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Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms

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1. Introduction

Neuropathic pain is a complex, heterogeneous disorder that affects approximately 8% of the total adult human population and comes with significant burden for both the patient and health care system.[13] The international association for the study of pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" and classifies chronic neuropathic pain as a disease under *International Classification of Diseases 11th Revision* (*ICD-11*).[89] Despite the development and use of many pharmacological drugs and guidelines for the treatment of chronic neuropathic pain over the years,[8] a substantial amount of neuropathic pain patients remain undertreated or untreated, with less than 50% of patients responding to pharmacological treatment.[30] The development of novel, last-resort interventional treatment therapies is crucial to also relief pain in these refractory patients.

Over the years, spinal cord stimulation (SCS) has proven to be a valuable last-resort treatment option (approximately 50% pain reduction in 50%-70% of patients) for a wide variety of refractory pain disorders, such as painful diabetic peripheral neuropathy (PDPN),[22,94] complex regional pain syndrome (CRPS),[42,43] and failed back surgery syndrome (FBSS).[53,77] The mechanism underlying Tonic SCS (see section 2) is partly understood, and evidence has been provided for a mechanism of action through both spinal (section 2.1) and supraspinal levels (section 2.2). Recently, new physiological targets for stimulation as well as novel SCS paradigms were introduced to bridge the gap between currently achieved pain relief (as obtained with Tonic SCS) and the desired pain relief. Literature on the effect of stimulation at new anatomical locations, such as dorsal root ganglion stimulation (DRGS) (see section 3), and the use of new subsensory SCS paradigms such as high-frequency (HF) SCS (see section 4.2) and Burst SCS (see section 4.3) are discussed. This review ends with concluding remarks and future directions for research.

2. Tonic spinal cord stimulation: mechanisms of action

2.1. Tonic spinal cord stimulation and spinal segmental mechanisms

Experimental studies on the effect of SCS have predominantly been performed in rodent models including the partial sciatic nerve ligation model (PSNL) (for review, see Smits et al.[97]). Electrodes are carefully inserted, either transcutaneous or through laminectomy, in the epidural space on top of the dura mater surrounding the spinal cord. Then, electrical pulses are administered to the dorsal columns of the spinal cord through an implantable pulse generator or an external stimulation device. Tonic SCS settings vary within a range of 30 to 80 Hz, 100 to 500 μs of pulse width, and an amplitude above sensory threshold.[71,73,93,97]

The concept of Tonic SCS emerged as a direct spin-off from the gate control theory.[65] Based on this gate control theory, it was postulated that antidromic stimulation of the non-nociceptive Aβ fibers in the dorsal columns could close a "spinal gate," located in the dorsal horn of the spinal cord.[92] Meanwhile, orthodromic stimulation of the Aβ fibers in the dorsal columns also caused paresthesias (ie, abnormal tingling sensation) in the area innervated by the stimulated fibers[9] (**Fig. 1**). Nowadays, during implantation of the SCS lead the physician makes sure these paresthesias overlap the painful area.[9,76] Closing of the "spinal gate" is mediated by inhibitory interneurons located in the upper laminae of the dorsal horn. In line with the gate control theory, these inhibitory interneurons, when antidromically activated by Tonic SCS, modulate the nociceptive signal through the release of gamma-aminobutyric acid (GABA). Indeed, experimental research has demonstrated that Tonic SCS decreases intracellular GABA immunoreactivity in the dorsal horn of chronic neuropathic rats.[39] At the same time, extracellular GABA levels in the spinal dorsal horn increase when applying Tonic SCS in chronic neuropathic rats.[18,61,104] Thus, enhanced GABA release in the spinal dorsal horn seems to be a vital aspect of the mechanisms underlying Tonic SCS. The mechanism underlying interference with nociception at the spinal cord level using Tonic SCS was further elucidated by the administration of pharmacological agents. Local intrathecal application of a $GABA_B$ receptor antagonist in the dorsal horn transiently abolished the stimulation-induced analgesic effect in neuropathic rats, and rats not receiving adequate reductions in tactile allodynia with Tonic SCS (non-responders) were turned into responders by administration of the $GABA_B$ receptor agonist baclofen.[17] The aforementioned preclinical

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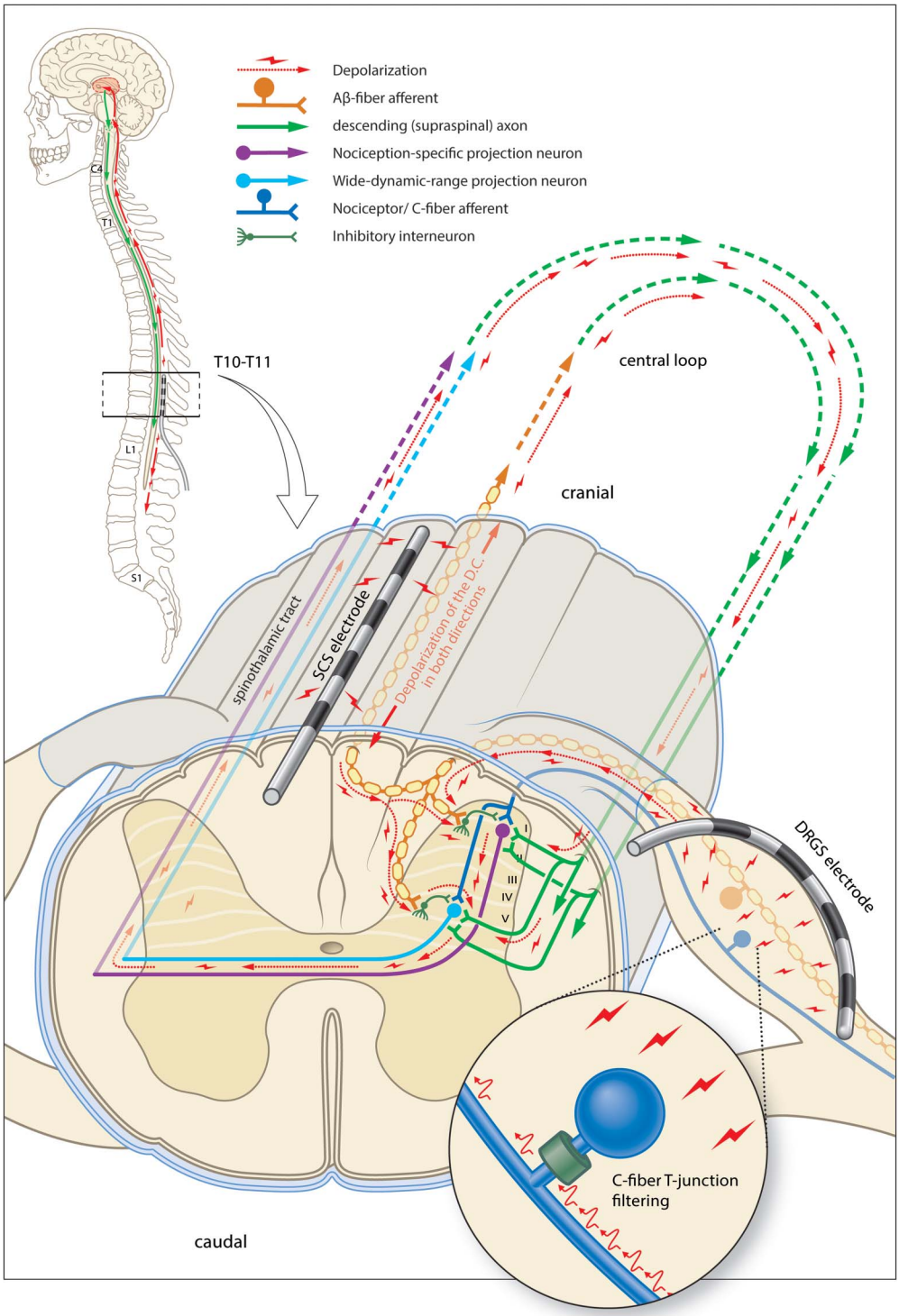

Figure 1. The spinal nociceptive network and mechanisms of action of SCS of the dorsal columns and DRGS. The spinal cord dorsal horn contains 2 types of second-order projection neurons: the nociceptive-specific (NS) projection neurons located in lamina I and the wide-dynamic range (WDR) projection neurons located in the deeper laminae. These projection neurons receive input from nociceptive afferents, but also from thickly myelinated, touch-affiliated, Aβ fiber afferents. Spinal cord stimulation (electrode placed on top of the dorsal columns) is believed to depolarize the touch-affiliated Aβ fibers, and this can occur in both the antidromic and orthodromic directions. Antidromically, SCS can activate GABAergic inhibitory interneurons located in the dorsal horn. Consequently, these inhibitory interneurons release GABA, which, after binding to its GABA receptor (either to $GABA_B$ or $GABA_A$ presynaptically or postsynaptically), inhibits the incoming signals from nociceptors and thereby closes the "spinal gate." In addition, SCS can also interfere with further processing of the nociceptive signal through the spinothalamic tract, thereby modulating supraspinal brain centers such as the thalamus, somatosensory cortex, cingulate cortex, and insula. Orthodromically, SCS can also depolarize Aβ fibers in the cranial direction, thereby further modulating supraspinal centers like the cuneate nucleus or gracile nucleus. After supraspinal integration of the signal, a descending feedback loop of both serotonergic and noradrenergic projections to the dorsal spinal horn further modulates and controls the "spinal gate." Dorsal root ganglion stimulation (electrode placed on top of the DRG) might engage mechanisms dependent on stimulation of non-nociceptive Aβ fibers (as occurs in SCS) as well as stimulation of nociceptive C fibers in the DRG. Recent studies suggest that DRGS may induce a conduction block through the C-type T-junction located in the DRG itself. This T-junction can act as a low-pass filter for action potentials (nociceptive signals) travelling from the periphery to the spinal cord. SCS, spinal cord stimulation; DRGS, dorsal root ganglion stimulation; GABA, gamma-aminobutyric acid.

findings were successfully translated to the clinic, where some neuropathic pain patients not responding to Tonic SCS were turned into responders with additional intrathecal administration of low (subeffective) doses of baclofen.[59,60,88] Hence, the presynaptic $GABA_B$-mediated inhibition of the communication between nociceptive afferents and the second-order neurons in the spinal dorsal horn is important in the mechanism underlying Tonic SCS. Nevertheless, also postsynaptic GABAergic modulation through $GABA_A$ receptors in conjunction with K^+/Cl^- cotransporter 2 (KCC2) expression is involved in neuropathic pain[15] and in the mechanism underlying Tonic SCS.[17,39,40]

A decreased GABA release as noted in animal models of neuropathic pain results in further enhanced and uncontrolled glutamate release of the nociceptive afferents, which in turn activates and opens the N-methyl-D-aspartate (NMDA) receptor due to removal of the Mg^{2+} block. Enhanced Ca^{2+} influx through the NMDA receptor then leads to central sensitization, which is a process fundamental to neuropathic pain.[119] From this, it was suggested that interference with the process of central sensitization through antagonism of the NMDA receptor might attenuate chronic neuropathic pain, a process that may also be involved in the antidromic mechanism underlying Tonic SCS. Indeed, a combined treatment of Tonic SCS and the intrathecal application of a subeffective dose of ketamine (a NMDA antagonist replacing the Mg^{2+} block) has been shown to convert SCS nonresponders into responders in a rat model of chronic neuropathic pain.[109] It needs to be stressed that these experimental findings have not yet been implemented and/or confirmed in clinical studies. Importantly, intrathecal administration of ketamine was shown to result in severe histological abnormalities, including central chromatolysis, nerve cell shrinkage, neuronophagia, microglial upregulation, and gliosis in a patient suffering from chronic intractable neuropathic pain.[116] Although it is very well possible that subeffective doses of ketamine can in fact be safely used in a clinical setting, more research is needed as to determine safe intrathecal administration dosages.

The main goal of Tonic SCS in the treatment of (experimental) chronic neuropathic pain is to stimulate the thickly myelinated Aβ fibers in the dorsal columns. It can, however, not be excluded that also incoming dorsal root fibers, including C and Aδ fibers, are directly stimulated through the relatively large-sized experimental electrodes as used in rodent studies.[97] This possible involvement of dorsal root fibers and the dorsal root as the site of action is further substantiated by electrophysiological analysis where not only stimulation of the dorsal column but also stimulation of the dorsal root attenuated dorsal horn neuronal hyperexcitability in nerve-injured rats.[33]

Although Tonic SCS and its spinal mechanisms are partly uncovered, recent studies indicate that much more complicated interactions and cell types are involved. Tonic SCS causes long-term depression of excitatory synaptic transmission in the superficial dorsal horn (lamina II), and this depression is blocked by antagonists of cannabinoid receptor type 1 (CB1).[91] Furthermore, the intrathecal application of AM251, a CB1 receptor antagonist, was able to block SCS-mediated reversal of mechanical hypersensitivity in rats.[105] The CB1 receptor is located on microglial cells,[105] which indicates that the endocannabinoid system, and in particular the CB1 receptor, plays a pivotal role in the reversal of hyperalgesia induced by SCS, and links the mechanism underlying Tonic SCS analgesia to glia-mediated control of nociception.[38]

2.2. Tonic spinal cord stimulation and suprasegmental mechanisms

Once activated, supraspinal cell regions are known to modulate the incoming nociceptive signals at the spinal level through descending fiber projections. Brainstem nuclei such as the locus coeruleus and the nucleus raphe magnus, but also the rostral ventromedial medulla, are activated by Tonic SCS and in turn modulate the spinal nociceptive signal (**Fig. 1**). The descending projections release a variety of neurotransmitters including serotonin (5-HT), which exerts an inhibitory effect (based on the receptor involved) on the incoming nociceptive fibers,[72,86,99,102,108] and this maintains long-term neuropathic pain.[117] Further detailed research on the spinal 5-HT receptors that contribute to the pain-relieving effects of Tonic SCS in chronic neuropathic rats was performed, and with use of intrathecal application of antagonists and agonists for the various serotonin receptors, it was shown that the activation of the 5HT-3 receptor seems to operate through spinal GABAergic interneurons.[101]

First evidence for a role of suprasegmental mechanisms underlying Tonic SCS was presented by El-Khoury et al.,[26] who demonstrated that Tonic SCS of the dorsal column nuclei reduces allodynia and hypersensitivity in an experimental model of chronic neuropathic pain, even after dorsal column transection below these nuclei. From this, it was suggested that the observed inhibition in terms of allodynia and hypersensitivity responses can be attributed to the activation of brainstem pain-modulating centers through rostral projections of the dorsal column nuclei.

That Tonic SCS can also modulate activation patterns in brain areas at subcortical and cortical levels has been shown in a rodent model of chronic neuropathic pain.[66,70] How Tonic SCS alters cortical processing has also been shown by clinical studies using imaging approaches such as functional magnetic resonance imaging (fMRI), positron-emission tomography, single-photon emission computed tomography, and 133-Xe inhalation (reviewed in Bentley et al.[11]). These cortical changes during Tonic SCS may represent direct effects from dorsal column stimulation or inhibition of nociceptive signals arising from the periphery, or they may reflect complex modulatory effects on somatosensory and affective processing. Early clinical fMRI work on the supraspinal effects of Tonic SCS has demonstrated modulation of brain regions associated with the lateral spinothalamic tract (l-STT).[46,52] The l-STT is responsible for the transmission of pain aspects such as the intensity and location of the painful stimulus. This l-STT pathway projects from the dorsal horn, through the thalamus, to cortical areas such as the somatosensory cortex.[10] An fMRI study performed in 8 patients receiving Tonic SCS demonstrated that this type of stimulation of the dorsal columns increased blood–oxygen level-dependent signals in somatosensory cortices, the sensorimotor cortex, and the insula.[52] Furthermore, a more recent fMRI study with 20 patients, who received Tonic SCS as treatment for FBSS, reported deactivation of the bilateral medial thalamus and its connections to the rostral and caudal cingulate cortex, and the insula.[74] In conclusion, over the years, literature on Tonic SCS has provided evidence for a mechanism of action through both spinal and supraspinal levels.

2.3. Tonic spinal cord stimulation and translation of experimental studies

It should be noted that most preclinical studies still rely on behavioral analysis based on Von Frey paw withdrawal testing, a technique unable to assess supraspinal cognitive-motivational aspects of pain.[123] Although the peripheral nerve injuries as used in experimental animal studies do definitely result in chronic pain, the rather exclusive use of Von Frey testing is much more related to assessment of nociception instead of pain.[12] This may underlie

the limited translation of experimental findings to the clinic.[115,123] Recently, an operant testing method was introduced, which assesses cognitive and motivational aspects of pain in rodents: the Mechanical Conflict-Avoidance System (MCAS).[34] With use of MCAS, Tonic SCS was shown to affect also the cognitive-motivational aspects of the presumed pain in chronic neuropathic rats.[70] This indicates that Tonic SCS, in addition to local spinal modulation, also recruits supraspinal brain areas, a finding further substantiated by fMRI analysis of brain areas including the anterior cingulate cortex (ACC).[66] These findings make clear that operant behavioral testing should be considered when analyzing the analgesic effects of SCS in chronic neuropathic pain because this is not only likely to increase the translation of experimental findings to the clinic but will also help to better understand the underlying mechanisms of action.

In addition, also other discrepancies between humans and rodents may impact direct translation of laboratory findings to the clinic. These include the standardized models used (in comparison with heterogeneous clinical populations), the use of motor thresholds (instead of perception thresholds in humans) for determining stimulation amplitude, the size of the electrode in relation to the dorsal columns (typically larger in rodents), differences in dorsal column anatomy, and the thickness of the cerebrospinal fluid layer that lies between the SCS lead and dorsal column fibers.[97] Therefore, it is important to always carefully consider these discrepancies when trying to extrapolate preclinical findings to the clinic.

2.4. Tonic spinal cord stimulation: which dorsal column fibers are stimulated?

Although both spinal and supraspinal activation are involved in Tonic SCS, it has been demonstrated that Tonic SCS results in greater reductions of mechanical allodynia in the rat when administered at the level where the injured sciatic nerve fibers enter the spinal dorsal horn (=T13), as compared to application at more rostral levels (=T11).[98] The anatomy of the dorsal column in the rat spinal cord makes the Aβ fibers initially localized dorsolateral within the columns at T13 (where injured fibers enter) but then rearranged to ventromedial positions at more rostral levels (T11).[95,98] Most ascending dorsal column Aβ fibers were also found to be lost from the dorsal columns, and only 15% reaches cervical levels.[95] Furthermore, computer modelling and calculations on the fraction of dorsal column fibers that are actually being stimulated (and depolarized) by Tonic SCS found that this is not likely to exceed 1% of the most superficially (dorsally) located afferents because the ability of the SCS electrode to depolarize dorsal column fibers decreases to the third power of the distance from the electrode.[35,36] As the behavioral findings on pain relief of Tonic SCS in a model of chronic neuropathic pain[98] are in line with the aforementioned anatomical and physiological principles, it is concluded that Tonic SCS primarily acts through a segmental, spinal, site of action (**Fig. 1**).

In the context of dorsal column anatomy, it should be stressed that these fiber systems not only include large myelinated Aβ fibers but also contain even larger numbers of unmyelinated fibers in the rat[54] and human,[87] something that is often neglected. Because of the importance of the dorsal columns in somatic sensation, and as the origin of these unmyelinated fibers is still not fully understood, it is extremely important to understand where these fibers originate. Although the unmyelinated fibers may belong to various categories including proprioceptive, corticospinal, or fibers descending from cells in the nucleus gracilis or cuneate,[54,75] unilateral dorsal root transection revealed that a significant fraction of the unmyelinated fibers in the fasciculus gracile ascend, presumably to the nucleus gracilis in the brain stem, and also that a significant number of these fibers branch.[81] Moreover, based on pharmacological intervention studies, it is strongly suggested that, at least at cervical levels, a subset of these unmyelinated fibers might be nociceptive and involved in noxious processing.[80] This then may shed a more complicated view on the mechanism underlying Tonic SCS because not only non-nociceptive Aβ fibers but also nociceptive unmyelinated C fibers are stimulated. In this context, it is interesting that a detailed protocol for the identification of superficial dorsal horn spinal cord neurons that receive peripheral input and project to the brain was recently presented.[96] This may allow for further identification of not only nociceptive-specific cells in the dorsal horn but also their possible (unmyelinated) ascending projections in the dorsal column.

2.5. Tonic spinal cord stimulation: limitations

Despite considerable improvements, there are, however, limitations to the efficacy of Tonic SCS. First, only 50% to 70% of patients with PDPN, CRPS, or FBSS achieve pain reductions of ≥50%.[22,42,43,53,77,94] Second, the average pain reduction is restricted to approximately 50% to 60%.[22,42,43,53,77,94] Third, Tonic SCS is often unable to satisfactory and specifically stimulate difficult-to-reach areas, such as the extremities or the groin. Fourth, placement of the leads on top of the dorsal columns makes this therapy susceptible to postural variations due to changes in distance between stimulation lead and stimulation target, leading to unpleasant paresthesias and/or overstimulation.[97] Last, with Tonic SCS, there is significant energy loss to the local environment such as the cerebrospinal fluid, before the electrical energy (charge) reaches the spinal cord dorsal columns.[73] It is important to note that recent developments in the field of SCS may result in overcoming these limitations. These developments will be discussed as related to either the use of new locations for stimulation (see section 3) and/or the use of new SCS paradigms (see section 4).

3. New stimulation location: the dorsal root ganglion

With DRGS, the leads are transcutaneously implanted in the epidural space on top of the dura mater surrounding the spinal cord but are then advanced laterally through the intervertebral foramen, to place the lead over the DRG of interest. Since the first fully implanted DRGS system in 2013,[58] DRGS has been successfully implemented for a wide variety of neuropathic pain disorders, including, but not limited to, discogenic low back pain,[37] CRPS type I and II,[24] postamputation pain,[27] and PDPN.[28] Yet, only one randomized clinical trial (RCT) on DRGS has been published to date.[24] This study found DRGS to be noninferior and superior to Tonic SCS for treating chronic intractable pain of the lower limbs attributed to CRPS type I and II. In addition, patients receiving DRGS were found to have less therapy habituation as compared to patients treated with Tonic SCS at 9 and 12 months.[57] Also the amount and intensity of paresthesias were found to be less with DRGS over Tonic SCS, and DRGS was found to be more stable in response to changes in body position as compared to Tonic SCS.[23] Finally, some DRGS patients even achieved paresthesia-free analgesia.[63]

Mechanistically, it was initially assumed that DRGS engages the spinal mechanisms dependent on stimulation of non-nociceptive Aβ fibers and GABA release in the dorsal horn of

the spinal cord as occurs in Tonic SCS of the dorsal columns. Although a recent computational study indeed suggested that DRGS may inhibit nociception by activating pain-gating mechanisms in the dorsal horn through repeated activation of large myelinated (Aβ) afferents,[31] another study found that the pain-relieving effect of DRGS is not likely to be dependent on GABA release in the spinal dorsal horn at the L4-L6 lumbar level.[47] Some experimental studies suggest that, instead, DRGS suppresses excitability of neurons with predominantly slow-conducting nociceptive fibers (C fibers).[44,48] Because of the unique pseudounipolar design of DRG neurons, the DRG is likely to act as an impediment or low-pass filter to electrical impulses traveling from the peripheral nociceptor to the spinal cord in response to electrical stimulation (**Fig. 1**).[44,48,49] Interestingly, a recent study by Du et al. found an extensive GABAergic communication network between sensory neuron somata inside the DRG. These authors showed that sensory neurons in the DRG express major proteins required for GABA synthesis and release and are capable of releasing GABA upon depolarization. From this, it was proposed that this GABAergic system in the DRG may act as a second gate, in addition to the aforementioned gate control theory (or first gate), and that DRGS might exert its analgesic action by engaging this second gate.[25] This proposed conduction block at the site of the DRG is consistent with the observation that DRGS attenuates blood–oxygen level-dependent signals of brain areas that are considered to be part of the pain matrix including the contralateral thalamic nuclei, and cortical S1 and S2 that were increased by noxious hind-limb stimulation in rats.[82]

Although promising, the therapeutic efficacy of DRGS should be confirmed and verified in additional large-scale RCTs including different pain etiologies. Future experimental studies are also needed to unravel the underlying mechanisms of DRGS, including the role of a hypothetical second (GABAergic) gate in the DRG itself.

4. The use of new spinal cord stimulation paradigms: high-frequency spinal cord stimulation and Burst spinal cord stimulation

4.1. Introduction

Next to novel physiological targets for stimulation, novel SCS paradigms were introduced to bridge the gap between currently achieved and desired pain relief. Two prominent examples, HF SCS and Burst SCS, were recently introduced to try to optimize the efficacy of SCS treatment for chronic neuropathic pain.[4,6,20,21,50,93,100,112] Both HF SCS and Burst SCS are generally applied at stimulation amplitudes below sensory threshold, which means the patient does not experience paresthesias during stimulation. This has offered researchers, for the first time since (Tonic) SCS was introduced in 1967,[92] the opportunity to perform double-blind placebo-controlled clinical studies.[2,19,51,83,90]

4.2. High-frequency spinal cord stimulation in neuropathic pain

High-frequency SCS is generally applied at a frequency above 1000 Hz, up until 10 kHz, with a pulse width at approximately 30 μs and an amplitude of typically 1 to 5 mA.[41] Hypotheses about the underlying mechanism of HF SCS vary.

Although Tonic SCS and its pain inhibition is accompanied by paresthesias, the subthreshold HF SCS paradigm is paresthesia-free (administered below sensory threshold) and does not activate or change the conduction properties of the dorsal column Aβ fibers.[14,45,55] Experimental research has shown that the dorsal column nuclei are activated with use of Tonic SCS, while with subthreshold HF SCS, the neurons in the gracile nucleus do not show a reduction of evoked responses upon peripheral stimulation in a chronic neuropathic pain model.[103] A hypothetical mechanism for HF SCS and its pain-relieving effect was brought forward by Chakravarthy et al., who suggested that the electrical current applied to the spinal cord surface may generate a weak and localized electric field of electrochemical disturbance in the spinal dorsal horn and dorsal root entry zone.[14,73] Hence, HF SCS in fact desynchronizes the communication between the nociceptive C fibers, which mainly terminate in the dorsal horn superficial laminae (Lamina 1-3), and the nociceptive specific neurons (**Fig. 1**). Besides the generation of a weak electrical field in the superficial dorsal horn, the hypotheses about the underlying mechanism of HF SCS also include (1) temporal summation which could play a role, where multiple pulses build on each other to achieve neuronal activation, and (2) a depolarization blockade that might occur and where propagating action potentials are differentially blocked by the HF stimulation.[7,14,45,73,122]

Until today, the optimal frequency for HF SCS has not yet been determined, and clinical evidence suggests that different HF SCS frequencies can yield clinically significant pain relief.[2–4,41,112]

4.3. Burst spinal cord stimulation in neuropathic pain

The Burst paradigm was introduced in 2010 by de Ridder et al.[21] This Burst waveform consists of 5 closely spaced monophasic spikes administered at 40 Hz interburst mode and 500 Hz intraburst frequency, with a pulse width of 1 ms and 1 ms interspike interval, delivered in constant current mode. The cumulative charge of the five 1 ms spikes is balanced during the 5 ms after the spikes, in a so-called passive recharge phase, which differentiates it from HF SCS and Tonic SCS, in which each pulse is immediately charge balanced after each spike, in a so-called active recharge phase.[19,21,50] This Burst pattern was chosen because it supposedly mimics naturally occurring neural bursting patterns in the central nervous system. Indeed, neurons responsible for encoding aspects of nociception from peripheral neurons[5,120,121] and the thalamus[29,56,85] have been reported to fire in bursting patterns. Although possible overlap between the original Burst waveform (as proposed and used by De Ridder et al.)[19,21] and the neural bursting patterns in the central nervous system, it is important to note that Burst parameters have not yet been optimized in relation to pain-relieving capacity because the parameter space has not been fully explored. For instance, effect differences of active vs passive charge recovery have not been characterized. Beyond charge recovery, many other parameters can be varied: interburst frequency, intraburst frequency, pulse width, shape of pulse, but also the number of pulses. Future research is needed to optimize burst programming as well as to elucidate how the physiological changes produced by different Burst SCS paradigms are reflected in preclinical behavior and in the clinic.[32]

Like HF SCS, the Burst paradigm has been reported to produce pain relief without inducing paresthesias in most patients, suggesting that stimulation is not activating dorsal column Aβ fibers.[16,107] However, although stimulation at low amplitude may be subthreshold with respect to neuronal activation, and subperception with respect to the patient's experience, large amounts of charge are still delivered to dorsal horn fibers, providing the pulse width and/or frequency are sufficiently large.[73] This could potentially set in motion additional

dorsal horn mechanisms that are not activated with suprathreshold Tonic SCS. Yet, the key difference between Tonic SCS and Burst SCS is believed to be located higher up the neuraxis, at supraspinal levels. Clinical evidence suggests that Burst SCS not only stimulates sensorimotor cortex areas through the l-STT (known to be involved in localization and intensity of pain), but also specifically stimulates the medial STT (m-STT), which is known to target limbic brain areas involved in cognitive-motivational and emotional aspects of pain, such as the amygdala, the ACC, and the insula.[19,20] In addition, it was found that Burst SCS improves pain aspects, including "the amount of attention patients pay to pain" as well as "changes in pain," as assed by the Pain Vigilance and Awareness Questionnaire, to a greater degree than Tonic SCS or placebo stimulation.[19] Interestingly, although Burst SCS resulted in significantly more improvement in terms of limb and back pain than placebo on the Visual Analog Scale, no significant differences between Burst and Tonic SCS were observed in terms of Visual Analog Scale scores.[19] These findings are further substantiated by the fact that Burst and Tonic SCS do share brain activation patterns of the l-STT as well as descending pain inhibitory pathways.[19,20] Combined, these data suggest that both Burst SCS and Tonic SCS are capable of modulating the l-STT, but Burst SCS adds to this by also modulating the m-STT. Modulation of the m-STT may hereby improve the affective component of the pain experience.

To further elucidate the mechanism underlying Burst SCS and pain relief, experimental studies are needed. As most experimental studies on the effect of Tonic SCS were performed in sciatic nerve injury models including the PSNL model (see section 2.1), it is important to use similar models to adequately compare and correlate findings. As the administration of both bicuculline ($GABA_A$) and phaclofen ($GABA_B$) receptor antagonists abolishes the pain-relieving effect of both Tonic SCS but also Burst SCS in a PSNL rat model of chronic neuropathic pain, it is concluded that Burst SCS, like Tonic SCS, is mediated through spinal GABAergic mechanisms.[67] Because Burst SCS is suggested to modulate structures at a supraspinal levels in a different manner as compared to Tonic SCS,[19,20] it is remarkable that the GABAergic mechanisms underlying these different stimulation waveforms, at least at a spinal level, show similarities.[67] On the other hand, with the use of escape latency in the MCAS,[34] the cognitive-motivational aspects of Burst SCS were analyzed and compared with Tonic SCS in a rat model of chronic neuropathic pain[70] (see also section 2.2). With the MCAS, Burst SCS exit latencies differed significantly from Tonic SCS exit latencies, and from this, it was concluded that Burst SCS specifically affects, much more than Tonic SCS, supraspinal areas responsible for the processing of cognitive-motivational aspects of pain. These findings were further substantiated with fMRI imaging[66]: fMRI analysis of Burst SCS in chronic neuropathic animals showed specific involvement and activation of limbic brain areas including the ACC as well as the amygdala and insula, areas known to be involved in cognitive and emotional aspects of pain. The behavioral and imaging studies on Burst SCS and Tonic SCS in pain relief in a neuropathic animal model strongly suggest that the mechanism underlying Burst SCS significantly differs from that of Tonic, although some overlap in underlying mechanism (eg, GABA release in dorsal spinal horn) does exist.

The fact that Burst SCS has been shown to result in a delayed wash-in and delayed wash-out analgesic effect in a chronic neuropathic pain model as compared to Tonic SCS[68,69] might provide some additional clues about the underlying mechanism. As the Burst SCS paradigm mainly activates ascending pathways including the l-STT and m-STT (**Fig. 1**), it is possible that Burst SCS subsequently modulates descending serotonergic and noradrenergic pathways. The latter may explain the delayed wash-in and wash-out effect observed in experimental studies. Although not substantiated by clinical data, first anecdotal reports on a delayed wash-in of Burst SCS do exist. In addition, results from a recent RCT found that Burst SCS microdosing, a paradigm that relies on the introduction of stimulation-off phases in-between stimulation-on phases, is as effective as standard Burst SCS, indeed indicating a delayed wash-out after Burst SCS.[114] The activation or deactivation of such a large supraspinal loop might take more time as compared to the fast antidromic spinal mechanism known to be pivotal in Tonic SCS (see section 2.1 and **Fig. 1**). Activation of a supraspinal loop implicates signal transfer at various levels in the brain including thalamus,[64] cortical brain areas, but also nuclei involved in the descending part of the loop such as the periaqueductal grey, ventromedio medial medulla, and nucleus raphe,[10,72] as well as signal transfer and distribution over the various cortical areas or pain matrix.[62]

That the mechanism underlying Burst SCS differs from Tonic SCS is further indicated by experimental studies on the effect of pulse amplitude and the suppression of mechanical hypersensitivity in a neuropathic rat model.[69] Burst SCS and mechanical hypersensitivity are characterized by a nonlinear relation effect, where Burst SCS is superior at an amplitude of 50% of motor threshold as compared to amplitudes of 33% and 66% of motor threshold. At the same time, the relation between pulse amplitude and effect with Tonic SCS is linear. Hence, the optimal Burst SCS amplitude (at 50% of motor threshold) was comparable with Tonic SCS at the high intensity (66% of motor threshold) for attenuating mechanical hypersensitivity, and interestingly, the charge delivered per second was much greater for Burst SCS than for Tonic SCS at comparable behavioral outcomes. From this, it is suggested that, with Burst SCS, a complex, nonlinear interplay between charge delivery, activation of neuronal elements, and pain relief does exist.[16,69]

5. Conclusions, future directions, and research agenda

Spinal cord stimulation and in particular Tonic SCS have been shown to represent a safe and effective last-resort therapy for patients with pharmacologically refractory pain conditions, especially those with FBSS, CRPS, and PDPN. Nevertheless, serious limitations exist (see section 2.5). Among the main limitations is that with Tonic SCS, only 50% to 70% of patients with refractory neuropathic pain achieve pain reductions of ≥50%, and the average pain reduction is restricted to approximately 50% to 60%. Then, there is also a loss of efficacy that occurs over short and long durations.[1,43,111] To overcome these limitations, research in the field of SCS and neuropathic pain recently introduced new stimulation locations like DRGS and new subsensory SCS paradigms such as HF SCS and Burst SCS. This increases options for the neuropathic pain patient and, at the same time, allows the possibility for individual and personalized treatment strategies. As the mechanisms of action are only rudimentary understood, and as the efficacy in terms of pain relief with use of these new locations and new SCS paradigms is not significantly surpassing that achieved with Tonic SCS, further research is needed. This then should be based on an orchestrated interplay between (reproducible) experimental animal studies and well-designed large, (preferably) nonindustry-sponsored clinical trials. In this context, the following research questions and research directions, in line with those formulated by the international association for the study of pain

special interest group Neuromodulation, need to be addressed (=research agenda):

(1) What are the segmental and supraspinal circuits involved in SCS? The use of modern, genetically identified cell types (optogenetics) allows further understanding of these circuits. The involvement and role of glial cells is needed and warrants further research.[110]
(2) How do different stimulation paradigms (ie, variations in frequency and/or intensity and/or pulse width) affect the spinal and supraspinal circuits, and what is the impact of the total charge and charge per pulse? As not only HF SCS (see section 4.2) and Burst SCS (see section 4.3), but also other stimulation paradigms such as high-density SCS[84,106,118] and 3D-guided SCS[113] have shown great promise, both experimental studies and large randomized studies are needed to understand and confirm these first and preliminary findings. Also the use of closed-loop SCS devices capable of measuring evoked compound action potentials is encouraged to better understand the relationship between stimulation, electrophysiological response, and neuromodulation, which may then have direct consequences for SCS design and programming.[78,79]
(3) Animal pain research should include operant behavioral testing and should no longer be exclusively based on paw withdrawal testing. Operant testing includes affective-emotional and cognitive aspects of pain and will likely improve clinical translation of findings.
(4) Implementation of imaging techniques (fMRI, positron-emission tomography scan) and correlation of involvement of supraspinal circuits as related to various SCS paradigms and stimulation locations (DRGS) and their effect on pain relief are needed.
(5) It is of utmost importance to understand the anatomy of the dorsal column and the role of unmyelinated (nociceptive) fibers (see section 2.4)

As Tonic SCS has been shown to affect cortical processing and thalamo-cortical communication, and the fact that new SCS paradigms like Burst SCS may specifically activate the m-STT and with that cortical brain areas involved in the motivational, affective, and emotional components of pain makes this therapy also interesting for treatment of pain-related comorbidities such as depression and stress. These comorbidities, also often difficult to treat pharmacologically, are known to be associated to activation of closely related or even similar cortical brain areas. Novel SCS paradigms, for instance, Burst SCS, may form a serious future option for modulating and treating not only chronic neuropathic pain but also its comorbidities.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Aiudi CM, Dunn RY, Burns SM, Roth SA, Opalacz A, Zhang Y, Chen L, Mao J, Ahmed SU. Loss of efficacy to spinal cord stimulator therapy: clinical evidence and possible causes. Pain Physician 2017;20: E1073–E80.
[2] Al-Kaisy A, Palmisani S, Pang D, Sanderson K, Wesley S, Tan Y, McCammon S, Trescott A. Prospective, randomized, sham-control, double blind, crossover trial of subthreshold spinal cord stimulation at various kilohertz frequencies in subjects suffering from failed back surgery syndrome (SCS frequency study). Neuromodulation 2018;21: 457–65.
[3] Al-Kaisy A, Palmisani S, Smith T, Harris S, Pang D. The use of 10-kilohertz spinal cord stimulation in a cohort of patients with chronic neuropathic limb pain refractory to medical management. Neuromodulation 2015;18:18–23; discussion.
[4] Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med 2014;15:347–54.
[5] Amir R, Michaelis M, Devor M. Burst discharge in primary sensory neurons: triggered by subthreshold oscillations, maintained by depolarizing afterpotentials. J Neurosci 2002;22:1187–98.
[6] Annemans L, Van Buyten JP, Smith T, Al-Kaisy A. Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). J Long Term Eff Med Implants 2014;24:173–83.
[7] Arle JE, Mei L, Carlson KW, Shils JL. High-frequency stimulation of dorsal column axons: potential underlying mechanism of paresthesia-free neuropathic pain relief. Neuromodulation 2016;19:385–97.
[8] Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological S. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113–e88.
[9] Barolat G, Massaro F, He J, Zeme S, Ketcik B. Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man. J Neurosurg 1993;78:233–9.
[10] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139:267–84.
[11] Bentley LD, Duarte RV, Furlong PL, Ashford RL, Raphael JH. Brain activity modifications following spinal cord stimulation for chronic neuropathic pain: a systematic review. Eur J Pain 2016;20:499–511.
[12] Borsook D, Hargreaves R, Bountra C, Porreca F. Lost but making progress—where will new analgesic drugs come from? Sci Transl Med 2014;6:249sr3.
[13] Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. PAIN 2008;136:380–7.
[14] Chakravarthy K, Richter H, Christo PJ, Williams K, Guan Y. Spinal cord stimulation for treating chronic pain: reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. Neuromodulation 2018;21:10–8.
[15] Coull JA, Boudreau D, Bachand K, Prescott SA, Nault F, Sik A, De Koninck P, De Koninck Y. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature 2003;424: 938–42.
[16] Crosby ND, Goodman Keiser MD, Smith JR, Zeeman ME, Winkelstein BA. Stimulation parameters define the effectiveness of burst spinal cord stimulation in a rat model of neuropathic pain. Neuromodulation 2015; 18:1–8; discussion.
[17] 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;66:287–95.
[18] Cui JG, O'Connor WT, Ungerstedt U, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. PAIN 1997;73:87–95.
[19] De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg 2013; 80:642–9 e1.
[20] De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. Neuromodulation 2016;19: 47–59.
[21] De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. Neurosurgery 2010;66:986–90.
[22] de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, Enggaard TP, Lenders MW. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. PAIN 2014;155:2426–31.
[23] Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burgher AH, Scowcroft J, Golovac S, Kapural L, Paicius R, Pope JE,

Samuel S, Porter McRoberts W, Schaufele M, Burton AW, Raza A, Agnesi F, Mekhail N. Comparison of paresthesia coverage of patient's pain: dorsal root ganglion vs. Spinal cord stimulation. An ACCURATE study sub-analysis. Neuromodulation 2019;22:930–6.

[24] Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Obray J, Scowcroft J, Golovac S, Kapural L, Paicius R, Kim C, Pope J, Yearwood T, Samuel S, McRoberts WP, Cassim H, Netherton M, Miller N, Schaufele M, Tavel E, Davis T, Davis K, Johnson L, Mekhail N. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. PAIN 2017;158:669–81.

[25] Du X, Hao H, Yang Y, Huang S, Wang C, Gigout S, Ramli R, Li X, Jaworska E, Edwards I, Deuchars J, Yanagawa Y, Qi J, Guan B, Jaffe DB, Zhang H, Gamper N. Local GABAergic signaling within sensory ganglia controls peripheral nociceptive transmission. J Clin Invest 2017; 127:1741–56.

[26] El-Khoury C, Hawwa N, Baliki M, Atweh SF, Jabbur SJ, Saade NE. Attenuation of neuropathic pain by segmental and supraspinal activation of the dorsal column system in awake rats. Neuroscience 2002;112: 541–53.

[27] Eldabe S, Burger K, Moser H, Klase D, Schu S, Wahlstedt A, Vanderick B, Francois E, Kramer J, Subbaroyan J. Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). Neuromodulation 2015;18:610–6; discussion 6–7.

[28] Eldabe S, Espinet A, Wahlstedt A, Kang P, Liem L, Patel NK, Vesper J, Kimber A, Cusack W, Kramer J. Retrospective case series on the treatment of painful diabetic peripheral neuropathy with dorsal root ganglion stimulation. Neuromodulation 2018;21:787–92.

[29] Emmers R. Thalamic mechanisms that process a temporal pulse code for pain. Brain Res 1976;103:425–41.

[30] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.

[31] Graham RD, Bruns TM, Duan B, Lempka SF. Dorsal root ganglion stimulation for chronic pain modulates Abeta-fiber activity but not C-fiber activity: a computational modeling study. Clin Neurophysiol 2019;130: 941–51.

[32] Gu JW, Joosten EAJ. Clarifying the scientific knowledge pertaining to burst waveforms in spinal cord stimulation. Neuromodulation 2019;22: 758–9.

[33] Guan Y, Wacnik PW, Yang F, Carteret AF, Chung CY, Meyer RA, Raja SN. Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010;113:1392–405.

[34] Harte SE, Meyers JB, Donahue RR, Taylor BK, Morrow TJ. Mechanical conflict system: a novel operant method for the assessment of nociceptive behavior. PLoS One 2016;11:e0150164.

[35] Holsheimer J. Computer modelling of spinal cord stimulation and its contribution to therapeutic efficacy. Spinal Cord 1998;36:531–40.

[36] Holsheimer J, Khan YN, Raza SS, Khan EA. Effects of electrode positioning on perception threshold and paresthesia coverage in spinal cord stimulation. Neuromodulation 2007;10:34–41.

[37] Huygen F, Liem L, Cusack W, Kramer J. Stimulation of the L2-L3 dorsal root ganglia induces effective pain relief in the low back. Pain Pract 2018; 18:205–13.

[38] Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci 2018;19: 138–52.

[39] Janssen SP, Gerard S, Raijmakers ME, Truin M, Van Kleef M, Joosten EA. Decreased intracellular GABA levels contribute to spinal cord stimulation-induced analgesia in rats suffering from painful peripheral neuropathy: the role of KCC2 and GABA(A) receptor-mediated inhibition. Neurochem Int 2012;60:21–30.

[40] Janssen SP, Truin M, Van Kleef M, Joosten EA. Differential GABAergic disinhibition during the development of painful peripheral neuropathy. Neuroscience 2011;184:183–94.

[41] Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. 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;123:851–60.

[42] Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343:618–24.

[43] Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008;108:292–8.

[44] Kent AR, Min X, Hogan QH, Kramer JM. Mechanisms of dorsal root ganglion stimulation in pain suppression: a computational modeling analysis. Neuromodulation 2018;21:234–46.

[45] Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. Neuromodulation 2014;17:242–54; discussion 54–5.

[46] Kiriakopoulos ET, Tasker RR, Nicosia S, Wood ML, Mikulis DJ. Functional magnetic resonance imaging: a potential tool for the evaluation of spinal cord stimulation: technical case report. Neurosurgery 1997;41:501–4.

[47] Koetsier E, Franken G, Debets J, Heijmans L, van Kuijk SMJ, Linderoth B, Joosten EA, Maino P. Mechanism of dorsal root ganglion stimulation for pain relief in painful diabetic polyneuropathy is not dependent on GABA release in the dorsal horn of the spinal cord. CNS Neurosci Ther 2020;26:136–43.

[48] Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. Neuromodulation 2013;16:304–11; discussion 10–1.

[49] Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. Neuromodulation 2015;18:24–32; discussion.

[50] Kriek N, Groeneweg G, Huygen FJ. Burst spinal cord stimulation in a patient with complex regional pain syndrome: a 2-year follow-up. Pain Pract 2015;15:E59–64.

[51] Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. 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; 21:507–19.

[52] Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, Frackowiak RS, Friston KJ, Jones AK. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci 2005;21:3133–42.

[53] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. PAIN 2007; 132:179–88.

[54] Langford LA, Coggeshall RE. Unmyelinated axons in the posterior funiculi. Science 1981;211:176–7.

[55] Lempka SF, McIntyre CC, Kilgore KL, Machado AG. Computational analysis of kilohertz frequency spinal cord stimulation for chronic pain management. Anesthesiology 2015;122:1362–76.

[56] Lenz FA, Garonzik IM, Zirh TA, Dougherty PM. Neuronal activity in the region of the thalamic principal sensory nucleus (ventralis caudalis) in patients with pain following amputations. Neuroscience 1998;86: 1065–81.

[57] Levy RM, Mekhail N, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Scowcroft J, Golovac S, Kapural L, Paicius R, Pope J, Samuel S, McRoberts WP, Schaufele M, Kent AR, Raza A, Deer TR. Therapy habituation at 12 Months: spinal cord stimulation versus dorsal root ganglion stimulation for complex regional pain syndrome type I and II. J Pain 2019. doi: 10.1016/j.jpain.2019.08.005.

[58] Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013;16:471–82; discussion 82.

[59] Lind G, Meyerson BA, Winter J, Linderoth B. Intrathecal baclofen as adjuvant therapy to enhance the effect of spinal cord stimulation in neuropathic pain: a pilot study. Eur J Pain 2004;8:377–83.

[60] Lind G, Schechtmann G, Winter J, Meyerson BA, Linderoth B. Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: long-term outcome of a pilot study. Eur J Pain 2008; 12:132–6.

[61] Linderoth B, Stiller CO, Gunasekera L, O'Connor WT, Ungerstedt U, Brodin E. Gamma-aminobutyric acid is released in the dorsal horn by electrical spinal cord stimulation: an in vivo microdialysis study in the rat. Neurosurgery 1994;34:484–8; discussion 8–9.

[62] Martucci KT, Mackey SC. Neuroimaging of pain: human evidence and clinical relevance of central nervous system processes and modulation. Anesthesiology 2018;128:1241–54.

[63] Mekhail N, Deer TR, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Scowcroft J, Golovac S, Kapural L, Paicius R, Pope J, Samuel S, McRoberts WP, Schaufele M, Kent AR, Raza A, Levy RM. Paresthesia-free dorsal root ganglion stimulation: an ACCURATE study sub-analysis. Neuromodulation 2020;23:185–95.
[64] Melzack R, Casey KL. Localized temperature changes evoked in the brain by somatic stimulation. Exp Neurol 1967;17:276–92.
[65] Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150:971–9.
[66] Meuwissen K, Van der Toorn A, Gu J, Zhang T, Dijkhuizen R, Joosten E. Burst and tonic spinal cord stimulation engage different supraspinal mechanisms: a functional magnetic resonance imaging study in peripherally injured chronic neuropathic rats. Pain Prac 2020. doi: 10.1111/papr.12879.
[67] Meuwissen KPV, de Vries LE, Gu JW, Zhang TC, Joosten EAJ. Burst and tonic spinal cord stimulation both activate spinal GABAergic mechanisms to attenuate pain in a rat model of chronic neuropathic pain. Pain Pract 2020;20:75–87.
[68] Meuwissen KPV, Gu JW, Zhang TC, Joosten EAJ. Burst spinal cord stimulation in peripherally injured chronic neuropathic rats: a delayed effect. Pain Pract 2018;18:988–96.
[69] Meuwissen KPV, Gu JW, Zhang TC, Joosten EAJ. Conventional-SCS vs. Burst-SCS and the behavioral effect on mechanical hypersensitivity in a rat model of chronic neuropathic pain: effect of amplitude. Neuromodulation 2018;21:19–30.
[70] Meuwissen KPV, van Beek M, Joosten EAJ. Burst and tonic spinal cord stimulation in the mechanical conflict-avoidance system: cognitive-motivational aspects. Neuromodulation 2019. doi: 10.1111/ner.12955.
[71] Meyerson BA, Linderoth B. Mode of action of spinal cord stimulation in neuropathic pain. J Pain Symptom Manage 2006;31(4 suppl):S6–12.
[72] Millan MJ. Descending control of pain. Prog Neurobiol 2002;66: 355–474.
[73] Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderoth B. Parameters of spinal cord stimulation and their role in electrical charge delivery: a review. Neuromodulation 2016;19:373–84.
[74] Moens M, Sunaert S, Marien P, Brouns R, De Smedt A, Droogmans S, Van Schuerbeek P, Peeters R, Poelaert J, Nuttin B. Spinal cord stimulation modulates cerebral function: an fMRI study. Neuroradiology 2012;54:1399–407.
[75] Niu J, Ding L, Li JJ, Kim H, Liu J, Li H, Moberly A, Badea TC, Duncan ID, Son YJ, Scherer SS, Luo W. Modality-based organization of ascending somatosensory axons in the direct dorsal column pathway. J Neurosci 2013;33:17691–709.
[76] North RB, Ewend MG, Lawton MT, Piantadosi S. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. PAIN 1991;44:119–30.
[77] North RB, Kumar K, Wallace MS, Henderson JM, Shipley J, Hernandez J, Mekel-Bobrov N, Jaax KN. Spinal cord stimulation versus re-operation in patients with failed back surgery syndrome: an international multicenter randomized controlled trial (EVIDENCE study). Neuromodulation 2011;14:330–5; discussion 5-6.
[78] Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. PAIN 2012;153:593–601.
[79] Parker JL, Obradovic M, Hesam Shariati N, Gorman RB, Karantonis DM, Single PS, Laird-Wah J, Bickerstaff M, Cousins MJ. Evoked compound action potentials reveal spinal cord dorsal column neuroanatomy. Neuromodulation 2020;23:82–95.
[80] Patterson JT, Chung K, Coggeshall RE. Further evidence for the existence of long ascending unmyelinated primary afferent fibers within the dorsal funiculus: effects of capsaicin. PAIN 1992;49:117–20.
[81] Patterson JT, Head PA, McNeill DL, Chung K, Coggeshall RE. Ascending unmyelinated primary afferent fibers in the dorsal funiculus. J Comp Neurol 1989;290:384–90.
[82] Pawela CP, Kramer JM, Hogan QH. Dorsal root ganglion stimulation attenuates the BOLD signal response to noxious sensory input in specific brain regions: insights into a possible mechanism for analgesia. Neuroimage 2017;147:10–8.
[83] Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M, Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation 2013;16:363–9; discussion 9.
[84] Provenzano DA, Rebman J, Kuhel C, Trenz H, Kilgore J. The efficacy of high-density spinal cord stimulation among trial, implant, and conversion patients: a retrospective case series. Neuromodulation 2017;20: 654–60.
[85] Radhakrishnan V, Tsoukatos J, Davis KD, Tasker RR, Lozano AM, Dostrovsky JO. A comparison of the burst activity of lateral thalamic neurons in chronic pain and non-pain patients. PAIN 1999;80: 567–75.
[86] Saade NE, Tabet MS, Soueidan SA, Bitar M, Atweh SF, Jabbur SJ. Supraspinal modulation of nociception in awake rats by stimulation of the dorsal column nuclei. Brain Res 1986;369:307–10.
[87] Saliani A, Perraud B, Duval T, Stikov N, Rossignol S, Cohen-Adad J. Axon and myelin morphology in animal and human spinal cord. Front Neuroanat 2017;11:129.
[88] Schechtmann G, Lind G, Winter J, Meyerson BA, Linderoth B. Intrathecal clonidine and baclofen enhance the pain-relieving effect of spinal cord stimulation: a comparative placebo-controlled, randomized trial. Neurosurgery 2010;67:173–81.
[89] Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD. Classification Committee of the Neuropathic Pain Special Interest G. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. PAIN 2019;160:53–9.
[90] Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. 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; 17:443–50.
[91] Sdrulla AD, Xu Q, He SQ, Tiwari V, Yang F, Zhang C, Shu B, Shechter R, Raja SN, Wang Y, Dong X, Guan Y. Electrical stimulation of low-threshold afferent fibers induces a prolonged synaptic depression in lamina II dorsal horn neurons to high-threshold afferent inputs in mice. PAIN 2015;156:1008–17.
[92] Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967;46:489–91.
[93] Shechter R, Yang F, Xu Q, Cheong YK, He SQ, Sdrulla A, Carteret AF, Wacnik PW, Dong X, Meyer RA, Raja SN, Guan Y. Conventional and kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. Anesthesiology 2013;119:422–32.
[94] Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, Kessels AG, van Kleef M. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care 2014;37:3016–24.
[95] Smith KJ, Bennett BJ. Topographic and quantitative description of rat dorsal column fibres arising from the lumbar dorsal roots. J Anat 1987; 153:203–15.
[96] Smith TM, Lee D, Bradley K, McMahon SB. Methodology for quantifying excitability of identified projection neurons in the dorsal horn of the spinal cord, specifically to study spinal cord stimulation paradigms. J Neurosci Methods 2019;330:108479.
[97] Smits H, van Kleef M, Holsheimer J, Joosten EA. Experimental spinal cord stimulation and neuropathic pain: mechanism of action, technical aspects, and effectiveness. Pain Pract 2013;13:154–68.
[98] Smits H, van Kleef M, Joosten EA. Spinal cord stimulation of dorsal columns in a rat model of neuropathic pain: evidence for a segmental spinal mechanism of pain relief. PAIN 2012;153:177–83.
[99] Song Z, Ansah OB, Meyerson BA, Pertovaara A, Linderoth B. The rostroventromedial medulla is engaged in the effects of spinal cord stimulation in a rodent model of neuropathic pain. Neuroscience 2013; 247:134–44.
[100] Song Z, Meyerson BA, Linderoth B. High-frequency (1 kHz) spinal cord stimulation-is pulse shape crucial for the efficacy? A pilot study. Neuromodulation 2015;18:714–20.
[101] Song Z, Meyerson BA, Linderoth B. Spinal 5-HT receptors that contribute to the pain-relieving effects of spinal cord stimulation in a rat model of neuropathy. PAIN 2011;152:1666–73.
[102] Song Z, Ultenius C, Meyerson BA, Linderoth B. Pain relief by spinal cord stimulation involves serotonergic mechanisms: an experimental study in a rat model of mononeuropathy. PAIN 2009;147:241–8.
[103] Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation 2014;17:226–34; discussion 34–5.
[104] Stiller CO, Cui JG, O'Connor WT, Brodin E, Meyerson BA, Linderoth B. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in

mononeuropathic rats. Neurosurgery 1996;39:367–74; discussion 74–5.
[105] Sun L, Tai L, Qiu Q, Mitchell R, Fleetwood-Walker S, Joosten EA, Cheung CW. Endocannabinoid activation of CB1 receptors contributes to long-lasting reversal of neuropathic pain by repetitive spinal cord stimulation. Eur J Pain 2017;21:804–14.
[106] Sweet J, Badjatiya A, Tan D, Miller J. Paresthesia-free high-density spinal cord stimulation for postlaminectomy syndrome in a prescreened population: a prospective case series. Neuromodulation 2016;19: 260–7.
[107] Tang R, Martinez M, Goodman-Keiser M, Farber JP, Qin C, Foreman RD. Comparison of burst and tonic spinal cord stimulation on spinal neural processing in an animal model. Neuromodulation 2014;17: 143–51.
[108] Tazawa T, Kamiya Y, Kobayashi A, Saeki K, Takiguchi M, Nakahashi Y, Shinbori H, Funakoshi K, Goto T. Spinal cord stimulation modulates supraspinal centers of the descending antinociceptive system in rats with unilateral spinal nerve injury. Mol Pain 2015;11:36.
[109] Truin M, Janssen SP, van Kleef M, Joosten EA. Successful pain relief in non-responders to spinal cord stimulation: the combined use of ketamine and spinal cord stimulation. Eur J Pain 2011;15:1049 e1–9.
[110] Vallejo R, Gupta A, Kelley CA, Vallejo A, Rink J, Williams JM, Cass CL, Smith WJ, Benyamin R, Cedeno DL. Effects of phase polarity and charge balance spinal cord stimulation on behavior and gene expression in a rat model of neuropathic pain. Neuromodulation 2020;23:26–35.
[111] van Beek M, Geurts JW, Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, van Kuijk SMJ, van Kleef M. Severity of neuropathy is associated with long-term spinal cord stimulation outcome in painful diabetic peripheral neuropathy: five-year follow-up of a prospective two-center clinical trial. Diabetes Care 2018;41:32–8.
[112] Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation 2013;16:59–65; discussion 65–6.
[113] Veizi E, Hayek SM, North J, Brent Chafin T, Yearwood TL, Raso L, Frey R, Cairns K, Berg A, Brendel J, Haider N, McCarty M, Vucetic H, Sherman A, Chen L, Mekel-Bobrov N. Spinal cord stimulation (SCS) with anatomically guided (3D) neural targeting shows superior chronic axial low back pain relief compared to traditional SCS-LUMINA study. Pain Med 2017;18:1534–48.
[114] Vesper J, Slotty P, Schu S, Poeggel-Kraemer K, Littges H, Van Looy P, Agnesi F, Venkatesan L, Van Havenbergh T. Burst SCS microdosing is as efficacious as standard burst SCS in treating chronic back and leg pain: results from a randomized controlled trial. Neuromodulation 2019; 22:190–3.
[115] Vierck CJ, Hansson PT, Yezierski RP. Clinical and pre-clinical pain assessment: are we measuring the same thing? PAIN 2008;135:7–10.
[116] Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH. Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain. PAIN 2005;117:231–5.
[117] Wang R, King T, De Felice M, Guo W, Ossipov MH, Porreca F. Descending facilitation maintains long-term spontaneous neuropathic pain. J Pain 2013;14:845–53.
[118] Wille F, Breel JS, Bakker EW, Hollmann MW. Altering conventional to high density spinal cord stimulation: an energy dose-response relationship in neuropathic pain therapy. Neuromodulation 2017;20: 71–80.
[119] Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. PAIN 1991;44:293–9.
[120] Wu G, Ringkamp M, Hartke TV, Murinson BB, Campbell JN, Griffin JW, Meyer RA. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J Neurosci 2001;21: RC140.
[121] Wu G, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, Campbell JN, Griffin JW, Meyer RA. Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci 2002;22:7746–53.
[122] Yang F, Carteret AF, Wacnik PW, Chung CY, Xing L, Dong X, Meyer RA, Raja SN, Guan Y. Bipolar spinal cord stimulation attenuates mechanical hypersensitivity at an intensity that activates a small portion of A-fiber afferents in spinal nerve-injured rats. Neuroscience 2011;199:470–80.
[123] Yezierski RP, Hansson P. Inflammatory and neuropathic pain from bench to bedside: what went wrong? J Pain 2018;19:571–88.