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Dorsal root ganglion stimulation for chronic pain: Hypothesized mechanisms of action

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Abstract

Dorsal root ganglion stimulation (DRGS) is a neuromodulation therapy for chronic pain that is refractory to conventional medical management. Currently, the mechanisms of action of DRGS-induced pain relief are unknown, precluding both our understanding of why DRGS fails to provide pain relief to some patients and the design of neurostimulation technologies that directly target these mechanisms to maximize pain relief in all patients. Due to the heterogeneity of sensory neurons in the dorsal root ganglion (DRG), the analgesic mechanisms could be attributed to the modulation of one or many cell types within the DRG and the numerous brain regions that process sensory information. Here, we summarize the leading hypotheses of the mechanisms of DRGS-induced analgesia, and propose areas of future study that will be vital to improving the clinical implementation of DRGS.

Keywords

dorsal root ganglion stimulation; electric stimulation; chronic pain; neuropathic pain; implanted neurostimulators

Introduction

Chronic pain remains one of the world's largest public health challenges, affecting hundreds of millions of people throughout the world.[66] Neurostimulation therapies are important tools in a pain physician's clinical toolbox to manage chronic pain conditions that are refractory to conventional medical management. Spinal cord stimulation (SCS) has been a mainstay neurostimulation therapy for chronic pain for more than 50 years, and is an effective tool

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in managing intractable neuropathic pain in the lower limbs.[73] Despite the overall success of SCS in treating many chronic pain conditions (e.g., failed back surgery syndrome), pain in specific areas, such as the groin, foot, low back, and knee, are difficult to accurately target with SCS. The complex anatomy of the spinal column, posture-related motion of the spinal cord in the thecal sac, and shunting of electrical current in the cerebrospinal fluid can limit the delivery of stimulation to the target fibers within the spinal cord.[67] Therefore, patients with intractable pain in regions that are difficult to target with SCS are often left with few alternatives, presenting a large need for innovations in neurostimulation for pain management.

Dorsal root ganglion stimulation (DRGS) is a novel neurostimulation therapy for managing medically refractory chronic pain.[25] As a single dorsal root ganglion (DRG) receives sensory information from a discrete region of the body, it was hypothesized that DRGS could be an effective strategy for managing pain in regions that are difficult to target with SCS. DRGS was approved by the United States Food and Drug Administration (FDA) in 2016 for the treatment of refractory complex regional pain syndrome (CRPS) in the lower limbs.[27] Despite currently only having FDA approval for CRPS in the lower limbs, DRGS has shown promise in managing other pain etiologies, such as painful diabetic neuropathy,[37] phantom limb pain,[36] and groin pain.[88] The ACCURATE clinical trial compared the safety and efficacy of SCS and DRGS in treating patients with intractable CRPS at 3 and 12 months post-implantation, and demonstrated that more patients were considered treatment successes (i.e., received ≥ 50% reduction in pain intensity) with DRGS than SCS.[26] However, a 50% reduction in pain intensity (measured via the visual analog scale (VAS)) does not always lead to an improved quality of life, or facilitate a patient returning to their activities of daily living.[57] Furthermore, more than a quarter of patients were not deemed treatment successes with DRGS, leaving them with few other pain management options because neurostimulation therapies are often a last-resort therapy in a clinician's treatment algorithm.[80] Presently, we do not have a clear scientific understanding of the physiological mechanisms of DRGS-induced pain relief. We believe that it is vital to elucidate these mechanisms, to: 1) understand why DRGS fails in some patients, to improve patient selection, and 2) innovate DRGS technologies to specifically target these mechanisms, to maximize pain relief in all patients.

Recently, there was an excellent review of human DRG anatomy;[51] therefore, we will highlight only the anatomy essential to understanding DRGS. The DRG is a swelling in the dorsal spinal root, which houses the cell bodies of all primary sensory neurons (PSNs) (Fig. 1) innervating a specific dermatome (i.e., region of the body). There are bilateral pairs of DRG at each vertebral level (Fig. 1A), which receive information from roughly the same dermatome on opposite sides of the body. All DRG are encased by the meninges of the spinal cord as the meninges transition into the epineurium surrounding peripheral nerves.[15] DRG reside in the neuroforamina (Fig. 1B), but the relative position of the DRG within the foramen may vary depending on the spinal level.[54] During the implantation of a DRGS system, electrode lead bodies are percutaneously inserted using a Touhy needle, guided through the epidural space of the spinal column using X-ray fluoroscopy, and routed into the intraforaminal space where the array of electrode contacts are placed along the dorsal side of

the DRG (Fig. 1A,B). The electrode lead(s) are connected to an implanted pulse generator, which resides in a body cavity usually around the posterior lateral flank.[28]

Extracellular electrical stimulation, like that utilized by DRGS, can affect different neural structures (e.g., cell bodies, axons, presynaptic terminals) depending on the parameters of the stimulus pulse (e.g., amplitude, frequency, pulse width, polarity).[78] Therefore, the morphological characteristics of DRG neurons, and their location in the DRG relative to the stimulating electrodes, will greatly affect which cells are being modulated by DRGS. Clinically, DRGS is typically applied with a bipolar stimulation configuration and a tonic pulse train with a pulse frequency around 20 Hz, a pulse duration between 200 and 300 μs, and a pulse amplitude on the order of several hundred μA to a few mA.[28] DRGS four-contact cylindrical electrode arrays are 1 mm in diameter with 1.25 mm long contacts, comparatively smaller than traditional SCS cylindrical electrode arrays.[6] The electrode is typically placed within the foramen such that the second and third contacts span the pedicle, with the second and third contacts typically assigned as the cathode and anode, respectively.[28] PSNs, the cells within the DRG, are pseudounipolar, i.e., their cell bodies have a single axon process called the stem axon, which bifurcates at a region called the T-junction into an axon that projects to the spinal cord (centrally projecting axon) and an axon that projects to the peripheral nervous system (peripherally projecting axon) (Fig. 1D).[29] Recent histological results demonstrated that in human lumbar DRG, cell bodies typically organize around the dorsomedial region of the ganglion, while axons of passage are more homogeneously distributed throughout the rest of the ganglion.[115] DRG cytoarchitecture is of great importance to the clinical implementation of DRGS (Fig. 1C). As distance from the stimulating electrode increases, extracellular potentials exponentially decrease, and therefore DRGS-induced activity may be focused on the most superficial neural elements. Such knowledge is crucial to designing stimulus waveforms that target the neural elements and PSN subtypes responsible for the pain-relieving effects of DRGS.

PSNs are a diverse class of neurons, with different types of neurons conveying different sensory modalities (e.g., touch, pain, itch). PSN axons are commonly classified as A-fibers (myelinated axons) and C-fibers (nonmyelinated axons). In this review, we will refer to DRG neurons with myelinated axons as A-neurons, and DRG neurons with nonmyelinated axons as C-neurons. C-neurons are traditionally thought to be nociceptors, though it is known that C-neurons consist of several molecularly defined subpopulations that convey a myriad of sensations, including innocuous or painful touch,[70] innocuous and painful thermal sensations,[55,127] chemical itch,[108] pleasant touch,[75] and some C-neurons code multiple types of sensations (i.e., polymodal C-neurons).[70,127] A-neurons are further stratified into Aα-, Aβ-, and Aδ-neurons. Aα-neurons are thickly myelinated, large-diameter muscle afferents, and can be further classified as group Ia neurons, which innervate muscle spindles and code muscle stretch, and Ib neurons which innervate golgi tendon organs and code muscle tension.[13] Aβ-neurons are also thickly myelinated, large-diameter afferents, though they are smaller in diameter than Aα-neurons. Aβ-neurons typically convey non-painful tactile stimuli,[1] though there have been reports of nociceptive signals conducted in the Aβ-fiber conduction velocity range,[8,32] and a subset of Aβ-neurons are important in transmitting mechanical itch.[93] Aδ-neurons are thinly myelinated, medium-diameter afferents, that typically convey innocuous or painful touch[31] or thermal sensations.[55] The

peripherally-projecting axon of a PSN terminates in a sensory end organ, depending on the type of sensations conveyed by that neuron.[1] The centrally-projecting axon enters the spinal cord (Fig. 1D), where it can send collaterals into the grey matter to form excitatory synapses with spinal neurons (e.g., interneurons in the dorsal horn), enter a white matter tract and project caudally or rostrally (e.g., to the brain stem), or project to both spinal and supraspinal targets.[14,119]

Previous reviews have covered several aspects of DRGS, including *in vivo* and *in vitro* studies of DRGS,[125] the DRG as a target for neurostimulation therapies,[38,65] and clinical evidence of DRGS efficacy.[53] However, to our knowledge, there has not been a review of the evidence supporting the current hypotheses of the physiological mechanisms of DRGS-induced pain relief. Therefore, our goal in this review is to summarize the evidence supporting the current hypotheses of DRGS mechanisms, and to provide an outlook on the scientific insight needed to facilitate technological innovations that will improve the efficacy of DRGS. We consider both the direct neural response to DRGS (i.e., the neuronal processes that are transiently modulated by DRGS-generated electric fields) and the indirect effects of DRGS (e.g., postsynaptic activation of neural circuits in the central nervous system, modulating the activity of non-neuronal targets). Due to the novelty of DRGS, there are few studies of the indirect effects of DRGS; therefore, much of our discussion will focus on the direct neural response to stimulation. We conclude by suggesting future research avenues towards painting the holistic picture of DRGS mechanisms.

Direct neural response to DRGS

Similar to other clinical neurostimulation therapies, DRGS interfaces with the body by generating spatiotemporally varying electric fields. These electric fields can perturb a cell's transmembrane voltage, and can lead to the opening or closing of voltage-sensitive ion channels. Stimuli of sufficient intensity can induce an action potential (AP), while subthreshold stimuli would result in a transient change in membrane potential that does not induce an AP. However, it is possible that subthreshold stimuli have modulatory effects, such as integrating or disrupting ongoing neural activity, or by influencing voltage-sensitive channels whose dynamic ranges are below the AP threshold. In this paper, we define the direct neural response to DRGS as any voltage-sensitive neurophysiological process that is induced, prevented, or characteristically altered by the transient electrical stimuli generated by DRGS. This definition includes effects, such as generating APs in a particular cell type leading to neurotransmitter release from presynaptic terminals or intracellular second messenger systems that are triggered by voltage-sensitive processes (e.g., calcium influx through voltage-sensitive calcium channels). We believe that there are three primary hypotheses on the direct neural response to DRGS: 1) the driving of feed-forward pain-inhibition circuitry, 2) augmenting low-pass filtering mechanisms at the T-junction of PSNs, and 3) suppressing the hyperexcitability of PSNs generated by chronic pain states.

Driving input into pain-gating networks

In their seminal paper in 1965, Melzack and Wall proposed the gate control theory of pain,[83] which states that activating large-diameter tactile afferents gates pain signals to the

brain by driving inhibitory networks in the spinal cord, while also being modulated by top-down control from supraspinal structures. Only two years later, Wall and Sweet used this theory to demonstrate temporary analgesia in humans by electrically stimulating peripheral nerves, and Shealy et al. developed the first clinical usage of SCS.[109,126] By stimulating the large diameter afferents in peripheral nerves and the dorsal columns of the spinal cord, respectively, these groups demonstrated the ability of exogenous electric fields to drive pain inhibition in humans, putatively by artificially driving feed-forward pain-inhibition networks in the spinal dorsal horn.[84] As many of the Aβ-axons that constitute the dorsal columns originate in the DRG,[90] and extracellular electrical stimulation preferentially activates large-diameter myelinated axons over small-diameter nonmyelinated axons,[99,101] DRGS may share mechanisms of action with SCS.

Computational modeling is an important tool in uncovering the mechanisms of neurostimulation therapies.[20] Bourbeau and colleagues used a combined biophysical and analytical model to study activation thresholds during microstimulation of the DRG with penetrating microelectrodes.[12] Their results suggest myelinated afferent activation thresholds would be on the order of microamperes, and that microstimulation can preferentially activate small-diameter myelinated afferents over large-diameter myelinated afferents. This finding is contrary to conventional understanding that larger-diameter axons have lower activation thresholds than smaller-diameter axons.[79] The authors suggested that this selectivity for small-diameter axons was due to smaller axons having more closely spaced nodes of Ranvier, increasing the probability that a node would be present near the penetrating microelectrode. However, their modeling framework was not designed to study clinical DRGS performed with non-penetrating macroelectrodes placed in the intraforaminal tissue, and it did not account for factors, such as the anatomy surrounding the DRG, which would affect the electric field delivered to DRG neurons. Furthermore, that study only modeled the axons in the DRG, assuming that cell bodies would not be excitable by extracellular stimulation, and it did not examine the effects on C-neurons. It is currently unclear if this selectivity is achievable with extragangliar electrodes, like those used in clinical DRGS.

Work from our laboratory implemented a field-cable modeling approach to study clinical DRGS, and compared the activation thresholds of Aβ-neurons with C-neurons.[48] We showed that when applying DRGS with clinical leads and stimulation parameters, DRGS drives the activity of Aβ-neurons without affecting the activity of C-neurons (Fig. 2). Our follow-up study further examined the effect of DRGS on Aα- and Aδ-neurons.[49] We showed that with clinical stimulation parameters, DRGS may activate Aδ-neurons that sense innocuous touch, without activating Aδ-neurons that sense mechanical pain. Furthermore, we showed that Aα-neurons may be widely activated during DRGS, but their low population within the DRG makes it difficult to determine their extent of activation in clinical scenarios.[115] However, our models did not account for calcium channels or dynamics in DRG neurons, which may affect a neuron's activation threshold, and likely affects the DRGS-influenced neural dynamics which operate on time-scales lasting seconds or longer,[45] suggesting that additional mechanisms might be at play. Though computer models provide an excellent framework with which to probe the mechanisms of DRGS, there are several limitations to the computational approach, such as simplified cellular morphologies, and a

lack of experimental data (e.g., spatiotemporal ion channel expression profiles) from which to build the models.

Currently, there are a few *in vivo* studies of DRGS mechanisms, specifically in the context of neurostimulation for pain. However, these initial studies have provided interesting results. Using a rat model of DRGS, Chao and colleagues confirmed our modeling predictions that Aβ-neurons have the lowest activation thresholds during DRGS.[22] Koetsier and colleagues showed that in rats, DRGS did not affect intracellular levels of gamma-aminobutyric acid (GABA) in the spinal cord dorsal horn, suggesting DRGS does not drive inhibitory circuitry in the spinal cord.[62] Instead, the authors suggested that DRGS may drive GABAergic pain-gating circuits local to the DRG. Du and colleagues recently found that many DRG neurons possess the cellular machinery necessary to synthesize and release GABA, including large-diameter 200 kDa neurofilament-positive neurons, such as Aβ-neurons.[33] They also demonstrated that optogenetically depolarizing these neurons caused behavioral changes indicative of reduced acute and chronic pain. Therefore, it is possible that clinical DRGS directly activates myelinated afferents, leading to a release of GABA within the DRG itself to inhibit pain perception (Fig. 2). However, these findings are preliminary, and more work is needed to understand the physiological consequences of *in vivo* GABA release in DRG, and whether clinical DRGS is capable of inducing somatic GABA release.

Furthermore, these data have not ruled out pain-gating inhibition in the dorsal horn as a mechanism of DRGS. Alternatively, DRGS may drive the release of other inhibitory neurotransmitters, such as glycine, in the dorsal horn. Aβ-neurons in the DRG have axonal projections to lamina ii_i and iii of the dorsal horn,[14] where they form feed-forward circuits with glycinergic interneurons that gate mechanical allodynia, a common phenotype of neuropathic pain.[76] It is possible that DRGS drives the activity of Aβ-projections to the dorsal horn, thereby increasing the glycinergic inhibitory tone in the spinal cord to gate neuropathic pain. Continued study of the complex pain-processing networks in the central nervous system is crucial to fully elucidating how DRGS-generated peripheral inputs reduce pain.

Additional studies have examined DRGS through the lens of other neurorehabilitation therapies, such as controlling bladder function,[16] or as a target to provide somatosensory feedback and control in neuroprosthetic systems.[9] Though these studies were not designed to provide evidence on the mechanisms of DRGS for pain relief, they still give insight into which types of DRG neurons respond to extracellular stimulation. For example, some studies found that low-amplitude intragangliar stimulation with penetrating microelectrodes elicits antidromic compound action potentials (CAPs) with conduction velocities in the Aβ- to Aα-range.[41,43,60] Other studies showed similar findings with an electrode array placed on the surface of the ganglion.[89] However, due to the small diameter of Aδ- and C-neuron axons, their APs can be difficult to resolve on CAP recordings, leaving the extent to which small-diameter axons are recruited during DRGS an open question.

Augmenting T-junction filtering

Several sources of experimental data have suggested that T-junction filtering could be a primary mechanism of DRGS-induced analgesia. Following frequency, the maximum

frequency train of APs that can be conducted through an axonal branch point, is used as a measure of T-junction filtering in PSNs. Gemes and colleagues showed that in excised rat DRG, A-neurons have significantly larger following frequencies than C-neurons, i.e., A-neurons can transmit higher frequency trains of APs across the T-junction than C-neurons.[44] Interestingly, peripheral nerve injury decreased the following frequency in A-neurons, but increased the following frequency in C-neurons, suggesting that in chronic pain states there is a coincident decrease of pain-gating signals and increase of painful signals entering the spinal cord. They also found that in C-neurons, increasing current through calcium-dependent ion channels (e.g., small conductance calcium-activated potassium (SK) channels) reduced the following frequency. This result suggests that a therapy designed to trigger calcium influx into C-neurons may enhance T-junction filtering and block pain signals from entering the central nervous system.

The T-junction, the region where the stem axon bifurcates into a spinally projecting axon and a peripherally projecting axon, is a morphological peculiarity nearly unique to DRG neurons (and the sensory neurons of the trigeminal ganglion).[29] The T-junction is a large node of Ranvier,[114] and the peripherally projecting axon is typically larger in diameter than the spinally projecting axon, though there may be differences in this diameter mismatch across cell types.[50] Furthermore, the cell bodies of DRG neurons have active ion channels, which allow peripherally generated APs to invade the soma.[2] These peculiarities can affect the transmission of afferent signals from the peripheral axon to the dorsal root axon. For example, in myelinated afferents, orthodromically propagating APs can generate ‘extra’ spikes in the initial segment, which rebound towards the T-junction and may occlude other orthodromic APs.[3] This self-generated occlusion seems to increase the number of short and long inter-spike intervals, while decreasing the number of intermediate inter-spike intervals. In nonmyelinated afferents, combinations of morphological and electrophysiological features, such as stem axon length and slow hyperpolarizing conductances, can produce a low-pass filtering effect on orthodromically propagating APs.[117] DRGS may provide analgesia by augmenting this filtering property in the DRG neurons responsible for pain pathophysiology.

The first computational study of clinical DRGS mechanisms examined the effect of DRGS on putatively nociceptive C-neurons. Kent and colleagues used a field-cable modeling approach to show that DRGS generates APs in C-neuron somata, which produces a net hyperpolarization by increasing the current through SK channels (Fig. 3B).[58] Somatic hyperpolarization electrotonically hyperpolarized the stem axon and T-junction (Fig. 3C) to an extent that blocked AP propagation into the dorsal root axon (Fig. 3C), both painful APs from the periphery (Fig. 3A) and DRGS-generated APs from the soma. However, to produce the T-junction filtering effect, it was necessary to apply DRGS with a stimulation amplitude greater than 9 mA, which is far greater than typical clinical stimulation amplitudes (1 mA on average).[28] It is important to note that anatomical simplifications and parameter selection (e.g., tissue conductivities, ion channel conductances) used in the field-cable model can dramatically affect the thresholds necessary to generate APs in modeled neurons.[131] Therefore, future studies should examine which parameters affect the fidelity with which DRGS can augment T-junction filtering.

Koopmeiners and colleagues utilized an *in vitro* approach to study the effect of extracellular electrical stimulation on Aδ- and C-neurons in excised rat DRG.[64] They demonstrated that field stimulation of excised DRG reduced the following frequency of putatively nociceptive neurons, while producing large transient increases in intracellular calcium concentration. Pan and colleagues then provided the first *in vivo* recordings of T-junction filtering in a rat model of DRGS for rheumatoid arthritis, though in this case, DRGS filtered antidromically propagating APs initiated via dorsal root stimulation and recorded via teased fiber recordings from the sural nerve.[92] These results add further evidence that DRGS may provide pain relief by filtering the transmission of APs at the T-junction, and that this phenomenon is likely either calcium-dependent or calcium-sensitive.

Recently, Chao and colleagues used an *in vivo* rat model to study the mechanisms of action of DRGS.[22] Using teased fiber dorsal root recordings, they demonstrated that when stimulating the sciatic nerve, the stimulation amplitude needed to activate nonmyelinated C-axons is more than 50 times greater than the amplitude needed to activate myelinated Aβ-axons, in agreement with conventional neurostimulation theory. However, when stimulating the DRG, the C-neuron activation threshold was only 1.5 times the Aβ-neuron threshold, contrary to previous modeling results.[48] Furthermore, they found that within approximately 30 seconds of starting DRGS applied at 80% of motor threshold, the orthodromically propagating C-component of the teased fiber recording disappeared, suggesting that prolonged DRGS augments T-junction filtering in nociceptive neurons after a brief wash-in period. These experimental results are exciting, and imply that DRGS activates many types of neurons simultaneously, suggesting multiple pain-relieving mechanisms may be happening concurrently.

As with all animal models of human technology, it is critical to ensure that *in vivo* models accurately recapitulate clinical scenarios. Therefore, the electric fields generated by DRGS in preclinical studies must adequately approximate the electric fields generated by clinical DRGS systems to ensure the conclusions of experimental studies accurately inform our clinical understanding of the technology. In this way, there are three interrelated factors that we think are worth careful consideration when designing future experimental studies of DRGS: 1) the dimensions of the stimulating electrode contacts, 2) the dimensions of the animal model's DRG and surrounding anatomy, and 3) the choice in stimulation parameters, particularly the pulse amplitude. Chao and colleagues used an in-house made electrode to apply bipolar DRGS that is necessarily smaller than the electrode leads used clinically, because the rat neuroforamina are considerably smaller than human neuroforamina. However, smaller electrode contacts will generate larger current densities in stimulated tissues compared to larger contacts for a given pulse amplitude, potentially lowering the activation threshold of small neurons (e.g., C-neurons). Furthermore, smaller neuroforamina, i.e., a more enclosed space surrounded by a bony structure, implies more current will enter the more conductive neural tissue, compared to the minimally conductive bone. A recent study of anatomical factors affecting the activation thresholds of neurons in the spinal cord dorsal columns emphasizes the importance of this latter point.[131]

Comparatively larger current densities resulting from smaller electrode contacts and neuroforamina make the already difficult task of choosing clinically relevant pulse

amplitudes for *in vivo* DRGS studies even more challenging. Koetsier and colleagues applied DRGS using an intensity of 66.7% motor threshold (i.e., the minimum amplitude at which DRGS causes muscle activation in the patient's or animal's stimulated myotome), whereas Chao and colleagues suggested that 80% motor threshold was the optimal stimulating intensity.[22,62] However, preliminary clinical data suggest that sensory thresholds (i.e., the minimum stimulation amplitude at which a human patient reports feeling paresthesias) can be between 33% and 70% of the motor threshold value.[39] This finding, taken with the clinical reports that some DRGS patients utilize sub-perception DRGS (i.e., DRGS with amplitudes that do not produce paresthesias) and achieve successful pain relief,[81,105] indicates further study is needed to determine how the 'optimal' pulse amplitude should be calculated in experimental studies to most accurately recapitulate clinical DRGS. Determining this relationship between experimental and clinical pulse amplitudes is a challenging problem because there are currently no clinically analogous methods for determining sensory thresholds in animal models.

Furthermore, neural activation generated when stimulating at a particular percent motor threshold in a preclinical model may not be directly analogous to the neural activation generated by stimulating at the same percent motor threshold in a human study, because of differences in DRG size across species. Muscle twitches resulting from DRGS are likely caused by: 1) direct activation of Ia afferents in the DRG causing postsynaptic activation of motor neurons in the ventral horn,[21] or 2) direct activation of motor axons in the ventral root. Because Ia afferents have low populations in both rodent[47] and human[115] DRG, activation of sufficient numbers of Ia afferents to produce a muscle twitch could suggest widespread neural activation throughout the DRG. Similarly, assuming the stimulating electrode is placed on the dorsal side of the DRG, direct activation of the ventral root – a structure farther from the stimulating electrode than the DRG – would suggest that DRGS was applied with a large pulse amplitude, thereby likely causing widespread activation throughout the DRG.

However, rat DRG are much smaller than human DRG. In the dorsal-ventral axis, lumbar rat DRG are likely less than 1 mm wide[30,98] while human lumbar DRG are approximately 6 mm wide,[51] placing rodent ventral roots and Ia afferents much closer to the stimulating electrode contact than in clinical scenarios. Because the voltage at a given point in space is inversely proportional to its distance from a current source, a given percent of a motor threshold in a rat likely causes more neural activation in the DRG than the same percent motor threshold would cause in a DRGS patient. Future work should develop rigorous methodologies for selecting stimulation parameters in both clinical and preclinical DRGS experiments which allow for direct comparison between the two types of data.

Suppressing PSN hyperexcitability

Spontaneous firing of APs despite a lack of sensory input and increased firing of APs in response to peripheral stimuli, are thought to be two biomarkers of several chronic pain etiologies. For example, ongoing input into nociceptive C-neurons, generated perhaps from a peripheral neuroma, may lead to pain perception without an external noxious stimulus.[107] Spontaneous activity in Aβ-neurons, which typically don't convey pain signals, is thought to

underly allodynia, a clinical symptom of neuropathic pain whereby previously non-painful stimuli cause pain.[4,19] Current evidence suggests that the DRG can be responsible for the development of neuropathic pain through hyperexcitability and spontaneous ectopic firing of PSNs. One proposed mechanism of DRGS is that electrical stimulation rectifies this hyperexcitability and aberrant activity.

Koopmeiners and colleagues measured the number of APs generated in response to current-clamp stimulation in excised DRG from healthy rats.[64] They demonstrated that putatively nociceptive neurons generate fewer APs in response to current clamp stimulation after exposure to 90 seconds of DRGS compared to before receiving DRGS, suggesting that DRGS reduces membrane excitability. Given that DRGS applied at an intensity that reduced membrane excitability also produced large increases in intracellular calcium, the authors hypothesized that the reduction of membrane excitability may be calcium-dependent or calcium-sensitive. It is currently unclear how different chronic pain etiologies affect neural dynamics and the response to DRGS, but these data provide evidence that justifies further study of DRGS' ability to suppress neuronal excitability.

In a tibial nerve-injured (TNI) rat model of DRGS, Chao and colleagues showed that DRGS raised the mechanical threshold to elicit AP firing in both C- and Aδ-neurons, and significantly reduced the firing frequency of C- and Aδ-neurons in response to mechanical stimulation.[22] As these data come from teased fiber recordings of dorsal root axons, it is difficult to ascertain whether these changes resulted from suppressing the excitability of the recorded cell, or from inducing T-junction filtering of orthodromically propagating APs (see previous section). However, the authors also showed that after DRGS, the average spontaneous firing frequency of C-neurons decreased, and other studies have shown that DRGS reduces spontaneous pain behavior in TNI rats,[91,130] suggesting that excitability suppression is a possible culprit of the reduction in nociceptor activity.

To date, there are relatively few studies explicitly examining the hypothesis of hyperexcitability suppression, and the biophysical mechanisms through which excitability suppression is achieved are unclear. Extracellular electrical stimuli with durations lasting on the order of 1 ms or shorter, such as those utilized by DRGS, are conventionally believed to induce neural activity by transiently perturbing voltage-gated sodium channels to generate action potentials, counterintuitive to the idea of stimulation-induced suppression of excitability. Therefore, it is likely that DRGS-induced reductions in membrane excitability are due to voltage-sensitive intracellular secondary messenger cascades.[46]

Indirect effects of DRGS

Though the direct response to electrical stimulation is usually the generation of an AP in a target cell, the ultimate goal of neuromodulation therapies is to cause the release of neurotransmitters that modulate downstream neural activity which produces clinical benefit – so-called indirect effects of stimulation. Indirect effects are likely widely distributed throughout the neuraxis, particularly when stimulated tissue projects to many structures throughout the nervous system. Furthermore, the indirect effects of neuromodulation therapies may extend to non-neuronal targets, such as glial cells. Due to the novelty

of DRGS, and the importance of first understanding which cells are directly affected by stimulation, there are as of yet few studies on the indirect effects DRGS. However, preliminary evidence suggests that DRGS may share indirect effects with conventional SCS, though continued study is vital to delineate the specific mechanisms unique to each therapy. Such knowledge may help improve patient selection and allow therapy assignment to be tuned to the pathophysiological differences across chronic pain etiologies.

Spinal/Segmental effects

The goal of DRGS – to stimulate a particular DRG to provide dermatome-specific pain relief – places fundamental importance on the effects of stimulation at the particular spinal segment receiving sensory information from a patient's painful region. A wide range of experimental techniques exist to objectively characterize the segmental effects of neurostimulation. For example, quantitative sensory testing (QST) and standard clinical electrophysiological assessments (e.g., electromyography) have proven useful in characterizing the mechanisms of action of SCS (for review, see [106]). Application of these techniques to patients receiving DRGS treatment could provide critical insight into the segmental effects of DRGS, and can be utilized in longitudinal studies to examine how the therapeutic effects of stimulation change over time, which are difficult to recapitulate using computational and preclinical models.

QST can assess a patient's sensory capacity and has been used to characterize SCS and DRGS patients' responses to both static stimuli (i.e., single transitory sensory stimuli) and dynamic stimuli (i.e., multiple stimuli). To date, there have been three studies using such experimental techniques to characterize the mechanisms of DRGS.[23,59,105] All three studies found that DRGS increased patients' pain thresholds in response to pressure stimuli localized to the patients' painful regions, though Kinfe and colleagues noted that the increase they observed was not statistically significant. A localized increase in pressure pain threshold suggests that DRGS modulates patients' perception of acute nociceptive pain, possibly through central mechanisms (e.g., segmental inhibition in the dorsal horn), or though peripheral mechanisms (e.g., suppression of nociceptive PSN activity), or both. DRGS may also affect patients' abilities to detect non-painful mechanical stimuli by modulating the activity of large-diameter Aβ-neurons. Kinfe and colleagues found that DRGS lowered detection thresholds in response to non-painful punctate stimuli,[59] while Chapman and colleagues found a similar, but non-statistically significant trend.[23] However, work from our laboratory found that in patients receiving DRGS or SCS treatment, vibration detection thresholds did not change during stimulation compared to pre-treatment values,[105] suggesting that continued study is needed to determine the effect of DRGS on patients' perception of innocuous mechanical stimuli.

Furthermore, these early studies showed that DRGS reduces temporal summation (TS).[59,105] TS is a dynamic QST metric that is typically measured by taking the difference between a patient's reported pain intensity in response to a train of noxious stimuli and their reported pain intensity in response to a single noxious stimulus of equal magnitude. TS is a proxy to measure the "wind-up" phenomenon in humans. Wind-up is an increased firing rate of dorsal horn neurons in response to painful stimuli, believed to be mediated by activation of

N-methyl-D-aspartic acid (NMDA) receptors on wide dynamic range neurons in the dorsal horn.[35] Therefore, a reduction in TS by DRGS suggests stimulation provides pain relief in part by reducing the firing rate of pain-coding neurons in the central nervous system. It is reasonable to expect that DRGS may reduce TS by activating inhibitory circuits in the spinal cord dorsal horn, by causing nociceptive signals to be filtered out within the DRG, or a combination of the two. Interestingly, patients receiving SCS that demonstrate enhanced TS prior to implantation reported less overall pain after implantation.[18] If SCS and DRGS both provide pain relief in part by driving the activity of Aβ-neurons, pre-implantation TS levels could similarly predict patients that will respond well to DRGS. Taken together, these preliminary studies indicate that DRGS may exert several concurrent effects on segmental pain processing, and demonstrate the utility of QST in studying the mechanisms of DRGS. Future work should include larger patient cohorts, examine the effects of pain etiology on changes in QST metrics, and determine if clinically quantifiable factors can be used as predictors for patient success with DRGS.

SCS has been shown to reduce the amplitude of some spinal cord reflex arcs, such as the H-reflex,[7] a mono-synaptic reflex mediated by large-diameter muscle afferents, and the nociceptive flexor withdrawal reflex (also known as the RIII-reflex),[7,11,42] a poly-synaptic reflex mediated by small-diameter nociceptors. Similar to TS, the nociceptive flexor withdrawal reflex is a proxy for assessing spinal excitability in humans. From these results, it is generally interpreted that SCS increases the inhibitory tone of the spinal cord, thereby decreasing the amplitude of the nociceptive reflex arc, and may reduce the amplitude of the H-reflex by causing AP collision in muscle afferents. Interestingly, the magnitude of attenuation of the nociceptive flexor withdrawal reflex correlates with SCS-induced pain relief, suggesting that the success of the therapy is at least partially attributable to facilitating segmental inhibition. We hypothesize one would see similar results using these measures to study DRGS, as computational and preclinical studies demonstrate that DRGS also generates APs in large-diameter afferents.[22,48,49] However, it may be possible that DRGS exerts a larger attenuating effect on the nociceptive flexor withdrawal reflex, through the combined mechanisms of increasing inhibitory tone in the spinal cord, and reducing the net small-diameter input entering the spinal cord via T-junction filtering.

Supraspinal effects of DRGS

The original gate control theory of pain emphasized the importance of ‘central control’ – descending efferent fibers which modulate the gate control system – to the experience of pain, and stimulation-induced neural activity likely modulates brain regions involved in descending control. For example, SCS-induced activation of Aβ-axons in the dorsal columns activates neurons in brainstem regions, such as the rostroventral medulla and locus coeruleus,[110,111] which in turn drive descending inhibition via serotonergic and noradrenergic efferents.[112,113] As DRGS likely also drives the activation of Aβ-neurons,[22,48,49] it may modulate similar supraspinal regions to SCS. However, as experimental data also suggest DRGS may directly affect the activity of small-diameter PSNs,[22] there may be considerable differences in the brain regions engaged by SCS and DRGS.

In the first study of the supraspinal regions involved in DRGS, Pawela and colleagues performed functional magnetic resonance imaging (fMRI) in a rat model of DRGS to examine the effect of DRGS on the blood oxygen-level dependent (BOLD) signal evoked by noxious electrical stimulation of the hindpaw.[95] They found that DRGS reduced the magnitude of the BOLD response in regions associated with the sensory-discriminative component of pain, such as the somatosensory cortices and the ventral posterolateral and ventral posteromedial nuclei of the thalamus, similar to findings from studies performing fMRI during SOS.[61,86,116] Interestingly, they also found that DRGS reduced the magnitude of the BOLD response in the nucleus accumbens – a limbic structure that may play a role in the motivational aspect of chronic pain – which was recently implicated as a potential supraspinal target of SCS in a rat fMRI study.[85] These results suggest that DRGS may provide pain relief through similar mechanisms to tonic SCS, though additional supraspinal mechanisms may also be at work. Continued study of the supraspinal mechanisms of DRGS will be critical, particularly studies performed in humans, as anesthesia used in non-human functional imaging studies adds additional confounds to interpreting results.

Parker and colleagues recently used magnetoencephalography (MEG) to study the effect of DRGS-induced pain relief on cognitive performance.[94] They found that patients receiving pain relief from DRGS displayed a reduction in gamma-band (30-Hz) activity in the somatosensory and anterior cingulate cortices (ACC) – brain structures that have been shown to be implicated in the pain-relieving effects of conventional tonic SCS and burst SCS, respectively.[103] It is hypothesized that burst SCS – a type of SCS that applies stimulation in high-frequency bursts – provides pain relief in part by modulating the medial spinothalamic pain pathway. This pathway flows from C-neurons in the DRG which project to lamina i of the dorsal horn,[14] to several brain regions including the ACC, and is associated with the affective and attentional components of pain. Therefore, Parker and colleagues' observation that DRGS-induced pain relief is accompanied by modulation of the ACC adds additional evidence that DRGS may directly act upon C-neurons, as suggested by previous computational and animal studies.[22,58] Interestingly, Parker and colleagues found a reduction in gamma-band activity in the ACC, while De Ridder and colleagues found an increase in alpha-band activity (8-10 Hz) in the ACC,[102] but neither study considered the effects of stimulation across the full power spectrum of neural activity. More work is needed to understand how different patterns of peripheral input affect the activity of different functional brain networks. This understanding could lead to the design of DRGS stimulation patterns that directly target different components of the pain matrix (i.e., sensory, affective, cognitive), allowing for the personalized design of a patient's stimulation parameters based on their individual needs.

Studying the effect of DRGS on somatosensory evoked potentials (SSEPs) may also give insight into the supraspinal effects of the therapy, and SSEPs have been used for several decades to characterize the effects of SCS. SSEPs consist of positive and negative voltage deflections as a sensory stimulus travels through the nervous system. SSEPs are often obtained by recording electroencephalogram signals from the scalp in response to an external stimulus (e.g., percutaneous nerve stimulation), and can provide insight into how a therapy affects sensory processing. Generally, SCS-induced activation of Aβ-axons in the dorsal columns decreases the amplitude of SSEPs,[17,68,69,96] and as DRGS likely acts in

part through similar mechanisms, we may expect similar findings. A recent study of the effect of DRGS on laser evoked potentials (LEPs) – an SSEP measured in response to noxious laser stimulation of the skin – showed that DRGS increases the N2-P2 amplitude of LEPs, and that larger N2-P2 amplitudes may be correlated with lower pain ratings.[87] Given that LEPs are designed to only study the cortical response to noxious stimulation, and that there are possible coincident effects of DRGS on small-diameter afferents which may produce different effects on SSEPs, continued investigation into the cortical effects of DRGS is necessary. A multi-modal approach to studying the supraspinal effects of DRGS will be necessary not only to understand the mechanisms of action of the therapy, but to also understand its effects on patients across pain etiologies and comorbidities.

Effects on glia

Historically, the non-neuronal effects of neurostimulation technologies have largely been ignored, except in the context of the foreign body response to implanted materials.[77] An area of basic research that remains underexplored is the effect of DRGS on satellite glial cells (SGCs), the glial cell present in the DRG.[52] SGCs are known to be important in the development and maintenance of chronic pain.[24] Though they do not generate APs, SGCs possess voltage-sensitive ion channels, and communicate directly with neurons in the DRG,[56] suggesting that they may be directly influenced by the DRGS-generated electric fields, or indirectly by DRGS-induced activity in PSNs. Though the effects of stimulation on glial cells have not yet been studied in the context of DRGS, early studies in SCS suggest it is an avenue well worth exploring.

SCS is most commonly applied to the lower thoracic spinal cord, where there are approximately 20 glial cells for every neuron.[104] A high density of glial cells around common SCS targets indicates that SCS-generated electric fields could modulate glial activity, depending on the electrophysiological characteristics of glial cells and how those characteristics are affected by SCS stimulus waveforms.[122] Differential targeted multiplexed programming-SCS (DTMP-SCS) was developed to concurrently drive neuronal and glial mechanisms of pain relief, by concurrently delivering a low-frequency SCS waveform (~50 Hz) and a high-frequency SCS waveform (~1200 Hz). Vallejo and colleagues demonstrated that in rats with spared nerve injuries, DTMP-SCS provided a greater reversal in chronic pain behavioral metrics, such as mechanical and thermal hypersensitivity, relative to low-frequency or high-frequency SCS alone.[123] Furthermore, spared nerve injury affected the expression levels of many glia-related genes, and DTMP-SCS drove the expression level of many of those genes back towards naive levels. These results suggest that simultaneously modulating the neuronal and glial components of pain may lead to greater pain relief than modulating the neuronal component alone.

It is currently unclear how DRGS modulates the SGC component of pain. However, SGCs being the singular glial cell type in the DRG may make DRGS an ideal use case to study the differential effects of neurostimulation on neurons versus glia, and how communication between neurons and glia are modulated by extracellular stimulation. It is worth investigating the extent to which current clinical DRGS stimulation waveforms affect SGC physiology, and if further innovation is necessary to modulate the SGC component

of pain (e.g., by multiplexing DRGS, similar to DTMP-SCS). Finally, in addition to the importance of glia in stimulation-induced pain relief, these studies also highlight the nascent but important study of omics, both to understand the mechanisms of neurostimulation therapies and as potential biomarkers of various chronic pain states.[118,124]

Looking forward

Several decades after helping construct the gate control theory of pain, Melzack synthesized a wide body of work across the medical and biological sciences into a new theory, the so-called neuromatrix theory. The neuromatrix theory places greater emphasis on not only the sensory component of pain, but also on the role of cognitive and affective components.[82] Much as the foundation of this new theory drew from evidence across several disciplines, so too should our approach towards elucidating the mechanisms of action of neurostimulation therapies to manage pain. We believe that it is unlikely that these therapies provide pain relief through a single mechanism, and that a holistic understanding of electrical stimulation induced pain relief is vital towards successful and consistent implementation of these therapies. Therefore, much work remains to be done through the combined efforts of basic neuroscience, engineering, and clinical pain research.

Presently, there is considerable disagreement between the conceptual understanding of neurostimulation biophysics and the available experimental data of DRGS mechanisms. One of the most striking results of the work of Chao and colleagues is that the ratio of C-neuron to Aβ-neuron activation threshold was dramatically lower than the corresponding ratios when stimulating the sciatic and saphenous nerves.[22] This result contrasts greatly with modeling studies comparing Aβ- and C-neuron activation thresholds.[48,49] These conflicting results suggest several potential explanations that warrant further study. Firstly, the recent discovery of GABAergic communication within the DRG, suggests possible synaptic action within the DRG itself.[33] Because GABA depolarizes C-neurons due to the atypical higher concentration of chloride within C-neurons than the extracellular space,[97] it is possible that DRGS drives GABA release from Aβ-neurons, which then depolarizes C-neurons to induce T-junction filtering as described above. However, it is unclear if GABAergic activation alone is sufficient to induce filtering. Secondly, there could be one or more features of the soma and stem axon complex of C-neurons that are missing from existing computer models that significantly reduce the activation thresholds of these neurons.

For example, much of our intuition of extracellular stimulation-induced neural activation comes from modeling studies of the peripheral nerve, characterized by long, straight axons.[79,99,100] In reality, DRG neurons have complex, winding stem axon trajectories[5,71,114,129] that haven’t been accounted for in previous models. These trajectories could produce complex spatiotemporal profiles of depolarization and hyperpolarization in response to DRGS, making prediction of neural activation difficult. In simplified models of retinal ganglion cells, the presence of a 90-degree bend in an axon was sufficient to produce complex spatial distributions of activation thresholds,[40] suggesting that more complex trajectories may require a new conceptual framework to predict neural activation. Furthermore, the effects of ephaptic coupling (i.e., transmembrane currents contributing to the extracellular potential at other parts of the cell) are typically ignored, but could be on the

order of several millivolts.[121] Because DRG neurons have tightly coiled stem axons closely apposed to large cell bodies (which would produce large transmembrane currents), intra- and inter-cellular ephaptic effects in the DRG could be significant. Future modeling work should aim to develop new intuitions of neural activation when stimulating cells with complex morphologies and axon trajectories, and use these novel intuitions to assist in interpreting experimental data of DRGS. Such intuitions will be critical to understanding not only the mechanisms of DRGS, but the mechanisms of other clinical neuromodulation therapies, including SCS.

In addition to complex stem axon trajectories, DRG neurons have active ion channels in their somata. Typically, APs are thought to be rarely generated in the soma,[78] but the presence of active ion channels in DRG somata, and the computer modeling predictions that some APs may initiate in the somata of DRG neurons,[48,58] suggest that this intuition may not apply to DRGS. There is a myriad of sodium[10] and potassium[120] channel isoforms important to physiological and pathological pain processing, many of which are expressed in DRG. In a recent study from our lab, we implemented two models of Aδ-neurons that were morphologically and electrically identical, except for the voltage-gated sodium channels that they expressed.[49] Aδ-neurons that expressed $Na_v1.6$ had lower activation thresholds than Aδ-neurons that expressed $Na_v1.7$ and $Na_v1.8$, suggesting that in addition to morphological properties, the electrophysiological properties of a given neuron are crucial in determining its response to extracellular stimulation. Future experimental data summarizing the types, densities, and spatial distributions of ion channels in DRG neurons will be critical to developing accurate computer models with which to study the mechanisms of DRGS.

In addition to accurately representing the electrophysiological characteristics of the neural systems under study, computational and experimental studies of neuromodulation therapies must utilize electric fields that are representative of the fields generated during clinical implementation of the therapies. Patient-specific modeling is a powerful technique in understanding and developing neurostimulation therapies, and for ensuring computer models mimic clinical implementation of the therapy.[72] This approach has already proven useful in investigating the mechanisms of SCS for pain.[74] Patient-specific DRGS models could provide evidence for why DRGS fails in some patients but not others, or serve as the basis for a clinical decision-support system to accelerate the time-consuming process of titrating an individual patient's stimulation parameters.

There is good agreement between experimental[22] and clinical[28] studies of preferred DRGS parameters, particularly that the preferred stimulation frequency is 20 Hz in both human patients and rats. The work of Gemes and colleagues showed that when stimulating *ex vivo* rat DRG, Aδ- and C-neurons typically produced the largest calcium transients in response to frequencies between 3-7 Hz, while Aβ-neurons produced the largest calcium transients in response to 20-50 Hz stimulation.[45] Furthermore, the calcium transients in putative nociceptors (i.e., Aδ- and C-neurons) had larger amplitudes and slower decay time constants than the Aβ-neurons. These results may suggest different calcium-dependent mechanisms of stimulation on different functional groups of DRG neurons. Augmented T-junction filtering of nociceptive signals is believed to be achieved through triggering of calcium-activated slow hyperpolarizing currents, which may suggest that larger amplitude,

slowly decaying levels of internal calcium may be more conducive to sustained filtering in nociceptors (Fig. 3). It is also possible that the release of GABA within the DRG from Aβ-neuron somata (Fig. 2) requires comparatively smaller increases in intracellular calcium and benefits from faster decay times to allow somatic neurotransmitter resources to quickly reprime for the next release event. Could 20 Hz DRGS then be a ‘happy medium’ between the optimal frequencies to produce the necessary diversity of somatic calcium transients in both nociceptive and non-nociceptive DRG neurons? Such a finding would further suggest DRGS provides pain relief by directly activating multiple types of PSNs.

In the more than five decades since Melzack and Wall proposed the gate control theory, a superb amount of effort has gone in to elucidating the specific neural circuits which govern pain processing and transmission in the dorsal horn (for review, see [14,34,128]). Much of the currently available data on DRGS mechanisms give evidence for the direct effects of stimulation, but it remains an open question as to how DRGS-induced peripheral input is integrated by neural networks in the central nervous system. With the advent of preclinical techniques to dissect neural circuits, such as optogenetics, calcium imaging in awake behaving animals, and transsynaptic tracing, it is now possible to elucidate the network dynamics that lead to chronic pain phenotypes. Applying these techniques to preclinical studies of DRGS could provide mechanistic knowledge into the systems-level effects of stimulation, and inform the design of novel DRGS technologies to specifically target these mechanisms.

To fully elucidate the mechanisms of DRGS, we must also understand how DRGS affects an individual patient’s pain experience (e.g., time course of pain relief, pain diagnosis, sensory profile). There is a dearth of clinical data on the temporal features of DRGS-induced analgesia, such as how long it takes for analgesia to onset (i.e., wash-in time) and offset (i.e., wash-out time). Preliminary clinical studies suggest that wash-in and wash-out times for DRGS are on the order of minutes,[22] with DRGS possibly having faster wash-out times than SCS.[63] Studying these phenomena in humans and comparing these temporal characteristics with clinical outcomes could provide insight into whether the analgesic effects of DRGS predominantly rely on faster mechanisms (e.g., transient induction or interruption of neural firing patterns), or slower mechanisms (e.g., inducing changes in synaptic plasticity).

Finally, using a mechanistic understanding of DRGS to design prospective clinical studies examining DRGS outcomes in patients with specific pain etiologies will be critical to determine which patient populations are best managed with DRGS. Determining if there are clinically measurable sensory features (e.g., mechanical allodynia, cold hypersensitivity) that correlate with DRGS-induced pain relief (e.g., through clinical studies performing QST), could not only provide further insights into the mechanisms of action of DRGS, but also improve patient selection. Furthermore, functional neuroimaging (e.g., fMRI, MEG) and clinical electrophysiology (e.g., electroencephalography) studies will be critical to investigating how DRGS modulates brain regions associated not just with the sensory component of pain, but also with the affective and cognitive components of pain. As DRGS has been shown to provide greater improvement in depression- and mood-related metrics than tonic SCS,[26] improving our understanding of how DRGS modulates the non-sensory components of the pain neuromatrix may further assist in patient stratification between

neurostimulation therapies. Continued study of the clinical manifestations of the effect of DRGS on the nervous system will be crucial to bridging the gap between our mechanistic understanding of DRGS-induced analgesia and improvements in patients' quality of life.

Conclusion

Dorsal root ganglion stimulation is an important tool in a pain physician's toolbox for managing intractable chronic pain. It is unlikely that any neuromodulation therapy acts through a single mechanism alone, and the growing body of evidence suggests that DRGS is no exception. Current evidence suggests that DRGS may provide pain relief by post-synaptic activation of pain-gating circuitry in the dorsal horn and possibly the DRG itself, by augmenting the low-pass filtering of painful signals at the T-junction of nociceptive neurons, and by reducing the intrinsic excitability of DRG neurons. Continued study of the mechanisms of action of DRGS, particularly into the supraspinal effects of DRGS, as well as the role of cognitive and affective networks in the patient response to DRGS, is warranted. DRGS is an excellent use case to develop new intuitions on the morphological and electrophysiological factors contributing to neural activation, which will be invaluable in innovating current, and developing novel, neurostimulation therapies for neurological disorders. Such innovation will be crucial to reduce the world-wide impact of chronic pain.

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Conflicts of interest:

SFL has equity in Hologram Consultants, LLC, is a member of the scientific advisory board for Abbott Neuromodulation, and receives research support from Medtronic, Inc. SFL also holds stock options, received past research support, and serves on the scientific advisory board of Presidio Medical, Inc. All other authors declare no competing interests.

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Perspective

This article synthesizes the evidence supporting the current hypotheses of the mechanisms of action of DRGS for chronic pain and suggests avenues for future interdisciplinary research which will be critical to fully elucidate the analgesic mechanisms of the therapy.

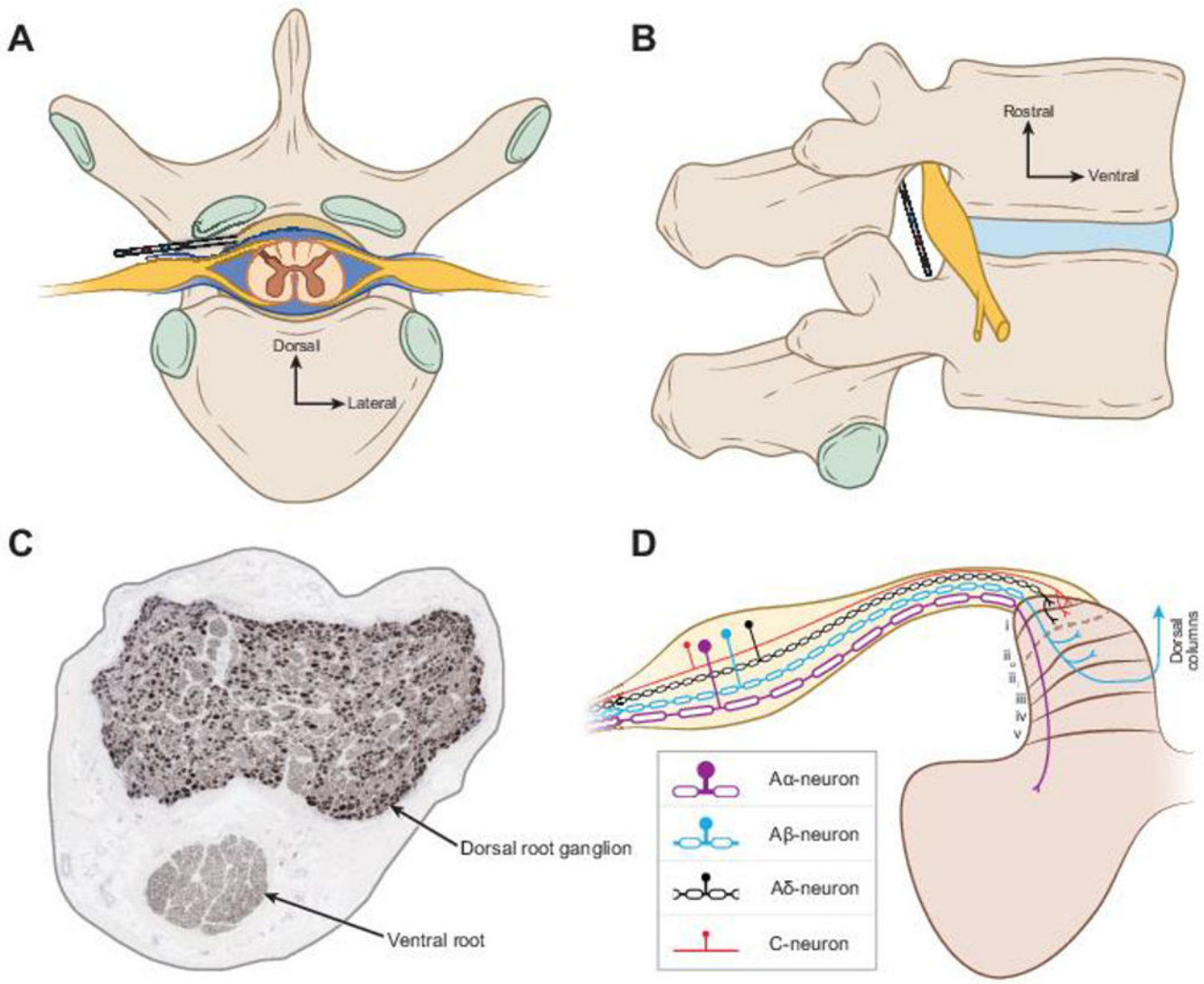

Figure 1:

DRGS and surrounding anatomy. A) Axial view of a human spinal column with a DRGS electrode array in place. B) Sagittal view of a DRGS electrode array in the foramen. C) Histology image of a human lumbar DRG stained for 200 kDa neurofilament.[115] Axons appear as miniscule dots; cell bodies appear as larger dark spots. D) Sensory neuron types in the DRG and their projections into the spinal cord. The first five lamina of the dorsal horn are labeled to indicate where different sensory neuron types send axon collaterals.

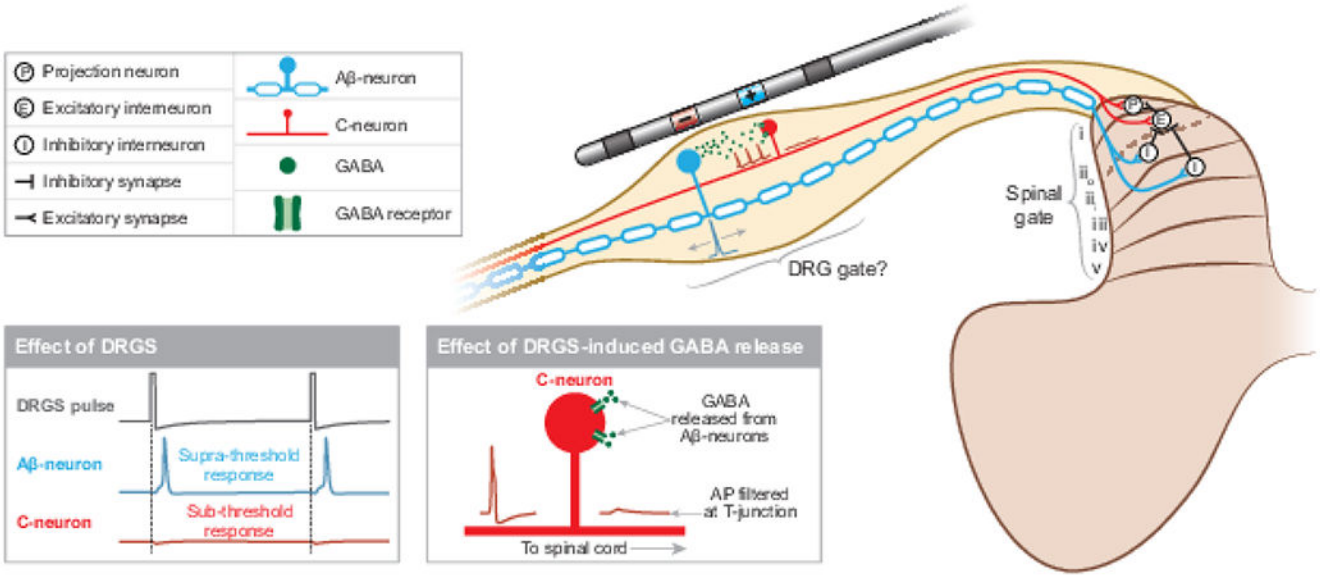

Figure 2:

DRGS may drive pain-gating mechanisms in the spinal cord dorsal horn, the DRG, or both. DRGS applies trains of electrical pulses which induce APs in Aβ-neurons, which activate inhibitory interneurons in lamina ii_i and iii in the dorsal horn. Concurrently, Aβ-neurons may release GABA within the DRG, which can act on C-neurons and potentially prevent ectopic APs from propagating to the spinal cord.

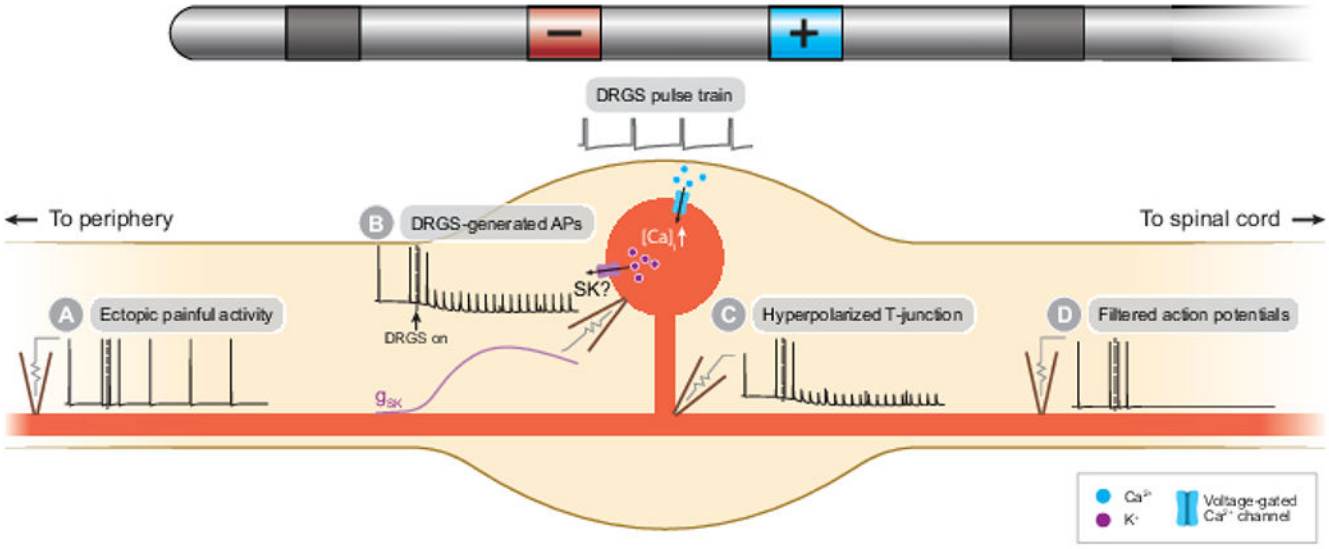

Figure 3:

DRGS may augment the low-pass filtering properties of nociceptive C-neurons. A) Ectopic APs indicative of spontaneous pain propagate along the peripheral axons of C-neurons towards the central nervous system. B) The DRGS pulse train induces APs in or near C-neuron somata causing calcium influx through voltage-gated calcium channels, putatively triggering potassium efflux through calcium-activated SK channels. C) Potassium efflux hyperpolarizes the soma, which electrotonically hyperpolarizes the T-junction. D) Orthodromically propagating APs are unable to propagate passed the hyperpolarized T-junction into the spinal axon.