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).98 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.50 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),22,24 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 transcortaneous 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.71,73,90,97

The concept of Tonic SCS emerged as a direct spin-off from the gate control theory.155 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.50 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 (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.89 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 GABAB 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 GABAB receptor agonist baclofen.17 The aforementioned preclinical
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 GABAA or GABAB, 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. Hence, the presynaptic GABA<sub>A</sub>-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 GABA<sub>A</sub>ergic modulation through GABA<sub>A</sub> receptors in conjunction with K<sup>P</sup> cotransporter 2 (KCC2) expression is involved in neuropathic pain and in the mechanism underlying Tonic SCS.17,38,40

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<sup>2+</sup> block. Enhanced Ca<sup>2+</sup> influx through the NMDA receptor then leads to central sensitization, which is a process fundamental to neuropathic pain.179 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<sup>2+</sup> 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 thinly myelinated A<sub>B</sub> fibers in the dorsal columns. It can, however, not be excluded that also incoming dorsal root fibers, including C and A<sub>B</sub> 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 I), and this depression is blocked by antagonists of cannabinoid receptor type 1 (CB1).31 Furthermore, the intrathecal application of AM251, a CB1 receptor antagonist, was able to block SCS-mediated reversal of mechanical hypersensitivity in rats.115 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 analogies to glia-mediated control of nociception.56

### 2.2. Tonic spinal cord stimulation and supraspinal 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 GABA<sub>A</sub>ergic interneurons.101

First evidence for a role of supraspinal 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.70 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.72 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.\textsuperscript{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).\textsuperscript{34} With use of MCAS, Tonic SCS was shown to affect also the cognitive-motivational aspects of the presumed pain in chronic neuropathic rats.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{98} The anatomy of the dorsal column in the rat spinal cord makes the A\textsuperscript{δ} fibers initially localized dorsolateral within the columns at T13 (where injured fibers enter) but then rearranged to ventromedial positions at more rostral levels (T11).\textsuperscript{95,96} Most ascending dorsal column A\textsuperscript{δ} fibers were also found to be lost from the dorsal columns, and only 15% reaches cervical levels.\textsuperscript{99} Furthermore, computer modeling 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.\textsuperscript{35,36} As the behavioral findings on pain relief of Tonic SCS in a model of chronic neuropathic pain\textsuperscript{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 A\textsuperscript{δ} fibers but also contain even larger numbers of unmyelinated fibers in the rat\textsuperscript{54} and human,\textsuperscript{67} 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 propriocceptive, corticospinal, or fibers descending from cells in the nucleus gracilis or cuneate,\textsuperscript{54,75} unilateral dorsal root transection revealed that a significant fraction of the unmyelinated fibers in the fasciculus gracilis ascend, presumably to the nucleus gracilis in the brain stem, and also that a significant number of these fibers branch.\textsuperscript{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 nocuous processing.\textsuperscript{80} This then may shed a more complicated view on the mechanism underlying Tonic SCS because not only non-nociceptive A\textsuperscript{δ} 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.\textsuperscript{94} 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%\textsuperscript{22,42,43,53,77,94} Second, the average pain reduction is restricted to approximately 50% to 60%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{75} 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,\textsuperscript{58} DRGS has been successfully implemented for a wide variety of neuropathic pain disorders, including, but not limited to, discogenic low back pain,\textsuperscript{37} CRPS type I and II,\textsuperscript{24} postamputation pain,\textsuperscript{27} and PDPN.\textsuperscript{28} Yet, only one randomized clinical trial (RCT) on DRGS has been published to date.\textsuperscript{29} 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.\textsuperscript{30} 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.\textsuperscript{31} Finally, some DRGS patients even achieved paresthesia-free analgesia.\textsuperscript{32}

Mechanistically, it was initially assumed that DRGS engages the spinal mechanisms dependent on stimulation of non-nociceptive A\textsuperscript{δ} 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 DRGns may inhibit nociception by activating pain-gating mechanisms in the dorsal horn through repeated activation of large myelinated (Aβ) afferents, a closer examination reveals that the pain-relieving effect of DRGns is not likely to be dependent on GABA co-release in the spinal dorsal horn at the L4-L6 lumbar level. Some experimental studies suggest that, instead, DRGns suppress excitability of neurons with predominantly slow-conducting nociceptive fibers (C fibers). 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). Interestingly, a recent study by Du et al. found an extensive GABAergic 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 DRGns might exert its analgesic action by engaging this second gate. This proposed conduction block at the site of the DRG is consistent with the observation that DRGns 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.

Although promising, the therapeutic efficacy of DRGns 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 DRGns, 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. 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, the opportunity to perform double-blind placebo-controlled clinical studies.

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. 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. 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. 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. 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 hypothesis 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.

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.

4.3. Burst spinal cord stimulation in neuropathic pain

The Burst paradigm was introduced in 2010 by de Ridder et al. 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. 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 nociceptive C-fibers and the thalamus 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.) 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. In fact, 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.

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. 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. This could potentially set in motion additional
dorsal horn mechanisms that are not activated with supra-threshold 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.\textsuperscript{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.\textsuperscript{15} 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.\textsuperscript{19} These findings are further substantiatied by the fact that Burst and Tonic SCS do share brain activation patterns of the i-STT as well as descending pain inhibitory pathways.\textsuperscript{19,20} Combined, these data suggest that both Burst SCS and Tonic SCS are capable of modulating the i-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\textsubscript{A}) and phaclofen (GABA\textsubscript{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.\textsuperscript{67} Because Burst SCS is suggested to modulate structures at a supraspinal levels in a different manner as compared to Tonic SCS,\textsuperscript{18,20} it is remarkable that the GABAergic mechanisms underlying these different stimulation waveforms, at least at a spinal level, show similarities.\textsuperscript{67} On the other hand, with the use of escape latency in the MCAS,\textsuperscript{34} the cognitive-motivational aspects of Burst SCS were analyzed and compared with Tonic SCS in a rat model of chronic neuropathic pain\textsuperscript{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:\textsuperscript{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, 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\textsuperscript{68,69} might provide some additional clues about the underlying mechanism. As the Burst SCS paradigm mainly activates ascending pathways including the I-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.\textsuperscript{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,\textsuperscript{64} cortical brain areas, but also nuclei involved in the descending part of the loop such as the periaqueductal grey, ventromedial medial medulla, and nucleus raphe,\textsuperscript{10,72} as well as signal transfer and distribution over the various cortical areas or pain matrix.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 gial 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 SCS84,106,118 and 3D-guided
SCS113 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 re-
sponse, 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 pharmacolog-
ically, 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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