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Spinal Cord Stimulation Control Modalities: Open-loop versus Closed-loop and Perspectives

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Abstract. Spinal cord stimulation is currently widely used in the treatment of chronic pain, which has a prominent effect on reducing pain in the trunk and limbs. With the development of related technology, spinal cord stimulation has shown great advantages in the field of pain management and a lot of stimulation methods have been born. This paper will first introduce the working principle of spinal cord stimulation and introduce several typical open-loop stimulation methods, including conventional tonic SCS, High Frequency SCS and Burst SCS. Then it will analyze the factors that affect the stimulation effect. The concept of electrically evoked compound action potentials (ECAPs) is explained, and then the closed-loop SCS controlled by ECAPs are introduced and their working principle is explained. Finally, the future development direction of this field is prospected, and it is believed that this field needs a convincing quantitative index. Finally, the possible development direction of technology is given.

Keywords: Spinal Cord Stimulation; gate control theory; electrically evoked compound action potentials; electrically evoked compound action potentials.

1. Introduction

Spinal cord stimulation (SCS) was developed from the gate control theory which proposed by Wall and Melzack in 1965, and has been wildly used to treat and relieve chronic pain in the trunk and limbs.With the continuous development of spinal cord physiology in recent years, researchers have gradually clarified the relationship between spinal cord stimulation and pain [1]. After decades of development in this field, a large number of spinal cord stimulation designs have been created to relieve chronic pain. Among them, traditional stimulation methods such as tonic SCS, high-frequency SCS, and burst SCS are representative and widely used in the commercial field. However, these stimulation methods are not suitable for all patients, data show that only 50%-70% of patients experience pain relief of more than 50%, and these methods are accompanied by abnormal perception, tolerance and battery life problems. As more technical details were discovered, the concept of closed-loop stimulation was born, which, unlike quantitative stimulation in the past, could provide personalized services by adjusting stimulation parameters through feedback from the patient's body to achieve the best stimulation effect. At present, related fields are trying to integrate artificial intelligence into the spinal cord stimulation system in order to achieve the optimal parameter setting and improve the stimulation effect.

This passage discusses the wide application of spinal cord stimulation in chronic pain management, highlighting its efficacy in reducing pain in the trunk and limbs. It introduces various open-loop stimulation methods like tonic SCS, High Frequency SCS, and Burst SCS, alongside factors affecting stimulation effectiveness. The concept of electrically evoked compound action potentials (ECAPs) is explained, leading to the introduction of ECAPs controlled closed-loop SCS . The future of the field requires a robust quantitative index and suggests potential technological advancements.

2. Open-loop SCS protocol

2.1. Operating principle of SCS

According to the gate control theory which proposed by Melzack and Wall, Nociception requires orderly relay conduction of a series of nerve fibers,.At the same time, the gate control theory emphasizes the influence of non-nociceptive input on pain perception. For example, touch, massage, or other sensory input can reduce or inhibit the transmission of pain signals by activating non-nociceptive fibers and stimulating neuronal gate controllers. Nociception and non-nociception transmit excitation to the spinal cord and thence to the brain through their respective primary afferent nerve fibers(C, Aδ fibers/Aβ fibers). The dorsal column (DC) fibers, which excite different inhibitory interneurons within an interneuron pool (INT), can be used to stimulate these interneurons when the patient experiences pain. through wide dynamic range (WDR) projection neurons in the dorsal horn (DH) and therefore prevent the transmission of pain (Fig. 1) [2].

SCS consists of an implantable pulse generator (IPG) and a wire with positive and negative electrodes connected to it. The electric field generated by the positive and negative electrodes could stimulate the target nerve to depolarize them. According to the above explanation of gate control theory, stimulating DC fibers can effectively inhibit and reduce many neuropathic pain [3].

So far, SCS has been widely applied in the treatment of Failed back surgery syndrome, Chronic legs ischaemia, Chronic angina refractory to treatment and other chronic pain in the extremities and trunk, some data show that there are currently 40,000 to 50,000 devices implanted each year, and close to one million people receive SCS treatment [4].

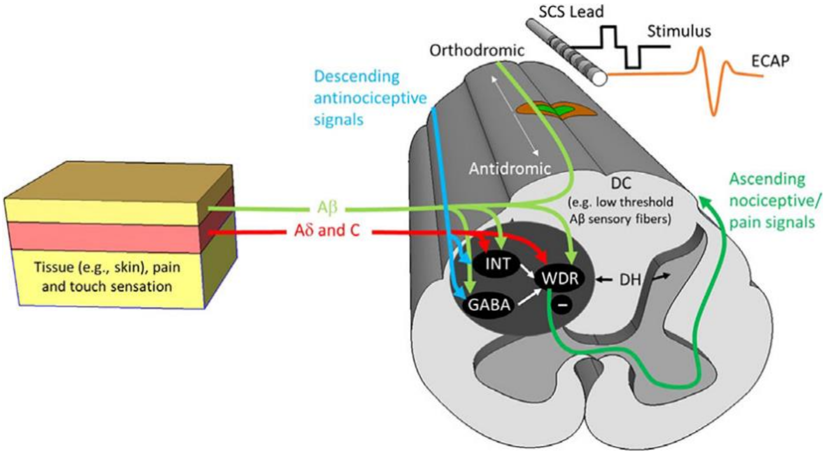

Fig. 1 This figure explains how spinal cord stimulation works. [2]

2.2. Stimulation Protocol

However, due to the complexity of the types and structures of spinal nerve cells, there is a lack of accurate judgment basis for the degree of pain relief of patients in the relevant field. Researchers usually take 50% of patients experienced a 50% reduction in pain as a vague standard to measure the effectiveness of the device. Under this premise, researchers first designed Conventional Tonic SCS Protocol, which has the typical frequency of 40–100 Hz, and pulse width about 100–500 μs.The conventional tonic SCS utilize the electrodes which implanted in the epidural space, activate Aβ fibers which carrying innocuous touch information in the dorsal columns by means of short-duration electrical pulses. These Aβ fibers produce collaterals that project into the dorsal horn and synapse on inhibitory interneurons whose post-synaptic activation can “close the gate” on nociceptive transmission so as to achieve the purpose of pain relief [5].

However, according to patient feedback, this conventional tonic SCS is not a perfect protocol. In fact, due to the large stimulation amplitude of traditional tetanic stimulation, which activates more Aβ fibers, produces excessive paesthesia (which is not welcomed by patients) and covers too much area, prolonged continuous stimulation may lead to phenomena that patients tolerate and thus reduce the effectiveness of the device. And this protocol of stimulation has serious limitations. Statistically, this protocol may be suitable for 50% to 70% of patients, but for pain caused by certain diseases, especially patients with axial low back pain and some patients with persistent spinal pain syndrome (psp), the non-response rate is particularly high.

Therefore, it is necessary to develop more versatile and effective stimulation schemes. Technological improvements over the past 40 years have made SCS more useful for an increasing number of patients. In addition to conventional tonic stimulation, high-frequency (HF) SCS and Burst SCS are the main stimulation schemes currently used in the commercial field, which are Paresthesia-free programming paradigms.

Some related studies have shown that HF SCS (especially 10-KHz SCS) show better analgesic effects than conventional tonic SCS.Moreover, HF SCS has a significant effect on patients who do not respond to conventional tonic SCS(In a group of patients with complex regional painsyndrome, the treatment was effective in 65%- 70% of cases based on patient feedback) [6]. However, the disadvantage still exists; the continuous high-frequency oscillation causes a great burden on the battery, reducing the battery life and is likely to produce overheating. Burst SCS solves this problem. Burst SCS improves on HF SCS by no longer using constantly high-frequency stimulation to complete the purpose of analgesia. Instead, it uses a specific frequency to operate periodically (about5 pulses at 500 Hz, delivered 40 times per second). This parameter mimics the human nerve firing and prolongs battery life without causing abnormal sensation to the patient. However, the research on avoiding abnormal feelings in patients has not been conclusive. The most likely speculation is that the mechanism difference between conventional tonic SCS, HF SCS and Burst SCS [7].

In addition to the several stimulus packages outlined above, an alternative approach is to SCS is performed with a subthreshold and subperception waveform. The current deficiency of this technique is the lack of treatment effect (tolerance).

3. Close-loop protocol

The therapeutic efficacy of spinal cord stimulation (SCS) depends on many variables, among which waveform parameters such as amplitude, frequency, and pulse width play a key role. Delving into the details of the waveform parameters reveals their subtle influence on the effect of spinal cord stimulation. For example, amplitude determines the strength of the transmitted electrical signal and thus affects the degree of neuromodulation. Modulation frequency regulates the transmission rate of electrical pulses, affects the temporal pattern of stimulation, and may alter the therapeutic effect. Pulse width, on the other hand, governs the duration of each pulse and affects the spatial distribution of the stimulus within the spinal cord. In essence, a comprehensive evaluation of the efficacy of SCS requires a thorough exploration of the intricate interactions between waveform parameters and other variables. Understanding how these components work together to contribute to the therapeutic outcome of SCS is essential to optimize its application in addressing various neurological disorders. These key parameters are in the hands of the enterprise as patents. In addition, factors such as implantation location, patient position, and electrode material have intricate effects on SCS outcomes. It is crucial to recognize the interrelated nature of these factors, as a single focus on any single factor may not provide a comprehensive understanding.

Despite the significance of these factors, a notable challenge in SCS research lies in the absence of standardized metrics to precisely measure treatment outcomes. The evaluation of SCS devices, particularly from the perspective of patients' sensory experiences,”50% of patients reduced 50% of pain” lacks the requisite accuracy. This gap underscores the pressing need for a reliable index that can effectively gauge the impact of stimulation.

In this context, the advent of electrically evoked compound action potentials (ECAPs) presents a promising avenue for researchers. When the spinal cord receives electrical stimulation surpassing a certain threshold, nerve fibers generate active potentials. The cumulative effect of these action potentials is referred to as the electrically evoked compound action potential (ECAP). Capturing electrophysiological signals from the dorsal aspect of the epidural space during SCS enables the acquisition of spinal ECAP signals.

While researchers have sought to record these potentials for years to glean insights into neural properties, challenges arise when attempting to measure ECAPs in close proximity to electrodes. The presence of artifacts generated during potential generation poses a significant obstacle to accurate measurements. However, ongoing studies and experiments, encompassing animal models, computer simulations, and human trials, have shown promising advancements. Researchers have successfully identified distinctions between spinal cord ECAP signals and stimulation artifacts, even in the complex environment of SCS. This innovative approach not only opens new avenues for understanding neural responses but also holds potential for establishing more precise benchmarks in assessing the efficacy of SCS therapies, thereby contributing to the ongoing evolution of spinal cord stimulation research.

The research of Calvert et al suggest that ECAP can be used to investigate the effects of SCS on spinal sensorimotor networks and to provide stimulation strategies to optimize the clinical benefits of SCS in managing chronic pain and sensorimotor recovery after SCI [8]. This makes it possible for the ECAP of to serve as a relevant reference for quantitative studies.

Previously introduced approved SCS therapies (including conventional tonic SCS, high-frequency SCS, Burst SCS, etc.) produce fixed output stimulation regardless of whether stimulation causes paresthesia in the patient, and the energy delivered from the electrode array is fixed regardless of the neural activity of the spinal cord fibers. These SCS systems do not fully take into account the changes in the electric field due to the normal physiological activities of the human body (such as heartbeat, breathing) and the possible changes in the position and distance between the electrode and the target spinal cord fiber caused by motion. When the distance between the electrode and the spinal cord decreases, the intensity of stimulation to the spinal cord may increase and the range of stimulation may expand Patients may manually modify stimulation current to reduce overstimulation and understimulation at the expense of optimal pain treatment when movement-induced changes in stimulation intensity are nontherapeutic (that is, outside the therapeutic usage range or window) (Fig. 2) [2].

Unlike open-loop SCS systems, which do not have spinal cord feedback to modify stimulation, a novel neuro-modulation system has been created. With the help of a feedback mechanism that uses electrically evoked compound action potential (ECAP) measurements to modify the stimulation output level following each stimulation pulse, this device provides closed-loop stimulation. The goal is to maintain the ECAP near the target amplitude. This way, ECAP-controlled SCS can modulate the energy delivered in real-time to ensure consistent activation of the spinal cord. On the other hand, modeling studies have shown that changes in posture can cause activation levels to vary from zero activation to more than five times the desired level in open-loop SCS systems. A comparative study of closed-loop versus open-loop patients showed that the use of ECAP-controlled closed-loop SCS reduces activation variation with posture by more than ten times, and eliminates periods of no activation (51 of 62 patients [82.3%] vs. 38 of 63 patients [60.3%]). This is the primary outcome that Mekhail et al. achieved [9].

This new closed-loop SCS approach provides more precise and tailored stimulation, taking into account the specific needs of each patient and the dynamic nature of the human body. A 2018 multicenter, prospective, randomized, double-blind, parallel-group clinical investigation measuring SC activation in ECAP-controlled closed-loop versus open-loop stimulation produced significant information about variations in safety, efficacy, and neurophysiological characteristics.

The ECAP-controlled closed-loop SCS system follows a specific process to deliver more precise stimulation. First, it generates a new stimulus based on the patient's requirements and the pain management goals. Then, it collects the electrically evoked compound action potential (ECAP) signal that is generated in response to the stimulus. This ECAP signal represents the neural response of the spinal cord fibers to the stimulation. The collected ECAP signal is then compared with a pre-set target amplitude. This target represents the desired level of neural activation for optimal pain relief. The system uses an algorithm to calculate the parameters of the new stimulus current based on the comparison between the collected ECAP signal and the target amplitude. The algorithm adjusts the stimulation output level after every stimulation pulse to maintain the ECAP close to the target amplitude. This process is conducted continuously, allowing the ECAP signal to gradually approach the target amplitude over time. As the system iteratively fine-tunes the stimulus parameters based on the collected ECAP signal, it aims to achieve an ideal treatment effect that provides consistent and effective pain relief for the patient.

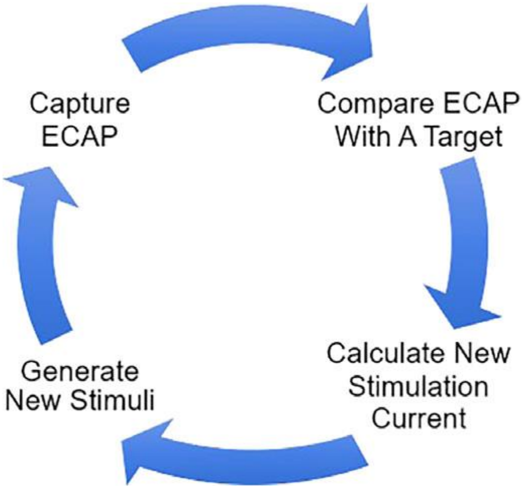

Fig. 2 This figure shows the mode of operation of ECAP controlled closed-loop stimulation. [2]

The closed-loop nature of this ECAP-controlled SCS system ensures that the stimulation energy delivered to the spinal cord is dynamically adjusted in real-time, accounting for changes in the patient's posture, movement, and other physiological factors. By constantly adapting the stimulation based on the ECAP feedback, this closed-loop approach significantly reduces the variation in activation levels caused by posture changes, minimizing the risk of over-stimulation or under-stimulation.

This advanced neuro-modulation system represents an important innovation in SCS therapy, as it offers improved precision and personalized treatment to patients, taking into account the dynamic nature of the human body and the unique needs of each individual.

4. Summary

Looking ahead, the future of spinal cord stimulation (SCS) technology appears promising as researchers continue to push the boundaries of innovation. While the current landscape showcases impressive advancements and a growing interest in integrating artificial intelligence into SCS. New designs continue to emerge, and new ideas about waveform parameters continue to evolve and significantly improve the patient experience, a critical challenge persists: the need for robust quantitative metrics. The essence of this challenge lies in the intricate interplay between electrical stimulation and neural activity, a relationship that remains elusive despite considerable progress. To address this hurdle, a cohort of researchers has embarked on an intensive exploration of electrically evoked compound action potentials (ECAPs). By delving deeper into the nuances of ECAP signals, they aim to unravel the intricacies of neural response to electrical stimulation, thus laying the groundwork for more precise and effective SCS techniques. Furthermore, pioneering studies hint at the potential of leveraging in vitro culturing of neurospheres alongside the analysis of neurosphere electrophysiological recordings. This innovative approach holds promise in deciphering the complex correspondence between electrical stimulation and neural activity, offering new avenues for understanding and optimizing SCS interventions.

In summary, while this paper provides a comprehensive overview of current SCS methodologies and sheds light on the frontier of SCS technology development, the quest to establish a rigorous connection between electrical stimulation and neural response remains a pressing challenge. However, ongoing research endeavors and emerging techniques offer valuable insights and pave the way for future exploration, fostering optimism for the continued advancement of SCS technology and its transformative impact on pain management.

Authors Contribution

The authors' names were listed in alphabetical order. Zhide Zheng is the first author and Jiacheng Cai is the second author.

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