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Review

Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain

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ABSTRACT

Spinal cord stimulation (SCS) is an established and cost-effective therapy for treating severe chronic pain. However, despite over 40 years of clinical practice and the development of novel electrode designs and treatment protocols, increases in clinical success, defined as the proportion of patients that experience 50% or greater self-reported pain relief, have stalled. An incomplete knowledge of the neural circuits and systems underlying chronic pain and the interaction of SCS with these circuits may underlie this plateau in clinical efficacy. This review summarizes prior work and identifies gaps in our knowledge regarding the neural circuits related to pain and SCS in the dorsal horn, supraspinal structures, and the Pain Matrix. In addition, this review discusses and critiques current experimental and computational models used to investigate and optimize SCS. Further research into the interactions between SCS and pain pathways in the nervous system using animal and computational models is a fruitful approach to improve this promising therapy.

Contents

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1. Introduction

Spinal cord stimulation is a treatment option for patients with refractory chronic pain including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and idiopathic conditions such as fibromyalgia and irritable bowel syndrome. (Wall and Melzack, 1996; Kumar et al., 2007; Guan, 2012) Over 30,000 individuals receive SCS devices annually for chronic pain, and SCS is a growing industry with global annual sales exceeding $1.8 billion. In conventional SCS, short duration current or voltage pulses are delivered at a constant frequency through an epidural electrode to excite the axons in the dorsal columns that carry sensory non-nociceptive information from the source of pain (Shealy et al., 1972; Oakley and Prager, 2002). Stimulation parameters such as amplitude, pulse duration, pulse repetition frequency, and the configuration of active electrode contacts are selected based on a combination of paresthesia location, pain relief, and comfort and can have a significant impact on clinical outcomes (Table 1) (Aló and Holsheimer, 2002; Cameron, 2004; Turner et al., 2004). Patients undergoing SCS report higher quality of life, greater pain relief, and more frequent resumption of normal activities and employment relative to individuals undergoing pharmacological treatment alone (Cameron, 2004; Kumar et al., 2007). For some indications, SCS along with conventional therapies (drugs, physical therapy) is both more efficacious and cost-effective than conventional therapies alone (Kumar et al., 2002; Kumar and Rizvi, 2013)

Despite the success of SCS, there remain significant opportunities to improve the clinical efficacy of SCS. Notably, SCS has a relatively low mean "success rate" for treatment and significant variation in efficacy (Fig. 1): only 58% of patients experienced successful outcomes – defined as a 50% or greater improvement in self-reported pain – based on data from two reviews of clinical studies and case series encompassing 1972 through 2013 (North et al., 1993; Taylor et al., 2013). Furthermore, success rate does not correlate with study year ($R=0.09$, $p=0.4$ t-test), indicating that the therapy is not improving with innovation and experience. As well, an analysis of 74 studies originally intended to reveal prognostic factors for SCS efficacy identified only one statistically significant trend: a *negative* correlation between study quality as assessed by Jadad score and reported clinical success (Taylor et al., 2005, 2013).

The lack in improvement in SCS efficacy over the years, the high variability of clinical success rates, and the apparent dependence of efficacy on pain etiology (Kumar et al., 1998)

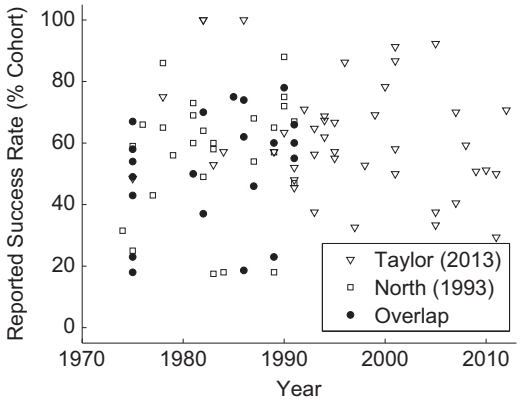

Fig. 1 – A scatter plot showing reported mean success rates from clinical studies on SCS over the period of 1973–2013 where "success" is defined as 50% or greater subjective pain relief reported by the patient. Studies mentioned solely in one review and studies mentioned in both reviews are delineated by different markers. Adapted from North et al. (1993), Taylor et al. (2013).

Table 1 – Critical stimulation parameters and sample ranges reported from clinical studies.

Parameter	Representative ranges
Stimulation frequency	50–150 Hz;[1] 15–750 Hz;[2] 80±29 Hz[b3]; 2–200 Hz[4]; 49±16.4 Hz[b5]
Stimulation amplitude[a]	2–5 V;[2] 2.8–5.4 V;[1] 3±1.5 V;[b3] 3.7±2.0 V[†5]
Waveform pulse width	150–500 μs[1]; 80–500 μsb[2]; 270±79 μs[b3]; 350±95.5 μs[b5]
Electrode geometry[1,2,3,6]	Bipolar, "guarded" tripolar, quadrupolar, other multipolar

[a] Constant voltage stimulation.
[b] Denotes mean±standard deviation instead of full range, as the latter was not reported in source.
[1] Abejon et al. (2005).
[2] Alo et al. (2002).
[3] Butyen (2003).
[4] North et al. (1993).
[5] Kumar et al. (2007).
[6] Aló and Holsheimer (2002).

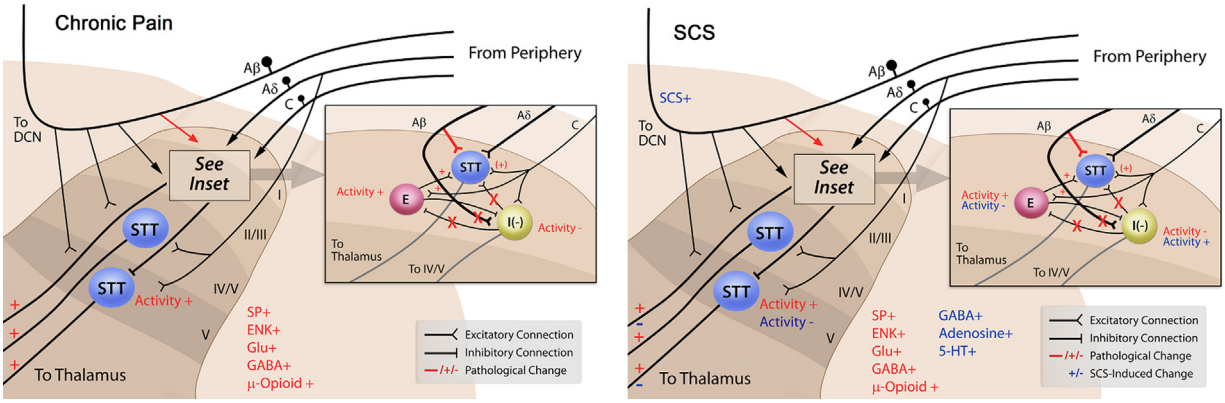

Fig. 2 – A schematic showing changes that occur to the circuitry and neurochemistry of the pain processing network in the dorsal horn during the induction and maintenance of neuropathic pain during SCS. The progression of neuropathic pain may involve but is not limited to increases in the levels of excitatory neurotransmitters and decreases in the levels of inhibitory neurotransmitters, aberrant sprouting of primary afferent fibers into laminae where they typically do not enter, and the loss of inhibitory controls either via interneuronal death or changes in the function of GABA receptors.

suggest that the state of understanding of the neurophysiology underlying chronic pain and SCS are incomplete. Theoretical and computational models of the neural circuitry underlying the nociceptive system may provide insights regarding the mechanisms of action of SCS. However, existing theoretical frameworks are largely untested, and few existing computational models exist. In particular, the Gate Control Theory (Melzack and Wall, 1965) provided the initial mechanism of action for SCS (Shealy et al., 1972) and is still considered a plausible depiction of the mechanisms of SCS (Linderoth et al., 2009; Guan, 2012). Experimental models of SCS provided insights into the effects of SCS on both the activity of sensory dorsal horn neurons and the behaviors of animal models of neuropathic pain (Linderoth and Foreman, 2006). Concurrently, computational models of SCS provided insights into anatomical substrates and geometric aspects of the SCS electrode important to dorsal column activation and led to electrode designs more capable of targeting specific dermatomes (Holsheimer and Wesselink, 1997). However, both experimental and computational models assume that the Gate Control Theory is sufficient to describe the mechanisms underlying SCS, and efforts to model the neural circuitry associated with SCS and to test proposed networks experimentally are sparse.

To facilitate the continued development and optimization of this promising therapy, we discuss in this review theoretical, experimental, and computational models that describe the mechanisms of SCS. We focus on the neural circuits related to neuropathic pain and SCS in the dorsal horn and supraspinal centers and identify clinically relevant gaps in our knowledge of these circuits that must be addressed. In addition, we review and critique existing experimental and computational models of SCS and discuss avenues for the development of novel network models of SCS that can improve our understanding of the mechanisms of SCS.

In this review, we consider conventional clinical SCS for the treatment of refractory neuropathic pain syndromes. Recently, high frequency SCS using pulse repetition frequencies in the kilohertz ranges was reported to provide pain relief without concomitant paresthesia (Al-Kaisy et al., 2014). The ability of HFSCS to suppress pain in animal models appears comparable to that of conventional SCS (Shechter et al., 2013; Song et al., 2014), but the mechanisms of action have not been investigated and may be distinct from those of conventional SCS (Shechter et al., 2013), so we will not discuss this therapy in this review. SCS for peripheral vascular disease and angina pectoris may achieve therapeutic effects through mechanisms distinct from those related to neuropathic pain (Meyerson and Linderoth, 2003; Linderoth et al., 2009), and these applications for SCS are also not discussed in detail.

2. Theoretical models for SCS

2.1. *The Gate Control Theory*

The Gate Control Theory proposed by Melzack and Wall (1965) presented a possible neuron network in the dorsal horn that could explain non-linearities in pain perception, and the theory provided possible mechanism by which pain could be relieved. The proposed network consists of a "transmission (T) cell" responsible for relaying pain signals to the body's "action system" that was modulated by excitatory inputs from peripheral A-fiber and C-fiber afferent inputs and inhibitory inputs from inhibitory interneurons ("SG Cells") in the substantia gelatinosa (Melzack and Wall, 1965). That the inhibitory interneuron could be activated by enhanced A-fiber activity via dorsal column stimulation and thereby suppress pain transmission (Woolf and Wall, 1982) served as initial and continued inspiration for SCS (Shealy et al., 1972; Linderoth et al., 2009). However, for the network described by the Gate Control Theory to be a valid mechanistic depiction of SCS, two specific observations regarding the effects of SCS on the dorsal horn circuit must be made: SCS must suppress the activity of "wide dynamic range" (WDR) dorsal horn projection neurons (Willis et al., 1974; Chung et al., 1979; Simone et al., 1991) through A-fiber mediated

mechanisms, and SCS-mediated inhibition must involve segmental inhibitory interneurons.

Extensive neurophysiological evidence exists to indicate that SCS suppresses WDR neuron activity, and recent studies have shown that this inhibition depends on A-fiber activity. Early single unit recording studies revealed that stimulation of the dorsal columns inhibits the activity of deep laminae (IV, V) WDR dorsal horn neurons (Hillman and Wall, 1969; Lindblom and Meyerson, 1975; Foreman et al., 1976; Duggan and Foong, 1985), and these studies are more extensively reviewed elsewhere (Linderoth and Foreman, 1999; Linderoth et al., 2009). SCS may also prevent WDR neuron sensitization due to long-term potentiation (LTP) of C-fiber inputs (Wallin et al., 2003) and wind-up induction (Guan et al., 2010), and SCS also inhibits WDR neurons in animal models of neuropathic pain (Yakhnitsa et al., 1999). Finally, recent work has shown that the suppression of neuronal activity in WDR neurons and pain alleviation during SCS in animal models of neuropathic pain requires activation of dorsal column fibers corresponding to A-fibers originating from the site of pain (Yang et al., 2011; Guan, 2012), supporting this feature in the Gate Control Theory architecture as well as SCS as a means to modulate pain.

As predicted by the circuit underlying the Gate Control Theory, inhibition of dorsal horn neurons involves spinal inhibitory mechanisms. SCS-induced inhibition of dorsal horn neurons is disrupted by cooling or lesioning of the dorsal horn caudal but not rostral to the stimulation site (Hillman and Wall, 1969; Foreman et al., 1976), and inhibition occurs with greater strength when the SCS electrode is placed at a spinal level close to the affected dermatome(s) (Smits et al., 2012). Studies demonstrating that bicuculline, a GABAa antagonist, reduces SCS-mediated inhibition of dorsal horn projection neurons (Duggan and Foong, 1985) and induces hyperalgesia and allodyina in otherwise healthy rats (Sivilotti and Woolf, 1994) implicate GABAergic inhibition from local interneurons as the driver of A-fiber mediated inhibition. Supporting this observation, hyperalgesia and allodynia in animal models of neuropathic pain can be reversed by the administration of the $GABA_A$ and $GABA_B$ agonists muscimol and baclofen (Hwang and Yaksh, 1997). Immunohistochemical labeling and electron microscopy demonstrate that WDR projection neurons possess GABAergic synaptic boutons (Lekan and Carlton, 1995), and the presynaptic neurons of GABAergic synapses on Lamina I projection neurons originate from inhibitory interneurons in laminae I–III of the dorsal horn (Todd, 2010; Zeilhofer et al., 2012), thus confirming the neuronal origin of spinal segmental GABAergic inhibition. Studies on the relationship between GABA and SCS (reviewed in Linderoth and Foreman, 1999) confirmed this finding in neuropathic rats and posited GABAergic modulation as a way to enhance the efficacy of SCS (Cui et al., 1996, 1998; Linderoth and Foreman, 1999; Schechtmann et al., 2010). The discovery of the relationship between GABA and SCS had clinical implications as well: clinical trials of SCS paired with the $GABA_B$ agonist baclofen demonstrated that the administration of baclofen during SCS enhanced the effect of SCS in 48 patients for which SCS alone was ineffective in relieving pain (Lind et al., 2004; Lind et al., 2007).

One aspect of the Gate Control Theory based explanation for the mechanisms of SCS that has not been investigated in detail is the occurrence of SCS-mediated *excitation* of dorsal horn neurons. Specifically, SCS has been also reported to excite dorsal horn WDR neurons, and in some cases, SCS excites and inhibits the same neuron (Foreman et al., 1976; Dubuisson, 1989). The interaction between SCS-mediated excitation and inhibition appears on the circuit underlying the Gate Control Theory and may be of clinical importance, as this balance of excitation and may partially explain why SCS-mediated pain relief is dependent on stimulation frequency, with 50–80 Hz being the most common clinical range (Oakley and Prager, 2002; Guan, 2012). However, few explanations exist for why applying Aβ-fiber threshold tactile or electrical stimulation directly to the receptive field of a WDR neuron may excite the neuron while SCS may putatively inhibit the neuron, and the relationship between SCS-mediated excitation and inhibition at different frequencies has not been explored.

2.2. *Beyond the Pain Gate*

Although the Gate Control Theory explains a number of features of pain relief from SCS, the network proposed by the Gate Control Theory is insufficient to describe all of the features of pain and SCS (Fig. 2), and clinical observations underscore some limitations of this theory. First, the Gate Control Theory alone cannot account for why SCS may produce pain relief over a receptive field in which allodynia, or pain from non-noxious stimulation of a local receptive field, also occurs (Campbell and Meyer, 2006). Second, SCS does not affect the perception of acute pain from the region of paresthesia, whereas the Gate Control Theory predicts that sustained activation of large myelinated fibers, such as is the case in clinical SCS, should mask all pain. Furthermore, the Gate Control Theory posits that suppression of spinal projection neurons is sufficient for all pain relief, but pain relief by SCS depends heavily on etiology. Specifically, SCS is approved by the United States Food and Drug Administration only for FBSS and complex regional pain syndrome, and trials of SCS for other indications such as phantom limb pain and spinal cord injury have yielded lower success rates (Kumar et al., 1998). Finally, pain relief provided by SCS can persist for up to 30 min after the cessation of stimulation (Lindblom and Meyerson, 1975), whereas the Gate Control Theory only predicts pain relief while large myelinated inputs (e.g. the dorsal columns) are activated preferentially over smaller unmyelinated fibers.

Inhibition from surrounding receptive beyond that hypothesized by the Gate Control Theory has been documented and may affect neuronal responses to SCS (Hillman and Wall, 1969; Menetrey et al., 1977). For example, mechanical and electrical stimulation of low-threshold afferents originating from receptive fields *surrounding* the primary excitatory receptive field of a neuron results in inhibition of that neuron (Hillman and Wall, 1969; Menetrey et al., 1977) and can be similar to inhibition induced by dorsal column stimulation (Foreman et al., 1976). These observations were corroborated by a recent study demonstrating that SCS inhibited the C-fiber component of a WDR neuron's response, while

A-fiber stimulation of a peripheral nerve corresponding to the local receptive field of the WDR neuron at the same frequency could not (Yang et al., 2014). Further supporting the importance of surround inhibition to pain modulation is the observation that receptive fields of dorsal horn projection neurons enlarge following peripheral nerve injury (Woolf and Wall, 1982), inflammation (Kawamata et al., 2005), or the intrathecal administration of bicuculline in the case of nociceptive-specific neurons (Kawamata et al., 2005). These observations, coupled with recent anatomical studies revealing GABAergic connections between dorsal horn neurons extending across several spinal levels (Todd, 2010; Szucs et al., 2013), suggest that a center-surround excitatory-inhibitory architecture may better represent the effects of peripheral afferent activity and SCS on dorsal horn neuron activity. Further exploration of the contribution of surround inhibition to the inhibitory effects of SCS and the design of SCS electrodes capable of exploiting surround inhibition could produce improvements in clinical pain relief.

In addition, WDR neurons responsive to both A-fiber and C-fiber inputs are not the only class of neuron present in the dorsal horn; low-threshold (LT) neurons that are responsive primarily to light touch and nociceptive-specific (NS) neurons that respond only to noxious mechanical and thermal stimulation are also prevalent in the dorsal horn (Chung et al., 1979). NS and WDR neurons are both active during noxious mechanical and thermal stimuli (Simone et al., 1991; Coghill et al., 1993), and NS and WDR neurons may encode distinct aspects of pain (Blomqvist and Craig, 2000). It is also likely that the networks underlying NS and WDR neuron behavior are different, as NS neurons located in superficial laminae of the dorsal horn are organized into modular networks (Zheng et al., 2010) but, unlike WDR neurons, do not appear to receive direct inputs from Aβ fibers (Todd, 2010; Torsney, 2011). In addition, NS neurons become sensitized after bicuculline administration (Torsney and MacDermott, 2006) and during the progression of neuropathic pain (Lavertu et al., 2013), suggesting that pathological changes involving these neurons contribute to chronic pain. In fact, a recently developed scheme states that rather than being defined by the output of one type of neuron from a single circuit, nociception is a population response comprising responses from distinct "microcircuits" that are each responsible for specific aspects of perception (Prescott and Ratté, 2012). This "microcircuit" hypothesis suggests that LT, WDR, and NS neurons are wired differently in the dorsal horn and by extension may respond differently to SCS; for example, NS neurons being active during noxious stimuli while unresponsive to SCS may explain why SCS does not inhibit acute pain. However, the responses of low-threshold and NS neurons to peripheral stimulation and SCS have not been extensively documented, and the connectivities depicted by the microcircuit theory have not been confirmed.

Along with these clinical observations, the Gate Control Theory does not account for progressive changes that accompany the transition between an acute injury and chronic pain (Woolf, 2011). Aberrant sprouting of myelinated fibers into laminae where they typically do not enter occurs following a peripheral nerve injury (Woolf et al., 1992), resulting in the formation or unmasking of excitatory connections onto neurons in the superficial dorsal horn (Kohno et al., 2003) and the sensitization of NS neurons (Kawamata et al., 2005; von Hehn Christian et al., 2012). The abnormal sprouting and unmasking of excitatory connections is correlated with the time course of hypersensitivity to mechanical and thermal stimuli in rats following nerve constriction or nerve crush (Woolf et al., 1995; Kim et al., 1997), suggesting a relationship between abnormal afferent sprouting and altered pain perception. Furthermore, the expression of synaptic receptors associated with excitation (AMPA, NMDA, NK1) increases following peripheral nerve injury over the same time frame as behavioral indications of pain (Goff et al., 1997; Bleakman et al., 2006; von Hehn Christian et al., 2012); the levels of other markers associated with the dorsal horn pain network (bNOS, μ-opioid receptors) in neuropathic animals also deviate significantly from normal and fluctuate over time in a manner that differed between animal models (Goff et al., 1997). This latter finding underscores the need to understand how specific changes in the dorsal horn network may affect responses to SCS, as differences in the mechanisms underlying different neuropathic pain syndromes may explain differential outcomes to SCS by etiology.

Progressive loss of inhibitory mechanisms occurs in conjunction with alterations in dorsal horn network connectivity, contributes to the progression of neuropathic pain, and is also not predicted by the Gate Control Theory. Loss of strong A-fiber mediated inhibition is evident in sensory dorsal horn neurons following a peripheral nerve lesion (Woolf and Wall, 1982), and at least some of this loss can be explained by the reduction in GABA-mediated IPSCs in the dorsal horn due to the death of GABAergic interneurons (Moore et al., 2002) or reductions in the amount of GABA released into the dorsal horn (von Hehn Christian et al., 2012). In particular, disruption of the expression of the KCC2 transporter following pathological changes in glial cell activity results in neuronal excitation when normally inhibitory GABAergic synapses are activated (Coull et al., 2005). Furthermore, activation of GABAergic inputs to neurons in which the KCC2 transporter is disrupted results in markedly increased levels of spontaneous and evoked activity in dorsal horn neurons (Keller et al., 2007), and dorsal horn projection neurons sensitized following a neurogenic injury may be "rescued" through the administration of the KCC2 activator CLP 257 (Lavertu et al., 2013). The role of KCC2 function in SCS remains unclear, as levels of KCC2 apparently do not correlate with increases in paw withdrawal threshold in neuropathic rats during SCS (Janssen et al., 2012), but understanding this relationship may provide insights into the specific inhibitory mechanisms underlying SCS. Finally, many nociceptive-specific neurons in superficial laminae of the dorsal horn receive polysynaptic excitatory inputs from Aβ fibers that are unmasked following the administration of bicuculline, suggesting that network changes combined with the loss of GABAergic inhibition both contribute to pathological nociception (Torsney and MacDermott, 2006; Torsney, 2011). The lack of accounting by clinical SCS treatment plans for pathological changes to the level of inhibition in the dorsal horn circuit may contribute to the degradation of SCS efficacy with continued disease progression (Taylor et al., 2005; Kumar et al., 2007), and understanding these changes may yield better treatment plans.

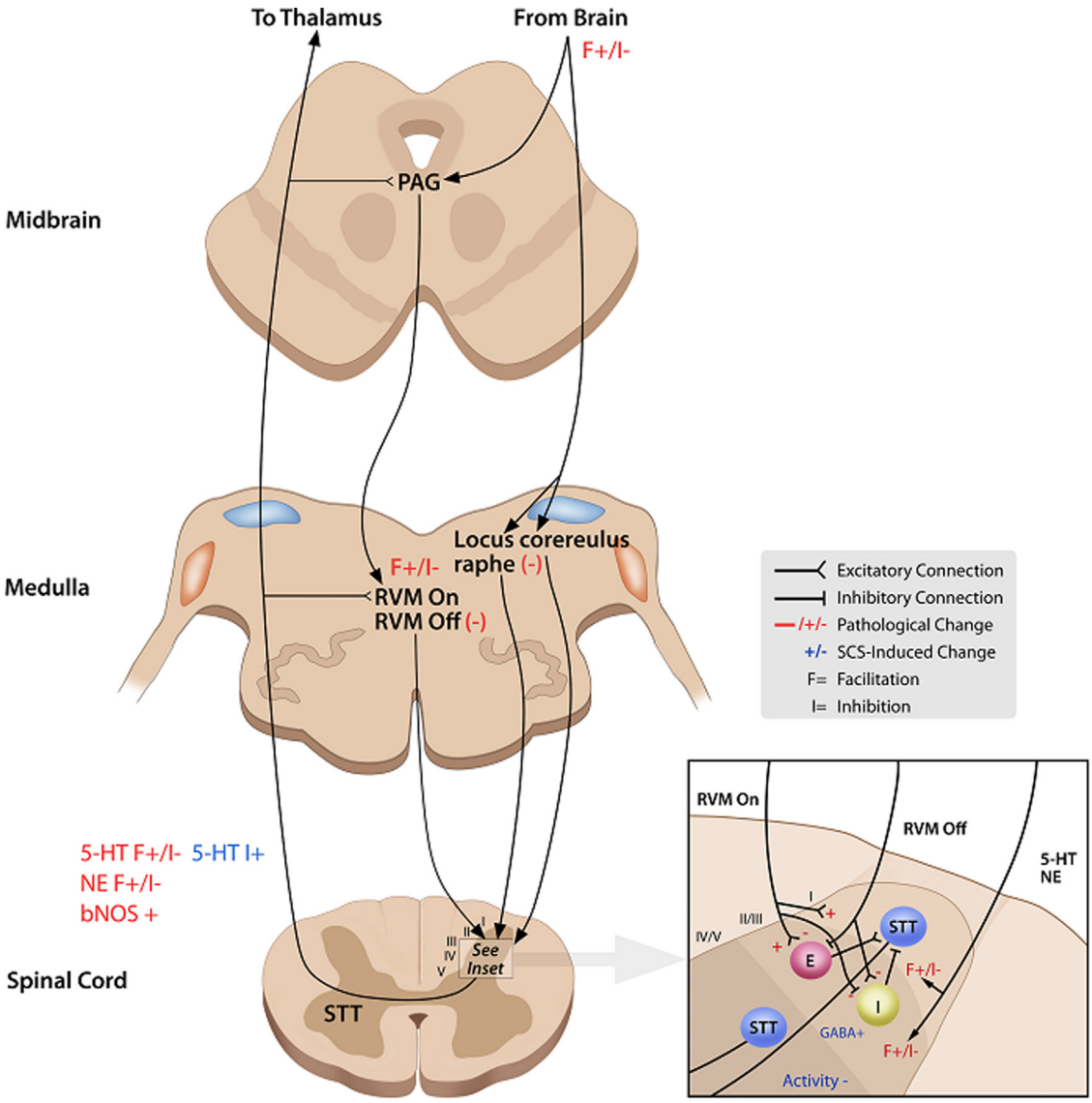

Fig. 3 – A schematic showing changes that occur to the circuitry and neurochemistry of supraspinal structures that exert descending modulation on the dorsal horn pain processing network during the induction and maintenance of neuropathic pain and during SCS. The progression of neuropathic pain involves but is not limited to imbalances in the relative levels of descending inhibition and facilitation and changes to the strengths of descending aminergic (5-HT, NE) connections.

2.3. *Supraspinal mechanisms*

In addition to segmental mechanisms, supraspinal projections play an important role in the development of neuropathic pain, and the mechanisms by which they contribute to the disruption of the balance of descending facilitation and inhibition have been reviewed elsewhere (Millan, 2002; Suzuki et al., 2004; Heinricher et al., 2009). Behavioral and electrophysiological studies also demonstrated that descending mechanisms play a role in SCS, they may be independent of segmental mechanisms (Tabet et al., 1986) (El-Khoury et al., 2002) (Fig. 3), and their temporal characteristics correlate with the period of pain relief that occurs after the cessation of SCS (Barchini et al., 2012).

Endogenous opioideric and serotoninergic (5-HT) systems are thought to be important in pain modulation, and both may contribute to pain relief from SCS. The degree to which opioidergic mechanisms contribute to SCS is controversial, as the administration of clinical doses of naloxone (up to 0.2 mg/kg) does not prevent SCS-mediated pain relief in humans (Freeman et al., 1983), but the administration of high doses of naloxone (10 mg/kg/h) eliminates some SCS-frequency dependent increases in paw withdrawal thresholds in rat models of neuropathic pain, suggesting that κ- and δ- rather than μ-opioid receptors may be involved in SCS (Sato et al., 2013). Opioidergic mechanisms may also be involved in other indications for SCS not covered by this review, such as SCS for angina (Ding et al., 2008). However, the role of 5-HT in modulating the behavioral effects of SCS for neuropathic pain is more clear: SCS efficacy and levels of 5-HT in the spinal cord of neuropathic rats are correlated (Song et al., 2009), and descending serotoninergic connections affected by

SCS modulate both $GABA_A$ and $GABA_B$ synapses (Song et al., 2011) independently of segmental mechanisms (Barchini et al., 2012). The relationship between 5-HT and GABA, particularly as it relates specifically to 5-HT_2, 5-HT_3, and 5-HT_4 receptors, is also a topic of recent interest and has been reviewed elsewhere (Guan, 2012), and understanding these mechanisms may lead to the development of novel treatment regimens that exploit serotoninergic pathways.

Despite progress in understanding 5-HT mechanisms underlying SCS, knowledge regarding the specific neuronal connections and circuits that mediate descending modulation remains sparse. The rostroventromedial medulla, considered to be a major source of descending facilitation and inhibition, receives ascending inputs from dorsal horn neurons (Millan, 2002; Heinricher et al., 2009), sends direct axonal projections to the dorsal horn (Fields et al., 1995), and affects the activity of both interneurons and projection neurons in the dorsal horn (Giesler et al., 1981; Heinricher et al., 2009). Recent work has also revealed direct effects by SCS on supraspinal neurons: neurons in the locus coeruleus exhibit more activity during SCS in neuropathic rats that show increased paw withdrawal thresholds than in non-responding rats, supporting the idea that SCS acts by modulating the activity of a spinal-supraspinal loop (Song et al., 2013). However, the specific connections between the dorsal horn and supraspinal centers that drive this activity are unknown. Further exploration of the links between SCS and RVM activity and the effects on descending facilitation and inhibition of such a link (Fig. 3) could provide new insights into the mechanisms underlying SCS and lead to the development of more effective therapies, especially as these circuits are believed to play a role in other forms of neuromodulation for pain, such as motor cortex stimulation (Viisanen and Pertovaara, 2010).

2.4. *The Pain Matrix*

The Pain Matrix, or the network of brain structures involved in pain processing in the brain, also plays a complex and critical role in the perception and evaluation of pain, and SCS may provide pain relief through its effects on the Pain Matrix (Tracey and Mantyh, 2007) (Fig. 4). Dorsal column stimulation alters the electrical activity of neurons in the thalamus and the somatosensory cortices (SI/SII) (Bantli et al., 1975; Qin et al., 2009), and more recent imaging studies led to the identification of specific relevant brain regions. Functional magnetic resonance imaging (fMRI) found that effective SCS was accompanied by increased activation of SI/SII; however, this study did not probe other regions of the brain or differentiate between SI/SII activation due to pain or paresthesia (Kiriakopoulos et al., 1997). A more comprehensive positron emission tomography (PET) imaging study in patients undergoing SCS effective for angina revealed increased activity in the ventrolateral PAG, left pulvinar (thalamus), left medial temporal gyrus, medial prefrontal cortex bilaterally, caudate nucleus, and posterior cingulate cortex and decreased activity in posterior insula, right inferior temporal gyrus, right inferior frontal gyrus, and right anterior cingulate cortex (Hautvast et al., 2006). As well, fMRI imaging during SCS effective for angina demonstrated that increased activation of cortical regions due to acute noxious stimuli, although extensive, are largely unaffected by SCS, suggesting that SCS specifically affects the activity of brain regions

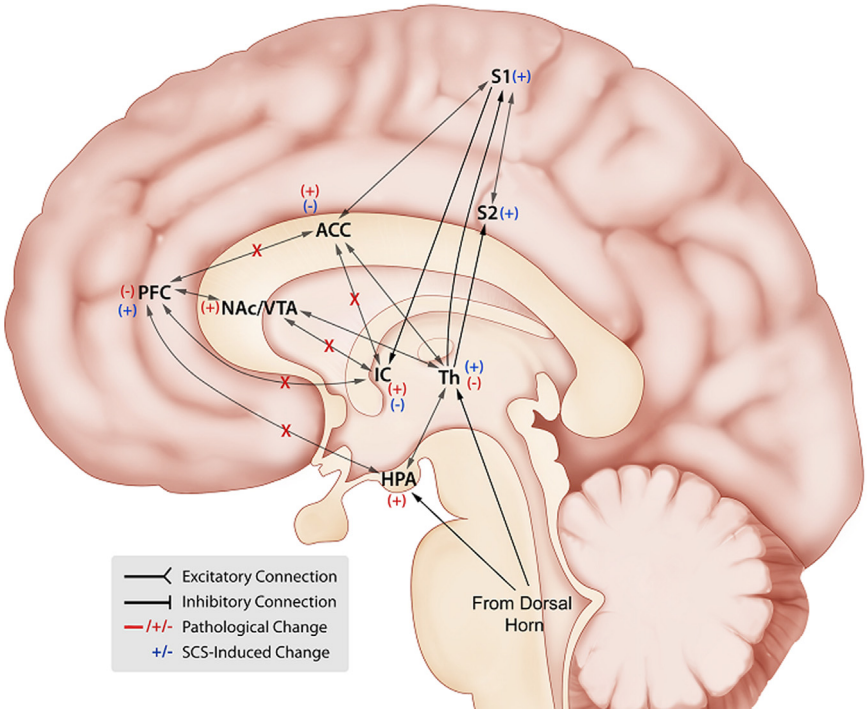

Fig. 4 – A schematic showing changes that occur to brain activation and the Pain Matrix during the progression of neuropathic pain and during SCS. The effects of SCS on the neurochemical brain are not well understood, but SCS has been shown to affect the activation of brain regions associated with pathological pain.

associated with the processing of pathological pain (Stancák et al., 2008).

Although a promising avenue of further research, few conclusions can currently be drawn about the effects of SCS on the Pain Matrix in neuropathic pain. Only three such studies assessing the effects of SCS on activity in the brain have been conducted, and they were primarily correlative in that they did not point to a specific network or changes in connectivity that could explain pain relief by SCS. In addition, these studies did not differentiate between changes in neural activity that underlie pain relief and changes that are epiphenomena associated with stimulation (e.g., paresthesia). Studies on the relationships between brain activity, pain, and modulation of the nervous system using electrical stimulation will delineate more clearly the neural networks involved in pain. In addition, the continued development of these ideas could lead to the formulation of fMRI activation profiles that signify pain and pain relief due to SCS, resulting in novel strategies for stimulation parameter selection or patient-specific treatments for pain (Bruehl et al., 2013).

3. Experimental models of SCS

The state of knowledge of both the underlying mechanisms of SCS and the most efficient and effective methods to deliver SCS remains incomplete. The effects of SCS on dorsal horn neurons are not entirely known, and the optimal set of stimulation parameters (electrode configuration, pulse duration, pulse amplitude, pulse repetition frequency) has yet to be determined. The combination of experiments in preclinical animal models and computational modeling has advanced the state of knowledge regarding the mechanisms of SCS and novel electrode geometries designed to deliver more spatially selective stimulation. The remainder of this review describes these experimental and computational approaches and their contributions to advancing SCS.

3.1. *Animal models and SCS*

Single unit recordings in anesthesized cats and non-human primates enabled characterized the excitatory and inhibitory effects of single pulses of dorsal column stimulation during natural peripheral inputs (brush, press, pinch, crush) and electrical stimulation of peripheral nerves (Hillman and Wall, 1969; Foreman et al., 1976; Lindblom et al., 1978). In some cases, neurons were specifically identified as projection neurons through stimulation of the contralateral spinothalamic tract (Hillman and Wall, 1969; Foreman et al., 1976). These studies provided experimental support for the Gate Control Theory and suggested that SCS had a net inhibitory effect on the activity of dorsal horn neurons. However, as these studies were conducted in healthy, anesthesized animals (Hillman and Wall, 1969; Foreman et al., 1976; Duggan and Foong, 1985), the relationship between SCS and behaviors associated with pathological pain could not be characterized, and the degree to which the results of these studies apply to neuropathic pain is unclear.

The development of rat models of chronic pain (Kim et al., 1997; Decosterd and Woolf, 2000) and protocols to assess awake animal behavior during SCS were vital to demonstrating that SCS can relieve pathological pain (Linderoth and Foreman, 2006). The first of these experiments demonstrated that decreases in mechanical withdrawal threshold following nerve injury were reversed by SCS (Meyerson et al., 1995). The role of segmental GABAergic systems (Cui et al., 1996, 1998), as well as descending 5-HT pathways (Song et al., 2011) in modulating the effects of SCS were clarified through the use of these behavioral models and have even led to clinical trials investigating the efficacy of combining SCS with GABAb agonists (Lind et al., 2008). However, a limitation in these studies is that they did not relate improvements in pain-related behaviors to activity of dorsal horn neurons, so only correlative relationships between pharmacological interventions and behavioral responses can be drawn from these studies. In other studies, SCS was shown to suppress the activity of dorsal horn neurons in neuropathic animals in response to natural stimulation of the hindpaw ipsilateral to sciatic nerve injury (Yakhnitsa et al., 1999), but pharmacological manipulations were not applied. More recent studies using neuropathic rats showed that SCS-mediated suppression of wind-up in dorsal horn neurons (Guan et al., 2010) and associated increases in mechanical withdrawal thresholds (Yang et al., 2011) are dependent on the activation of Aβ afferents originating from the injured nerve, but these studies did not verify that recorded neurons were projection neurons whose activity is directly correlated to pain (Simone et al., 1991). Recordings of the responses of projection neurons to SCS during pharmacological interventions and in neuropathic pain models are necessary to provide insights into the direct effects of SCS on pain suppression.

3.2. *Computational modeling of SCS*

Experimental models have contributed to understanding the neurophysiological mechanisms underlying pain relief by SCS, while computational models of SCS have been used to inform the development of electrodes capable of delivering targeted SCS. Motivation for early models of SCS by Coburn and colleagues came from “chance observations” (Coburn and Sin, 1985) that SCS could elicit effects on pain, motor deficits, bladder dysfunction, and a range of other disorders with spinal pathologies (e.g., spinal cord injury, cerebral palsy, peripheral vascular disease) (Cook and Weinstein, 1973; Illis et al., 1978, 1980). Coburn and colleagues developed finite element models of the electrical environment of the spinal cord and coupled them to simple biophysical models of neural elements present in the cord (Coburn, 1985; Coburn and Sin, 1985). Extracellular voltages calculated using these models were comparable to values recorded from both primate and human cadaver spinal cords (Coburn and Sin, 1985), and model-generated strength-duration relationships between axon excitation thresholds and stimulation pulse durations matched clinically observed relationships between stimulation amplitude, stimulation pulse width, and paresthesia threshold (Coburn, 1985). These results suggested that computational models of spinal cord anatomy and neuronal biophysics could be used together to model the clinical effects of SCS.

Subsequent model based design of innovative SCS electrodes incorporated more biophysical realism and increased understanding of how electrode geometries and tissue properties affect SCS efficacy. Holsheimer and colleagues added anisotropy and inhomogeneity to tissue electrical properties and determined the electrical and geometric factors that contributed most to determining the neural elements activated by SCS (Struijk et al., 1991, 1992, 1993a, 1993b; Holsheimer and Wesselink, 1997; Wesselink et al., 1998a, 1998b). Furthermore, these anatomically -based models revealed that the medial-lateral position of the electrode (Struijk et al., 1991), the thickness of the cerebrospinal fluid layer (Struijk et al., 1991), the curvature of dorsal root fibers (Struijk et al., 1992, 1993b), and the presence of axon collaterals (Struijk et al., 1992, 1993b) all substantially affected thresholds of dorsal column fibers. Importantly, the modeling results were validated by clinical measurements of paresthesias (Struijk et al., 1993a). Using these models, Holsheimer and colleagues developed a "guarded tripole" electrode geometry that preferentially depolarized dorsal column fibers over dorsal root fibers and exhibited the capability to activate more selectively the dorsal column fibers originating from the site of peripheral pain. This design was predicted to be an improvement over previous electrode configurations, as the increased dorsal column fiber selectivity was expected to provide better paresthesia coverage over the source of pain, corresponding to better "gating" according to the Gate Control theory (Shealy et al., 1972) as well as reduced parethesias from regions beyond the source of pain due to dorsal root activation (Holsheimer and Wesselink, 1997; Aló and Holsheimer, 2002). The design was used in a clinical study to estimate the diameters of activated dorsal column fibers at various points along the spinal cord (Holsheimer and Wesselink, 1997; Wesselink et al., 1998a, 1998b) The results of this experiment provided data on the realistic morphology and distribution of fibers in the dorsal column that can be used in future electrode designs, and recent SCS electrodes have employed the "guarded tripole" geometry with varying degrees of clinical success (Wesselink et al., 1998b; Alo et al., 2002; Butyen, 2003; Abejon et al., 2005). Further development and refinement of finite element models of spinal cord stimulation have allowed computational assessments of the neural elements activated by SCS (Aló and Holsheimer, 2002) and the development of electrode geometries capable of focusing stimulation to specific regions of the dorsal horn (Sankarasubramanian et al., 2011).

Implicit in finite element modeling studies of SCS is that the Gate Control Theory sufficiently describes the neural network of the dorsal horn and therefore the neurophysiological basis of pain relief due to SCS (Holsheimer, 2002). However, the effects of SCS on the dorsal horn pain circuit have not been explicitly modeled. Although biophysical models of many neuron types and neuronal systems are numerous and frequently used (Hines and Carnevale, 1997), very few models of dorsal horn neurons have been published, and to date, no network models are capable of reproducing the inhibitory effects of SCS. Existing models of dorsal horn neurons represent tonic (Melnick et al., 2004; Prescott and De Koninck, 2005), phasic (Prescott et al., 2008), and single-spiking (Prescott et al., 2008) cells and reproduce observations made from isolated dorsal horn neurons, but these neuronal models work in isolation rather than within a functional dorsal horn network. The few network models of the dorsal horn that exist are either pure mathematical functions (Britton et al., 1996; Britton and Skevington, 1996), or biophysical models (Farajidavar et al., 2008; Aguiar et al., 2010) that do not reproduce A-fiber inhibition, thus limiting their utility in modeling the effects of SCS. The development of network models of pain circuits in the dorsal horn and supraspinal centers will enable the development of more effective SCS treatment strategies.

4. Conclusion

SCS is a promising surgical treatment for chronic pain refractory to conservative medical management. The plateau in clinical efficacy reflects an incomplete understanding of the systems underlying pain and points to the need to consider the neural circuits and systems involved in chronic pain and its treatment. Although some efforts have been undertaken to determine the connectivity of neurons in the dorsal horn and how SCS interacts with these networks, the true nature of the dorsal horn pain processing circuit and supraspinal (midbrain and cortical) influences of SCS remain poorly understood and present opportunities for future research. A combination of experimental studies to identify and characterize the specific neural elements affected by SCS and the development of computational biophysical models of the dorsal horn network will provide greater insight into both the neural substrate of pain, the transition from acute to chronic pain, and the effects of SCS on pain transmission. This knowledge, when combined with existing computational models of SCS and animal models of pain, will pave the way to new approaches to improve the clinical efficacy of SCS and, ultimately, the quality of life of patients suffering from chronic pain.

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REFERENCES

Abejon, D., Reg, E., Pozo, C.d., Contreras, R., Insausti, J., 2005. Dual spinal cord stimulation for complex pain: preliminary study. Neuromodulation 8, 105–111.

Aguiar, P., Sousa, M., Lima, D., 2010. NMDA channels together with L-type calcium currents and calcium-activated nonspecific cationic currents are sufficient to generate windup in WDR neurons. J. Neurophysiol. 104, 1155–1166.

Al-Kaisy A., Van Buyten J.-P., Smet I., Palmisani S., Pang D., Smith T., 2014. 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 medicine n/a-n/a.

Aló, K.M., Holsheimer, J., 2002. New trends in neuromodulation for the management of neuropathic pain. Neurosurgery 50, 690–704.

Alo, K.M., Redko, V., Charnov, J., 2002. Four year follow-up of dual electrode spinal cord stimulation for chronic pain. Neuromodulation 5, 79–88.

Bantli, H., Bloedel, J., Thienprasit, P., 1975. Supraspinal interactions resulting from experimental dorsal column stimulation. J. Neurosurg. Pediatr. 42, 296–300.

Barchini, J., Tchachaghian, S., Shamaa, F., Jabbur, S., Meyerson, B., Song, Z., Linderoth, B., Saade, N., 2012. Spinal segmental and supraspinal mechanisms underlying the pain-relieving effects of spinal cord stimulation: an experimental study in a rat model of neuropathy. Neuroscience 215, 196–208.

Bleakman, D., Alt, A., Nisenbaum, E.S., 2006. Glutamate receptors and pain. Semin. Cell Dev. Biol. 17, 592–604.

Blomqvist, A., Craig, A.D., 2000. Is neuropathic pain caused by the activation of nociceptive-specific neurons due to anatomic sprouting in the dorsal horn?. J. Comp. Neurol. 428, 1–4.

Britton, N.F., Chaplain, M.A.J., Skevington, S.M., 1996. The role of N-methyl-D-aspartate (NMDA) receptors in wind-up: a mathematical model. Math. Med. Biol. 13, 193–205.

Britton, N.F., Skevington, S.M., 1996. On the mathematical modelling of pain. Neurochem. Res. 21, 1133–1140.

Bruehl, S., Apkarian, A.V., Ballantyne, J.C., Berger, A., Borsook, D., Chen, W.G., Farrar, J.T., Haythornthwaite, J.A., Horn, S.D., Iadarola, M.J., Inturrisi, C.E., Lao, L., Mackey, S., Mao, J., Sawczuk, A., Uhl, G. R., Witter, J., Woolf, C.J., Zubieta, J.-K., Lin, Y., 2013. Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges. J. Pain 14, 103–113.

Butyen, J.-P.V., 2003. The performance and safety of an implantable spinal cord stimulation system in patients with chronic pain: a 5-year study. Neuromodulation 6, 79–87.

Cameron, T., 2004. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J. Neurosurg. Spine 100, 254–267.

Campbell, J.N., Meyer, R.A., 2006. Mechanisms of neuropathic pain. Neuron 52, 77–92.

Chung, J.M., Kenshalo, D.R., Gerhart, K.D., Willis, W.D., 1979. Excitation of primate spinothalamic neurons by cutaneous C-fiber volleys. J. Neurophysiol. 42, 1354–1369.

Coburn, B., 1985. A theoretical study of epidural electrical stimulation of the spinal cord—Part II: Effects on long myelinated fibers. IEEE Trans. Biomed. Eng. 32, 978–986.

Coburn, B., Sin, W.K., 1985. A theoretical study of epidural electrical stimulation of the spinal cord—Part I: Finite element analysis of stimulus fields. IEEE Trans. Biomed. Eng. 32, 971–977.

Coghill, R.C., Mayer, D.J., Price, D.D., 1993. Wide dynamic range but not nociceptive-specific neurons encode multidimensional features of prolonged repetitive heat pain. J. Neurophysiol. 69, 703–716.

Cook, A.W., Weinstein, S.P., 1973. Chronic dorsal column stimulation in multiple sclerosis. Preliminary report. N. Y. State J. Med. 73, 2868–2872.

Coull, J.A., Beggs, S., Boudreau, D., Boivin, D., Tsuda, M., Inoue, K., Gravel, C., Salter, M.W., De Koninck, Y., 2005. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature 438, 1017–1021.

Cui, J.-G., Linderoth, B., Meyerson, B.A., 1996. Effects of spinal cord stimulation on touch-evoked allodynia involve GABAergic mechanisms. An experimental study in the mononeuropathic rat. Pain 66, 287–295.

Cui, J., Meyerson, B., Sollevi, A., Linderoth, B., 1998. Effect of spinal cord stimulation on tactile hypersensitivity in mononeuropathic rats is potentiated by simultaneous GABAB and adenosine receptor activation. Neurosci. Lett. 247, 183–186.

Decosterd, I., Woolf, C.J., 2000. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain 87, 149–158.

Ding, X., Hua, F., Sutherly, K., Ardell, J.L., Williams, C.A., 2008. C2 spinal cord stimulation induces dynorphin release from rat T4 spinal cord: potential modulation of myocardial ischemia-sensitive neurons. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R1519.

Dubuisson, D., 1989. Effect of dorsal-column stimulation on gelatinosa and marginal neurons of cat spinal cord. J. Neurosurg. 70, 257–265.

Duggan, A.W., Foong, F.W., 1985. Bicuculline and spinal inhibition produced by dorsal column stimulation in the cat. Pain 22, 249–259.

El-Khoury, C., Hawwa, N., Baliki, M., Atweh, S., Jabbur, S., Saade, N., 2002. Attenuation of neuropathic pain by segmental and supraspinal activation of the dorsal column system in awake rats. Neuroscience 112, 541–553.

Farajidavar, A., Saeb, S., Behbehani, K., 2008. Incorporating synaptic time-dependent plasticity and dynamic synapse into a computational model of wind-up. Neural Net. 21, 241–249.

Fields, H.L., Malick, A., Burstein, R., 1995. Dorsal horn projection targets of ON and OFF cells in the rostral ventromedial medulla. J. Neurophysiol. 74, 1742–1759.

Foreman, R.D., Beall, J.E., Coulter, J.D., Willis, W.D., 1976. Effects of dorsal column stimulation on primate spinothalamic tract neurons. J. Neurophysiol. 39, 534–546.

Freeman, T.B., Campbell, J.N., Long, D.M., 1983. Naloxone does not affect pain relief induced by electrical stimulation in man. Pain 17, 189–195.

Giesler Jr, G., Gerhart, K., Yezierski, R., Wilcox, T., Willis, W., 1981. Postsynaptic inhibition of primate spinothalamic neurons by stimulation in nucleus raphe magnus. Brain Res. 204, 184–188.

Goff, J., Burkey, A., Goff, D., Jasmin, L., 1997. Reorganization of the spinal dorsal horn in models of chronic pain: correlation with behaviour. Neuroscience 82, 559–574.

Guan, Y., 2012. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. Curr. Pain Headache Rep. 16, 217–225.

Guan, Y., Wacnik, P.W., Yang, F., Carteret, A.F., Chung, C.-Y., Meyer, R.A., Raja, S.N., 2010. Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 113, 1392–1405.

Hautvast, R., Horst, G., DeJong, B., DeJongste, M., Blanksma, P., Paans, A., Korf, J., 2006. Relative changes in regional cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris. Eur. J. Neurosci. 9, 1178–1183.

Heinricher, M.M., Tavares, I., Leith, J.L., Lumb, B.M., 2009. Descending control of nociception: specificity, recruitment and plasticity. Brain Res. Rev. 60, 214–225.

Hillman, P., Wall, P.D., 1969. Inhibitory and excitatory factors influencing the receptive fields of lamina 5 spinal cord cells. Exp. Brain Res. 9, 284–306.

Hines, M.L., Carnevale, N.T., 1997. The NEURON simulation environment. Neural Comput. 9, 1179–1209.

Holsheimer, J., 2002. Which neuronal elements are activated directly by spinal cord stimulation. Neuromodulation 5, 25–31.

Holsheimer, J., Wesselink, W., 1997. Optimum electrode geometry for spinal cord stimulation: the narrow bipole and tripole. Med. Biol. Eng. Comput. 35, 493–497.

Hwang, J.H., Yaksh, T.L., 1997. The effect of spinal GABA receptor agonists on tactile allodynia in a surgically-induced neuropathic pain model in the rat. Pain 70, 15–22.
Illis L.S., Sedgwick E.M., Tallis R.C. (1978) Clinical results of spinal cord stimulation. In: Proceedings of the VIIth International Symposium Exern Contr Human Extremities, 523–523 Dubrovnick, Yugoslavia.
Illis L.S., Sedgwick E.M., Tallis R.C., 1980. Spinal cord stimulation in multiple sclerosis: clinical results. J. Neurol. Neurosurg. Psychiatry 43, 1-14.
Janssen, S., Gerard, S., Raijmakers, M., Truin, M., Van Kleef, M., Joosten, E., 2012. Decreased intracellular GABA levels contribute to spinal cord stimulation-induced analgesia in rats suffering from painful peripheral neuropathy: the role of KCC2 and GABA< sub> A</sub> receptor-mediated inhibition. Neurochem. Int. 60, 21–30.
Kawamata, M., Koshizaki, M., Shimada, S.G., Narimatsu, E., Kozuka, Y., Takahashi, T., Namiki, A., Collins, J.G., 2005. Changes in response properties and receptive fields of spinal dorsal horn neurons in rats after surgical incision in hairy skin. Anesthesiology 102, 141–151.
Keller, A.F., Beggs, S., Salter, M.W., De Koninck, Y., 2007. Transformation of the output of spinal lamina I neurons after nerve injury and microglia stimulation underlying neuropathic pain. Mol. Pain 3, 27.
Kim, K.J., Yoon, Y.W., Chung, J.M., 1997. Comparison of three rodent neuropathic pain models. Exp. Brain Res. 113, 200–206.
Kiriakopoulos, E.T.M.D., Tasker, R.R.M.D., Nicosia, S.M.A., Wood, M.L. P., Mikulis, D.J.M.D., 1997. Functional magnetic resonance imaging: a potential tool for the evaluation of spinal cord stimulation: technical case report. Neurosurgery August 41, 501–504.
Kohno, T., Moore, K., Baba, H., Woolf, C., 2003. Peripheral nerve injury alters excitatory synaptic transmission in lamina II of the rat dorsal horn. J. Physiol. 548, 131–138.
Kumar, K., Malik, S., Demeria, D., 2002. Treatment of chronic pain with spinal cord stimulation versus alternative therapies: cost-effectiveness analysis. Neurosurgery July 51, 106–116.
Kumar, K., Rizvi, S., 2013. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. Pain Med..
Kumar, K., Taylor, R.S., Jacques, L., Eldabe, S., Meglio, M., Molet, J., Thomson, S., O'Callaghan, J., Eisenberg, E., Milbouw, G., Buchser, E., Fortini, G., Richardson, J., North, R.B., 2007. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 132, 179–188.
Kumar, K., Toth, C., Nath, R.K., Laing, P., 1998. Epidural spinal cord stimulation for treatment of chronic pain—some predictors of success. A 15-year experience. Surg. Neurol. 50, 110–121.
Lavertu, G., Côté, S.L., De Koninck, Y., 2013. Enhancing K–Cl co-transport restores normal spinothalamic sensory coding in a neuropathic pain model. Brain.
Lekan, H.A., Carlton, S.M., 1995. Glutamatergic and GABAergic input to rat spinothalamic tract cells in the superficial dorsal horn. J. Comp. Neurol. 361, 417–428.
Lind, G., Schechtmann, G., Winter, J., Meyerson, B.A., Linderoth, B., 2008. Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: long-term outcome of a pilot study. Eur. J. Pain 12, 132–136.
Lind, G., Meyerson, B.A., Winter, J., Linderoth, B., 2004. Intrathecal baclofen as adjuvant therapy to enhance the effect of spinal cord stimulation in neuropathic pain: a pilot study. Eur J Pain 8, 377–383.
Lind G., Schechtmann G., Winter J., Linderoth B., 2007. Drug-enhanced spinal stimulation for pain: a new strategy. In: Operative Neuromodulation, Springer, pp 57–63.
Lindblom, U., Meyerson, B.A., 1975. Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. Pain 1, 257–270.
Lindblom, U., Tapper, D.N., Wiesenfeld, Z., 1978. The effect of dorsal column stimulation on the nociceptive response of dorsal horn cells and its relevance for pain suppression. Pain 4, 133–144.
Linderoth, B., Foreman, R.D., 1999. Physiology of spinal cord stimulation: review and update. Neuromodulation 2, 150–164.
Linderoth, B., Foreman, R.D., 2006. Mechanisms of spinal cord stimulation in painful syndromes: role of animal models. Pain Med. 7, S14–S26-S14-S26.
Linderoth, B., Foreman, R.D., Meyerson, B.A., 2009. Mechanisms of action of spinal cord stimulation. Textbook of Stereotactic and Functional Neurosurgery, 2331-2348. McGraw Hillpp.
Melnick, I.V., Santos, S.F.A., Szokol, K., Szucs, P., Safronov, B.V., 2004. Ionic basis of tonic firing in spinal substantia gelatinosa neurons of rat. J. Neurophysiol. 91, 646–655.
Melzack, R., Wall, P.D., 1965. Pain mechanisms: a new theory. Science 150, 971–979.
Menetrey, D., Giesler Jr, G., Besson, J., 1977. An analysis of response properties of spinal cord dorsal horn neurones to nonnoxious and noxious stimuli in the spinal rat. Exp. Brain Res. 27, 15–33.
Meyerson, B.A., Linderoth, B., 2003. Spinal cord stimulation: mechanisms of action in neuropathic and ischemic pain. Electrical Stimulation and the Relief of Pain, vol. 15. The Netherlands: Elsevier B.V161–182.
Meyerson, B.A., Ren, B., Herregodts, P., Linderoth, B., 1995. Spinal cord stimulation in animal models of mononeuropathy: effects on the withdrawal response and the flexor reflex. Pain 61, 229–243.
Millan, M., 2002. Descending control of pain. Prog. Neurobiol. 66, 355–474.
Moore, K., Kohno, T., Karchewski, L., Scholz, J., Baba, H., Woolf, C., 2002. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. J. Neurosci. 22, 6724–6731.
North, R.B., Kidd, D.H., Zahurak, M., James, C.S., Long, D.M., 1993. Spinal cord stimulation for chronic, intractable pain: experience over two decades. Neurosurgery 32, 384–395.
Oakley, J.C., Prager, J.P., 2002. Spinal cord stimulation: mechanisms of action. Spine 27, 2574–2583.
Prescott, S.A., De Koninck, Y., 2005. Integration time in a subset of spinal lamina I neurons is lengthened by sodium and calcium currents acting synergistically to prolong subthreshold depolarization. J. Neurosci. 25, 4743–4754.
Prescott, S.A., De Koninck, Y., Sejnowski, T.J., 2008. Biophysical basis for three distinct dynamical mechanisms of action potential initiation. PLoS Comput. Biol. 4, e1000198.
Prescott, S.A., Ratté, S., 2012. Pain processing by spinal microcircuits: afferent combinatorics. Curr. Opin. Neurobiol. 22, 631–639.
Qin, C., Yang, X., Wu, M., Farber, J.P., Linderoth, B., Foreman, R.D., 2009. Modulation of neuronal activity in dorsal column nuclei by upper cervical spinal cord stimulation in rats. Neuroscience 164, 770–776.
Sankarasubramanian, V., Buitenweg, J., Holsheimer, J., Veltink, P., 2011. Electrode alignment of transverse tripoles using a percutaneous triple-lead approach in spinal cord stimulation. J. Neural Eng. 8, 016010.
Sato, K., King, E., Johanek, L., Sluka, K., 2013. Spinal cord stimulation reduces hypersensitivity through activation of opioid receptors in a frequency-dependent manner. Eur. J. Pain 17, 551–561.
Schechtmann, G., Lind, G., Winter, J., Meyerson, B.A., Linderoth, B., 2010. Intrathecal clonidine and baclofen enhance the

pain-relieving effect of spinal cord stimulation: a comparative placebo-controlled, randomized trial. Neurosurgery 67, 173–181.
Shealy, C.N., Mortimer, J., Hagfors, N.R., 1972. Dorsal column electroanalgesia. Survey Anesthesiol. 16, 15–16.
Shechter, R., Yang, F., Xu, Q., Cheong, Y.-K., He, S.-Q., Sdrulla, A., Carteret, A.F., Wacnik, P.W., Dong, X., Meyer, R.A., 2013. Conventional and kilohertz-frequency spinal cord stimulation produces intensity-and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. Anesthesiology 119, 422–432.
Simone, D.A., Sorkin, L.S., Oh, U., Chung, J.M., Owens, C., LaMotte, R. H., Willis, W.D., 1991. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J. Neurophysiol. 66, 228–246.
Sivilotti, L., Woolf, C.J., 1994. The contribution of GABAA and glycine receptors to central sensitization: disinhibition and touch-evoked allodynia in the spinal cord. J. Neurophysiol. 72, 169–179.
Smits, H., van Kleef, M., Joosten, E.A., 2012. Spinal cord stimulation of dorsal columns in a rat model of neuropathic pain: evidence for a segmental spinal mechanism of pain relief. Pain 153, 177–183.
Song, Z., Ansah, O., Meyerson, B., Pertovaara, A., Linderoth, B., 2013. Exploration of supraspinal mechanisms in effects of spinal cord stimulation: role of the locus coeruleus. Neuroscience 253, 426–434.
Song, Z., Meyerson, B.A., Linderoth, B., 2011. Spinal 5-HT receptors that contribute to the pain-relieving effects of spinal cord stimulation in a rat model of neuropathy. Pain 152, 1666–1673.
Song, Z., Ultenius, C., Meyerson, B.A., Linderoth, B., 2009. Pain relief by spinal cord stimulation involves serotonergic mechanisms: an experimental study in a rat model of mononeuropathy. Pain 147, 241–248.
Song, Z., Viisanen, H., Meyerson, B.A., Pertovaara, A., Linderoth, B., 2014. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodul.: Technol. Neural Interface.
Stancák, A., Kozák, J., Vrba, I., Tintera, J., Vrána, J., Polácek, H., Stancák, M., 2008. Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome patients. Eur. J. Pain 12, 137.
Struijk, J., Holsheimer, J., van der Heide, G., Boom, H., 1992. Recruitment of dorsal column fibers in spinal cord stimulation: influence of collateral branching. IEEE Trans. Biomed. Eng. 39, 903–912.
Struijk, J.J., Holsheimer, J., Barolat, G., He, J., Boom, H.B.K., 1993a. Paresthesia thresholds in spinal cord stimulation: a comparison of theoretical results with clinical data. IEEE Trans. Rehabil. Eng. 1, 101–108.
Struijk, J.J., Holsheimer, J., Boom, H.B.K., 1993b. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. IEEE Trans. Biomed. Eng. 40, 632–639.
Struijk, J.J., Holsheimer, J., van Veen, B.K., Boom, H.B.K., 1991. Epidural spinal cord stimulation: calculation of field potentials with special reference to dorsal column nerve fibers. IEEE Trans. Biomed. Eng. 38, 104–110.
Suzuki, R., Rygh, L., Dickenson, A., 2004. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol. Sci. 25, 613–617.
Szucs, P., Luz, L.L., Pinho, R., Aguiar, P., Antal, Z., Tiong, S.Y.X., Todd, A.J., Safronov, B.V., 2013. Axon diversity of lamina I local-circuit neurons in the lumbar spinal cord. J. Comp. Neurol. 521, 2719–2741.
Tabet, M.S., Soueidan, S.A., Bitar, M., Atweh, S.F., Jabbur, S.J., 1986. Supraspinal modulation of nociception in awake rats by stimulation of the dorsal column nuclei. Brain Res. 369, 307–310.
Taylor, R., Van Buyten, J., Buchser, E., 2005. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. Spine 30, 152–160.
Taylor, R.S., Desai, M.J., Rigoard, P., Taylor, R.J., 2013. Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. Pain Pract.
Todd, A.J., 2010. Neuronal circuitry for pain processing in the dorsal horn. Nat. Rev. Neurosci. 11, 823–836.
Torsney, C., 2011. Inflammatory pain unmasks heterosynaptic facilitation in lamina I neurokinin 1 receptor-expressing neurons in rat spinal cord. J. Neurosci. 31, 5158–5168.
Torsney, C., MacDermott, A.B., 2006. Disinhibition opens the gate to pathological pain signaling in superficial neurokinin 1 receptor-expressing neurons in rat spinal cord. J. Neurosci. 26, 1833–1843.
Tracey, I., Mantyh, P.W., 2007. The cerebral signature for pain perception and its modulation. Neuron 55, 377–391.
Turner, J., Loeser, J., Deyo, R., Sanders, S., 2004. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain 108, 137–147.
Viisanen, H., Pertovaara, A., 2010. Roles of the rostroventromedial medulla and the spinal 5-HT1A receptor in descending antinociception induced by motor cortex stimulation in the neuropathic rat. Neurosci. Lett. 476, 133–137.
von Hehn Christian, A., Baron, R., Woolf Clifford, J., 2012. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 73, 638–652.
Wall, P.D., Melzack, R., 1996. Textbook of Pain. Churchill Livingstone, Edinburgh.
Wallin, J., Fiskå, A., Tjølsen, A., Linderoth, B., Hole, K., 2003. Spinal cord stimulation inhibits long-term potentiation of spinal wide dynamic range neurons. Brain Res. 973, 39–43.
Wesselink, W.A., Holsheimer, J., Boom, H.B.K., 1998a. Analysis of current density and related parameters in spinal cord stimulation. IEEE Trans. Rehabil. Eng. 6, 200–207.
Wesselink, W.A., Holsheimer, J., Nuttin, B., Boom, H.B.K., King, G.W., Gybels, J.M., de Sutter, P., 1998b. Estimation of fiber diameters in the spinal dorsal columns from clinical data. IEEE Trans. Rehabil. Eng. 45, 1355–1362.
Willis, W.D., Trevino, D.L., Coulter, J.D., Maunz, R.A., 1974. Responses of primate spinothalamic tract neurons to natural stimulation of hindlimb. J. Neurophysiol. 37, 358–372.
Woolf, C., Wall, P., 1982. Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. Brain Res. 242, 77–85.
Woolf, C.J., Shortland, P., Coggeshall, R.E., 1992. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature 355, 75–78.
Woolf, C.J., Shortland, P., Reynolds, M., Ridings, J., Doubell, T., Coggeshall, R.E., 1995. Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy. J. Comp. Neurol. 360, 121–134.
Woolf, C.J.W., 2011. Central sensitization: implications for the diagnosis and treatment of pain. Pain 152, S2–S15-S12-S15.
Yakhnitsa, V., Linderoth, B., Meyerson, B.A., 1999. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. Pain 79, 223–233.
Yang, F., Carteret, A., Wacnik, P., Chung, C.-Y., Xing, L., Dong, X., Meyer, R., Raja, S., Guan, Y., 2011. 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 199, 470–480.

Yang, F., Xu, Q., Cheong, Y.K., Shechter, R., Sdrulla, A., He, S.Q., Tiwari, V., Dong, X., Wacnik, P.W., Meyer, R., Raja, S.N., Guan, Y., 2014. Comparison of intensity-dependent inhibition of spinal wide-dynamic range neurons by dorsal column and peripheral nerve stimulation in a rat model of neuropathic pain. Eur. J. Pain.

Zeilhofer, H.U., Wildner, H., Yévenes, G.E., 2012. Fast synaptic inhibition in spinal sensory processing and pain control. Physiol. Rev. 92, 193–235.

Zheng, J., Lu, Y., Perl, E.R., 2010. Inhibitory neurones of the spinal substantia gelatinosa mediate interaction of signals from primary afferents. J. Physiol. 588, 2065–2075.