

**REVIEW**

# Clinical application study of neuromuscular electrical stimulation for premature ejaculation

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**Abstract**

Premature ejaculation (PE) is a highly prevalent male sexual dysfunction that significantly impairs psychological well-being, interpersonal relationships, and quality of life. Although pharmacological treatments, such as selective serotonin reuptake inhibitors and topical anesthetics, remain the mainstay of therapy, their clinical effectiveness is often limited by adverse effects, suboptimal efficacy, and poor long-term adherence. In recent years, neuromuscular electrical stimulation (NMES) has emerged as a potential non-pharmacological therapeutic option for PE, attracting increasing clinical and research interest. This narrative review provides a comprehensive overview of the neurophysiological mechanisms underlying ejaculation and the pathophysiology of PE, with a particular focus on the theoretical rationale and clinical evidence supporting NMES therapy. We summarize findings from available animal experiments and human clinical studies evaluating low-frequency electrical stimulation, highlighting its effects on intravaginal ejaculatory latency time, ejaculatory control, and patient-reported outcomes. In addition, we discuss the proposed peripheral and central mechanisms of action of NMES, including modulation of pelvic floor muscle activity, alteration of penile sensory thresholds, regulation of autonomic nervous system balance, modulation of spinal and supraspinal reflex pathways and neurotransmitter signaling, and improvement of pelvic microcirculation. Integrative perspectives from traditional Chinese medicine are also briefly discussed. Overall, existing evidence suggests that NMES may offer a safe and well-tolerated adjunctive approach for the management of PE. However, the current literature is limited by small sample sizes, heterogeneous stimulation protocols, insufficient standardization, and a lack of high-quality randomized controlled trials. Further large-scale, rigorously designed studies are required to establish standardized treatment parameters, clarify underlying mechanisms, and define the long-term efficacy and safety of NMES. Until such evidence is available, NMES should be regarded as an exploratory or adjunctive therapy rather than a first-line treatment for premature ejaculation.

**Keywords**

PE; Ejaculatory response; Physiological mechanisms; NMES therapy

# Estudio de aplicación clínica de la estimulación eléctrica neuromuscular para la eyaculación prematura

## Resumen

La eyaculación prematura (EP) es una disfunción sexual masculina altamente prevalente que afecta significativamente el bienestar psicológico, las relaciones interpersonales y la calidad de vida. Aunque los tratamientos farmacológicos como los inhibidores selectivos de la recaptación de serotonina y los anestésicos tópicos siguen siendo la base principal del tratamiento, su utilidad clínica suele estar limitada por efectos adversos, eficacia subóptima y mala adherencia a largo plazo. En los últimos años, la estimulación neuromuscular eléctrica (ENME) ha surgido como una opción terapéutica no farmacológica potencial para la EP, atrayendo un creciente interés clínico e investigativo. Esta revisión narrativa ofrece una visión integral de los mecanismos neurofisiológicos subyacentes a la eyaculación y la fisiopatología de la EP, con un enfoque particular en la justificación teórica y la evidencia clínica que respalda el tratamiento con ENME. Resumimos los hallazgos de los experimentos animales disponibles y estudios clínicos humanos que evalúan la estimulación eléctrica de baja frecuencia, destacando sus efectos en el tiempo de latencia intravaginal de eyaculación, el control eyaculatorio y los resultados reportados por los pacientes. Además, discutimos los mecanismos periféricos y centrales propuestos de acción de la ENME, incluyendo la modulación de la actividad del suelo pélvico, la alteración de los umbrales sensoriales penianos, la regulación del equilibrio del sistema nervioso autónomo, la modulación de las vías reflejas espinales y supraspinales y la señalización de neurotransmisores, así como la mejora de la microcirculación pélvica. También se discuten brevemente perspectivas integrativas de la medicina tradicional china. En general, la evidencia existente sugiere que la ENME podría ofrecer un enfoque adyuvante seguro y bien tolerado para el manejo de la EP. Sin embargo, la literatura actual está limitada por tamaños de muestra pequeños, protocolos heterogéneos de estimulación, insuficiente estandarización y una falta de ensayos controlados aleatorizados de alta calidad. Se requieren estudios más a gran escala y diseñados rigurosamente para establecer parámetros de tratamiento estandarizados, aclarar los mecanismos subyacentes y definir la eficacia y seguridad a largo plazo de la ENME. Hasta que se disponga de tal evidencia, la ENME debe considerarse como una terapia exploratoria o adjunta, en lugar de un tratamiento de primera línea para la EP.

## Palabras Clave

PE; Respuesta eyaculatoria; Mecanismos fisiológicos; Terapia con estimulación neuromuscular eléctrica

## 1. The nosology and current therapeutic approaches for premature ejaculation

### 1.1 Clinical definitions and classification

Premature ejaculation (PE) is one of the most common sexual dysfunctions in men. The global prevalence of lifelong PE is estimated to be 2–5%, while acquired PE affects approximately 3–4% of men [1]. The earlier medical term of PE was proposed by Masters and Johnson in 1970, who described it as “the inability of a man to delay ejaculation long enough for his partner to reach orgasm in 50% of attempts at sexual intercourse” [2]. Over time, a more standardized and authoritative definition was established. The International Society for Sexual Medicine (ISSM) proposed that PE should be diagnosed based on three core criteria: (1) a short intravaginal ejaculatory latency period (IELT), which refers to the duration of penile insertion into the vagina until ejaculation; (2) a reduced ability to delay ejaculation; and (3) negative personal consequences, such as distress, frustration, or dissatisfaction experienced by the patient and/or their sexual partner.

Traditionally, PE has been classified into two major categories: primary (lifelong) and secondary (acquired). Primary PE refers to ejaculation that consistently occurs too rapidly from the onset of sexual activity. Secondary PE develops after a period of normal ejaculatory function and is often associated with identifiable medical or psychological factors. More recently, an expanded classification system has been proposed, dividing PE into four types, including primary PE, secondary

PE, variable PE, and PE-like ejaculatory dysfunction.

### 1.2 Etiology and evolving perspectives

The etiology of PE is multifactorial and has evolved significantly over time. In the early 20th century, PE was predominantly regarded as a psychological disorder. It was believed that psychological factors influenced ejaculation by affecting the ejaculatory center in the brain. A study by Rajkumar RP *et al.* [3] demonstrated that sexual performance anxiety is significantly associated with PE subtypes, particularly acquired subtypes [4], suggesting that anxiety may play a causal role in the development of subtype PE. As a result, early treatment strategies primarily focused on psychological interventions. Behavioral therapies, including modifications of sexual habits and cognitive approaches, were developed based on this psychological framework. With advances in sexual medicine, PE has gradually been recognized as a condition involving both psychological and physiological mechanisms [5]. Current evidence indicates that PE is associated with factors such as increased penile sensitivity, dysregulation of central neurotransmitters (particularly 5-hydroxytryptamine), and may occur secondary to other medical conditions [6].

### 1.3 Established treatments and their limitations

Multiple therapeutic strategies have been developed to address the diverse etiologies of PE. Currently, treatment options can

be broadly categorized into behavioral therapy, pharmacological therapy, and surgical intervention. Behavioral therapy focuses on ejaculatory control through partner-based techniques. Classic methods include the “squeeze” technique introduced by Masters and Johnson in 1970 and the “stop–start” technique described by Semans in 1956 [7]. Although these approaches may show short-term benefits, their efficacy is difficult to standardize and objectively assess, and their long-term effectiveness remains uncertain.

Pharmacological therapy remains the mainstay for PE treatment. (1) Local anesthetic drugs, such as lidocaine and procaine, are commonly used to reduce penile sensitivity. A eutectic formulation containing lidocaine (150 mg/mL) and procaine (50 mg/mL) has recently been introduced, and clinical trials demonstrated consistent efficacy in approximately 88% of patients, with a six-fold increase in median baseline IELT [8]. Moreover, local side effects are generally mild and transient, including penile hypesthesia, erectile difficulty, erythema, and localized burning sensations [9]. (2) Dapoxetine, which has been certified by Europe, is now used in clinical practice. Its primary mechanism involves inhibiting the reuptake of 5-hydroxytryptamine to achieve the body’s high content of 5-hydroxytryptamine and serotonin. As serotonin is an inhibitory central neurotransmitter, this mechanism contributes to delayed ejaculation. The pharmacological effect depends on dapoxetine binding to the serotonin transporter protein [10]. Common side effects include dizziness, headache, vomiting, delayed ejaculation, and withdrawal syndrome. Selective serotonin reuptake inhibitors (SSRIs) discontinuation syndrome encompasses a range of psychological and neurological symptoms. (3) Other pharmacological options include phosphodiesterase type 5 inhibitors (PDE5i) and tricyclic antidepressants (TCAs). However, these agents are generally not recommended as first-line treatments in clinical practice.

Surgical intervention for PE has been largely abandoned. Studies have found that patients who have undergone dorsal neurectomy may result in permanent loss of penile sensitivity or persistent numbness, raising significant safety concerns [11].

## 2. Neurophysiological basis of ejaculation and the pathophysiology of PE

### 2.1 Peripheral and spinal neural pathways

The ejaculatory response is regulated by the peripheral nervous system. Sympathetic nerves are responsible for the coordinated contraction of the smooth muscles within the seminal tract, which promotes the forward movement of semen. Parasympathetic nerves are responsible for the secretion of semen and the prevention of semen reflux. The pudendal nerve is responsible for the motor innervation of the urethral smooth muscle and the urethral sphincter [12].

In addition to peripheral control, ejaculation is tightly regulated by the spinal cord. Sympathetic nerves originate from the dorsal grey column and the intermediolateral cell column of the thoracolumbar spinal segments. Parasympathetic nerves emanate from the sacral parasympathetic nucleus located at

the sacral spinal levels. Somatic fibers of the pudendal nerve emanate from the ventral horn nuclei of spinal segments S2–S4. Recent studies have identified a specialized neuronal network within the lumbar spinal cord known as the spinal ejaculatory generator (SGE) [13]. The SGE plays a critical role in synchronizing ejaculatory-related spinal neurons, thereby coordinating the ejaculatory reflex.

### 2.2 Central nervous system regulation

The ejaculatory response is also controlled by central nervous system mechanisms. These include sensory integrative as well as excitatory-inhibitory actions within specific brain regions. Key structures involved in sensory and integrative control include the posterior medial division of the bed nucleus of the stria terminalis (BNSTpm), the posterior dorsal region of the medial amygdala (MPOA), the parafascicular thalamic small cell component (SPFp), and the posterior dorsal preoptic nucleus (PNpd) [12].

### 2.3 Pathophysiology of PE

The normal male sexual response cycle consists of four stages: arousal, ejaculation, orgasm, and extinction [14]. Sexual arousal begins when the brain receives sexual stimuli and initiates descending excitatory signals. The ejaculatory response consists of two distinct phases, *i.e.*, ejaculation and expulsion. Ejaculation refers to the passage of semen from the seminal vesicles to the prostatic urethra, and expulsion begins when the semen reaches the urethra and refers to the passage of semen from the prostatic urethra to the outside of the body and is controlled by rhythmic contractions of the pelvic and urethral smooth muscles [15].

Rhythmic contractions of the perineal musculature, along with coordinated activity of the internal and external urethral sphincters, facilitate the forward movement of the semen. Orgasm results from the central processing of sensory inputs combined with contractions of the ejaculatory organs. Current research indicates that ejaculation is primarily mediated through a central neural conduction pathway. Various sexual stimuli received by the penile skin are transmitted via the dorsal nerve of the penis to higher cerebral centers, where excitatory impulses are generated. These signals are subsequently relayed from the cerebral sexual excitation centers to the spinal ejaculatory center, which in turn coordinates the activity of sympathetic, parasympathetic, and somatic motor nerves to execute the ejaculatory process [16–18]. The generation and modulation of excitatory impulses in the brain are regulated by the neurotransmitters 5-hydroxytryptamine and dopamine. 5-hydroxytryptamine acts as an inhibitory “brake”, and a reduction in its level leads to a decrease in the ability to control ejaculation. In contrast, dopamine serves as an excitatory “throttle”, with increased dopaminergic activity facilitating and promoting the ejaculatory response [19].

## 3. Neuromuscular electrical stimulation as a novel therapeutic intervention

### 3.1 Principles and rationale

During sexual activity, patients with PE often experience difficulty maintaining a relaxed psychological state and report reduced sexual satisfaction. This persistent dissatisfaction can negatively affect mental health and may lead to psychological issues such as anxiety and fear. In severe cases, PE may also strain the intimate relationship between the couple, leading to the problem of a dysfunctional family. Therefore, PE represents a clinically significant condition that requires timely and effective intervention. Current treatment options for PE mainly include behavioral therapy, pharmacological treatment, and minimally invasive interventions. However, these approaches are frequently associated with adverse effects, including nausea, headache, dizziness, diarrhea, and ejaculatory disorders [20]. Consequently, there is a growing need for novel therapeutic strategies that offer improved efficacy with fewer side effects.

Neuromuscular Electrical Stimulation (NMES) is a safe, non-invasive physiotherapeutic modality that remains relatively underexploited in the field of male sexual medicine [16]. NMES involves the application of electrical currents to stimulate motor nerves or muscle fibers, thereby inducing controlled muscle contractions. This technique integrates principles derived from traditional Chinese medicine with modern electrophysiological theory. Low-frequency electrical stimulation devices are used to deliver pulsed currents to achieve therapeutic effects.

One of the earliest clinical applications of electrical stimulation involved activation of the peroneal nerve to enhance muscle function and correct foot drop in patients with post-stroke hemiplegia [21]. Since then, electrical stimulation therapy has been widely adopted in rehabilitation medicine, sports science, and health management. The therapeutic efficacy of electrical stimulation can be optimized while minimizing tissue damage by carefully adjusting parameters such as frequency, pulse width, pulse modulation, amplitude, electrode placement, and the use of variable frequency pulse patterns. The standard procedure for NMES protocols involves precise placement of electrode pads over the target muscles. Stimulation frequencies are typically adjusted to 20–50 Hz, depending on the patient's tolerance level. Each treatment session generally lasts 20–30 minutes, with multiple consecutive sessions administered as a treatment course [22]. NMES has recently gained increasing recognition as a potential therapeutic approach for PE. Shechter *et al.* [23] treated the perineal region of 23 patients with lifelong PE using a commercial electrical stimulation device and observed a more than fourfold increase in ejaculation latency following treatment. Similarly, Cizmeci *et al.* [18] applied NMES to 24 male Wistar albino rats and demonstrated a significant prolongation of ejaculation time. Aydos *et al.* [24] treated 60 patients with PE using TPTNS and observed a statistically significant prolongation of IELT after treatment. In a clinical trial conducted by Uribe *et al.* [25], transcutaneous electrical nerve stimulation significantly increased IELT by 4.8-fold, 6.8-fold, and 5.4-fold at 3, 6, and 12 months, respectively. In addition, literature has suggested that low-frequency electrical stimulation applied to specific body surface regions, when combined with pharmacological

therapy, is more effective than drug treatment alone.

### 3.2 Clinical evidence from animal and human studies

Several studies have investigated the application of low-frequency electrical stimulation for the treatment of PE. The key findings from representative animal and human studies are summarized in Table 1 (Ref. [18, 21, 26–28]).

### 3.3 Limitations of the existing evidence

Despite encouraging results, the current evidence base has several notable limitations. Most studies involved small sample sizes, limiting statistical power. Randomization and blinding procedures were often insufficient, and sham-controlled designs were frequently absent. In several studies, NMES was combined with other therapeutic modalities, complicating the evaluation of its independent efficacy. Furthermore, follow-up periods were generally short, restricting assessment of long-term outcomes and durability of treatment effects.

## 4. Proposed mechanisms of NMES in the management of PE

### 4.1 Peripheral neuromuscular effects

Electrical stimulation is widely used as a physiotherapeutic modality in cardiovascular and cerebrovascular medicine, obstetrics and gynecology, surgical, and rehabilitation medicine [16]. However, its application in the field of andrology remains limited, and its underlying mechanisms of action are not yet fully elucidated. Based on current understanding of the physiological process underlying PE, ejaculation can be described as follows: During sexual activity, sensory stimulation of the penile skin and glans is transmitted via the dorsal penile nerve, pudendal nerve, and sacral (S2–S4) plexus, with ascending conduction to the hypothalamus and cerebral cortex. When cortical excitability reaches a threshold, efferent signals are transmitted to the spinal cord, triggering ejaculation [29]. PE may result from hypersensitivity of the peripheral penile afferent nerves and increased excitability of the efferent nerves of the ejaculatory center. Therefore, we hypothesize that several peripheral mechanisms may explain the therapeutic effects of NMES. First, the ejaculatory response depends largely on rhythmic contractions of the pelvic floor muscles and urethral smooth muscles [30]. NMES induces continuous activation of the pelvic cavernous and bulbocavernosus muscles, resulting in sustained contraction of the pelvic muscles in a state of tension. During sexual intercourse, the ejaculation-related muscles cannot contract rhythmically, thus achieving the effect of delaying ejaculation. Second, the pudendal nerve provides motor innervation to the urethral smooth muscle as well as the internal and external urethral sphincters. Forward ejaculation requires complete synchronization between smooth muscle contraction and the urethral sphincter relaxation. Continuous neuromuscular stimulation of the pudendal nerves may disrupt this synchronization, thereby delaying ejaculation. Third, excessive sensitivity of the glans penis, particularly the frenulum region located at the 6 o'clock position, is a key contributor to

**TABLE 1. Clinical and experimental studies investigating low-frequency electrical stimulation for premature ejaculation.**

| Participants/Model   | Intervention  | Outcome Measures  | Key Results   |
|--|---|---|---|
| 66 patients with premature ejaculation and penile hypersensitivity, randomized into an NMES group, a local anesthetic group, and a combined treatment group. | Low-frequency NMES applied five times per week; local anesthetic group received compound lidocaine cream; combined group received both treatments; total treatment duration was 3 months.                                 | Intravaginal ejaculatory latency time (IELT); Premature Ejaculation Diagnostic Tool (PEDT); spousal satisfaction. | Chen <i>et al.</i> [26] reported that all groups showed significant improvement after treatment ( $p < 0.05$ ). The combined therapy group demonstrated superior improvements in IELT, PEDT scores, and spousal satisfaction compared with either monotherapy, while no significant difference was observed between NMES alone and anesthetic alone ( $p > 0.05$ ). |
| One case of lifelong (congenital) premature ejaculation.   | Percutaneous dorsal penile nerve stimulation with electrodes placed over the dorsal penile nerve; frequency 20 Hz, pulse width 200 $\mu$ s, current 20–60 mA; 30 minutes per session, three times per week, for 6 months. | IELT measured during treatment and follow-up up to 60 weeks.  | Moussa <i>et al.</i> [21] observed an increase in IELT from 40 seconds at baseline to an average of 3 minutes and 54 seconds after treatment, with further prolongation to approximately 5 minutes at 60-week follow-up.  |
| 86 patients with premature ejaculation (treatment group: 56; control group: 30).   | Treatment group received vacuum negative-pressure hydrodynamic massage combined with low-frequency electrical pulse acupoint stimulation 3–5 times per week; control group received psychotherapy.                        | IELT; erectile function improvement; adverse reactions.   | Zhuang <i>et al.</i> [27] found a significantly higher overall efficacy rate in the treatment group (76.8%) compared with the control group (30%) ( $p < 0.05$ ). Erectile function improved in 71.88% of patients with mild erectile dysfunction, and no obvious adverse reactions were reported.  |
| 90 patients with premature ejaculation divided into combined therapy, paroxetine-only, and low-frequency pulse-only groups.                                  | Combined therapy with paroxetine plus low-frequency pulse stimulation; control groups received paroxetine alone or low-frequency pulse therapy alone; treatment duration was 8 weeks.                                     | IELT; PEDT scores; overall treatment efficacy.  | Tan <i>et al.</i> [28] demonstrated that IELT was longest in the combined therapy group (6.48 $\pm$ 0.13 min), followed by the paroxetine-only group and the pulse-only group ( $p < 0.05$ ). PEDT score reduction and overall efficacy were also highest in the combined group (83%).  |
| 24 male Wistar rats divided into control, high-frequency burst, and low-frequency stimulation groups (n = 8 per group).                                      | High-frequency burst stimulation at 80 Hz and low-frequency stimulation at 2 Hz, both with a pulse width of 200 $\mu$ s, applied to the bulbospongiosus muscle.   | Ejaculation latency; seminal vesicle pressure parameters; bulbospongiosus electromyographic activity.             | Cizmeci <i>et al.</i> [18] reported that ejaculation latency was significantly prolonged in the low-frequency stimulation group compared with both the high-frequency burst and control groups ( $p < 0.05$ ).  |

NMES: neuromuscular electrical stimulation.

PE [31]. Low-frequency electrical stimulation stimulates the nerves of the pudendal and pelvic nerves by means of a continuous, mild electric current. This repeated stimulation promotes neural adaptation and increases the sensory threshold of the penile afferent nerves, thereby reducing hypersensitivity. Fourth, ejaculation is a spinal reflex predominantly mediated by the sympathetic nerves. When sexual excitement reaches climax, sympathetic over-excitement will trigger ejaculation. Low-frequency electrical stimulation can balance the autonomic nervous system and prolong ejaculation by inhibiting sympathetic overexcitation [32]. Fifth, long-standing PE may lead to the establishment of an abnormal, rapid ejaculation reflex arc [33]. Low-frequency electrical stimulation may function as a “reset mechanism”. Through frequent application of controlled electrical stimulation, NMES may facilitate reorganization of spinal and supraspinal reflex pathways, thereby restoring a more regulated ejaculatory response. Sixth, low-frequency electrical stimulation therapy improves local blood circulation in the pelvic region, and better blood flow increases oxygen and nutrient delivery to neural and muscular tissues, supporting functional recovery and maintenance [34]. Improved pelvic blood flow may also have a positive effect on prostatitis and pelvic pain syndromes, inflammatory conditions that are often important factors in exacerbating PE [35].

## 4.2 Central neuromodulatory effects

Previous studies have demonstrated the presence of Onuf’s nucleus within the human sacral medulla, which inhibits the motor responses of the bulbocavernosus and sciatic cavernous muscles. Electrical stimulation of the dorsal penile nerve has been shown to inhibit parasympathetic ejaculatory activity and modulate the function of the Onuf’s nucleus [36]. Through this central modulation, NMES may suppress excessive motor activation of ejaculation-related muscles, thereby delaying ejaculation (Fig. 1).

## 4.3 Integrative and traditional medicine perspectives

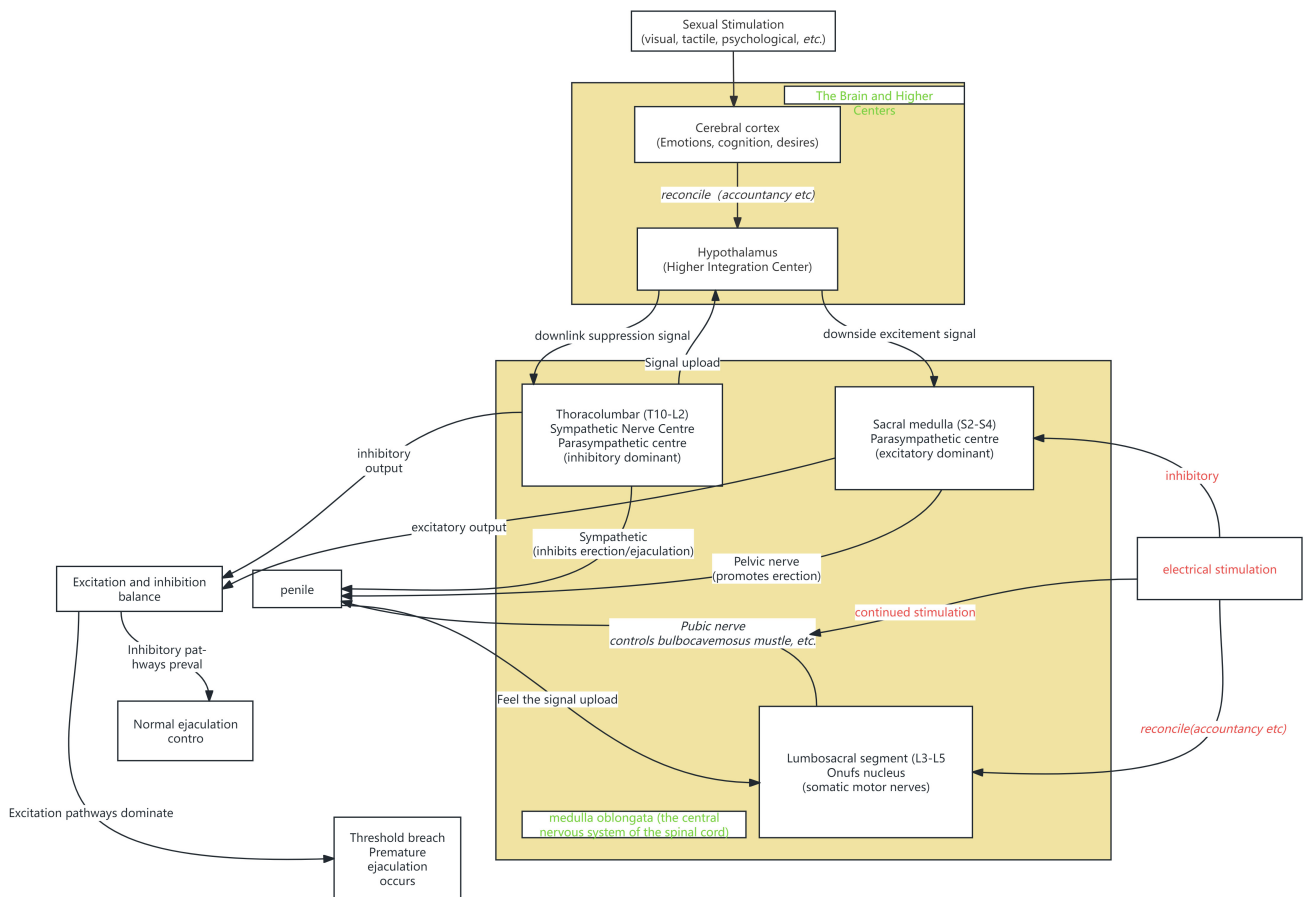
(1) Transcutaneous NMES may be interpreted within the framework of traditional Chinese medicine (TCM). According to TCM theory, PE is associated with an imbalance between yin and yang, mental unrest, and dysfunction of the liver and kidney system. Research has suggested that low-frequency electrical stimulation is believed to exert therapeutic effects by regulating yin and yang, enhancing psychological health, and improving the functions of the liver and kidney system. By combining the meridian theory of TCM with the digital electronic theory, low-frequency electrical stimulation in the form of electrical signals instead of traditional acupuncture stimulates the patient’s sex-related acupoints, such as kidney acupoints, Qihai, Guanyuan, and Sanyinjiao. This approach may increase the ejaculatory threshold and enable the PE patient to reach the normal ejaculation response time [27]. Electrical stimulation induces rhythmic contraction of the pelvic floor muscles, which are highly overlapped with the concept of “tendon” in TCM. In TCM, tendons bind bones and support organ function, and pelvic floor weakness is considered a manifestation of “tendon insufficiency” [37]. Through NMES,

acupoints are activated to stimulate meridian qi in a manner analogous to traditional acupuncture. When qi is sufficiently activated at the target sites, therapeutic effects are achieved, leading to strengthening of the associated tendons and musculature. This enhancement improves the restraining and regulatory control of the Jing Guan. This is like the real-life “squat” and the “Kegel exercise” [38] in the gym. According to TCM, “the heart is the master of God’s clarity”, and all emotions are attributed to the heart [39]. PE is closely associated with the patient’s nervousness. Continuous and regular low-frequency electrical stimulation itself has the effect of “calming and tranquilizing the mind”; continuous stimulation of acupoints such as Hundred Houses of Justice and the Divine Gate of God can tranquilize the mind and heart, ease the liver, and relieve the patient’s nervousness and anxiety [40].

(2) NMES may also exert therapeutic effects through modulation of the opioid neurotransmitter release. Endogenous opioid neurotransmitters are naturally released during sexual activity to reduce pain perception. Tramadol has been used clinically as a pain reliever and as a treatment for PE. It works as a weak opioid agonist, acetylcholine receptor antagonist, and 5-HT receptor antagonist to treat PE. Previous research reported that tramadol significantly increased intravaginal ejaculation latency in patients with PE [41]. NMES at specific frequencies promotes the release of opioid neurotransmitters from the central nervous system [42]. The analgesic effect of low-frequency electrical stimulation (4 Hz) was counteracted with a low dose of the opioid antagonist naloxone, whereas it was ineffective against the analgesic effect produced by high-frequency electrical stimulation (120 Hz), suggesting that low-frequency NMES produces opioid central neurotransmitters [43], which in turn prolongs the vaginal ejaculation latency.

(3) NMES may further influence ejaculation through nitric oxide (NO)-related signaling pathways. The NO-cGMP (Nitric Oxide-Cyclic Guanosine Monophosphate Pathway) and NO-cAMP (Nitric Oxide-Cyclic Adenosine Monophosphate Pathway) signaling pathways are not only involved in the relaxation of smooth muscle in the human penis, but may also affect smooth muscle relaxation in the vas deferens, seminal vesicles, prostate, urethra, and skeletal muscle [44]. It has been found that serum nitric oxide levels in patients with primary PE are generally lower than normal levels, and that intravaginal ejaculatory latency values are positively correlated with nitric oxide values [45]. Low-frequency electrical stimulation promotes endogenous production and release of NO and cGMP, leading to sympathetic inhibition and reduced penile smooth muscle contraction, thereby delaying ejaculation. Subsequently, transcutaneous NMES has been reported to increase NO and cGMP levels at local acupoints, and the increase in signaling molecules further promoted the efficacy of electrical stimulation.

(4) Nerve fibers in humans include fine and coarse nerve fibers. Fine nerve fibers specialize in transmitting noxious, painful signals and temperature sensations, including the hypersensitivity stimuli produced by PE. Coarse nerve fibers, on the other hand, transmit harmless mechanical sensations such as tactile pressure and vibration, including the slight vibration sensation produced by low-frequency electrical stimulation [46]. Based on the theory of pain gating [47], when



**FIGURE 1. A schematic representation of the neural conduction pathway involved in PE, and the proposed mechanisms of action of low-frequency electrical stimulation.** Low-frequency electrical stimulation delays ejaculation by continuously stimulating the bulbocavernosus muscle, resulting in the inability of ejaculation-related muscles to contract rhythmically. It also delays ejaculation by continuously stimulating the pudendal nerves, resulting in the inability of the urethral smooth muscles and the internal and external urethral sphincters to synchronize and coordinate. Electrical stimulation modulates the sacral plexus and acts on the parasympathetic segment to inhibit contraction of the sciatic cavernous and bulbocavernosus muscles. Concurrently, modulation of Onuf's nucleus within the sacral spinal cord suppresses motor output to these muscles, collectively contributing to delayed ejaculation.

the coarse nerve fiber signal is dominant, the activity of the coarse nerve fibers activates inhibitory neurons in the spinal cord and suppresses the sensation of pain. When electrical stimulation is applied, the vibration sensation predominates, the oversensitive stimulation transmitted by the fine nerve fibers is suppressed, and the pain sensation disappears. The signals from the penis that could lead to PE are suppressed or diminished by the “interference signals” (gross nerve activity) generated by the electrical stimulation, so that the strength of the overstimulation signals to the brain is greatly reduced. Eventually, the ejaculation threshold is raised, and it takes longer and more intense stimulation to make the patient ejaculate (Fig. 2).

(5) Psychological factors, including anxiety and tension, play a critical role in PE. After the delayed effect is produced by low-frequency electrical stimulation treatment, the negative effects of anxiety and tension can be significantly relieved, and a positive cycle can be formed [48]. The process of low-frequency electrical stimulation improves sexual technique by advancing the patient's perception of the onset of ejaculation

and the state of the pelvic muscles to improve the time to ejaculation.

## 5. Adverse reactions of NMES therapy for PE

NMES therapy for PE is generally well tolerated and associated with minimal adverse effects. Reported side effects are typically mild and transient, including temporary discomfort during stimulation, localized skin irritation at electrode sites, and mild soreness of the perineal muscles. Importantly, no serious adverse events have been reported in published studies to date. However, long-term safety data remain limited, and further studies with extended follow-up are required to comprehensively evaluate the safety profile of NMES therapy.

## 6. Conclusion and future perspectives

Premature ejaculation is a highly prevalent sexual dysfunction that significantly impairs quality of life and is frequently

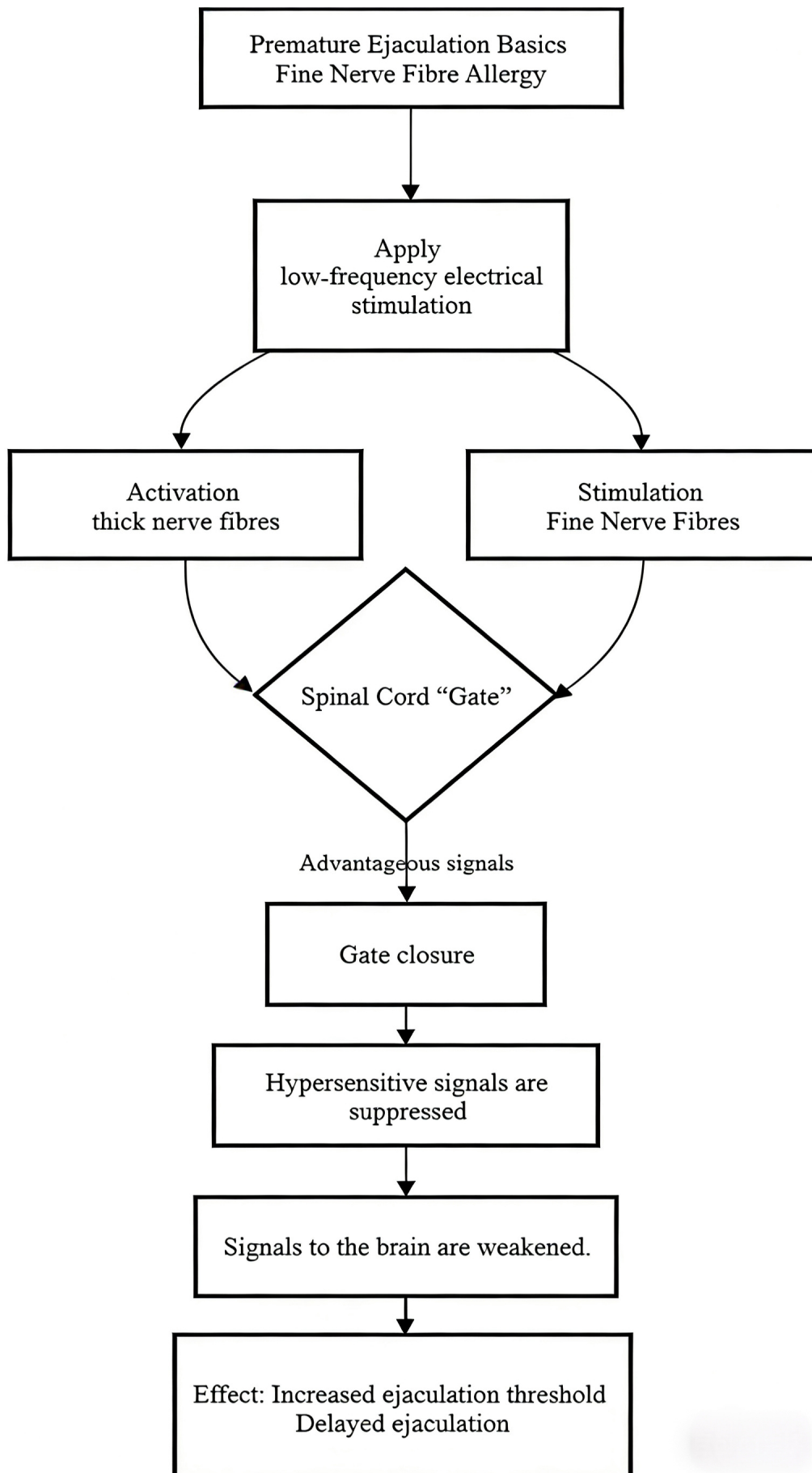


FIGURE 2. One of the principles of low-frequency electrical stimulation for PE, the theory of pain gating.

associated with psychological disorders such as anxiety and depression. It also negatively affects partner relationships and overall marital harmony. Therefore, elucidating the etiology and underlying mechanisms of PE, as well as developing effective therapeutic strategies, remains an important goal of clinical research.

Currently, Dapoxetine and specific lidocaine/pramidine sprays constitute the mainstay of PE treatment [9]. However, the clinical efficacy of these pharmacological agents is often limited. Their use is further constrained by frequent side effects and the high discontinuation rate, making sustained naturalization of the sexual function difficult to achieve. Encouragingly, accumulating evidence suggests that NMES therapy represents a promising alternative or adjunctive approach for PE management. This treatment requires no drugs, has mild side effects, and promises to bring back the natural process of sexual intercourse. Nevertheless, NMES therapy currently faces several limitations. These include the absence of standardized treatment protocols, a lack of trained professional, insufficient mechanistic understanding, limited high-quality evidence from large-scale randomized trials, prolonged treatment duration, and variable patient adherence. Accordingly, NMES should presently be considered an adjunctive or exploratory therapy rather than a first-line treatment option. Future research should focus on conducting large-scale, well-designed clinical trials to validate the efficacy and safety of NMES therapy. Further efforts are needed to clarify its underlying mechanisms, establish standardized treatment parameters, optimize combination strategies, and improve stimulation device performance. In addition, strengthening multidisciplinary collaboration, simplifying treatment procedures, reducing costs, and enhancing patient education may facilitate wider clinical adoption. With continued research and technological refinement, NMES therapy has the potential to become a valuable therapeutic option for PE in the future.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## AUTHOR CONTRIBUTIONS

BYZ—conceptualization, writing—original draft, writing—review & editing. XY—conceptualization, data curation. JRZ—formal analysis, methodology. GXZ—conceptualization, writing—review & editing. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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