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(REVIEW ARTICLE)

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How multi-site, peripheral, non-invasive electrical stimulation (MSPES) impact three major mechanisms in the Central Nervous System

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Abstract

With technological advancement, electrical stimulation (ES) has been increasingly used in various clinical settings to treat acute and chronic pain conditions. It has become popular with both patients and health professionals. However, its clinical effectiveness is still controversial, with some studies supporting it, whereas others contradict its clinical use. Although ES has been used for decades, it has recently been clarified how it produces analgesia or reduces pain. Furthermore, there is likely more than one mechanism of action. This descriptive review describes the fundamental mechanisms and the necessary details of possible pathways and networks that ES modulates. It also covers literature findings concerning ES: basic science, experimental pain; clinical trials; and systematic reviews; to update the reader on the latest developments in its description.

Keywords: Electrical stimulation; Neuromodulation; Opioid receptors; Somatosensory stimulation; Serotonin

1. Introduction

The brain instructs the hand to reach for an object, and the hand informs the brain that it has executed the instructions. Movements such as reaching for an object require the involvement of many areas of the nervous system. The motor regions of the frontal lobe plan and command the movements required to reach for the object. Pathways convey messages to the muscles from the frontal lobe to the spinal cord. Motor neurons of the spinal cord transmit the message to the muscles involved in the specific task. Sensory information from the visual cortex is required to direct the hand to the object, and sensory information from sensory receptors in the hand is needed to verify that the cup is grasped.

The basal ganglia participate in the moving process by calculating and estimating the force required to make the grasp. The cerebellum takes part by correcting errors in the movement as it is performed. ES is a common clinical technique known to induce changes in corticomotor excitability. While some types of ES is applied to induce a tetanic motor contraction, the ES at the sub-motor threshold (sensory) intensifies corticomotor excitability. This mechanism may underpin changes in corticomotor excitability in response to afferent input generated by ES. The ES of paralyzed muscles can be used to restore or replace motor function in individuals with upper motor neuron damage from causes such as stroke or spinal cord injury (SCI). Understanding the mechanisms underlying these opposite changes in corticomotor excitability still needs to be discovered.

In some conditions, such as stroke or incomplete SCI, ES may be part of a therapy regimen that helps restore volitional movement and function. In other conditions, such as severe stroke or complete SCI, permanent ES applications are

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needed to replace the lost neuromuscular function. This way, ES can be used for numerous benefits to modulate physiology. These include.

- Stimulating muscular blood flow,
- Increasing strength,
- Reducing muscle pain, and
- Improving psychological recovery.

These benefits are accomplished through the natural action of ES.

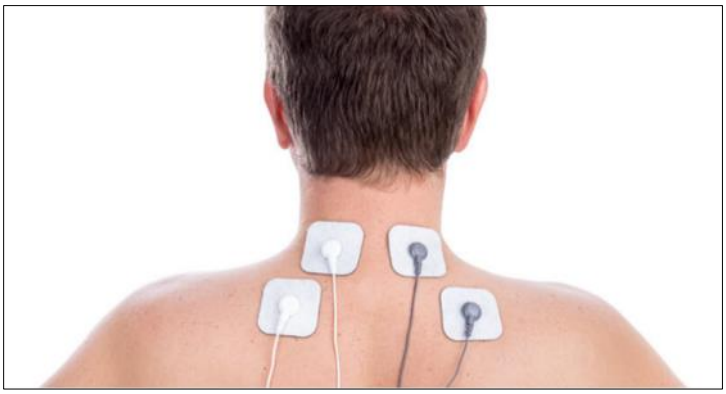

Figure 1 Example of electrode placement in electrical muscle stimulation

2. Description

For this descriptive essay on ES, three mechanisms in the body have been selected that react to ES on the body's surface. Several scenarios can be described to understand the body mechanism that reacts to ES. The idea is to update the reader on the latest development in its description. It also covers literature findings concerning ES: basic science, experimental pain, clinical trials, and systematic reviews. The three areas are.

- Transcutaneous electrical nerve stimulation produces its effects by activating opioid receptors.
- Serotonin levels in the spinal cord increase with ES
- The long-term effect of daily somatosensory stimulation with ES on the reorganization of the motor cortex

2.1. Transcutaneous electrical nerve stimulation produces its effects by activating opioid receptors.

Low-frequency ES (1–20 Hz) activates mu-opioid receptors, and high-frequency ES (50–150 Hz) activates delta-opioid receptors.

ES is a commonly used nonpharmacologic and non-invasive treatment for pain. Although several clinical studies show the effectiveness of ES for pain, there is still much controversy over which conditions to treat with ES and the adequate parameters to use. Prior reports show that ES reduces pain through both peripheral and central sites in the spinal cord and brainstem that utilize opioids and serotonin, and ES activates muscarinic receptors. (Chang and Cuatrecasas,1979). Among these, the μ-opioid receptor (MOR) plays a vital role in analgesia. Many of these receptors at various levels in the central nervous system are associated with pain transmission (Arvidsson et al., 1995). Peripherally, at the site of ES application, opioid and α-2 noradrenergic receptors are involved in ES-induced analgesia (Sluka, 2008).

One type of ES is the application of electrical current via electrodes placed on the skin for pain control. It can be applied with varying frequencies, from low (< 10 Hz) to high (> 50 Hz). Intensity may also be varied from sensory to motor activation. Sensory intensity is when the patient experiences a firm yet comfortable sensation without motor fiber contraction. High intensity typically involves a motor contraction but should not be painful. Higher-frequency stimulation is usually delivered at sensory intensity, and low-frequency stimulation is delivered at motor intensity. Prior literature based on laboratory experiments shows that various frequencies activate central mechanisms that produce analgesia regardless of intensity.

Studies have demonstrated that opioids modulate synaptic transmission in pain pathways and produce analgesic effects. Three different types of classical receptors are activated by opioids, namely μ, δ, and k-opioid receptors. It can be observed that low-frequency ES activates μ-opioid receptors in the spinal cord and the brainstem, whereas high-frequency ES activates δ-opioid receptors in the spinal cord and the brainstem (Sluka et al., 1999; Kalra, Urban, and Sluka, 2001; Sluka, and Chandran, 2002).

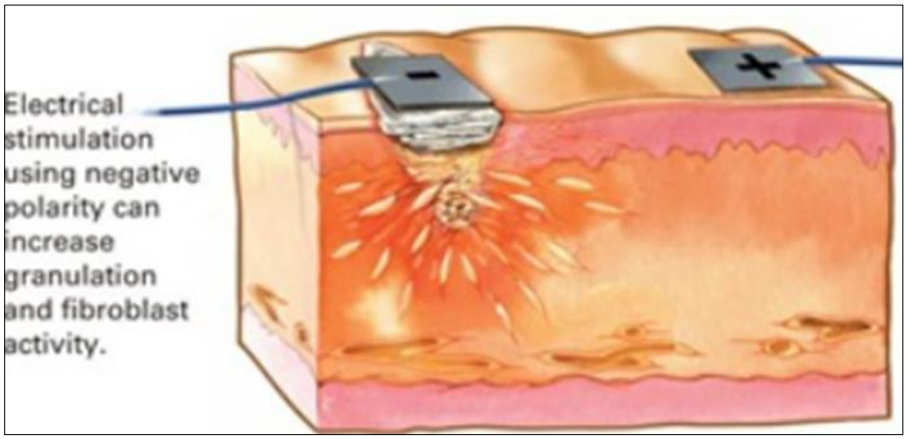

Figure 2 Schematic picture of increased granulation and fibroblast activity, ES increases levels of endogenous opioids in the spinal fluid.

ES is commonly used to relieve pain (Sluka et al., 2007). The literature on the clinical application of ES is extensive. The gate control theory of pain is commonly used to explain the actions of high-frequency ES, whereas the release of endogenous opioids typically explains low-frequency ES. The study shows how mu, delta, and kappa opioid receptors in antihyperalgesia are produced by low- and high-frequency ES using an animal inflammation model (Sluka et al., 2007). Antagonists to mu (naloxone), delta (naltrinodole), or kappa (nor-binaltorphimine) opioid receptors were transmitted to the spinal cord by micro-dialysis. Joint inflammation was induced by injecting kaolin and carrageenan into the knee-joint cavity.

The withdrawal latency to heat was measured before, during, and after inflammation. The data showed that the withdrawal latency decreased as inflammatory responses increased. Additionally, administering a drug or artificial cerebral spinal fluid had no significant effects on the withdrawal latency compared to control groups + ES. High- (100 Hz) or low-frequency (4 Hz) ES produced approximately 100% inhibition of hyperalgesia. Low doses of naloxone, selective for mu-opioid receptors, blocked the antihyperalgesia produced by low-frequency ES. High doses of naloxone, which also blocks delta and kappa opioid receptors, prevented the antihyperalgesia produced by high-frequency ES. Spinal blockade of delta opioid receptors dose-dependently prevented the antihyperalgesia produced by high-frequency ES.

2.2. Serotonin levels in the spinal cord increase with ES

In addition to opioids, serotonin plays a role in the analgesia produced by ES. Specifically, an increased serotonin release in the spinal cord produces analgesia by activating the spinal 5-HT2A and 5-HT3 receptors (Radhakrishnan et al., 2003). Peripheral 5-HT is released from plasma and activates 5-HT1 and 5-HT2 receptors on peripheral blood vessels to enhance vascular permeability (Pierce et al., 1996). The effects of serotonin are complicated, but it is believed that release from the brainstem structure produces analgesia (Stein, Schafer, and Machelska, 2003). On the other hand, serotonin injected peripherally produces edema and pain in humans and hyper-analgesia in rodents (Hughes & Sufka, 1991).

The above would result in edema and enhance the release of pronociceptive and proinflammatory substances such as bradykinin and eicosanoids. Peripherally released serotonin can produce pain directly by activating 5-HT3 receptors on A/C afferent fibers (Hughes & Sufka, 1991). Thus, the effects of serotonin peripherally are to produce edema and pain. Therefore, the peripheral effects of ES can be examined for its ability to modulate edema and pain induced by peripherally applied 5-HT.

2.3. The long-term effect of daily somatosensory stimulation with ES on the reorganization of the motor cortex

The somatosensory system shows what the body is up to by providing information about bodily sensations, such as touch, temperature, pain, position in space, and movement of the joints. The somatosensory system differentiates what the world does "*to us* from what we do *to it*." For example, when someone is pushed sideways, the somatosensory system tells the individual they have been pushed. Similarly, if someone lunges laterally, the somatosensory system tells the individual about that movement. The reason is that somatosensation is closer to movement than the other senses. If one loses sight, hearing, or even both, he or she can still move around, and the same is true of other animals.

The somatosensory system is unique among sensory systems because it is distributed throughout the entire body. It is not just localized in the head, like vision, hearing, taste, and smell. Somatosensory receptors are found in all body parts, and neurons from these receptors carry information to the spinal cord. Within the spinal cord, two somatosensory pathways project to the brain and, eventually, to the somatosensory cortex. One part of the somatosensory system, the vestibular system, is confined to a single organ, however. The vestibular system, located in the middle ear, contributes to the human sense of movement and balance.

Multisite Peripheral Electrical Stimulation (MPES) can significantly increase the cortical motor representation of skeletal muscles (Meesen et al., 2010). Observations and measurements suggest that ES-induced modulations in cortical motor representations (or tactile sensitivity) extended beyond the boundaries of the stimulated zone, indicating the spread of activation from stimulated to non-stimulated parts of the somatosensory network. This mechanism highlights the potential of somatosensory stimulation as a beneficial complementary therapy in neurorehabilitation. It is also shown that ES-induced enlargements in cortical motor maps were not restricted to the stimulated muscle but extended to other hand and forearm muscles. (Ridding et al. 2001)

3. Examples from literature

3.1. Case- (a)

The primary purpose of ES is to provide symptomatic relief by stimulating either the pain gate mechanism or the opioid system by exciting sensory nerves. The different methods of applying ES relate to these different physiological mechanisms. The effectiveness of ES varies depending on the type and severity of pain being treated, but research suggests that it provides significant relief compared to a placebo intervention. There is an extensive research base for ES in both clinical and laboratory settings. It is worth noting that the term ES could represent ANY electrical stimulation using skin surface electrodes that intend to stimulate nerves.

Table 1 Sample types of ES Applications

	Conventional ES (High)	**Acupuncture-like ES (Low)**	**Brief intense ES**	**Sub- Motor threshold ES (Low)**
Physiological Intervention	Activates large diameter non-noxious afferent elicit segmental analgesia.	Produce muscle twitch to activate small diameter motor afferent to elicit additional segmental analgesia.	Activates small diameter noxious afferents to elicit peripheral nerve blockade and additional segmental analgesia.	Activates small diameter motor afferents to induce spinal cord mechanisms and cortex response.
Clinical Technique	Low intensity /High Frequency at the site of pain to produce a firm but comfortable sensation.	High intensity/Low frequently over muscle or Acupuncture points to produce a firm but comfortable contraction.	High intensity /High frequency to produce maximum paresthesia	Low intensity/Low frequency producing sensory effects to induce a neuromotor response and analgesic effects
Duration of stimulation	30 min	No more than 20 min	No more than 5 min	60 minutes or longer or intermittent

In the clinical context, it is assumed to use ES to provide symptomatic pain relief. In a clinical setting, it is typically expected that ES will be used to relieve symptomatic pain. In a clinical setting, it is typically expected that ES will be used to relieve symptomatic pain. Opioids reduce pain, but they also have a lot of adverse side effects. The μ-, δ-, and κ-

opioid-opioid receptors, encoded by the three beforementioned genes, mediate all the activities of opioids. (Evans et al., 1992; Kieffer et al., 1992; Mestek et al., 1995; Simonin et al., 1995) The structures of opioid receptors, which are members of the superfamily of G protein-coupled receptors (GPCRs), have been solved at high resolution by X-ray crystallography.(Granier et al., 2012; Huang et al., 2015; Che et al., 2018). Upon activation by an agonist, opioid receptors couple to pertussis toxin-sensitive heterotrimeric Gi/o protein, which dissociates into Gαi/o and Gβγ subunits so they can interact with several intracellular effector systems (Law et al., 2000; Waldhoer et al., 2004; Stein, 2016).

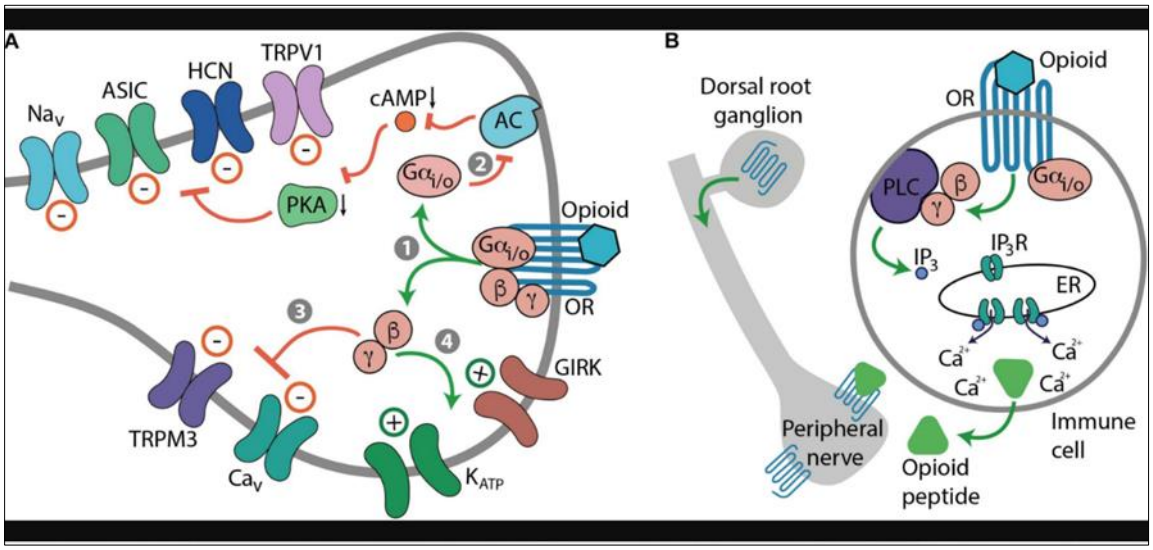

Figure 3 Mechanisms of opioid-induced analgesia. (A) Cellular effects are mediated by neuronal opioid receptors (OR). Activation of OR by an opioid lead to the dissociation of Gi/o proteins into Gαi/o and Gβγ subunits (step 1). Gαi/o inhibits AC, cAMP formation, and PKA activity, which blocks various ion channels, including TRPV1, HCN, ASIC, and Nav channels (path 2). Gβγ blocks Cav and TRPM3 channels (path 3) and activates GIRK and KATP channels (path 4). Ultimately, these actions lead to decreased neuronal excitability, which culminates in analgesia. (B) Cellular effects mediated by OR in immune cells. Activation of leukocyte Gi/o-coupled OR leads to a Gβγ-mediated activation of PLC and production of IP3, which activates IP3R in the endoplasmic reticulum (ER) to release intracellular Ca2+, which results in the secretion of opioid peptides from immune cells. The released opioid peptides activate the neuronal OR and decrease pain.

3.2. Case-(b)

Many previous studies have shown that ES reduces secondary mechanical hyperalgesia of the legs induced by knee joint inflammation (Sluka, Lisi, and Westlund, 2006; King et al., 2005; Radhakrishnan & Sluka, 2005; Vance et al., 2007; Sabino et al., 2008). More recently, (Ainsworth et al., 2006) have shown that primary mechanical hyperalgesia induced by joint inflammation was reduced in response to both high- and low-frequency ES. The compression withdrawal threshold was decreased at 24 hours and two weeks following inflammation onset but not when applied 4 hours after inflammation onset. Thus, it can be argued that because inflammation has already wholly developed, ES inhibits primary hyperalgesia associated with inflammation in a time-dependent manner (Vance et al., 2007).

The site of electrode application of ES is typically at the site of injury. However, as ES activates central mechanisms, applications outside the site may also be effective. Recently, two studies confirmed this hypothesis by showing that applying ES to the contralateral hind limb reduces hyperalgesia of the inflamed limb (Sabino et al., 2008; Ainsworth et al., 2006). Furthermore, when hyperalgesia developed bilaterally after a unilateral injury, applying either high- or low-frequency ES to the inflamed or the contralateral side reduced the hyperalgesia bilaterally (Ainsworth et al., 2006). In a different pain model, Somers and Clemente (2006) have investigated the sites of electrode placement that would best prevent the development of allodynia in a chronic constriction injury (CCI). Repeated daily high-frequency TENS for 12 days with electrodes on the skin covering either ipsilateral or contralateral paraspinal muscles reduced the development of mechanical hyperalgesia.

Low-frequency ES applied to acupuncture points in the ipsilateral or contralateral hind limbs decreased the development of thermal hyperalgesia, but only when ES was delivered on the contralateral side (Somers & Clemente, 2006). Thus, applying TENS to either the ipsilateral or the contralateral hind limb is effective once hyperalgesia develops. It is generally thought that ES produces analgesia by activating cutaneous afferent fibers at the application

site. However, by differentially blocking primary afferents with local anesthetics, Radhakrishnan and Sluka (2005) showed the importance of deep tissue afferents in the analgesia produced by ES. Specifically, blockade of cutaneous afferents with an anesthetic cream (eutectic mixture of lidocaine and prilocaine) during ES application did not affect the analgesia produced by both high- and low-frequency ES.

3.3. Case- (c)

For instance, fish that inhabit deep and dark caves cannot see at all, yet they can move about normally. Furthermore, animals like the butterfly that cannot hear can still move very well. If an animal were to lose its body senses, however, its movements would quickly become so impaired that it would not be able to survive. Some aspects of somatosensation are essential to movement. Considering the motor system, the study started at the cortex and followed the motor pathways to the spinal cord. The human body is covered with sensory receptors. They are located in both surface, and deeper layers of the skin and are also embedded in muscles, tendons, and joints.

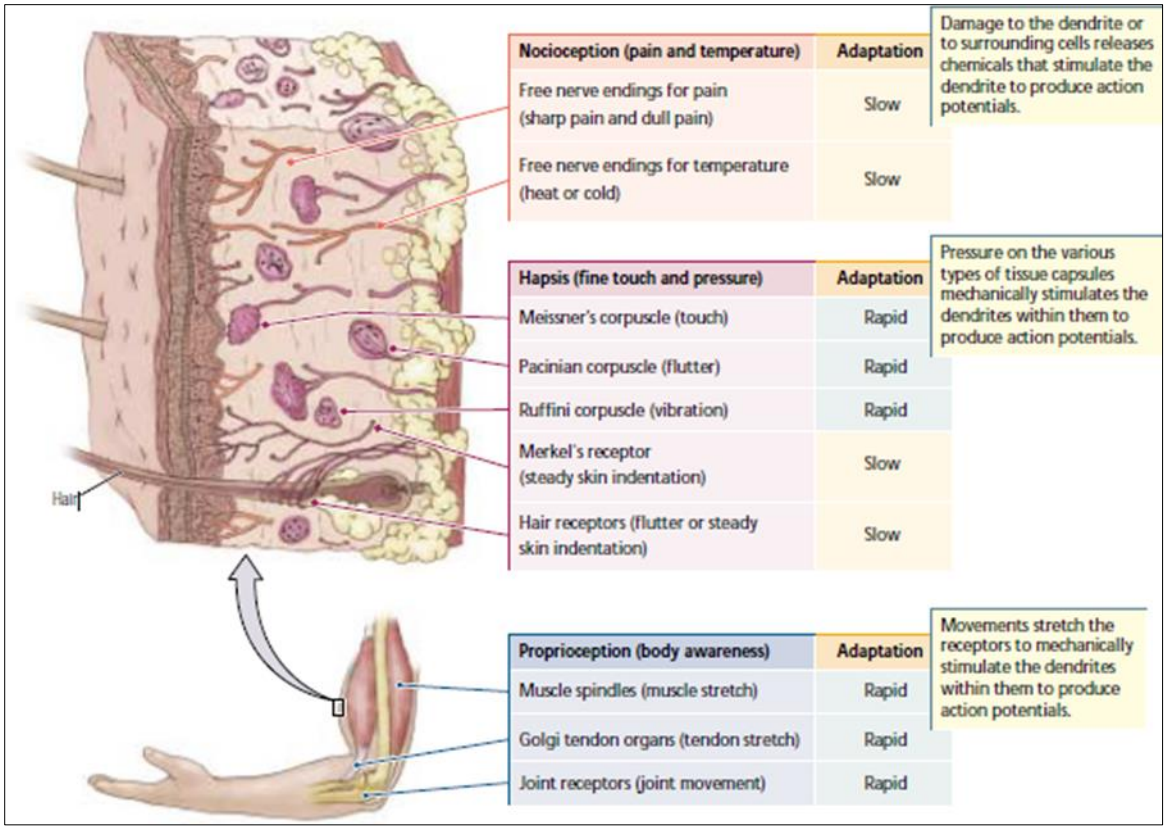

Figure 4 Schematic picture of somatosensory receptors located in the skin

[The perceptions derived from the body's senses depend on different receptors located in different parts of the skin, muscles, joints, and tendons - Patrick, 2020]

The body consists simply of the ending of a sensory neuron dendrite. On others, the dendrite is covered by a unique capsule or a sheath of connective tissue to adjacent tissue. The density of sensory receptors varies significantly in different parts of the body, not only in the skin but also in the muscles, tendons, and joints. The density variation is one reason different body parts are more or less sensitive to somatosensory stimulation. Parts of the body that are very sensitive to touch or capable of fine movements— including the hands, feet, lips, and eyes—have many more somatosensory receptors than other body parts. Sensitivity to different somatosensory stimuli is also a function of the kinds of receptors found in a particular region.

4. Conclusion

According to basic scientific findings, the analgesic activity of ES may be mediated by peripheral and central nervous system pathways. Stimulation intensity is a critical factor in reaching the intended mechanisms for the effectiveness of ES. The stimulation parameters are honed in experimental pain research and clinical trials to get optimal pain relief.

Science shows the positive treatment effects of ES for relieving chronic musculoskeletal pain and functional neuromotor outcomes, and randomized controlled trials consistently demonstrate the effectiveness of ES for acute, emergent, and postoperative pain conditions. Studies further demonstrate that various pharmacological and nonpharmacologic methods can be used to avoid resistance to repeated ES treatment. While ES can induce a tetanic motor contraction, the ES at the sub-motor threshold (sensory) intensifies corticomotor excitability. ES of paralyzed muscles' neurological pathways can be used to enhance, restore or replace cortico-motor function in individuals with upper motor neuron damage. Considering the documented effects of ES, it can play an important part in neurorehabilitation, and its applications influence not only pain-reducing mechanisms but also numerous other neurological actions.

Compliance with ethical standards

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Disclosure of conflict of interest

There was no conflict of interest while authoring this article.

Statement of ethical approval

The present research work does not contain any studies performed on animals/human subjects by any of the authors.

Statement of informed consent

This article did not require informed consent.

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