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REVIEW



Burst and high frequency stimulation: underlying mechanism of action

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ABSTRACT

Introduction: Paresthesia-free spinal cord stimulation (SCS) techniques, such as burst and high-frequency (HF) SCS, have been developed and demonstrated to be successful for treating chronic pain, albeit via different mechanisms of action. The goal of this review is to discuss the mechanisms of action for pain suppression at both the cellular and systems levels for burst and HF SCS. In addition, we also discuss the neuromodulation devices that mimic these paradigms.

Areas covered: The authors performed a literature review to unravel the mechanisms of action for burst and HF SCS coupled with booklets and user manuals from neuromodulation companies to understand the programmable parameters and operating ranges. Burst SCS modulates the medial pathway to suppress pain. On cellular level, burst SCS is independent on activation of γ -aminobutyric acid (GABA) receptors to inhibit neuronal firing. HF SCS blocks large-diameter fibers from producing action potentials with little influence on smaller fibers, increasing pain suppression as frequency increases.

Expert commentary: The neuromodulation industry is in a phase of intense innovation characterized by adaptive stimulation to improve patients' experience and experiment with alternative frequencies and novel stimulation targets.

ARTICLE HISTORY

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KEYWORDS

Burst stimulation; HF stimulation; tonic stimulation; pain; charge per second; charge per pulse; medication; dosage

1. Introduction

Pain is described as a wide range of unpleasant sensory and emotional experiences associated with actual or potential damage [1]. Pain is subdivided into two types: nociceptive and neuropathic pain. Nociceptive pain is physiological in that it is caused by the stimulation of sensory fibers through the activation of nociceptors. Neuropathic pain is the result of damaged, dysfunctional, or injured sensory nerve fibers and is therefore, in principle, pathological [2]. This latter type of pain can be felt as a sharp prickle, a burning sensation, or a dull muscular ache and can range intensity from mildly uncomfortable to completely disabling [3]. Moreover, analgesic medication often has an insufficient effect on neuropathic pain [4]. Spinal cord stimulation (SCS) provides a valuable option when neuropathic pain is intractable with medication [5]. The first clinical trial of SCS was tested in 1967 by Shealy et al. to treat cancer pain by stimulating the dorsal columns [6]. The US FDA approved SCS in 1989 to relieve chronic discomfort from neuropathic pain in the arms and legs. Besides treating neuropathic pain, SCS has been effective in patients with neurogenic lower urinary tract dysfunction resulting from spinal cord injury [7].

2. Blocking pain: the gate control theory

The gate control theory, proposed by Melzack and Wall in the mid-1960s, asserts that non-painful input received by the dorsal horn of the spinal cord closes a 'gate' to painful input, which blocks the sensation of pain from travelling to the central nervous system. According to this theory, the

activation of myelinated, afferent A β fibers inhibits pain transmission by the thinly myelinated A δ fibers and the unmyelinated C fibers [8]. A schematic of gate control is shown in Figure 1. SCS is based on this gate control theory of pain, with the aim of activating A β fibers to suppress pain transmission by the smaller fibers. Activating A β fibers induces paresthesia, and the extent of pain suppression is contingent on the amount of coverage of the painful area by paresthesia [8].

3. Tonic stimulation

SCS is being used to treat neuropathic pain, failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), angina pectoris, and ischemic limb pain [10–12]. SCS is advantageous in part because it is minimally invasive, making it a safer and more cost-effective technique than surgical methods. Furthermore, SCS can achieve targeted pain relief and even reduce opioid use, all with little to no side effects [13]. Traditionally, SCS therapy is delivered via tonic stimulation, usually with a frequency between 40 and 50 Hz, an amplitude between 2 and 4 mA, and a pulse width that falls between 300 and 500 μ s. The mechanism of action of SCS can be understood through both spinal and supraspinal mechanisms [14,15]. Electrical stimulation produces both orthodromic and antidromic action potentials. The action potential travels antidromically into the dorsal horn, where A β fibers synapse with the wide-dynamic-range neurons and release inhibitory neurotransmitters such as γ -amino butyric acid (GABA) and adenosine. The orthodromic potentials travel to the dorsal

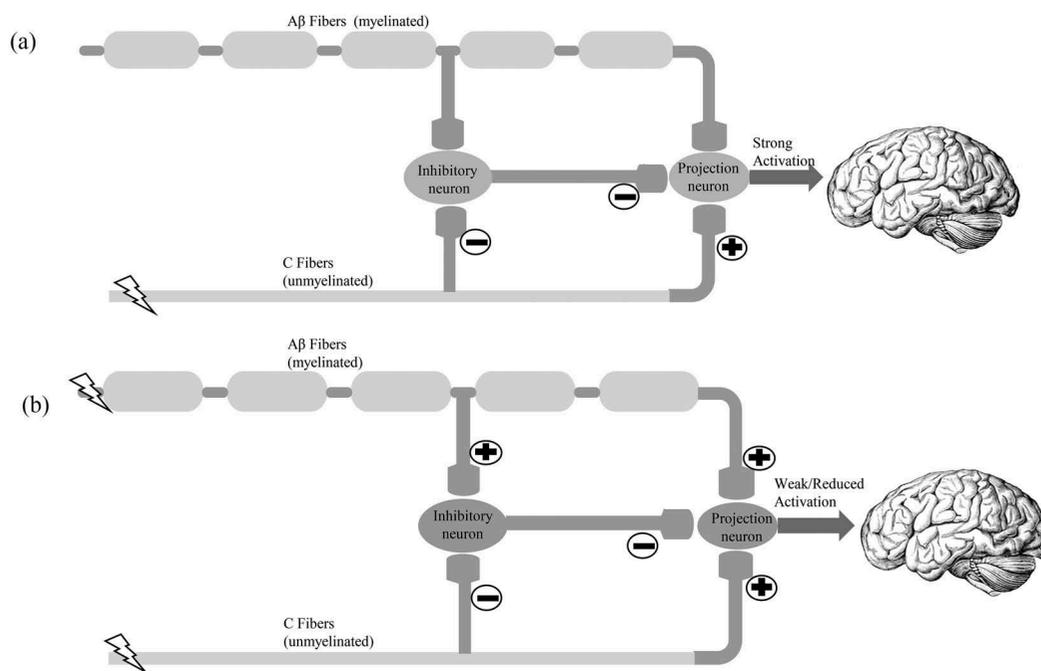


Figure 1. The schematic diagram of gate control theory. Firing of projection neuron determines pain. The inhibitory neuron decreases the chance of projection neuron being activated. (a) Firing of C fibers inhibits the inhibitory neuron, increasing the chance of projection neuron being activated, and sending pain signals to brain. (b) Firing of A β fibers activates the inhibitory neuron, reducing the chance of projection neuron being activated, sending in weak pain signal to brain. Inhibition neuron and projection neuron are labelled in figure. The bolt represents the activation for C and A β fibers (figure adapted from Melzack [9]).

column, inducing inhibition via serotonergic and noradrenergic pathways [16,17].

At a systemic level, different pathways are responsible for processing different aspects of pain signals, as shown in Figure 2. A lateral pain system processes the discriminative components (location, intensity, and character) of the pain, mediated by the lateral thalamic nuclei and the somatosensory cortex. Concomitantly, a medial pain system involving the medial thalamic nuclei and the anterior cingulate cortex has been associated with the emotional and motivational aspects of pain, comprising such elements as the unpleasantness of the pain stimulus. In addition, a descending inhibition pain system involving the rostral and pregenual anterior cingulate cortices, with connections to the

thalamus, the parahippocampal area, the periaqueductal gray, and the rostroventral part of the medulla oblongata. Imaging modalities such as functional magnetic resonance imaging demonstrate that tonic stimulation mainly modulates the lateral pain pathway, as visualized by blood-oxygen-level-dependent changes in the sensory thalamus and somatosensory cortices, but not in the dorsal anterior cingulate cortex or the insula [18]. A positron-emission tomography study further corroborated this hypothesis by demonstrating that activity increases in the thalamus contralateral to the painful limb as well as in the bilateral parietal association cortex, the anterior cingulate cortex, and prefrontal areas [19]. Hence, tonic stimulation only minimally modulates the medial pain system. Correlation analysis indicates that

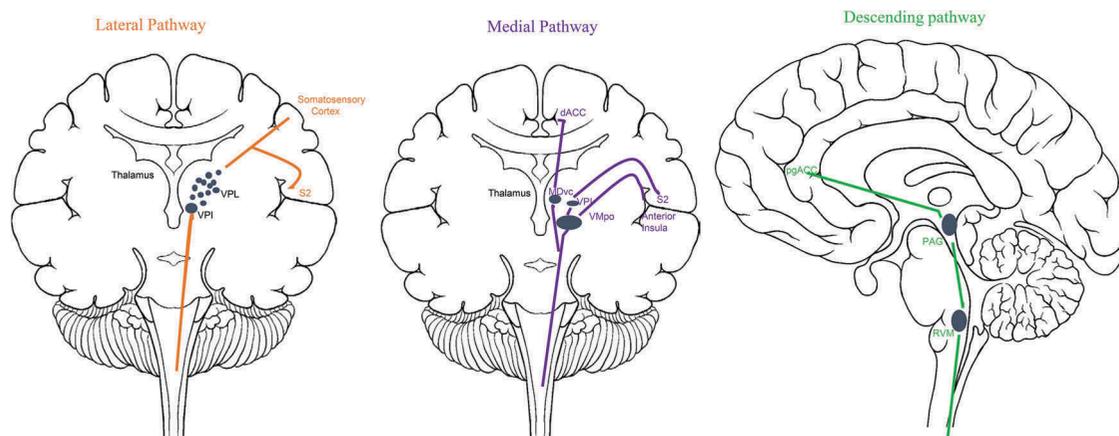


Figure 2. Lateral, medial, and descending pain pathways. The lateral ascending pathway processes the discriminatory component of pain, whereas the medial ascending pathway processes the affective, attentional component to pain. The descending pathway suppresses the pain (figure adapted from De Ridder [34]).

the amount of pain suppression is related to the activation of the pregenual anterior cingulate cortex and the dorsolateral prefrontal cortex, i.e. to the amount of mobilization of the descending pain inhibitory pathway [20].

4. Paresthesia-free stimulation

Although pain patients with an SCS device are able to cope with paresthesia when receiving tonic stimulation, many find the sensation to be unpleasant, particularly during positional changes. Paresthesia-free stimulation techniques have recently been developed, such as burst SCS and high-frequency (HF) SCS [21,22]. Figure 3 shows the waveform for tonic stimulation, burst SCS, and HF SCS, respectively.

4.1. Burst SCS

Burst SCS is a stimulation mode that uses small bursts of pulses rather than a continuous stream of pulses. More specifically, burst stimulation is a series of five 1000- μ s pulses at a frequency of 500 Hz, with an interspike interval of 1000 μ s, and spike trains repeated at a rate of 40 Hz. The cumulative charge of five 1000- μ s spikes is charge-balanced passively and immediately after the burst.

In recent years, burst stimulation has proven to be effective in FBSS pain relief, and clinical trials have demonstrated its ability to help FBSS sufferers to reduce analgesic intake [22,23]. More recent, prospective, randomized, double-blind, and placebo-controlled studies on FBSS show that burst stimulation decreases the perceived pain intensity and pain quality more effectively than either classic tonic stimulation or 500-Hz tonic stimulation [24]. Relative to a placebo, burst SCS was significantly better for multimodal pain measures, including both the perception of pain and the emotional component related to pain [25]. In addition, burst SCS has been reported to reduce neuropathic pain better than tonic SCS without generating paresthesia in patients [21,25,26].

Initial research also attempted to investigate the effects of burst SCS on animal models. An early study by Tang and coworkers explored possible differences in the mechanisms of action of burst SCS on nociceptive spinal networks and the gracile nucleus supraspinal relay in animal models [27,28]. In their study, visceromotor reflexes (a nociceptive response) and the extracellular activity of either L6-S2 spinal neurons or gracile nucleus neurons were recorded during noxious somatic stimulation (pinching) and visceral stimulation (colorectal distension [CRD]) in anesthetized rats. At 90% motor threshold (MT), spinal neuronal responses to CRD and pinching reduced similarly by both tonic and burst SCS. However, at low intensity (60% MT), only burst SCS significantly decreased the nociceptive somatic response. This supports the idea that burst stimulation has a greater inhibitory effect on neuronal responses to noxious somatic stimuli than to noxious visceral stimuli.

Another study investigated the effectiveness of burst SCS on the reduction of neuronal responses to noxious stimuli by altering stimulation parameters such as the width, amplitude, and number of pulses in rat models of cervical radiculopathy [29]. In this study, neuronal firing was recorded in the spinal dorsal horn before and after burst SCS. The percent reduction of the firing of wide dynamic range (WDR) and high-threshold neurons after SCS and the percentage of neurons responding to SCS were quantified for each parameter and correlated to the charge per burst delivered during stimulation. The width, amplitude, and number of pulses all correlated significantly to the suppression of neuronal firing after SCS. For example, setting the burst SCS paradigm to seven pulses at 500 Hz with a 1000- μ s pulse width and an intensity of 90% MT reduced the neuronal firing by approximately 45% across 85% of the neurons that responded to the stimulation. When the pulse width was adjusted from 1000 μ s to 250 μ s, neuronal firing was reduced to approximately 15% with only 65.4% of the neurons responding to the stimulation. In addition, the

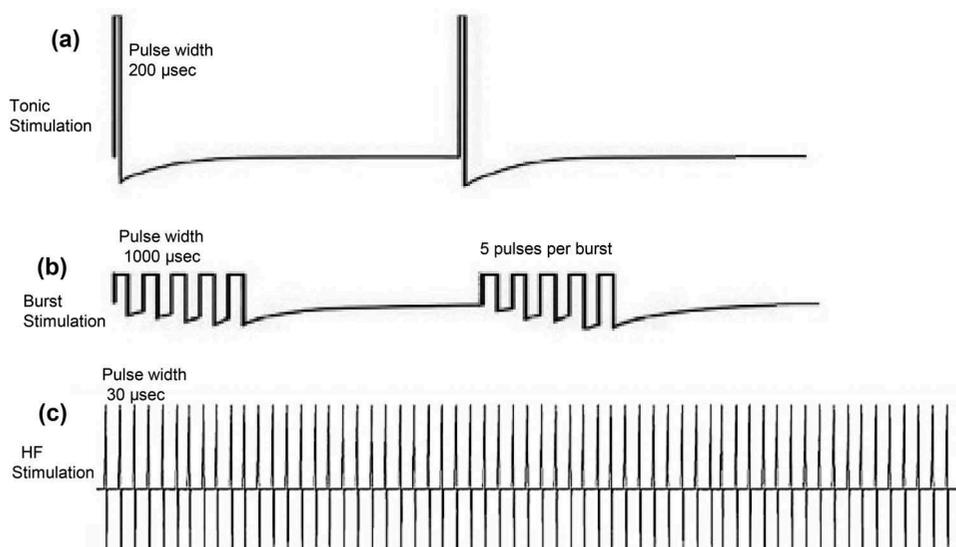


Figure 3. Waveforms for (a) Tonic stimulation: frequency between 40–50 Hz, amplitude between 2–4 mA, and a pulse width of 200 μ s; (b) Burst Spinal Cord Stimulation: series of five 1000- μ s pulses at a frequency of 500 Hz, interspike interval of 1000 μ s, and each train repeated at 40 Hz, cumulative charge of five 1000- μ s spikes is charge-balanced passively and immediately after the burst of 5 spikes; (c) High Frequency Spinal Cord Stimulation: frequency at 10 kHz, amplitude of 2.2 mA.

pulse frequency and amplitude significantly affected the percentage of responsive neurons. Furthermore, both burst and tonic SCS reduce spinal dorsal horn WDR neuronal firing and tactile allodynia to the same degree after painful nerve root compression. However, on the cellular level, burst SCS does not seem to rely on GABA release and the activation of GABA receptors to inhibit neuronal firing [30].

Another preclinical study examined the effect of bipolar tonic stimulation (50 Hz, 0.2 ms, 5 min) of the dorsal column and lumbar dorsal roots on the response of WDR in rats after L5 spinal nerve injury. Within 15 min of dorsal column or dorsal root stimulation, the spontaneous activity of WDR neurons was significantly reduced in nerve-injured rats. Stimulation also significantly attenuated WDR neuron responses to mechanical stimuli in nerve-injured rats. Dorsal column stimulation blocked windup of WDR neuronal response to repetitive intracutaneous electrical stimulation in nerve-injured and sham-operated rats, whereas dorsal root stimulation inhibited windup only in sham-operated rats [31,32].

Taken together, these findings imply that burst and tonic SCS modulate different cellular mechanisms [30]. Recently, it was shown that burst SCS influences the anti-inflammatory interleukin (IL)-10 in FBSS patients [33]. This, in turn, improved pain-associated comorbidities such as disrupted sleep cycles and depressive symptoms, suggesting a possible association between burst SCS and anti-inflammatory IL-10 in alleviating chronic back pain. In addition, it has been suggested that burst SCS is now paresthesia-free due to the lower amplitude and the overall larger pulse width. This could induce subthreshold firing of A β fibers [21]. The latter finding suggests that burst stimulation suppresses pain via the gate control mechanism before clinical paresthesia is even reached.

On a systemic level, changes in source-localized electroencephalography were analyzed to elucidate the relationships between different frequency bands in tonic and burst stimulation [25]. Significantly more alpha activity was seen in burst stimulation as opposed to tonic stimulation in the dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex, the primary somatosensory cortex, and the posterior cingulate cortex. These findings suggest that burst stimulation has a profound effect on medial, lateral, and descending pathways, whereas tonic stimulation influences the lateral pain pathways [34]. The question remains, however, how burst SCS reaches the brain without – according to animal research – altering the firing rate of the gracile nucleus. The gracile nucleus processes proprioceptive information from the dorsal column such as touch, pressure, and vibration [35]. One hypothesis is that burst SCS modulates the medial pain pathway directly via C-fiber activation, ending in lamina1 connections to the medial thalamic nuclei and anterior cingulate cortex. Another existing question is regarding the mechanism by which burst stimulation suppresses pain. One possible answer to this question is that burst stimulation disrupts synchronous firing of the high-threshold C-fibers related to pain perception [36–38]. This could be caused by reducing synchrony or generating inhibitory postsynaptic potentials which are maximal at 500-Hz bursts [39]. Another possibility is that burst SCS exerts its pain-improving effects by activating the antinociceptive low-threshold tactile C-fibers.

4.2. HF simulation

Recently, HF SCS has been developed to improve the clinical results of tonic SCS. HF SCS involves the use of kilohertz tonic stimulation – up to 10 kHz – to treat neuropathic pain without paresthesia. HF SCS has been evaluated for safety and efficacy through a multicenter, randomized, controlled trial for chronic back and leg pain. The patients were implanted at the thoracic (T8 to T11) level. After 24 months, back pain decreased to a greater degree with HF SCS (approximately 70%) than with traditional SCS (approximately 40%) [40].

HF SCS has the ability to generate rapid and reversible conduction block – a block of neural activity – by inactivating sodium channels along several nodes of Ranvier, as demonstrated in a peripheral nerve model and confirmed by animal models [41,42]. Indeed, it has been proposed that HF SCS blocks paresthesia by stopping large-diameter fibers from generating action potentials (fibers greater than 15–18 μ m begin to shut down at 4 kHz and 8–9 μ m fibers begin to shut down at 8 kHz) and, instead, activating medium- and small-diameter fibers that reduce WDR cell signaling encoding neuropathic pain [43]. However, recent computer simulation models show that conduction block thresholds are almost always outside of the clinical amplitude range. This fits with other research that states that, before a conduction block is generated with HF SCS, there is an initial increase in action potential firing called the onset response. This onset response can be observed by recording increased activity in WDR and manifests behaviorally as a feeling of discomfort during the first few minutes of stimulation [44]. Although this onset response has been observed in animal models of HF SCS, no paresthesia or other subjective perceptions have been reported during clinically effective HF SCS in human patients [22]. These findings suggest that HF SCS may not function explicitly through direct activation or conduction block of spinal cord fibers, but rather through more complex and subtle mechanisms for pain relief.

Recent studies have examined the effects of pulse rate on clinical outcomes in HF SCS. A murine study by Shechter et al. found no differences in efficacy between HF SCS at 1 kHz and 10 kHz for inhibiting the mechanical hypersensitivity [45]. In another study, North et al. published results from a randomized crossover clinical study of low-frequency suprapercception SCS vs. subperception SCS at 1 kHz. They tested whether subperception SCS at 1 kHz was sufficient to provide effective pain relief in human subjects. Indeed, 95% of the 22 patients who completed the study reported improvement in average, best, and worst pain as determined using a numeric rating score [46]. Furthermore, significant improvement in pain sensory thresholds have been reported in chronic pain patients with HF as low as 1.15 kHz compared to tonic stimulation [47]. Furthermore, a recent, randomized, controlled, multicentered, double-blind, crossover study suggested that for back pain there was no observable difference between 1 and 10 kHz stimulation [48]. These results suggest that there are clinical and basic questions that remain to be explored.

More recently, three working hypotheses were introduced to test the aforementioned findings: (1) that HF stimulation induces a depolarization block; (2) that HF SCS induces the desynchronization of neural signals from clusters of neurons firing; and (3) that impulses reaching a neuron within a certain

time frame may depolarize it and fire an action potential although every individual impulse is insufficient [49]. However, further research is needed to confirm these alternative explanations for the clinical effect of HF SCS. Furthermore, a systems approach is needed, since it could lead to a better understanding of the supraspinal mechanisms involved. A more recent hypothesis based on simulated clinical and pre-clinical data asserts that both burst and HF SCS might modulate the medial system in contrast to low-frequency stimulation, which may improve pain suppression.

4.3. Stimulation parameters

A rational way to characterize the stimulation paradigm, including the amplitude, charge per pulse, and the current delivered to the spinal cord, was first described in a report comparing burst SCS with conventional stimulation [21]. For burst stimulation, a low amplitude may exert a suppressing effect while increasing the amplitude may actually be detrimental. The burst waveform delivers pulses at an HF and at an amplitude much lower than tonic stimulation. The average amplitude for burst stimulation is 0.6 mA, ranging from 0.05–1.6 mA, which is significantly lower than the average amplitude for tonic stimulation, i.e. 3.1 mA, ranging from 0.5–3.9 mA. In fact, a recent study involving burst and tonic SCS demonstrated that in a large population, very low amplitudes (0.1 mA) are beneficial [50]. However, the amplitude impacts both the number of fibers recruited and the intensity of paresthesia. Thus, it is necessary to optimize the stimulation paradigm so as to achieve pain suppression without inducing paresthesia.

The burst stimulation follows an inverted U-curve profile for optimization of amplitude and pain suppression (De Ridder, personal communication). One of the ways to achieve this optimization is to start at a low amplitude, e.g. 0.1 mA, and progressively increase the amplitude over several days until no extra pain suppression can be obtained by further increasing the amplitude. This indicates that the optimal amplitude has been reached, i.e. the zenith of the inverted U-curve. The other approach is just the opposite of the first: start at a high amplitude, e.g. at paresthesia threshold, and progressively decrease the amplitude until pain reduction is maximized. Further studies need to be performed to explain and confirm this proposed inverted U-curve relationship between amplitude and pain suppression.

Charge per pulse is another parameter to characterize stimulation paradigm. The charge per pulse is calculated by multiplying the current amplitude by the pulse width. The charge per second, or the amount of electrical charge delivered to the spinal cord, is calculated by determining the charge per pulse and multiplying that value by the number of pulses delivered per second. The charge per pulse for burst stimulation (0.654 μC) is lower compared to that for tonic stimulation (1.03 μC). But the charge per second is higher for burst stimulation (130.8 $\mu\text{C/s}$) than for tonic stimulation (47.7 $\mu\text{C/s}$) [51]. HF stimulation is characterized by a lower charge per pulse (0.11 μC) and a higher charge per second (480 $\mu\text{C/s}$) when compared to tonic stimulation, a trend similar to the initial non-cycling burst stimulation [51]. A comparison between burst stimulation and HF stimulation

reveals that burst stimulation has a higher charge per pulse but that HF stimulation delivers more charge per second. The reason for this high charge per pulse for burst stimulation is a wider pulse width, i.e. 1000 μs as opposed to 30 μs for HF stimulation. The high charge per second for HF stimulation depends on the duty cycle, i.e. the percentage of 'on' vs. 'off' time in the pulse pattern. An increase in the duty cycle increases the proportion of 'on time' during stimulation, increasing the charge delivered over time. The duty cycle can be increased by increasing the frequency, increasing the pulse width, or a combination of both. However, a burst SCS study demonstrated that reducing the duty cycle from 20% to 10% by decreasing the pulse width from 1000 to 500 μs did not change the pain-relieving benefits for chronic back pain patients [52]. Furthermore, a comparison between burst stimulation with a duty cycle of 20% and 500-Hz tonic stimulation with a duty cycle of 18.5% reported better outcomes in pain relief for burst stimulation, despite the fact that the overall charge delivery was higher during tonic stimulation [24]. These results suggest that burst stimulation is capable of providing pain relief irrespective of changes in the duty cycle and that the charge is not important in human studies, contrary to what was shown in animal data [24].

4.4. Clinical comparison

From a clinical perspective, both burst and HF SCS seem to result in better pain suppression than classical tonic stimulation, without inducing paresthesia and with similar efficacy. On average, preoperative pain improves from 8 to 5 on a 10-point scale with classical tonic stimulation, but improves from 8 to 3 with burst and HF SCS [21,23,26,53]. Furthermore, in a direct comparison, Kinfe and colleagues reported that both burst and HF SCS can reduce back pain effectively [54]. For this study, 16 consecutive FBSS patients randomly received either burst or HF SCS. Burst SCS induced significant pain suppression in the limbs, whereas HF SCS did not. Interestingly, both burst and HF SCS resulted in similar suppression in back pain and similar improvements in depression and sleep [54]. This suggests that, from a clinical point of view, both burst and HF SCS stimulate the medial pain pathways resulting in improvements in both mood and sleep. A long-term follow-up on the same group compared the safety and efficacy of burst SCS vs. HF SCS for predominant back pain in FBSS patients and found that the responsiveness to burst SCS was superior to that of HF SCS [55]. The question remains: what is the mechanism of action for pain suppression in burst and HF SCS? Early clinical studies using burst or HF stimulation for the treatment of pain were not designed to elucidate the underlying mechanism but rather to test the efficacy of these methods.

5. Neuromodulation devices on the market

Patents on neurostimulation methods began in 1971 with the submission of 'Electrode implant for the neuro-stimulation of the spinal cord' in US 3724467A by Avery and Wepsic [56]. The implantable device was designed as a thin and flexible strip of physiologically inert plastic. A

plurality of electrodes was embedded in two layers of this plastic. The conductive lead wires were encapsulated in plastic, electrically coupled into the electrodes, and extending at the same angle as the spine's posterior process. The subsequent patents, US 6871099 B1 and US 20140277266 A1 in 2001 and 2013, were regarding the implantable stimulators, which were small enough to be located within or near the spinal area using a power source/storage device such as rechargeable battery [57,58]. The recharging system was later replaced with a wireless system and internal pulse generators (IPGs) controlled through software on a smartphone or tablet.

The current neuromodulation devices, i.e. IPGs, use technology that was originally developed for pacemakers [59]. The pacemakers were adapted to stimulate nervous tissue but were never specifically designed for it. The first IPGs from Medtronic were therefore using constant voltage, whereas later developments from Boston Scientific and St. Jude Medical/Abbott were based on constant current. What they all had in common, however, was that they delivered tonic pulses charge-balanced after each positive pulse. The Medtronic RestoreSensor neurostimulator received CE Mark approval in Europe in 2010. The FDA evaluated the benefits of the unique AdaptiveStim™ feature with RestoreSensor and approved it for clinical practice in 2011. The RestoreSensor integrates an accelerometer, known as AdaptiveStim technology, allowing the IPG to sense the patient's body position and automatically adjust the program, cycling between preselected settings that have been chosen for each position or activity.

The design of a stimulation system producing a combination of burst and tonic stimulation to alter the neuronal activity of a predetermined site to treat the neurological conditions was presented in US 8364273 B2 [60]. This design was implemented by Boston Scientific and St. Jude Medical/Abbott. The Boston Scientific Precision Spectra IPG is a tonic waveform generator, consisting of 32 independently controlled channels, allowing for more focused pain targeting. The Precision Spectra IPG is capable of delivering a burst pattern with active recharge. The Boston's burst design charges after every individual spike, whereas the Abbott's burst stimulation charges after the end of monophasic spikes.

Abbott's IPG, Prodigy™ (commercialized as Protégé in Europe), was approved by the FDA in 2016. The Prodigy is a 16-channel, constant-current pulse generator capable of delivering both tonic and burst waveforms. Amplitudes for tonic stimulation are programmed to a level that is perceived by the individual participant to produce comfortable levels of paresthesia. Burst stimulation is delivered in groups of five pulses with a 1-ms pulse width repeated 40 times per second. Charge balance occurs during the 5 ms after each burst with passive repolarization.

Patent US 8359102 B2 concerns selective HF SCS for inhibiting pain with reduced side effects [61]. This HF therapy, which gained European CE Mark approval in 2010 and the FDA approval in 2015, has been used to treat both back and leg pain. The Nevro is a constant-current, tonic waveform, 16-channel IPG. Each of the 16 outputs can be programmed as cathode or anode. It is capable of stimulating spinal cord nerves through the leads connected to any combination of the output terminals, using a single current source. The main advantage is that patients do not experience paresthesia, in contrast to conventional SCS.

A description of the external specifications for the available neurostimulators by different companies is shown in Table 1.

6. Conclusion

Paresthesia-free techniques such as burst and HF SCS have been proven to suppress chronic pain of the back and limbs [21,25,26]. However, researchers have been trying to entangle the mechanism of action for these techniques on pre-clinical models, but to date, nobody has been able to definitively explain how pain is suppressed using burst and HF SCS [27–30,41,42]. A suggested way for understanding the mechanism of action could be to implement imaging modalities which can exhibit changes in pain pathways before and after treatment. Further, clinicians need to explore novel targets of stimulation, experiment with alternative frequencies, and improve patient experience of stimulation.

Table 1. Specifications of different neurostimulators available on the market.

Characteristics	St. Jude Medical Prodigy	Boston Scientific Precision Spectra	Medtronic Restoresensor	Nevro HF
System type	Constant current	3D Finite Element model, constant current at each contact	Constant voltage	Constant current
No. of contacts	16	32	16	16
No. of power sources	1	32	1	1
Maximum pulse width	500 µs	1000 µs	1000 µs	20 µs to 1 ms
Maximum frequency	1200 Hz	1200 Hz	1200 Hz	10,000 Hz
Maximum voltage	12 V	15 V	10.5 V	15 mA
Imaging modality options	CT, CT with contrast, PET, X-ray, ultrasound	CT, CT with contrast, PET, X-ray, ultrasound	CT, CT with contrast, PET, X-ray, ultrasound	CT, CT with contrast, PET, X-ray, ultrasound
Height	4.8 cm (1.89 in)	4.6 cm (1.81 in)	5.4 cm (2.1 in)	5.3 cm (2.08 in)
Length	5.3 cm (3.09 in)	5.5 cm (2.16 in)	5.4 cm (2.1 in)	4.75 cm (1.87 in)
Thickness	0.95–1.1 cm (0.37–0.43 in)	1.08 cm (0.43 in)	1.06 cm (0.41 in)	1.25 cm (0.49 in)
Weight	29.0 g (1.0 oz)	30.0 g (1.05 oz)	45.0 g (oz)	32.0 g (1.1 oz)

HF: high-frequency; CT: computed tomography; PET: positron-emission tomography.

7. Expert commentary

Over the past four decades, SCS has been well established as a safe and effective therapeutic tool for treating patients with chronic pain, which is difficult to treat with medications. Classic SCS is targeted at the dorsal columns with electrodes positioned in the posterior epidural space. The first SCS device was placed in the subarachnoid space; later attempts were made to stimulate the dorsal, lateral, and ventral surfaces of the spinal cord [62–64]. The dorsal epidural space exhibited a sufficiently wide therapeutic window to keep SCS clinically feasible. The dawn of SCS in treating neuropathic pain led researchers and clinicians to find new stimulation targets. One of these is the dorsal root ganglion (DRG), an intraspinal structure that can be reached via a trans-spinal approach. There are many advantages of targeting DRG with electrical stimulation. Not only has it been implicated in the development and maintenance of chronic pain in CRPS, but it is also relatively immobile owing to its anatomical location and is surrounded by a much thinner layer of cerebrospinal fluid [65]. Another stimulation target for the treatment of pain is the uppermost most of spinal for e.g. C2 nerve, the part comprising the occipital nerves known as occipital nerve stimulation. Occipital stimulation has been used for the treatment of cluster headaches, targeting the occipital and trigeminal nerves. A standard percutaneous electrode inserted at the level of C2 demonstrated significant improvement in terms of duration and intensity of cluster headache attacks, as well as other related functional and impairment metrics [66]. While other neuromodulation modalities may take up to several months to achieve improvement in symptoms, occipital stimulation achieved immediate improvement. This immediacy of effect may make occipital SCS a preferred approach for patients with intractable symptoms.

Some of the challenges for SCS include selecting appropriate patients and the overall cost of implantation. Careful patient selection is vital for the selection of SCS therapy. Considerations include chronic pain, failure of conventional treatment for at least 6 months, no major psychiatric disorders, the ability to give informed consent for the procedure, and the willingness to stop inappropriate drug use before implantation.

The issue of pain and psychiatric disorders is a matter of ongoing controversy among clinicians and researchers. Certain psychological illnesses serve as contraindications to implant [67]. This may be problematic, however, as it excludes a large group of patients who would otherwise benefit. There is no consensus regarding which psychological characteristics to assess or which tests to administer [68]. A better understanding of psychosocial issues is needed before instituting SCS therapy.

Another concern is the high initial cost of SCS. A recent study investigating the cost-effectiveness of conventional medical management with SCS in patients with FBSS compared a summary of the total direct and indirect costs incurred in 12 months prior and 24 months after SCS [69]. The costs were scaled to €2009. The total SCS treatment costs were equivalent to €6567/patient/year. The year of implantation incurred a significant increase in cost of €20,902/patient year, mainly attributed to the high cost of the SCS device itself. SCS was perceived as a treatment of last resort, when most medical and surgical invasive therapies have already failed [70].

Recent research has found that SCS therapy can benefit patients battling chronic pain by reducing or stabilizing the use of opioids. In a new study, researchers examined opioid usage data from more than 5400 patients prior to and after receiving SCS implant. Researchers found that average daily opioid use declined or stabilized for patients receiving successful SCS therapy compared to patient use of opioids prior to implantation [48]. A recent pilot study assessed the feasibility of SCS in patients suffering from refractory angina followed by a six-month follow-up. The results showed a reduction in angina frequency and improvement in generic quality, exercise capacity, and Seattle Angina Questionnaire for patients treated with SCS [71].

In spite of the challenges involved in SCS, it can be both efficient and beneficial for treating chronic pain by reducing wait times before implantation and decreasing device-related complications. A longitudinal observational report supported the use of SCS in the early stages of neuropathic pain. Kumar and Wilson showed that pain treatment success rates decreased from approximately 85% for a delay of less than 2 years to 9% for a delay of 15 years or longer. The situation has improved, with patients now awaiting 4.5 years on average for an implant with a success rate of approximately 45% [72]. The long-term complication rate for SCS is around 18% and may be 32% for the first 6 months [12,73,74]. Complications can be divided in three categories: (1) hardware based, (2) biologically based, and (3) other. Hardware-based complications are lead migration (13%), fracture (9%), and hardware malfunction (3%). Biologically based complications are related to infection (3–5%), cerebrospinal fluid leak (0.3%), and pain located at the site of the incision, electrode, or IPG. Other complications include battery exhaustion, which occurs regardless of manufacturer; batteries must be replaced after 3 or 4 years depending upon the usage. The use of octopolar leads and complex programming have reduced the surgical revision rate from 15% to 3.8% [75]. Novel fixation devices have recently been marked to reduce the incidence of lead migration. Improved titanium and silicone anchors and tissue adhesive provide significant holding compared to early generation of silicon anchors. These tools help reduce the fracture risk [76,77].

New research seeks to understand the mechanism of action of HF SCS. Preclinical studies have shown that HF SCS suppresses pain via conduction block by inactivation of sodium channels. However, human studies have been performed at frequencies as low as 1 kHz to treat chronic back pain. Several mechanisms of action have been proposed thus far with no consensus. Since SCS devices are changing to become MRI compatible [78], researchers will be able to employ different imaging modalities such as functional MRI in order to understand how different regions of the brain coordinate during neuropathic pain. The SCS have shown to reduce depression and pain-related disability on Beck Depression Inventory and Pain Disability Index (PDI) in patients treated with lumbar, thoracic, or cervical neurostimulators [79]. This suggests that SCS could further be translated to treat axis 1 pathologies such as schizophrenia, bipolar disorder, depression, addiction, and anxiety.

8. Five-year view

The evolution of different stimulation paradigms such as tonic, burst, and HF marks the beginning of a new trend in spinal cord, brain, and peripheral nerve stimulation. It is likely that the future of neuromodulation involves not only better targeting but also the development of new stimulation techniques that can more effectively communicate with the nervous system. Some techniques likely to emerge in the near future are pseudorandom burst stimulation, pleasure stimulation, noise stimulation, and reconditioning stimulation [80]. These new techniques will also require the development of adjustable or upgradable IPGs that mimic the current evolution in smartphones, tablets, etc. In other words, a generic, open-platform hardware will be required onto which new stimulation designs can be downloaded, analogous to applications for smartphones. Current neuromodulators – including Precision Spectra, which is capable of handling different stimulations; Prodigy, which mimics the bursts in the nervous system; and RestoreSensor, which is capable of changing its settings based on body position – all have such a platform for future upgrades.

Key issues

- The gate control theory, proposed by Melzack and Wall, suggests that the activation of myelinated afferent A β fibers inhibits pain transmission to the central nervous system.
- Spinal cord stimulation (SCS) is the most common therapy for the treatment of chronic pain. The US FDA approved SCS in 1989 to relieve chronic discomfort from neuropathic pain in the arms or legs. The therapy now accounts for 70% of all neuromodulation treatments.
- SCS therapy is classically delivered via tonic stimulation, referring to the frequency of the electrical energy delivered to interrupt pain signals to the brain.
- Recently, new, paresthesia-free stimulation techniques have been developed, such as burst SCS and high frequency (HF) SCS.
- At a systems level, De Ridder and coworkers have demonstrated that burst SCS modulates the lateral (discriminatory), medial, and descending pain pathways.
- HF SCS treats pain by blocking neural conduction in peripheral nerves. The neural conduction block inhibits the pain signal by blocking large fibers (fibers greater than 15–18 μ m begin to shut down at 4 kHz and 8 or 9 μ m fibers begin to shut down at 8 kHz).
- Burst stimulation has a higher charge/pulse compared to HF stimulation, which has a higher high charge/sec.
- The future of neuromodulation not only involves better targeting, but also the development of new stimulation techniques that can better communicate with the nervous system, such as pseudorandom burst stimulation, pleasure stimulation, noise stimulation, and reconditioning stimulation.
- The development of adjustable or upgradable internal pulse generators (IPGs) is also required to implement the newly developed stimulation paradigms.

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