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ORIGINAL ARTICLE

Efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in anejaculation: A randomized controlled trial

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Abstract

Background: Anejaculation represents significant psychological distress and sexual and reproductive challenges among male individuals and couples. Effective fertility management options are available to address the reproductive challenges associated with anejaculation. However, there is a lack of methods to reverse the condition itself.

Objectives: This study aims to assess the effectiveness and safety of repetitive transcranial magnetic stimulation (rTMS) in patients suffering from anejaculation.

Methods: A total of 94 patients with anejaculation individuals were randomly assigned to receive high-frequency (HF) stimulation on the left dorsolateral prefrontal cortex (DLPFC), low-frequency (LF) stimulation on the right DLPFC, and sham stimulation for 4 weeks, with daily sessions of stimulation occurring on five consecutive weekdays each week.

Results: After 4 weeks of rTMS treatment, the patients in both the HF and LF groups exhibited a similar reduction in their male sexual health questionnaire for ejaculatory dysfunction bother/satisfaction score, Hamilton Anxiety Scale score, Hamilton Depression Scale score, and Pittsburgh Sleep Quality Inventory score, which were statistically significant compared with sham treatment. Additionally, there were no significant differences observed in erectile function and cognitive function across the three groups. However, there were notable disparities in the cure rates between HF- and LF-group patients (16.1% vs. 54.8%, $p = 0.001$). Additionally, it is worth noting that only two HF group patients and one LF group patient experienced spontaneously resolving minor adverse effects during the treatment process. At the 8-week follow-up, among patients who initially responded to the treatment, only one from the HF group experienced a relapse.

Discussion and conclusion: The findings of this study demonstrate that rTMS represents a secure and efficacious remedy for anejaculation patients.

KEYWORDS
ejaculation, ejaculatory disorders, repetitive transcranial magnetic stimulation

1 | INTRODUCTION

Anejaculation is a distinct form of ejaculatory dysfunction consisting of the absence of antegrade ejaculation, which must be distinct from delayed or retrograde ejaculation, and male anorgasmia.[1–3] Indeed, people suffering from anejaculation are unable to ejaculate during sexual stimulation.[4] This condition represents a source of personal and couple distress, as it carries fertility complications for the affected individuals despite their sexual arousal and usually intact erectile function.[5] Effective fertility management options, including penile vibratory stimulation, electroejaculation, and surgical sperm retrieval, are available to address the reproductive challenges associated with anejaculation. Unfortunately, there is a lack of methods to reverse the condition itself.[6,7] Besides infertility issues, anejaculation continues to pose significant distress in patients' sexual lives as a threat to sexual enjoyment.[8]

The ejaculatory reflex is influenced by a range of physiological and psychological factors.[9] Ejaculation generators are key spinal centers that modulate excitatory and inhibitory inputs from the brain, allowing the coordinated release of semen during sexual climax.[1,10–12]

The prefrontal cortex plays a role in sexual behavior, with ejaculation correlating with reduced activity in this brain region.[13,14] In particular, the left dorsolateral prefrontal cortex (DLPFC) is often associated with cognitive and emotional processing, including aspects of reward, pleasure, and ultimately, sexual satisfaction.[15] Stimulation of this region may enhance positive emotions and cognitive processes related to sexual arousal and response. By contrast, inhibiting the right DLPFC, which is often implicated in inhibitory control and negative emotional processing, could potentially reduce inhibitions and barriers to sexual function, facilitating a more natural sexual response.[16] Such specific compartmentation is reflected by ejaculation disorders that arise when these brain regions are hit by cerebrovascular/oncological/psychiatric events.[17–21] For these reasons, anejaculation might also be associated with disruptions in brain function.

Repetitive transcranial magnetic stimulation (rTMS) is a highly used technique employed for the treatment of multiple mental and neurological diseases.[22–24] Because of its low risk/benefit ratio, safety, non-invasiveness, coupled with high efficacy, recent findings suggest its potential use in the treatment of male sexual dysfunction.[25–27] rTMS can effectively modulate neuronal activity, either enhancing or suppressing their excitability, thereby impacting neural network function.[28,29] rTMS can exert an impact on the synaptic connections among neurons, thereby facilitating their interactions. This modulation of neural plasticity holds promise for ameliorating mental and brain disorders through reconfiguring aberrant patterns of neuronal activity.[30] By stimulating specific regions of the brain, alterations in metabolic rates can occur, thereby influencing neurotransmitter levels, neuronal firing, and synaptic connectivity.[31] Consequently, rTMS exhibits considerable potential for addressing central disorders. Nevertheless, the utilization of this technique in the context of ejaculation dysfunction remains unexplored.

Hence, there is a pressing need to investigate the potential of rTMS as a treatment for anejaculation. Understanding its efficacy and safety in the context of anejaculation could pave the way for innovative therapeutic approaches. This study aims to fill this research gap by rigorously evaluating the effectiveness and safety of rTMS in addressing anejaculation, offering hope for improved treatment outcomes and quality of life for individuals affected by this condition.

2 | MATERIALS AND METHODS

2.1 | Participants

The present study protocol obtained approval from the Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University and performed clinical trial registration at the Chinese Clinical Trial Register (ChiCTR2400081530). A total of 94 right-handed male subjects suffering from chronic anejaculation were recruited from the First Affiliated Hospital of Anhui Medical University (Figure 1). Anejaculation was defined as the complete inability to ejaculate vaginally.[2]

Prior to their involvement, written informed consent was obtained from all participants. Furthermore, all procedures were conducted in accordance with the principles of the Declaration of Helsinki. The implementation of this study adhered to the CONSORT guideline (Figure 1).

The study employed the following inclusion criteria: (1) Patients who experienced an inability to ejaculate vaginally despite adequate sexual stimulation. (2) Patients who reported symptoms of anejaculation during all instances of sexual intercourse since their initial experience, without the individual desiring delay and causing significant distress. (3) Patients who have nocturnal emissions. (4) Patients who were engaged in a stable heterosexual relationship for a minimum duration of 6 months. (5) Patients who obtained an International Index of Erectile Function (IIEF-5) score exceeding 21 points. Conversely, the exclusion criteria encompassed: (1) Patients with a history of epileptic seizures or substance abuse. (2) Patients with a history of any severe medical (in particular, endocrine and urological), neurological (in particular central and peripheral traumas and degenerative diseases), and psychiatric conditions. (3) Patients who are left-handed. (iv)Patients who use medications that might affect sexual function.

2.2 | Clinical evaluation

All enrolled patients underwent a comprehensive medical evaluation process, encompassing thorough anamnesis, physical examination, and laboratory analysis. Testosterone levels were measured through blood tests. To evaluate participants' distress over anejaculation, the Hamilton Depression Scale (HAMD), for depressive symptomatology, the Hamilton Anxiety Scale (HAMA), for anxious symptoms,

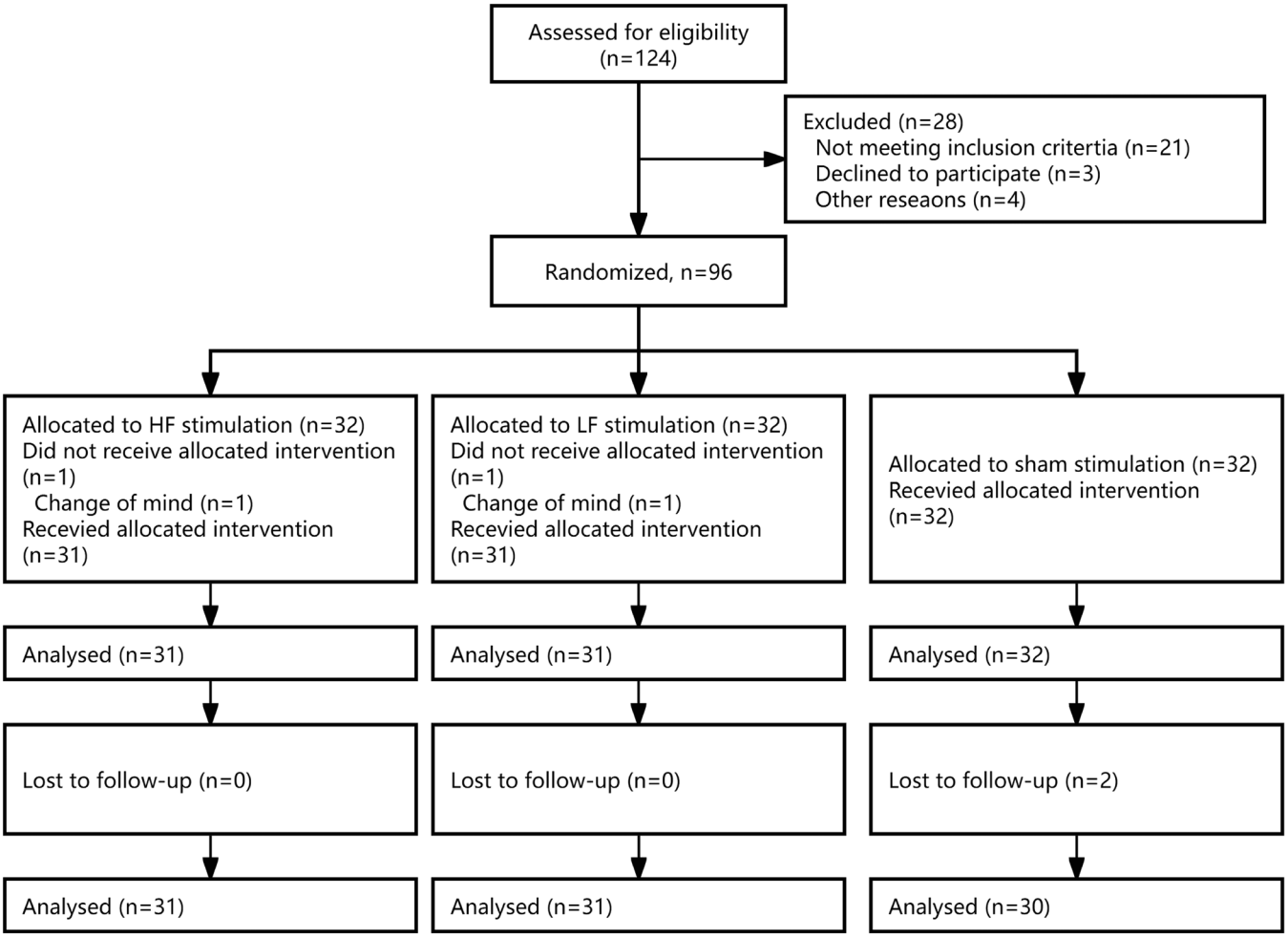

FIGURE 1 Flowchart of screening, randomization, and follow-up.

and the Pittsburgh Sleep Quality Inventory (PSQI), for insomnia severity were used.[32] Montreal Cognitive Assessment (MoCA) questionnaire was used to assess the cognitive function of patients. The evaluation of erectile function employed the abridged International Index of Erectile Function 5 (IIEF-5).[33] Ejaculatory dysfunction was evaluated using the Male Sexual Health Questionnaire for ejaculatory dysfunction (MSHQ-EjD) bother/satisfaction score, a specialized questionnaire designed to gauge concerns and satisfaction related to ejaculation.[34] All questionnaire assessments were conducted at baseline, post-stimulation at week 4, and again at week 8.

2.3 | rTMS treatment protocol

rTMS treatment and data collection were performed in the ward of the First Affiliated Hospital of Anhui Medical University. This study employed two distinct protocols of rTMS as separate treatment modalities, with the dorsolateral prefrontal cortex (DLPFC) serving as the targeted stimulation site. Specifically, the left high-frequency (HF) protocol involved the application of high-frequency (10 HZ) stimulation to the left DLPFC, while the right low-frequency (LF) protocol entailed the application of low-frequency (1 HZ) stimulation to the right DLPFC. These protocols are widely recognized and have demonstrated efficacy in the treatment of various mental and brain disorders.[35,36]

Consenting patients were randomly allocated into three groups, namely the HF group, LF group, and sham stimulation group with a 1:1:1 ratio. The patients were allocated randomly using the sealed envelope technique, employing a block-randomized computer-generated list with a block size of 6. The randomization code remained confidential and undisclosed to all investigators until the completion of the study. The andrologists responsible for evaluating the scales were unaware of the group assignment of the participants and each other. Furthermore, all participants, researchers, physiotherapists administering rTMS, and data analysts remained blinded until the database was unblocked.

All rTMS treatments were administered using a magnetic stimulator (VISHEE Medical Technology). Before the initial treatment, the resting motor threshold (RMT) was assessed using a standard figure-of-eight coil connected to the magnetic stimulator.[37] The participants were seated in a comfortable chair with armrests and instructed to maintain a state of relaxation. The coil was positioned tangentially to

TABLE 1 Demographic and clinical characteristics at baseline.

Variables	HF ($n = 31$)	LF ($n = 31$)	Sham ($n = 32$)	p-value
Age (years)	27.74 ± 3.61	26.61 ± 3.37	27.13 ± 3.45	0.445
Height (cm)	170.56 ± 4.64	171.30 ± 5.50	171.96 ± 3.96	0.504
Weight (kg)	70.08 ± 5.55	72.76 ± 6.01	72.04 ± 6.19	0.187
Place of residence, no. (%)				0.869
Urban	17 (54.8%)	19 (61.3%)	19 (59.4%)	
Rural	14 (45.2%)	12 (38.7%)	13 (40.6%)	
Educational level (years)	10.94 ± 2.06	11.52 ± 2.45	11.59 ± 2.77	0.512
Alcohol use, no. (%)	13 (41.9%)	15 (48.4%)	12 (37.5%)	0.680
Smoking, no. (%)	7 (22.6%)	12 (38.7%)	11 (34.4%)	0.370
Testosterone (nmol/L)	21.41 ± 6.88	21.97 ± 6.14	22.63 ± 5.10	0.727

Note: Data are presented as mean ± standard deviation or counts (%).
Abbreviations: HF, high-frequency group; LF, low-frequency group; Sham, sham stimulation group.

the head and at an approximate angle of 45° to the midline. The motor-evoked potential (MEP) was recorded using surface electromyography. The RMT was determined as the minimum stimulus intensity required to elicit a minimum of five motor-evoked potentials with an amplitude exceeding 50 μV in 10 consecutive trials.

The HF and LF patient groups were subjected to 1200 pulses per session of outpatient rTMS over the course of treatment, administered at 110% RMT. In contrast, the sham stimulation group received sham stimulation. The stimulation protocol encompassed a 4-week treatment period, with daily sessions of stimulation occurring on 5 consecutive weekdays each week for all groups.

2.4 | Statistical analyses

Given the pilot and proof-of-concept nature of this investigation, no power analysis was required to compute the sample size. The data were analyzed using SPSS (Version 22). Normality was assessed using the Shapiro–Wilk test. Appropriate statistical tests, including the Kruskal–Wallis test, Wilcoxon signed-rank test, paired t-test, chi-square test, and ANOVA, were employed to ascertain any significant disparities. Statistical significance was defined as p-values below 0.05.

3 | RESULTS

3.1 | Clinical characteristics

A total of 94 eligible participants were enrolled in the study and were randomly assigned to three groups (Figure 1). All participants completed a 4-week intervention protocol, with only two patients lost to follow-up at the 8-week mark (Figure 1). Table 1 summarizes sample characteristics, highlighting no significant differences observed among the three groups in terms of age, height, weight, place of residence, education, lifestyle habits, and testosterone levels at baseline.

TABLE 2 The incidence of side effects in the three groups.

Side effects (n, %)	HF ($n = 31$)	LF ($n = 31$)	Sham ($n = 32$)
Seizure	0	0	0
Headache	1 (3.2%)	1 (3.2%)	0
Pain at stimulation site	1 (3.2%)	0	0
Total	2 (6.5%)	1 (3.2%)	0

Note: Data are presented as presented as counts (%).
Abbreviations: HF, high-frequency group; LF, low-frequency group; Sham, sham stimulation group.

3.2 | Treatment-emergent adverse event

The monitoring of adverse events was conducted during the rTMS intervention. The analysis of reported adverse events revealed a comparable occurrence rate among the different rTMS groups (Table 2). Common side effects observed in rTMS studies include pain at the stimulation site and headaches. However, these discomforts were observed to resolve spontaneously following the stimulation.

3.3 | Evaluation of post-rTMS treatment at week 4

As presented in Table 3, the initial scores of IIEF-5, MSHQ-EjD bother/satisfaction, HAMA, HAMD, MoCA, and PSQI were similar among all patients in the three groups. Following a 4-week course of rTMS treatment, a significant reduction in MSHQ-EjD bother/satisfaction score was observed in patients in the HF and LF groups, which were statistically significant compared with sham treatment. Additionally, no significant changes were noted in erectile function and cognitive function across the three groups (Figure 2, Table 4). These findings indicated that rTMS treatment effectively alleviated ejaculation distress and enhanced ejaculation satisfaction in the patients. On top of all of that, it was observed that a total of five patients (16.1%) in the HF group and 17 patients (54.8%) in the

TABLE 3 Questionnaire assessment at baseline.

Variables	HF ($n = 31$)	LF ($n = 31$)	Sham ($n = 32$)	p-value
IIEF-5	23.19 ± 0.91	23.16 ± 0.90	22.88 ± 0.83	0.343
MSHQ-EjD bother/satisfaction	4.26 ± 0.82	4.32 ± 0.83	4.16 ± 0.68	0.532
HAMA	4.03 ± 1.94	4.16 ± 2.00	4.09 ± 1.78	0.965
HAMD	4.39 ± 1.91	4.32 ± 1.78	4.28 ± 2.00	0.976
MoCA	28.13 ± 1.02	28.68 ± 1.17	28.53 ± 1.11	0.158
PSQI	4.16 ± 1.90	3.65 ± 1.96	4.56 ± 1.79	0.160

Note: Data are presented as mean ± standard deviation.

Abbreviations: HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HF, high-frequency group; IIEF-5, International Index of Erectile Function 5; MoCA, Montreal Cognitive Assessment; MSHQ-EjD, the Male Sexual Health Questionnaire for ejaculatory dysfunction; LF, low-frequency group; PSQI, Pittsburgh Sleep Quality Inventory; Sham, sham stimulation group.

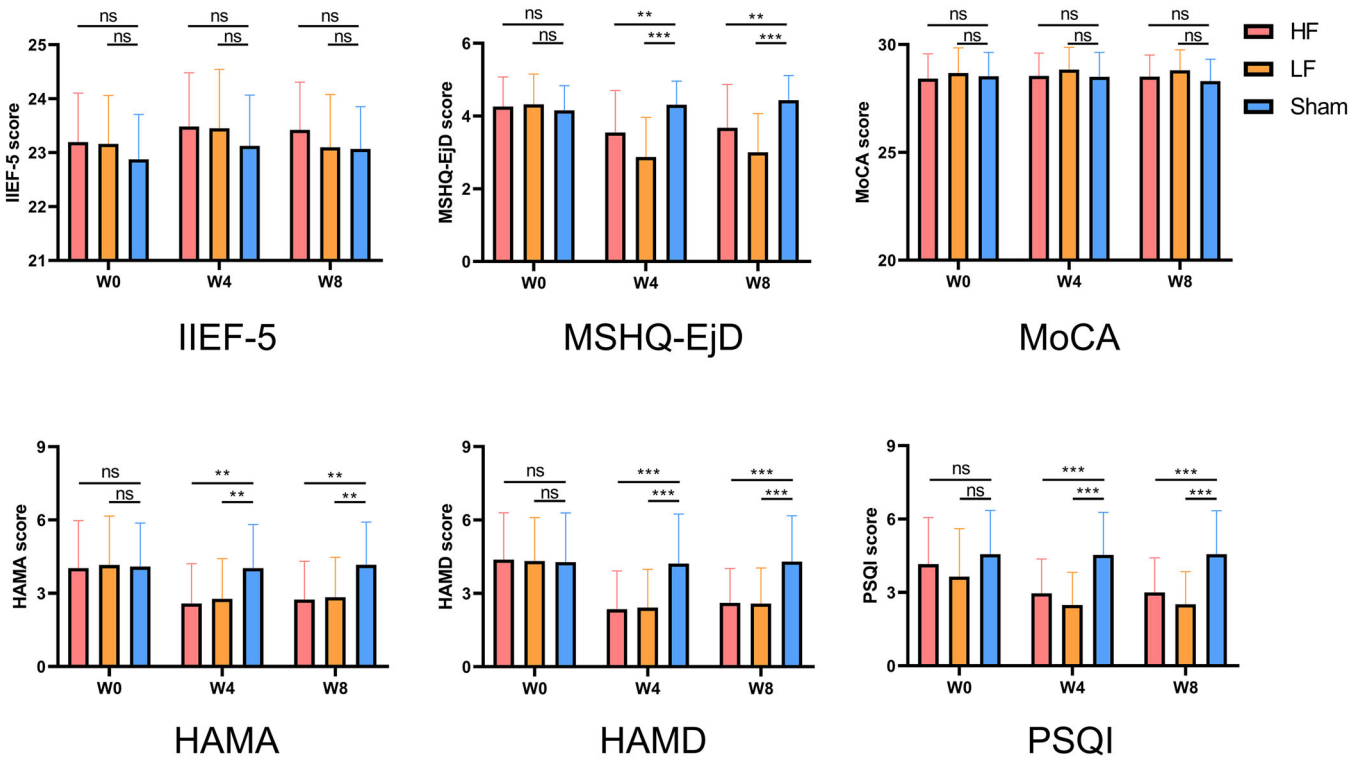

FIGURE 2 Mean performance at baseline (W0), after 4 weeks of treatment (W4), and 8 weeks after treatment beginning (follow-up; W8) in the HF, LF, and sham groups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, compared with each sham group. HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HF, high-frequency group; IIEF-5, International Index of Erectile Function 5; MoCA, Montreal Cognitive Assessment; MSHQ-EjD, the Male Sexual Health Questionnaire for ejaculatory dysfunction; LF, low-frequency group; PSQI, Pittsburgh Sleep Quality Inventory; Sham, sham stimulation group.

LF group achieved successful vaginal ejaculation following treatment (Table 4). There were notable disparities in the cure rates between the two cohorts of patients ($p = 0.001$). This finding suggested that rTMS, particularly when utilizing a right-sided low-frequency stimulation protocol, might effectively improve anejaculation. Furthermore, the administration of rTMS for a duration of 4 weeks resulted in a similar reduction in HAMA, HAMD, and PSQI scores among patients in both the HF and LF groups, which were statistically significant compared with sham treatment (Figure 2, Table 4). This outcome indicated that both HF and LF protocols have a positive impact on the psychological well-being and sleep quality of individuals.

3.4 | Evaluation at week 8 follow-up

The follow-up examination was conducted four weeks after the completion of rTMS therapy. The findings indicated that improvements in the psychological well-being, sleep quality, and satisfaction with

TABLE 4 Questionnaire assessment among three groups at three times.

Variables	Group	Times			*p*-value	
		W0	W4	W8	W4 vs. W0	W8 vs. W0
IIEF-5	HF	23.19 ± 0.91	23.48 ± 1.00	23.42 ± 0.89	0.079	0.052
	LF	23.16 ± 0.90	23.45 ± 1.09	23.10 ± 0.98	0.119	0.591
	Sham	22.88 ± 0.83	23.13 ± 0.94	23.07 ± 0.78	0.092	0.134
MSHQ-EjD bother/ satisfaction	HF	4.26 ± 0.82	3.55 ± 1.15	3.68 ± 1.19	0.001	0.007
	LF	4.32 ± 0.83	2.87 ± 1.09	3.00 ± 1.06	<0.001	<0.001
	Sham	4.16 ± 0.68	4.31 ± 0.64	4.43 ± 0.68	0.197	0.074
Intravaginal ejaculation	HF	0	5 (16.1%)	4 (12.9%)	0.020	0.039
	LF	0	17 (54.8%)	17 (54.8%)	<0.001	<0.001
	Sham	0	0	0	–	–
HAMA	HF	4.03 ± 1.94	2.58 ± 1.63	2.74 ± 1.57	<0.001	<0.001
	LF	4.16 ± 2.00	2.77 ± 1.65	2.84 ± 1.63	<0.001	<0.001
	Sham	4.09 ± 1.78	4.03 ± 1.79	4.17 ± 1.74	0.423	0.712
HAMD	HF	4.39 ± 1.91	2.35 ± 1.56	2.61 ± 1.41	<0.001	<0.001
	LF	4.32 ± 1.78	2.42 ± 1.57	2.58 ± 1.46	<0.001	<0.001
	Sham	4.28 ± 2.00	4.22 ± 2.03	4.30 ± 1.88	0.325	0.103
MoCA	HF	28.13 ± 1.02	28.55 ± 1.06	28.52 ± 1.00	0.148	0.200
	LF	28.68 ± 1.17	28.84 ± 1.04	28.81 ± 0.95	0.059	0.271
	Sham	28.53 ± 1.11	28.50 ± 1.14	28.30 ± 1.02	0.564	0.084
PSQI	HF	4.16 ± 1.90	2.97 ± 1.40	3.00 ± 1.41	<0.001	<0.001
	LF	3.65 ± 1.96	2.48 ± 1.34	2.52 ± 1.34	<0.001	<0.001
	Sham	4.56 ± 1.79	4.53 ± 1.74	4.57 ± 1.77	0.572	0.083

Note: Data are presented as mean ± standard deviation or counts (%).

Abbreviations: —, not available; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HF, high-frequency group; IIEF-5, International Index of Erectile Function 5; LF, low-frequency group; MoCA, Montreal Cognitive Assessment; MSHQ-EjD, the Male Sexual Health Questionnaire for ejaculatory dysfunction; PSQI, Pittsburgh Sleep Quality Inventory; Sham, sham stimulation group; W0, at baseline; W4, after stimulation at week 4; W8, follow-up at week 8.

ejaculation of patients persisted up to 8 weeks after the beginning of treatment regimens (Figure 2, Table 4). Significantly, only one patient who exhibited a positive response to the therapy experienced a relapse (Table 4).

4 | DISCUSSION

This study represents a proof of concept of the effectiveness and safety of rTMS in treating anejaculation. Ejaculatory dysfunction encompasses four distinct types, namely premature ejaculation, retrograde ejaculation, delayed ejaculation, and anejaculation.[4] Among these, anejaculation is considered the most severe manifestation of delayed ejaculation.[38] While premature ejaculation and retrograde ejaculation have received considerable research attention, delayed ejaculation, and anejaculation have been relatively understudied despite their significant negative impact on sexual and reproductive health as major producers of social, intrapsychic, and relational distress.[39]

Our findings indicate that rTMS shows promise in improving anejaculation and ejaculation and sexual satisfaction compared with sham stimulation. Particularly, the right low-frequency stimulation protocol exhibits a cure rate exceeding 50%. Our results gain significant relevance given that a dearth of effective remedies for anejaculation exists. Besides showing improved treatment outcomes, our research findings indicate that rTMS confirms to be a secure, non-invasive, almost side-effect-free tool, to alleviate the symptom of anejaculation and subsequent distress. Moreover, rTMS is a cost-effective treatment option that can alleviate the financial strain on patients.

The frontal cortex is frequently used as a stimulation site for rTMS. It has been found to significantly treat conditions such as depression, anxiety, and sleep disorders, consistent with the findings of our investigation.[24,35] In line with this, a similar connection has been observed between the frontal cortex and sexual behavior. Prior research has demonstrated that heightened activation in the frontal brain regions plays a crucial role in sustaining visual attention toward stimuli that hold motivational significance, consequently resulting in enhanced response inhibition of sexual arousal and erection responses.[40] Furthermore, the disruption of frontal brain regions may result in a state of hypersexuality due to the diminished inhibitory influence on sexual behavior.[41] The involvement of the pre-frontal

cortex in ejaculation control has also been established, as a significant decline in functionality across the pre-frontal cortex has been observed during ejaculation.[42] Recent findings have demonstrated a reduced functional integration between the pre-frontal cortex and subcortical regions in patients with anejaculation, indicating inadequate control of the pre-frontal cortex over subcortical regions.[43] Correspondingly, rTMS has the potential to influence the site of stimulation and the distal cortical functions in a synergistic manner, thereby promoting the reconstruction of the functional area of the cerebral cortex data network and facilitating the restoration of normal functional connections.[44]

Previous neuroimaging studies have indeed revealed a comprehensive network of cortical and subcortical brain regions, such as the frontal cortex, parietal lobes, insula, striatum, amygdala, and thalamus, that play a crucial role in the processing of erotic stimuli.[45,46] In light of these findings, a multidimensional model of sexual behavior is postulated, encompassing cognitive, emotional, motivational, and autonomic aspects. It is plausible that specific brain regions mediate distinct components of this model.[47] The cognitive aspects of sexual behavior, such as the evaluation and attentional processes toward sexual stimuli, are attributed to the frontal and parietal cortex.[48,49] On the other hand, the amygdala, thalamus, and striatum are implicated in the autonomic and emotional components of the model, encompassing sensations of sexual intensity, emotional arousal, and pleasure experienced during the processing of erotic stimuli.[50,51] Notably, during the orgasmic phase, the brain's right hemisphere exhibits its distinctive and essential function.[52] The initial investigation into male orgasm utilizing single photon emission computed tomography (SPECT) revealed a reduction in cerebral blood flow in all cortical regions except for the right prefrontal cortex, which experienced a significant increase in blood flow.[53] Furthermore, during the ejaculation phase, neocortical activation was almost exclusively observed on the right side, specifically in the inferior occipital gyrus, lingual gyrus, inferior parietal lobule, precuneus, and inferior frontal gyrus.[54] The presence of brain lesions in specific areas has been found to be correlated with sexual dysfunction, particularly in cases where lesions are located in the right hemisphere, leading to a higher likelihood of experiencing ejaculatory disorders. Additionally, it has been observed that post-unilateral lesion hypersexuality is significantly more prevalent among individuals with right-hemisphere lesions compared with those with left-hemisphere lesions. Furthermore, the occurrence of ictal orgasm is significantly more frequent in individuals with right-hemisphere seizure foci compared with those with left-hemisphere seizure foci.[52] A case had been reported of a man with a right temporofrontal lesion who developed extreme hypersexuality but lost his ability to achieve orgasm.[52,55] These findings suggest that ejaculation primarily relies on the functioning of the right hemisphere, which may help explain why patients in our study who received left versus right stimulation had significantly different outcomes.

Despite the promising effect sizes obtained in the present study, which is now extended to patients with delayed ejaculation, several limitations warrant future attention. First, it is imperative to conduct additional multi-center clinical trials with a larger sample in order to validate the generalizability of our findings. Second, the efficacy of various stimulation protocols remains unexplored because of constraints imposed by sample size limitations, as we solely focused on investigating the efficacy of the two most commonly used rTMS protocols. Moreover, while we explored the ability to ejaculate, we did not examine the effect of rTMS on the orgasmic intensity in both members of the couple. We plan to use a validated tool such as the male and female Orgasmomenter.[56,57] Lastly, the mechanism underlying the therapeutic effects of transcranial magnetism in the treatment of anejaculation was not investigated in this study, which may be achieved using functional magnetic resonance and other methods in the future.

5 | CONCLUSION

The findings of this study demonstrate that repetitive transcranial magnetic stimulation represents a secure and effective remedy for individuals suffering from anejaculation.

AUTHOR CONTRIBUTIONS

Ming Wang, Dangwei Peng, and Xiansheng Zhang formulated the idea of the article and supervised the research. Qiushi Liu, Hui Gao, Weinan Wang, Juncheng Ma, Zihang Chen, and Wangheng Zhang performed the research. Ming Wang, Tommaso B. Jannini, and Emmanuele A. Jannini analyzed the data and wrote the manuscript. Emmanuele A. Jannini, Hui Jiang, and Xiansheng Zhang reviewed the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The 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.

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