OXFORD

Mechanism of Action in Burst Spinal Cord Stimulation: Review and Recent Advances

Krishnan Chakravarthy, MD, PhD,* Michael A. Fishman, MD,† Xander Zuidema, MD, PharmD,‡ Corey W. Hunter, MD,§ and Robert Levy, MD, PhD¶

*San Diego Health Sciences, University of California, San Diego, California; †Center for Interventional Pain and Spine, Exton, Pennsylvania, USA; ‡Department of Anesthesiology and Pain Management, Diakonessenhuis Utrecht, Utrecht, the Netherlands; §Ainsworth Institute of Pain Management, New York, New York; ¶Institute for Neuromodulation, Boca Raton, Florida, USA

Correspondence to: Krishnan Chakravarthy, MD, PhD, Department of Anesthesiology, UC San Diego Health Sciences, 3350 La Jolla Village Dr., San Diego, CA 92161, USA. E-mail: kvchakravarthy@ucsd.edu.

Abstract

Objective. This is a comprehensive, structured review synthesizing and summarizing the current experimental data and knowledge about the mechanisms of action (MOA) underlying spinal cord stimulation with the burst waveform (as defined by De Ridder) in chronic pain treatment. **Methods.** Multiple database queries and article back-searches were conducted to identify the relevant literature and experimental findings for results integration and interpretation. Data from recent peer-reviewed conference presentations were also included for completeness and to ensure that the most up-to-date scientific information was incorporated. Both human and animal data were targeted in the search to provide a translational approach in understanding the clinical relevance of the basic science findings. **Results/Conclusions.** Burst spinal cord stimulation likely provides pain relief via multiple mechanisms at the level of both the spinal cord and the brain. The specific waveforms and temporal patterns of stimulation both play a role in the responses observed. Differential modulation of neurons in the dorsal horn and dorsal column nuclei are the spinal underpinnings of paresthesia-free analgesia. The burst stimulation pattern also produces different patterns of activation within the brain when compared with tonic stimulation. The latter may have implications for not only the somatic components of chronic pain but also the lateral and affective pathway dimensions as well.

Key Words: Burst; Spinal Cord Stimulation; Mechanism of Action; Analgesia; Neurophysiology; Imaging

Background

The gate control theory of pain modulation, proposed by Melzack and Wall in 1965 [1–3], served as the proposed mechanism of action of spinal cord stimulation (SCS) upon its introduction in 1967 [4]. Using this model, it was suggested that electrical stimulation of the spinal cord dorsal columns activated larger-diameter fibers that

could modulate, or "gate," the conduction of painful signals so as to provide pain relief. In 1967, Shealy et al. first demonstrated the potential effectiveness of stimulating the dorsal columns in humans to treat chronic pain [4]. Soon thereafter, some of the first SCS devices were produced by Medtronic in the late 1960s, with relatively widespread acceptance during the 1970s and 1980s.

Since that time, SCS has gained a significant position in the treatment algorithm for neuropathic and ischemic pain states and become part of the standard treatment for various recalcitrant pain conditions [5]. In recent years, there have been substantial technological advances in SCS system design with respect to varying the form of electrical energy being delivered to the cord; the use of SCS has been further advanced by the identification of new, more effective neural targets.

For 50 years, the SCS industry incrementally improved the hardware of these devices, leading to smaller batteries, percutaneous steerable electrodes, wireless connectivity, and magnetic resonance imaging (MRI) compatibility, among others. Over the past decade, the push for superiority in the neuromodulation space has focused on the development of novel stimulation patterns [6]. Paresthesia-based therapies have largely been supplanted by a variety of proprietary parameters that minimize or eliminate paresthesias altogether, as well as devices that allow for a variety of stimulation patterns purported to allow for better customization of therapy and improve clinical outcomes [7,8]. With this recent flood of innovations, it is important that initial reports of efficacy are validated by others and reported in peer-reviewed papers. This paradigm shift to nontraditional stimulation patterns has been reported to improve outcomes for patients with chronic pain, yet the specific mechanism(s) of action of different SCS modalities remains hypothetical and elusive [9]. Our objective is to provide more insight into one of these nontraditional stimulation patterns, burst spinal cord stimulation, and to critically review the current peer-reviewed studies of its mechanism of action.

Mechanism of Action in SCS

A great deal of work has been done to elucidate the mechanism of action behind the use of conventional (tonic, low-frequency) SCS in neuropathic pain states [3, 10, 11]. The pathophysiology of neuropathic pain involves changes in expression and function of a variety of neurotransmitter systems working throughout the nervous system [12]. At the level of the spinal cord, wide–dynamic range (WDR) neurons in the dorsal horn display increases in excitatory neurotransmitters, with concomitant decreased expression of inhibitory molecules [3,10, 11]. SCS has been shown to increase release of the inhibitory neurotransmitter GABA in the spinal cord and also induce a subsequent decrease in glutamate levels in experimental animals. [13–15]. The $GABA_B$ receptor has been shown to be particularly instrumental in this response, as shown by the conversion of non-responders to responders by adding intrathecal baclofen [16]. In support of this, long-term follow-up of seven patients who received this combination therapy reported durable relief at more than five years of follow-up [17]. Other molecules have also been implicated in the response of SCS to the patient's condition, including activation of

the cholinergic system with release of acetylcholine (ACh) and adenosine. Furthermore, multiple other neurotransmitters have been indicated in the response to SCS, including adenosine, serotonin (5-HT), and norepinephrine (NE) [3].

Overview of Novel Stimulation Algorithms

Within the last decade, there has been an increased interest in, and use of, stimulation patterns that deviate from low-frequency tonic SCS. Conventional SCS has traditionally had limited success in treating axial back pain due to anatomic and neurophysiologic reasons [21]. These approaches include high-frequency SCS (HF-SCS), with stimulation frequencies at 10 KHz, and burst SCS stimulation, described by De Ridder (five-pulse train with internal frequency of 500 Hz delivered at 40 Hz utilizing a passive recharge pattern and waveform) [22,23]. These stimulation patterns are hypothesized to evoke different underlying mechanisms of action [3,24,25] when compared with low-frequency tonic SCS. The underlying differences in neurophysiologic responses are translationally observed with lack of reliance on paresthesias as well as increases in clinical efficacy. Multiple studies with level 1 evidence have demonstrated the superiority of these novel therapies as compared with conventional stimulation for back and leg pain [22,23,26]. This review will focus on burst SCS as first described by De Ridder (Abbott, Plano, TX, USA).

Preclinical Data on Burst SCS Waveform

Several preclinical studies have helped to elucidate the potential mechanisms underlying burst SCS–induced analgesia. Although some neurons generate single action potentials with a following pause outlasting the relative refractory period, some neurons fire in a burst of action potentials that results in a follow-on quiescent period. These bursts are suggested to ride on a calcium current–mediated plateau, or active phase, in neurons, which differentiates them from clustered tonic firing not involving phasic calcium–mediated or sustained membrane depolarizations [27,28]. These variations in firing patterns in the dorsal column of the spinal cord compared with traditional tonic firing are purported to translate to differential downstream modulation of both the lateral and medial aspects of the spinothalamic tract, resulting in unique clinical effects.

Effects of Burst Patterns on Neurons
The bursting activity of neurons in vivo has a number of effects not seen with tonic firing. These include enhanced postsynaptic responses to presynaptic action potentials, enhanced strength in synaptic connectivity in both the short and long term, and differential activation of parallel, connected anatomical pathways. Swadlow and Gusev demonstrated increased cortical neuronal activity generated from stimulating the thalamus in burst compared

with tonic stimulation. Cortical neuronal activity was not only more activated with burst stimulation, but also resulted in a faster time to impulse reaching baseline, allowing for novel neocortical spikes for future neuronal activity [29,30].

Burst firing patterns in the medial thalamic and intra-laminar nuclei may evoke short- and/or long-term plasticity in the nociceptive thalamic–anterior cingulate pathway [31]. The medial thalamic complex is believed to potentiate anterior cingulate cortex neuronal activity by its burst firing pattern, which has been shown to enable a temporal response and processing of peripheral persisting noxious stimuli (e.g., pain). In addition, the maintenance and transition from acute to chronic pain may be dependent on oscillatory firing patterns within the thalamic–cingulate network responsible for both pain attention and memory and pain-induced fear and anxiety behavior [31–33].

Remy and Spruston demonstrated that delivering a single burst of stimulation to the Schaffer collateral pathway in the hippocampus produced long-term potentiation (LTP) at the excitatory synapse between the Schaffer collateral and postsynaptic CA1 neurons [34]. This demonstrates the heightened effect of burst stimulation within the central nervous system and provides the substrate of spinal burst stimulation to evoke long-lasting synaptic changes within the pain-associated neural network in the brain as well.

Neurophysiological Effects of Burst SCS

Several preclinical studies have examined the differences in neurophysiological effects of burst vs tonic SCS at stimulation intensities at 90% of the motor threshold. Figure 1 shows a diagram of proposed effects of burst SCS in the spinal cord. Crosby and colleagues, using a rodent model of cervical nerve root compression, demonstrated that burst SCS significantly reduced the number of paw withdrawals in response to 4-gm von Frey filament stimulations [35]. They also demonstrated that burst stimulation generated significant reductions in WDR dorsal horn neuron firing that were evoked by both toe pinch and 26-gm von Frey filament, suggesting that burst and tonic patterns had the same effect during noxious stimulation. Tang et al. also demonstrated that using amplitudes of 90% of the motor threshold, both tonic and burst SCS significantly suppressed neuronal responses to acute noxious pinch compared with baseline (30.6% and 41.5%) [36]. On the other hand, when stimulating with amplitudes of 60% of the motor threshold during acute noxious pinch, the authors found that burst stimulation produced a 47% reduction in dorsal horn neuron firing from baseline, whereas tonic stimulation did not produce any significant effects. This suggested that both the pattern and amplitude of stimulation have an impact on the neurophysiological response. It is unclear if this relationship differs for tonic and burst

stimulation clinically, but the potential differences in mechanism of action may lead to a fundamentally different relationship between pulse amplitude and pain relief and may need to be considered in programming patients. In addition, Tang et al. were also able to demonstrate that compared with tonic stimulation, burst stimulation did not affect selected neuronal activity in the gracile nucleus (Figure 2). WDR and low-threshold neurons in the gracile nucleus whose activity was decreased by 20% with tonic stimulation were not inhibited by burst stimulation, which the authors attributed to lower absolute stimulation intensity. More importantly, these findings could explain why patients do not feel paresthesia with burst SCS as the gracile nucleus is the tactile sensory target for much of the information ascending from the dorsal columns [36].

Two weeks after production of a rat sciatic nerve injury, burst stimulation at 90% of the motor threshold, delivered at an interburst frequency of 4 or 40 Hz and intraburst frequencies of 60, 500, or 1,000 Hz, was compared with tonic stimulation at 16, 60, or 160 Hz. Burst SCS reduced hyperalgesia and restored physical activity to a greater degree than tonic stimulation. Physical activity was defined as measuring distance, crossings, rearing, and grooming. The authors concluded that burst SCS may reduce pain-related disability, along with decreasing hypersensitivity, by inhibiting dorsal horn neuronal activity [37].

Effect of Burst Stimulation Parameters and Waveform on WDR Activity

In a rodent model, Crosby and colleagues demonstrated that increasing either the number of pulses in a burst, the pulse width, or the stimulation amplitude led to decreased WDR activity in the dorsal horn [38]. They further demonstrated that increasing the intraburst frequency was essential to recruiting more high-threshold neurons with burst SCS [38]. They also found a linear correlation between increasing the charge per burst and decreases in WDR neuronal firing. It is clear from their results that specific stimulation parameters are essential to optimizing the results of burst SCS.

Additional work has also linked features of the burst pulse train to modulation of dorsal horn neuronal activity [39]. Stimulating with a burst pulse train having increasing pulse amplitude over the course of each burst and a passive recharge phase produced significant reductions in dorsal horn neuron firing relative to baseline, whereas an alternative burst waveform with a fixed-pulse amplitude and an active recharge phase had the opposite effect, with significant increases in dorsal horn neuronal firing. Similarly, a computational SCS modeling study suggested that the dorsal column fibers that are directly impacted by stimulation have different responses depending on the burst pattern used, even when all other parameters (e.g., amplitude, frequency, pulse width) are held
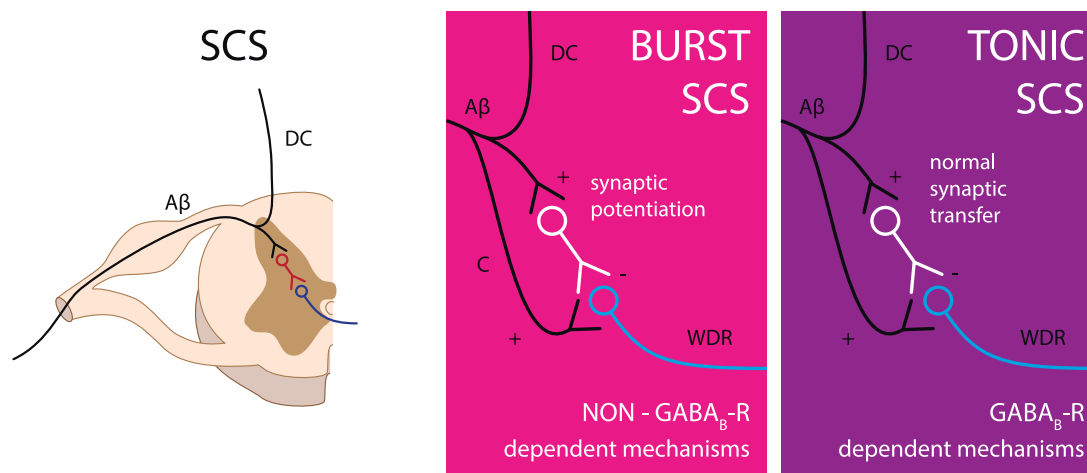
Figure 1. Comparison of cellular responses and potential mechanisms of action within the dorsal horn of the spinal cord between tonic and burst spinal cord stimulation. Note that synaptic potentiation and underlying neurochemical signaling are proposed differences between the two different stimulation patterns.
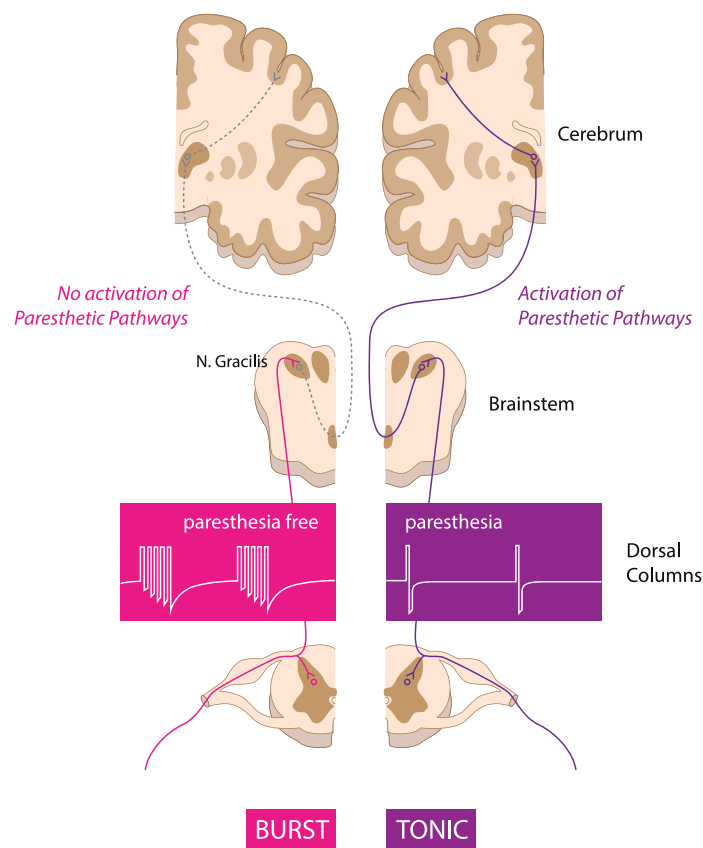

Figure 2. Stimulation of the spinal cord with burst or tonic spinal cord stimulation (SCS) yields different responses in the brainstem dorsal column nuclei (DCN; nucleus gracile). Tonic SCS evokes robust alterations in cellular discharge in the DCN, whereas burst does not evoke similar responses. The DCN pathway is responsible for the sensations of paresthesias during stimulation, so a differential activation of this pathway can account for the paresthesia-free analgesia evoked with burst SCS but not tonic SCS.

constant (Figure 3) [40]. Crosby and colleagues were also able to demonstrate that the effects observed with burst SCS, unlike tonic stimulation, are not dependent on GABAergic signaling. In their study, Crosby and colleagues applied a GABA$_B$ receptor antagonist to the

dorsal surface of the spinal cord in rodents with nerve root compression to evaluate the role of GABA$_B$ receptor activation during burst and tonic SCS [35]. The authors discovered that the GABA$_B$ receptor antagonist completely eliminated the effects of tonic SCS on
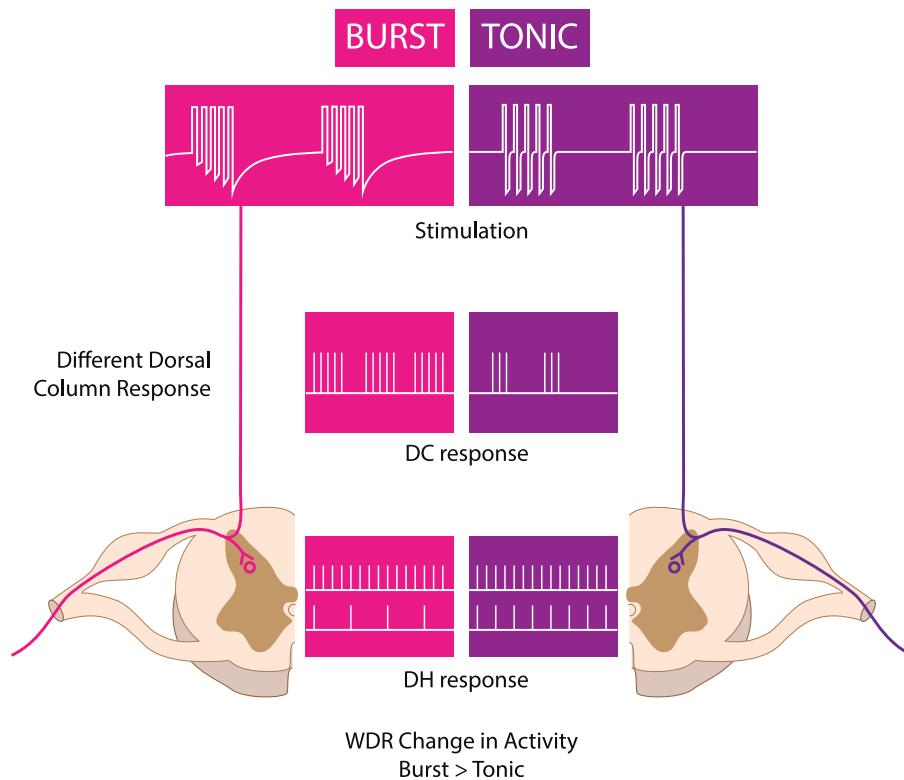
Figure 3. The signature of a neurostimulation signal can have a direct and indirect (downstream) impact on neurophysioloigic function. Burst patterns utilizing passive vs active recharge patterns evoke differential activity patterns in both the dorsal columns and neurons in the upper laminae of the dorsal horn.

attenuation of WDR neuron activity during noxious stimulation, but this effect was not present with burst SCS. These data agree with other work suggesting that there is pivotal role for GABAergic inhibition in tonic SCS [41–43]. Despite the apparent lack of a specific role of GABA_B receptors in burst SCS, the reductions in WDR firing observed must be driven by some as-yet to be determined neurochemical signaling mechanism. Further research is required to elucidate the neurochemical mechanism(s) of action of burst stimulation.

The effect of tonic SCS is reduced by opioid antagonists, suggesting that the effect of SCS may be mediated by the descending inhibitory pathways, which include both enkephalinergic and dynorphinergic fibers [44,45]. Stimulation of the periacqueductal gray (PAG) also results in the release of NE and 5-HT at the distal projections of the descending inhibitory tract [46]. Given the differences in how burst SCS alters neural processing of nociceptive and painful information (both spinally and supraspinally), there may also be differences in how this stimulation modality activates descending inhibitory pathways from the PAG, ventromedial medulla, and/or parabrachial brainstem regions [47]. Research also indicates that the anterior cingulate cortex (ACC) is directly involved in top-down modulation of cells in the dorsal horn [48]; this is of particular interest in that burst SCS has been demonstrated to activate the ACC [32]. In toto, this suggest that burst SCS may have an impact on pain

through a spino–cortical–spinal circuit, thereby causing both central and spinal effects through indirect activation of multiple pathways.

Variations in Burst Waveform

The neurophysiological impact of different burst SCS waveforms (passive recharge phase vs active recharge phase) (Figure 4a) was evaluated in a preclinical study [49]. Neuronal firing rates were measured in the spinal dorsal horn on day 7 after painful cervical nerve root compression at the C7 level (N = 5 Holtzman rats). Recordings were collected during a forepaw noxious pinch stimulus at baseline and after five minutes of burst SCS with passive or active recharge delivered at the midline C4 level at 90% of the motor threshold (measured at 0, 2, 5, 10, and 15 minutes after SCS). Burst with passive recharge significantly reduced neuronal firing rates evoked by noxious pinch stimuli compared with baseline ($P < 0.04$), whereas burst with active recharge significantly increased neuronal firing rates compared with baseline ($P < 0.006$) (Figure 4b). Moreover, burst with passive recharge significantly reduced spontaneous firing rates compared with baseline in the period after noxious pinch stimuli ($P < 0.03$). These results indicate that specific burst SCS patterns may vary widely in their therapeutic effects and raise questions about the differential impact of different burst waveform patterns and their
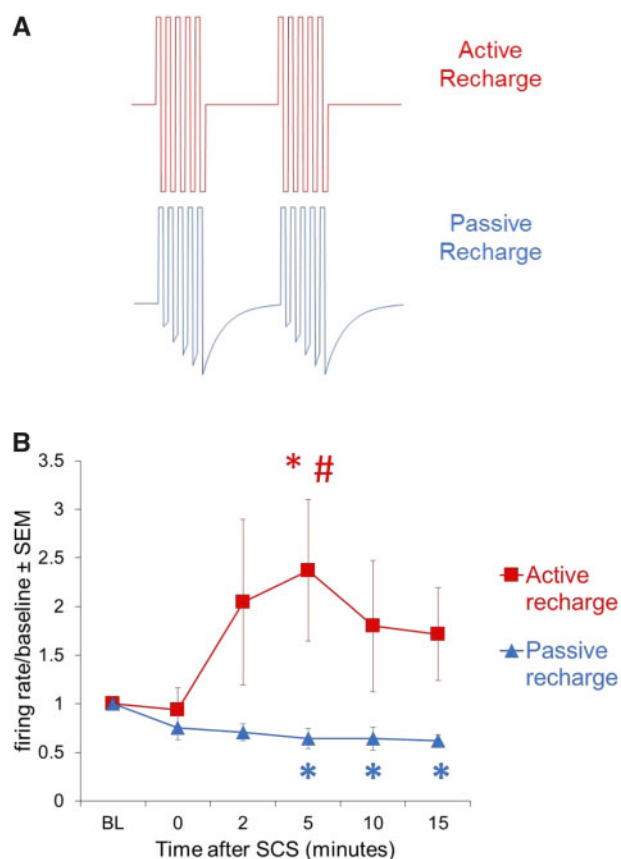
Figure 4. A) Illustration of burst waveforms with active recharge or passive recharge. B) Changes in spinal neuron firing rate from baseline after burst with active recharge or passive. Following burst spinal cord stimulation (SCS) with passive recharge, the normalized firing rate was significantly lower overall ($P = 0.019$) and at five, 10, and 15 minutes relative to baseline (blue $*P < 0.04$). Conversely, five minutes after burst SCS with active recharge, the normalized firing rate was increased relative to baseline ($^{\#}P < 0.006$) and zero minutes (red $*P < 0.003$). Figures used with permission from Weisshaar et al. [83].

role in developing or reversing SCS habituation in a subset of patients.

Clinical Data on Burst SCS Pattern

In addition to the preclinical animal research aimed at understanding the basic physiologic mechanism(s) of burst SCS, mechanistic research has also been conducted in humans [3, 24]. Because the individual perception of pain is the result of a complex integration of sensory, emotional, and cognitive components, work has been focused on not only understanding the spinal processing of the somatic components of pain and the impact of burst SCS, but also on its potential effects on higher-level processing of pain and secondary systemic effects on immune and neurohumoral function.

Electrophysiological Studies

The introduction of paresthesia-free methods of SCS-induced analgesia, such as burst SCS, has raised questions about how SCS-induced pain relief can be effective without stimulation of Aβ fibers and thus inducing sensation(s). If this paresthesia-free SCS does not act through an Aβ fiber mechanism, then the mechanism of action by which burst SCS impacts neural function in chronic pain patients remains unclear. As previously described, animal research has shown that traditional SCS suppresses dorsal horn WDR firing responses to noxious stimuli. This effect is more prominent with burst SCS compared with tonic SCS [36]. As a result of the animal data noted above, we now have rational hypotheses for 1) the reported superior pain-relieving effects of burst SCS, 2) the ability for burst SCS to work in patients who have failed low-frequency tonic SCS therapy, and 3) how burst SCS may influence neural function in a manner different from tonic SCS. These animal data are now supported by data from humans concerning the neurophysiologic effects of burst SCS.

Somatosensory evoked potentials (SSEPs) result from stimulation of somatosensory pathways (Aβ, Aδ, and C fibers) and can be recorded both orthodromically and antidromically. In 2018, Falowski studied the influence of different types of SCS waveforms (low- and high-frequency tonic, burst SCS, and other pulse train patterns) on SSEPs and electromyographic (EMG) signals [50]. He found that the SSEP signal of the tibial nerve was lost after stimulation with burst SCS, demonstrating an inhibitory effect that this stimulation pattern can have on somatic sensory transduction. Compared with tonic stimulation, the amount of energy needed to inhibit the SSEP signal was 50–75% lower with burst SCS. EMG recordings that were taken with leads placed at T8–T10 (with low-frequency tonic stimulation) showed, by concomitant muscle contraction, activation of proximal muscles at low amplitudes, which progressed to the distal muscles with higher stimulation amplitudes. Interestingly, burst stimulation activated the distal muscles (gastrocnemius → quadriceps → iliopsoas) first at lower amplitudes and more proximal muscles at higher amplitudes. One possible explanation for this observation is that burst SCS might penetrate deeper into the dorsal columns than tonic stimulation. In the dorsal columns, distal somatic afferent fibers enter laterally and then course medially as the dorsal column extends rostrally and more proximal fibers are added laterally. Thus, modulation of fibers within the dorsal column with burst SCS seems to be in a different order with increasing amplitude when compared with low-frequency tonic SCS. Of further interest is that burst SCS elicited only one large EMG signal, whereas other stimulation patterns with active recharge produced four equipotent EMG signals [50]. These latter data demonstrate that neurophysiologic recordings show differences based on precise waveform signatures (passive vs active recharge), suggesting differential activation of somatic pathways.

Differences in the ability of burst SCS vs tonic SCS to evoke neurophysiologic alterations in the human nervous system are not confined to the spinal cord. Bocci et al.
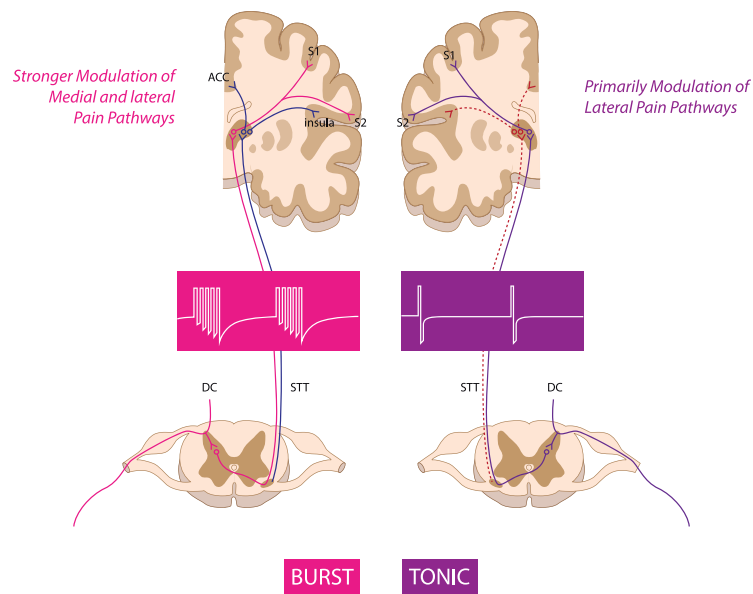
Figure 5. Burst and tonic evoke differential responses in cerebral regions involved with both discriminatory/somatic aspects of pain and brain regions involved in affective and emotional components of pain.

have used laser evoked potentials (LEPs) to elicit a painful heat stimulus while recording from the brain [51]. Unlike the SSEP response, only small-diameter fibers (Aδ and C fibers) are activated with LEPs, which are, therefore, more selective for afferent pain signals. The LEP signal travels via the spinothalamic tract and can then be detected by transcranial Ag/AgCl electrodes. The LEPs were measured in patients with chronic back pain while undergoing different modes of spinal cord stimulation, including low-frequency tonic, HF-SCS, and burst SCS. The authors observed that burst SCS stimulation reduced the brain LEP signal significantly more than HF-SCS and LF-SCS, the latter two patterns not showing any difference from baseline. They concluded that because the middle-latency N1 and late P2 waves, representing different cortical pain projections, were influenced by burst SCS, burst SCS must modulate both the lateral and medial pain pathways [51].

Prior studies have shown that neural activity of the somatosensory cortex and ACC (lateral and medial spino–thalamo–cortical pathway components, respectively) is altered by stimulation of the spinal cord using burst SCS [8]. Specifically, EEG recordings during tonic, burst, and placebo SCS found that burst SCS produced synchronized activity of the dorsal ACC, whereas tonic and placebo SCS did not. This indicates that in addition to somatosensory modulation, burst SCS also modulates the medial spino–thalamo–cortical pathways, which are believed to communicate the affective or emotional part of pain processing (Figure 5) [32, 63–65].

Neuroimaging Studies

Functional neuroimaging studies have provided insight not only into regions of the brain that are activated by painful conditions but also the connectivity between specific brain regions involved in both the discriminatory and affective components of pain [52]. With various pathways subserving these two pathophysiologic components of chronic pain, recent findings have highlighted the ability of spinal cord stimulation to specifically and regionally affect different brain regions.

Effect of Tonic Stimulation on Medial and Lateral Pathways

Pain perception is multidimensional and involves multiple anatomic pathways that extend from the peripheral nervous system to various regions of the brain. It is believed that the discriminative (somatosensory) component of pain perception (e.g., anatomic location, character, and intensity of pain) follows the lateral pathway via the anterior neo–spinothalamic tract, which projects mainly to the S1 and S2 regions of the sensory cortex via the sensory thalamus [32]. The affective/emotional part of pain perception follows the medial pathway via the paleo–spinothalamic tract, which projects to the operculum of the insula and ACC via medial thalamic nuclei [8, 53]. Morton et al. have described the intricacies of brain activation during the pain experience by using functional neuroimaging techniques, extending the possibilities of studying pain perception during functional neurostimulation [54].

In conjunction with this approach, brain positron emission tomography (PET) imaging of subjects receiving a painful stimulus shows clear activation of S1, S2, the insula, and the ACC. The ACC is putatively responsible, at least in part, for the affective part of pain processing [55]. Similarly, Rasche et al. performed blood oxygenation level–dependent (BOLD)–functional MRI (fMRI)

imaging in failed back surgery syndrome (FBSS) patients during tonic SCS. They showed that tonic SCS alters mainly the lateral somatosensory pathway, and to a lesser extent the structures (prefrontal cortex, ventral posterolateral nucleus of the thalamus, cingulate gyrus) of the medial affective pathway [56]. Further, BOLD-fMRI imaging studies in FBSS patients during tonic SCS showed increased activation of the medial primary sensorimotor cortex (SM1), the contralateral posterior insula, and the ipsilateral secondary somatosensory cortex (S2). Decreased activation was observed in the bilateral primary motor cortices (M1) and the ipsilateral primary somatosensory cortex (S1). The authors postulated involvement of the motor cortex in the pain matrix of FBSS patients treated with tonic SCS [57]. In contrast, a larger BOLD-fMRI study in 20 FBSS patients examined the brain regions of importance during short-term and long-term administration of tonic SCS in good responders [58, 59]. In the short term, the authors found a correlation between good pain relief from SCS and functional activation in the brainstem, the rostral ACC, the cerebellum, and the bilateral dorsolateral prefrontal cortex. All of these results are consistent with secondary effects of pain relief.

Deogaonkar and colleagues [60] performed a whole-brain connectivity analysis in conditions of optimal tonic SCS settings, as well as with SCS switched off. With optimal tonic SCS settings, the authors found a general trend toward decreased connectivity between S2 and limbic/emotional (middle cingulate cortex) areas and increased integration of somatosensory regions into the default mode network (DMN; medial prefrontal, precuneus, and lateral parietal cortex). The authors demonstrated that the above-mentioned alterations in the pain matrix activation are correlated with reductions in pain intensity. These data did not infer an impact on other dimensions of pain such as the psychological impact of suffering. Also, as only low-frequency tonic stimulation was utilized, the study did not examine if other stimulation patterns may have, comparatively, more pronounced effects [61, 62].

Effect of Burst Stimulation on Medial and Lateral Spino–Thalamo–Cortical Pathways

Similar findings to the aforementioned source-localized EEG results have been found utilizing PET–computed tomography (CT) imaging in a subanalysis of the SUNBURST study (Figure 6) [62]. When the same patients were exposed to either burst SCS or tonic SCS, somatosensory and motor structures, as well as subregions of the ACC (e.g., daACC, pACC), showed different patterns of activation. Mechanistically, following painful stimuli, medial thalamic cells fire in a burst pattern, thus potentiating the anterior cingulate cortex. Furthermore, the evolution of acute to chronic pain might be a result of low-frequency firing patterns within the spino–thalamo–

cingulate complex, thus facilitating pain-induced attention, memory, fear, and anxiety behavior [24, 33, 66, 67]. More recently, the ACC has been shown to influence nociceptive input coming into the spinal cord, which may provide a sensory–affective loop involving spino–cortico–spinal projections [48]. Thus, the integrative interactions between the somatic and affective properties of pain may not just be influenced independently by burst SCS in the cerebrum but also have a downstream impact on spinal somatic information processing. From this work, it is clear that neuronal bursting patterns play important roles in both normal and pathophysiologic processing of sensory information. To what extent, however, burst SCS impacts multiple sensory processes in chronic pain has yet to be fully elucidated. It is clear from multiple studies utilizing different brain activity monitoring approaches that the specific pattern used in burst SCS modulation of somatosensory fibers does have a different impact on multiple brain regions controlling central neural pain processing, including both somatosensory and cognitive dimensions.

Support for Burst SCS as a Placebo-Controlled Therapy

Burst SCS is a biomimetic, low-energy stimulation paradigm in which a short pulse train of high-frequency spikes (internal frequency 500 Hz) are delivered at 40 Hz [32, 63, 64]. Burst stimulation was initially used to treat noise-like tinnitus [68–70] and then was translated to modulate pain pathways, in which it was noted that burst stimulation was efficacious not only in modulating discriminatory aspects of pain, but in the affective response to pain as well [24]. Furthermore, burst SCS does not evoke paresthesias, allowing for placebo-controlled studies for comparison with tonic stimulation [64].

In 2013, De Ridder et al. published a randomized trial in which burst, tonic, and placebo were compared in 15 patients [64]. A subgroup of these patients also underwent source-localized electroencephalography (EEG) under baseline, tonic, burst, and placebo conditions. This study found that burst stimulation improved back, limb, and general pain VAS scores by 51%, 53%, and 55% and tonic stimulation by 30%, 52%, and 31%, respectively. Pain now, least pain, and worst pain were improved by 50%, 73%, and 36% by burst stimulation, whereas tonic stimulation improved these parameters by 26%, 46%, and 13%, respectively. Burst was significantly better than placebo for all measurements. Percent reductions in the back, leg, and overall pain were 18.9%, 11.7%, and 10.9% for the placebo group, compared with 51.3%, 52.7%, and 55.0% for the burst SCS group. These findings are consistent with those of two other placebo-controlled studies utilizing burst SCS [71, 72]. The Pain Vigilance and Awareness Questionnaire, which measures attention to pain and attention to changes in
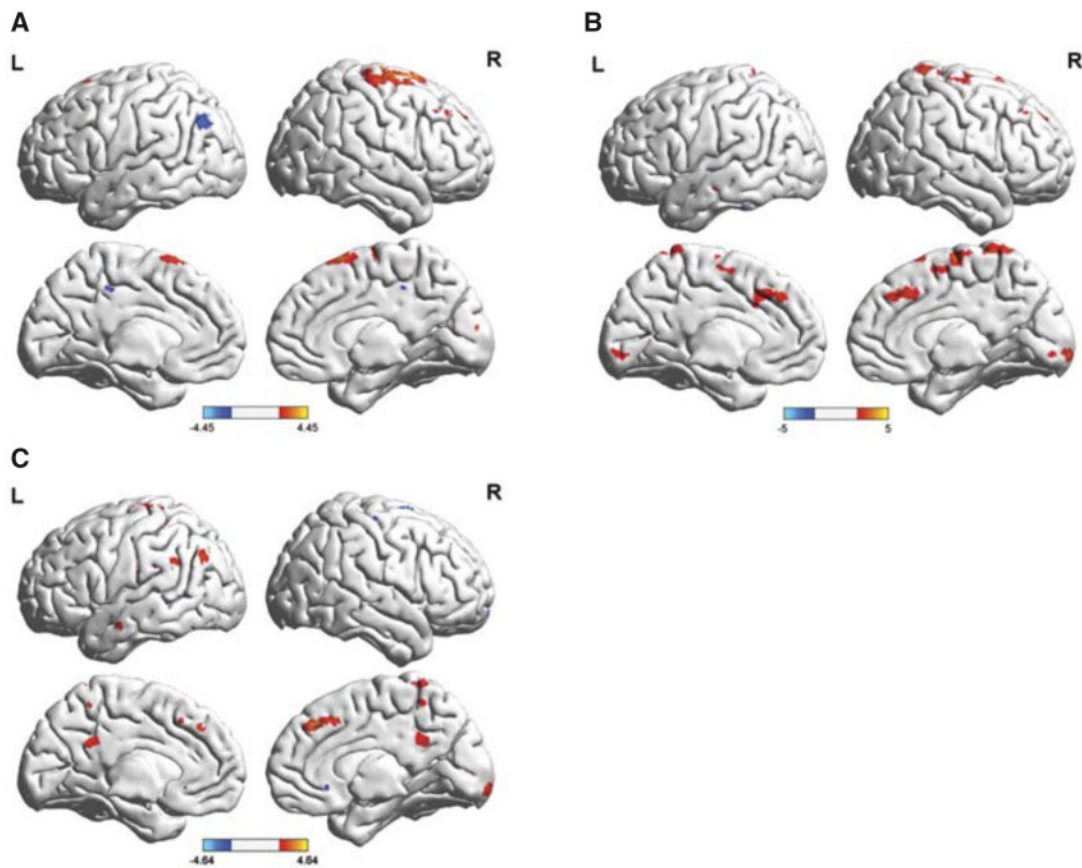
Figure 6. Positron emission tomography–computed tomography scans demonstrating areas of brain activation from tonic and burst spinal cord stimulation. A) Significant increases ($P < 0.01$) in premotor and supplementary motor cortex activity were observed during tonic stimulation when compared with baseline (NO STIM). B) Significant increases ($P < 0.01$) in neural activity were observed in premotor cortex, supplementary motor cortex, and dorsal cingulate cortex activity during burst stimulation when compared with baseline (NO STIM). C) Significant increases ($P < 0.01$) in neural activity were observed in the sensorimotor, anterior cingulate, and posterior cingulate cortex during burst stimulation when compared with tonic stimulation. A significant decrease ($P < 0.01$) in neural activity was observed in the anterior cingulate cortex during burst stimulation when compared with tonic stimulation. Figures used with permission from Yearwood et al. [62].

pain, was also administered in this study. This measure was statistically improved in the burst group as compared with both placebo and tonic stimulation. An anatomic correlation relating this to the medial spino–thalamo–cortical pathway was identified on EEG, which demonstrated burst activation of the dorsal anterior cingulate and right dorsolateral prefrontal cortex significantly greater than with tonic stimulation. In other words, this pilot study showed that burst stimulation was superior to tonic and placebo not only in pain reduction, but also that it produced differential changes in cerebral activation in brain regions known to be involved in psychological dimensions of pain.

Key RCT Data

An industry-sponsored, multicenter RCT with crossover design comparing tonic stimulation with burst stimulation by Deer et al. was published in 2018 [23]. In the study, 100 subjects who responded to a trial of tonic stimulation were implanted with a device capable of both

burst and tonic stimulation and were randomized to receive one stimulation for the first 12 weeks of the study and the other stimulation mode for the subsequent 12 weeks. The baseline mean VAS score for all subjects was 74.7 mm, and following the crossover phases, the average VAS score after 12 weeks was 48.7 mm for tonic stimulation and 43.5 mm for burst stimulation. After the randomization period, subjects were treated with the stimulation mode of their choice and followed out to one year. Patients overwhelmingly preferred burst stimulation (70.8%) as compared with tonic (18.8%), and some patients had no preference (10.4%). Eighty subjects reported pain diaries at the one-year visit, at which time the average VAS score was 42 mm for all parameters tested, with 68% of subjects utilizing burst as their most used program type. This study demonstrated that burst therapy was statistically both noninferior and superior to tonic SCS, although this difference was not clearly clinically significant. Of greater interest, however, was the profound patient preference for burst stimulation over tonic stimulation not fully explained by the small

differences in VAS scores. This suggests that although somatosensory measures of pain relief were similar between the burst SCS and tonic SCS groups, the additional significant impact on the affective (medial) pathways resulted in the profound patient preference for burst SCS. Subanalysis utilizing PET-CT imaging of these patient groups highlighted that both medial and lateral pathways were upregulated in the burst SCS treatment groups compared with tonic stimulation, which only modulated the lateral pathway [62].

Effect of Burst SCS Therapy on the Neuroimmune Axis—An Alternate Mechanism of Action?

Within the past 20 years, the role of the immune system in chronic pain conditions has been the subject of intensive investigation [74]. In particular, the role that microglial cells and neural–microglial interactions play has been the focus of much attention [74, 75]. Recent research suggests that a mechanism of analgesic action of SCS (including burst SCS) may involve effects upon glial cells and neuroinflammation. In support of this hypothesis, increases in anti-inflammatory cytokine interleukin 10 (IL-10) levels in cerebrospinal fluid and blood have been observed after treatment with SCS [76–78]. Similarly, Lind et al. found multiple proteins, including molecules involved in immune function, to be changed following SCS. In 2017, Kinfe and colleagues found serum anti-inflammatory IL-10 levels from FBSS patients to be four times higher with burst SCS compared with baseline, whereas levels of pro-inflammatory high mobility group box 1 protein (HMGB1) did not change significantly. Although this aspect of SCS is just starting to be examined, these initial findings suggest a role for the immune system in the clinical effects of burst SCS that might be positively modulating the autonomic–immunologic system.

Additional Clinical Insights from MOA Data

As with other therapies, the concept of a neuromodulation "dose" of therapy is an important consideration. The concept of therapeutic window will be relevant to how we apply stimulation therapy in the future. Animal studies in SCS have shown that alterations in WDR neuronal modulation have a dose dependency. Similarly, pain-related behaviors in rat models of neuropathic pain have demonstrated a dose response to SCS [9]. Studies of tonic SCS suggest that paresthesias are required to obtain pain relief; thus, the dose of stimulation must be sufficient to induce paresthetic sensations [79, 80]. In contrast, burst SCS dose was shown to reach a plateau, with no difference at 500 Hz vs 1,000 Hz on clinical pain intensity outcomes [81]. Given the effects that presynaptic burst patterns can have on sustained synaptic

strength, it was hypothesized that intermittent periods of burst SCS may also provide adequate and sustained pain relief. In a multicenter pilot study, burst SCS stimulation utilizing cycling paradigms (five seconds on stim and five seconds off stim) was found to be as effective as continuous burst SCS, with a trend toward patient preference for burst cycling [82]. Although further data are needed, these preliminary results equate well with what is currently understood about burst SCS. More importantly, they highlight the use of the lowest dose needed to produce the desired therapeutic outcome. Given the minimal long-term safety data on newer neurostimulation modalities and the lack of clear dose–response curves using novel stimulation patterns, attention to limiting dose becomes potentially important.

Conclusions

As a consequence of the particular pattern of pulses administered during burst stimulation as compared with traditional tonic stimulation, there are different neuromodulatory effects observed that are 1) directly impacted by the electrical field and 2) impacted by the orthodromic and antidromic effects of stimulation. These effects can likely be modulated not only by the pattern of the electrical pulses being delivered to the central nervous system, but also by the shape of the pulses—both individually and as a pattern within the burst itself. Clinically, these findings seem to translate to a variety of positive clinical benefits, which include superior pain relief without the need for paresthesias, increased patient preference, the potential for directly impacting affective and emotional components of pain, and the ability to affect downstream peripheral immune function.

Acknowledgments

References

1. Melzack R, Wall PD. Pain mechanisms: A new theory. Science 1965;150(3699):971–9.

2. Kumar K, Abbas M, Rizvi S. The use of spinal cord stimulation in pain management. Pain Manag 2012;2 (2):125–34.

3. Linderoth B, Foreman RD. Conventional and novel spinal stimulation algorithms: Hypothetical mechanisms of action and comments on outcomes. Neuromodulation 2017;20(6):525–33.

4. Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. J Neurosurg 1970;32 (5):560–4.

5. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The Neuromodulation Appropriateness Consensus Committee. Neuromodulation 2014;17(6):515–50; discussion 550.

6. De Ridder D, Vanneste S. Visions on the future of medical devices in spinal cord stimulation: What medical device is needed? Expert Rev Med Devices 2016;13(3):233–42.

7. Deer TR, Campos LW, Pope JE. Evaluation of Abbott's BurstDR stimulation device for the treatment of chronic pain. Expert Rev Med Devices 2017;14(6):417–22.

8. De Ridder D, Perera S, Vanneste S. Are 10 kHz stimulation and burst stimulation fundamentally the same? Neuromodulation 2017;20(7):650–3.

9. Li S, Farber JP, Linderoth B, et al. Spinal cord stimulation with "conventional clinical" and higher frequencies on activity and responses of spinal neurons to noxious stimuli: An animal study. Neuromodulation 2018;21(5):440–7.

10. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. Int Rev Neurobiol 2012;107:87–119.

11. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: Review and update. Neuromodulation 1999;2(3):150–64.

12. West SJ, Bannister K, Dickenson AH, et al. Circuitry and plasticity of the dorsal horn–toward a better understanding of neuropathic pain. Neuroscience 2015;300:254–75.

13. Bhadra N, Foldes E, Vrabec T, et al. Temporary persistence of conduction block after prolonged kilohertz frequency alternating current on rat sciatic nerve. J Neural Eng 2018;15(1):016012.

14. Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. Neuromodulation 2014;17(3):242–54; discussion 254–5.

15. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. Muscle Nerve 2005;32(6):782–90.

16. Cui J-G, O'Connor WT, Ungerstedt U, et al. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. Pain 1997;73(1):87–95.

17. Lind G, Schechtmann G, Winter J, et al. Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: Long-term outcome of a pilot study. Eur J Pain 2008;12(1):132–6.

18. Kumar K, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: A 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008;63(4):762–70; discussion 770.

19. Kumar K, North R, Taylor R, et al. Spinal cord stimulation vs. conventional medical management: A prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). Neuromodulation 2005;8(4):213–8.

20. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007;132(1):179–88.

21. Deer T, Pope J, Hayek S, et al. Neurostimulation for the treatment of axial back pain: A review of mechanisms, techniques, outcomes, and future advances. Neuromodulation 2014;17(Suppl 2):52–68.

22. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: The SENZA-RCT randomized controlled trial. Anesthesiology 2015;123(4):851–60.

23. Deer T, Slavin KV, Amirdelfan K, et al. Success using neuromodulation with BURST (SUNBURST) study: Results from a prospective, randomized controlled trial using a novel burst waveform. Neuromodulation 2018;21(1):56–66.

24. Chakravarthy K, Kent AR, Raza A, Xing F, Kinfe TM. Burst spinal cord stimulation: Review of preclinical studies and comments on clinical outcomes. Neuromodulation 2018;21(5):431–9.

25. Chakravarthy K, Richter H, Christo PJ, et al. Spinal cord stimulation for treating chronic pain: Reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. Neuromodulation 2018;21(1):10–8.

26. Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. Neurosurgery 2016;79(5):667–77.

27. Nunemaker CS, Satin LS. Episodic hormone secretion: A comparison of the basis of pulsatile secretion of insulin and GnRH. Endocrine 2014;47(1):49–63.

28. Nunemaker CS, Satin LS. A tale of two rhythms: A comparative review of pulsatile endocrine systems regulating insulin and GnRH secretion. Cell Sci Rev 2005;2:92–126.

29. Swadlow HA, Gusev AG. The impact of 'bursting' thalamic impulses at a neocortical synapse. Nat Neurosci 2001;4(4):402–8.

30. Sherman SM. Tonic and burst firing: Dual modes of thalamocortical relay. Trends Neurosci 2001;24(2):122–6.

31. Shyu BC, Vogt BA. Short-term synaptic plasticity in the nociceptive thalamic-anterior cingulate pathway. Mol Pain 2009;5:51.

32. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: Different and common brain mechanisms. Neuromodulation 2016;19(1):47–59.

33. Shum FWF, Wu L-J, Zhao M-G, et al. Alteration of cingulate long-term plasticity and behavioral sensitization to inflammation by environmental enrichment. Learn Mem 2007;14(4):304–12.

34. Remy S, Spruston N. Dendritic spikes induce single-burst long-term potentiation. Proc Natl Acad Sci U S A 2007;104(43):17192–7.

35. Crosby ND, Weisshaar CL, Smith JR, et al. Burst and tonic spinal cord stimulation differentially activate GABAergic mechanisms to attenuate pain in a rat model of cervical radiculopathy. IEEE Trans Biomed Eng 2015;62(6):1604–13.

36. Tang R, Martinez M, Goodman-Keiser M, et al. Comparison of burst and tonic spinal cord stimulation on spinal neural processing in an animal model. Neuromodulation 2014;17(2):143–51.

37. Gong WY, Johanek LM, Sluka KA. A comparison of the effects of burst and tonic spinal cord stimulation on hyperalgesia and physical activity in an animal model of neuropathic pain. Anesth Analg 2016;122(4):1178–85.

38. Crosby ND, Goodman Keiser MD, Smith JR, et al. Stimulation parameters define the effectiveness of burst spinal cord stimulation in a rat model of neuropathic pain. Neuromodulation 2015;18(1):1–8; discussion 8.

39. Kent AR, Weisshaar C, Agnesi F, Kramer J, Winkelstein BA. Measurement of evoked compound action potentials during burst and tonic spinal cord stimulation. Paper presented at: 20th Annual North American Neuromodulation Society Meeting (NANS); Jan 19–22, 2017; Las Vegas, NV.

40. Kent AR, Venkatesan L, Kramer J, Min X. Dorsal column fiber response is dependent on the temporal pattern of burst spinal cord stimulation. Paper presented at: 20th Annual North American Neuromodulation Society Meeting (NANS); Jan 19–22, 2017; Las Vegas, NV.

41. Zhang TC, Janik JJ, Grill WM. Modeling effects of spinal cord stimulation on wide-dynamic range dorsal horn neurons: Influence of stimulation frequency and GABAergic inhibition. J Neurophysiol 2014;112(3):552–67.

42. Cui JG, Linderoth B, Meyerson BA. Effects of spinal cord stimulation on touch-evoked allodynia involve GABAergic mechanisms. An experimental study in the mononeuropathic rat. Pain 1996;66(2):287–95.

43. Stiller CO, Cui JG, O'Connor WT, et al. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. Neurosurgery 1996;39(2):367–74; discussion 374–5.

44. Sato KL, King EW, Johanek LM, et al. Spinal cord stimulation reduces hypersensitivity through activation of opioid receptors in a frequency-dependent manner. Eur J Pain 2013;17(4):551–61.

45. Sivanesan E, Maher DP, Raja SN, Linderoth B, Guan Y. Supraspinal mechanisms of spinal cord stimulation for modulation of pain: Five decades of research and prospects for the future. Anesthesiology 2019;130(4):651–65.

46. Guan Y, Wacnik PW, Yang F, et al. Spinal cord stimulation-induced analgesia: Electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010;113(6):1392–405.

47. Heinricher MM, Tavares I, Leith JL, et al. Descending control of nociception: Specificity, recruitment and plasticity. Brain Res Rev 2009;60(1):214–25.

48. Chen T, Taniguchi W, Chen QY, et al. Top-down descending facilitation of spinal sensory excitatory transmission from the anterior cingulate cortex. Nat Commun 2018;9(1):1886.

49. Weisshaar CL, Kent AL, Venkatesan L, Winkelstein BA. High-frequency and burst SCS on acute spinal neuronal activity in a rat model of painful radiculopathy. Paper presented at: Annual Meeting of the North American Neuromodulation Society (NANS); January 19–22, 2017, Las Vegas, NV.

50. Falowski SM. An observational case series of spinal cord stimulation waveforms visualized on intraoperative neuromonitoring. Neuromodulation 2019; 22(2):219–28.

51. Bocci T, et al. Neurophysiological comparison among tonic, high frequency, and burst spinal cord stimulation: Novel insights into spinal and brain mechanisms of action. Neuromodulation 2019;22(2):219–28.

52. Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38(2):86–95.

53. Ahmed S, Yearwood T, De Ridder D, et al. Burst and high frequency stimulation: Underlying mechanism of action. Expert Rev Med Devices 2018;15(1):61–70.

54. Morton DL, Sandhu JS, Jones AK. Brain imaging of pain: State of the art. J Pain Res 2016;9:613–24.

55. Rainville P, et al. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997;277(5328):968–71.

56. Rasche D, Siebert S, Stippich C, et al. Spinal cord stimulation in failed-back-surgery-syndrome. Preliminary study for the evaluation of therapy by functional magnetic resonance imaging (fMRI) [in German]. Schmerz 2005;19(6):497–500, 502–5.

57. Stancak A, et al. Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome patients. Eur J Pain 2008;12(2):137–48.

58. Moens M, Sunaert S, Mariën P, et al. Spinal cord stimulation modulates cerebral function: An fMRI study. Neuroradiology 2012;54(12):1399–407.

59. Moens M, Droogmans S, Spapen H, et al. Feasibility of cerebral magnetic resonance imaging in patients with externalised spinal cord stimulator. Clin Neurol Neurosurg 2012;114(2):135–41.

60. Deogaonkar M, Sharma M, Oluigbo C, et al. Spinal cord stimulation (SCS) and functional magnetic resonance imaging (fMRI): Modulation of cortical connectivity with therapeutic SCS. Neuromodulation 2016;19(2):142–53.

61. De Ridder D, Vanneste S. Does tonic spinal cord stimulation really influence the medial pain system? Neuromodulation 2016;19(2):227–8.

62. Yearwood TL, Falowski S, Venkatesan L, Vanneste S. Comparison of neural activity in chronic pain patients during tonic and burst spinal cord stimulation: A SUNBURST sub-study. Paper presented at: North American Neuromodulation Society and the Neural Interfaces Conference (NANS-NIC); June 25–29, 2016; Baltimore, MD.

63. De Ridder D, Vanneste S, Plazier M, et al. Mimicking the brain: Evaluation of St Jude Medical's prodigy chronic pain system with burst technology. Expert Rev Med Devices 2015;12(2):143–50.

64. De Ridder D, Plazier M, Kamerling N, et al. Burst spinal cord stimulation for limb and back pain. World Neurosurg 2013;80(5):642–9.e1.

65. Kulkarni B, Bentley DE, Elliott R, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci 2005;21(11):3133–42.

66. Shyu BC, Vogt BA. Short-term synaptic plasticity in the nociceptive thalamic-anterior cingulate pathway. Mol Pain 2009;5:51.

67. Cohen AS, Coussens CM, Raymond CR, et al. Long-lasting increase in cellular excitability associated with the priming of LTP induction in rat hippocampus. J Neurophysiol 1999;82(6):3139–48.

68. De Ridder D, Vanneste S, van der Loo E, et al. Burst stimulation of the auditory cortex: A new form of neurostimulation for noise-like tinnitus suppression. J Neurosurg 2010;112(6):1289–94.

69. Meeus O, Blaivie C, Ost J, et al. Influence of tonic and burst transcranial magnetic stimulation characteristics on acute inhibition of subjective tinnitus. Otol Neurotol 2009;30(6):697–703.

70. De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A. Theta, alpha and beta burst transcranial magnetic stimulation: Brain modulation in tinnitus. Int J Med Sci 2007;4(5):237–41.

71. Schu S, Slotty PJ, Bara G, et al. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation 2014;17 (5):443–50.

72. Kriek N, Groeneweg JG, Stronks DL, et al. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. Eur J Pain 2017;21 (3):507–19.

73. Colagiuri B, Schenk LA, Kessler MD, et al. The placebo effect: From concepts to genes. Neuroscience 2015;307:171–90.

74. Grace PM, Hutchinson MR, Maier SF, et al. Pathological pain and the neuroimmune interface. Nat Rev Immunol 2014;14(4):217–31.

75. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 2009;10(1):23–36.

76. Muhammad S, Chaudhry SR, Yearwood TL, et al. Changes of metabolic disorders associated peripheral cytokine/adipokine traffic in non-obese chronic back patients responsive to burst spinal cord stimulation. Neuromodulation 2018;21(1):31–7.

77. Kinfe TM, Muhammad S, Link C, et al. Burst spinal cord stimulation increases peripheral antineuroinflammatory interleukin 10 levels in failed back surgery syndrome patients with predominant back pain. Neuromodulation 2017;20(4):322–30.

78. Lind A-L, Wu D, Freyhult E, et al. A multiplex protein panel applied to cerebrospinal fluid reveals three new biomarker candidates in ALS but none in neuropathic pain patients. PLoS One 2016;11 (2):e0149821.

79. Holsheimer J, Buitenweg JR. Review: Bioelectrical mechanisms in spinal cord stimulation. Neuromodulation 2015;18(3):161–70; discussion 170.

80. Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: Analysis of technical drawbacks and solutions. Neurosurgery 1997; 40(5):990–6; discussions 996–9.

81. Van Havenbergh T, Vancamp T, Van Looy P, et al. Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. Neuromodulation 2015;18(1):9–12; discussion 12.

82. Vesper J, Schu S, Slotty P, Poeggel-Kraemer K, Littges H, Van Looy P, Agnesi F, Venkatesan L, Van Havenberg T. BurstDR^{TM} microdosing is as efficacious as standard BurstDR^{TM} in treating chronic back and leg pain. Paper presented at: Annual Meeting of the North American Neuromodulation Society; Jan 11–14, 2018; Las Vegas, NV.

83. Weisshaar CL, Kent AR, Venkatesan L, Winkelstein BA. Comparison of burst SCS paradigms on acute spinal neuronal activity in a rat model of painful radiculopathy. Paper presented at: American Society of Regional Anesthesia and Pain Medicine (ASRA); Nov 17–19, 2016; San Diego, CA.