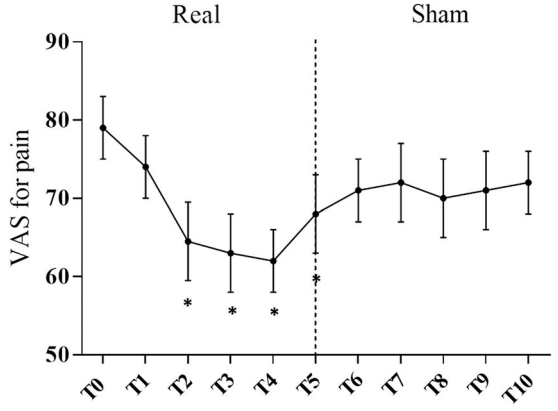

FIGURE 2 Mean changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on the VAS for pain score over time in patients with BPS/IC. Repeated measures analysis of variance (ANOVA) disclosed a significant within-subject effect at T1, T2, T3, T4, and T5 compared with T0

No significant changes were detected in any of the parameters at the time points considered in the Sham Stimulation Phase.

3.2 | Effect on urinary LUT symptoms

As regards the OABq score, no significant global effect was detected in the Real Stimulation Phase but within-subject simple contrast showed a significant effect at T3 ($P = 0.014$) compared to T0 (Figure 3). RM ANOVA identified a significant overall effect in the Real Stimulation Phase ($F[5,50] = 4030$, $p = 0.049$); the within-subject simple contrast detected a significant improvement in bladder emptying at T2 ($P = 0.031$) and T3 ($P = 0.049$) compared with T0.

3.3 | Effect on quality of life

The within-subject simple contrast test detected a significant overall effect in the SF-36 subscore related to physical pain in the Real Stimulation Phase ($F[5,50] = 2636$, $P = 0.034$); the within-subject simple contrast revealed a significant effect at T3 (0.013) and T4 (0.027) compared with T0 (Figure 4). A significant overall reduction was also observed for the SF-36 subscore related to emotional status ($F[5,50] = 3096$, $P = 0.016$).

As regards changes in *CSI* score, no significant overall effect was detected in the Real Stimulation Phase but the within-subject simple contrast did reveal a significant effect at T2 ($P = 0.005$), T3 ($P = 0.009$), and T4 ($P = 0.003$) compared with T0.

The results at the start of the sham session were statistically similar to those recorded at the baseline.

No serious adverse events were reported during the study. The following minor adverse events were reported: two patients complained of a mild headache in the hours following the real-rTMS treatment, though only in the first week of

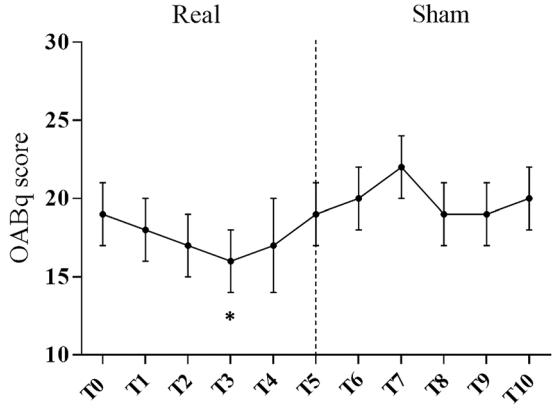

FIGURE 3 Mean changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on the OABq score over time in patients with BPS/IC. Repeated measures analysis of variance (ANOVA) disclosed a significant within-subject effect at T3 compared with T0

stimulation; another patient presented a lipothymic episode during the first session of rTMS-stimulation due to psychophysical discomfort, though she resumed and completed the study without any further problems.

4 | DISCUSSION

The present study confirms that high frequency rTMS performed daily for 20 min for 2 weeks over the M1 in an area corresponding to the pelvic region can modulate the subjective perception of pain frequency/urgency and bladder emptying in patients with BPS during treatment and for at least 3 weeks thereafter. The study also confirms that this kind of neuromodulation is safe.

The clinical improvement perceived by our patients was not due to a reduction in the depressive component, as is confirmed by the fact that the BDI score did not change significantly during the study. The BDI was analyzed because rTMS is also used as a safe and effective clinical application in the treatment of major depressive disorder.[43]

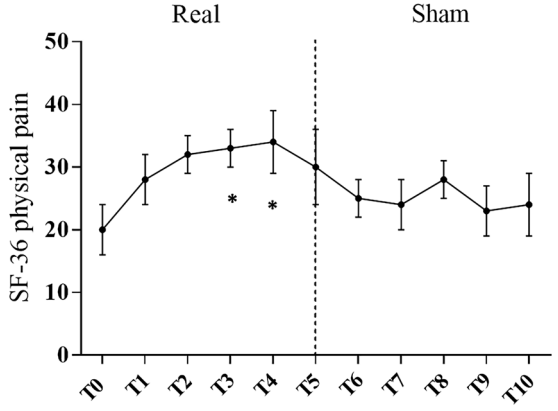

FIGURE 4 Mean changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on the SF-36 subscore related to physical pain over time in patients with BPS/IC. Repeated measures analysis of variance (ANOVA) disclosed a significant within-subject effect at T3 and T4 compared with T0

Repetitive TMS over cortical motor areas induces a plasticity process mediated by the activation of NMDA receptors and AMPA receptors as well as by the modulation of calcium currents.[44,45] This technique has emerged in recent years as an interesting and promising new treatment for pain.[29,46–49] The efficacy of high-frequency rTMS over the M1 on chronic neuropathic pain that is resistant to drugs has already been demonstrated in previous studies conducted on a range of diseases.[50–61] In general, the clinical effect begins a few days after the end of the rTMS cycle, lasts less than a week after a single stimulation session, and 2-3 weeks after repeated cycles of rTMS.[50,51,57,58] This beneficial effect observed after repeated stimulation is a key factor that warrants being able to administer this treatment in clinical practice, even though it has yet to be characterized more thoroughly.[27,29,49,62–64] Furthermore, rTMS may prove effective in the treatment of neuropathic pain with a central genesis by modulating, at the level of the cortex, the activity of related sub-cortical circuits of the brain areas involved in pain processing (such as the thalamus, the anterior cingulate cortex and the orbital-frontal region) that modulate the emotional component of pain, and by facilitating the inhibitory mechanisms of the descending pain pathway at the periaqueductal gray (PAG) level.[65,66] Since the same systems, that is, the prefrontal cortex, limbic system, and PAG, are also involved in urinary bladder control, it may also be possible to use rTMS to treat urinary disorders.[67,68] Indeed, our patients displayed a significant improvement in bladder emptying, daily urinary frequency, nicturia, and urge incontinence. This clinical improvement assumes an even greater value if we consider that our patients had a long history of disease and of chronic pain as well as a high incidence of related CSS, which are likely to have been due to a delayed diagnosis in many of them (made on average 10 years after onset, range: 0-37 years). rTMS probably increases the motor cortical output, produces a greater modulation of the motor emotional system, and enhances control over the pontine micturion centre.[68] Neuroimaging studies have confirmed that rTMS induces changes at the subcortical level.[69–74] The results of those studies combined with our findings are in keeping with the recent MRI characterization of the abnormal microstructure of cerebral white matter in women with BPS, particularly in the anterior thalamic region, the forceps major and the inferior longitudinal fascicle, and suggest that the brain is invoved in the neuropathology of CPP.[75,76] High frequency rTMS appears to improve the emptying phase even in patients with multiple sclerosis, possibly as a result of improved excitability in the cortico-spinal tract, and the consequent facilitation of the synergistic

contraction of the detrusor muscle and urethral sphincter.[67] The data available are not, however, sufficient to draw definitive conclusions because there are few long-term follow-up studies, and the patient populations in those studies that have been conducted are highly heterogeneous and the stimulation parameters used excessively variable.

The fact that the clinical efficacy of rTMS on pain and urinary disorders in our patients was observed above all in the weeks after the end of the rTMS session, and not during the treatment itself, indicates that synaptic strengthening is achieved over a long period of time. This finding confirms data previously obtained by applying high-frequency rTMS at the M1 level in patients with refractory chronic neuropathic pain.[50,51,57,58]

Last, a possible placebo effect was excluded thanks to the observation of a temporal latency between the treatment and the clinical effect. This time-related analgesic effect is hypothesized to depend on an adaptation of rTMS-induced cortical plasticity and on the activation of the descending pain control system.[51,77–79] A carry-over effect may also be excluded owing to the cross-over study design and a proper wash-out period. In our series, sham treatment did not produce any significant improvement in either treatment group.

5 | CONCLUSIONS

The lack of definitive treatments for neuropathic pain and urinary disorders in many patients with BPS/IC raises the need for new treatment options.

rTMS applied by using an H-coil over the M1 in an area corresponding to the pelvic region in patients with BPS/IC seems to induce an improvement in CPP and in associated urinary disorders. It might act by modulating brain plasticity through a process of functional reorganization of the neuronal connections at the cortex level and consequently by modifying the excitability of sub-cortical areas such as the cingulate gyrus and the orbital-frontal region (accompanied by modulation of the emotional component of pain), of the thalamus (involved in pain processing), and of PAG (with effects on the descending inhibitory pathway). However, the interpretation of these results is somewhat limited by the small number of patients enrolled in our study. New, rigorously designed, longer-lasting studies on larger numbers of patients are warranted.

As rTMS has no pharmacological or surgical side effects and does not interfere with other pharmacological treatments, it may prove to be an effective therapeutic tool that can be combined with other therapies. Furthermore, its use is currently a unique pharmacological resource as it is indicated specifically for complex pain syndromes with a neuropathic component that are resistant to other treatments. A more accurate and thorough knowledge of the correlation between the symptomatology and the pathophysiology of pain will most certainly lead to further clinical progress.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare in relation to the data reported in the present manuscript.

PUBLICATION STATUS

The paper has not been submitted before.

AUTHORS' CONTRIBUTION

OE, MC, CC, FV, and IM: clinical assessment, interpretation of the clinical data. TG: technical execution of rTMS. LV, GP, and CM: execution of urodynamic examination. OE, CM, CM, and IM: preparation of the manuscript, review. OE, MC, GC, TG, CM, CC, FV, and IM: approval of the manuscript. CM and OE contributed equally to the paper; they share the contribution as first Authors.

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