

Neuromodulation for Pain Treatment

Building a Foundation for Future Study

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Over the last 20 yr, the field of neuromodulation has undergone a surge of innovation in device design that includes miniaturization, enhanced durability, multicontact arrays, wireless systems, closed-loop modulation, new waveforms, and accessibility to new targets in the nervous system. Accompanying these technological leaps is an ever-increasing utilization to treat pain. Although increased utilization may be partly due to practical issues related to more favorable reimbursement and an increase in the number of physicians performing implants, enhanced effectiveness should be the underlying tenet for expanding indications.

Determining clinical outcomes for pain treatment in general is challenging, but the study of neuromodulation has been particularly plagued by concerns regarding bias, reproducibility, blinding, control group selection, and translatability of preclinical models.^{1–3} Preclinical animal models are the foundation for new discovery; however, their generalizability to patients relies on the validity of models to mimic human biology and measures of assessment that reflect pain and suffering, which are impossible to directly measure in noncommunicative animals. In this issue of *ANESTHESIOLOGY*, Yu *et al.* describe their development of a rat model of dorsal root ganglion field stimulation to demonstrate analgesia for not only neuropathic pain but also nociceptive pain from knee osteoarthritis, and in animals without injury.⁴ These findings raise important questions regarding the use of animal models in the study of electrical stimulation for different types of pain, study design, and anatomical targets for selective stimulation.



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Most data on neuromodulation derive from poorly or uncontrolled clinical studies, with preclinical work often performed in retrospect. This is in contrast to fields such as cardiology and oncology, which typically follow the standard progression from preclinical findings to large-scale clinical trials before widespread implementation. The paucity of clinical outcome data highlights our incomplete understanding of the mechanistic basis of neuromodulation. The key components of a translatable animal model for neuromodulation include selective stimulation of anatomical targets, matching intensity and duration of treatment, injury models that correlate with human biology, and the accurate interpretation of behaviors ostensibly associated with pain.

The quantification of animal pain behaviors is fraught with experimental subjectivity from variable inter- and intraexperimental methods, equipment, housing, and other environmental conditions unique to every laboratory. The hope is that these factors remain static throughout the experimental process so that they equally influence all animals. Even in this ideal scenario, the extrapolation of raw animal data to people is based on the premise that they actually correlate with a subjective, human experience (*i.e.*, pain). Thus, behavioral findings typically serve as the basis for phenotypic differentiation that leads to complementary molecular investigation or other nonbehavioral experiments. Given these limitations, the authors have conducted an array of different behavioral experiments that minimize the impact of misinterpreting any single technique. In addition to identifying changes in somatosensory response, their

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assessment of reflexive, functional, and affective behaviors allows further insight into mechanisms of electrical stimulation-induced analgesia that modulate supraspinal processes that may influence decision-making and the affective component of pain.

Yu *et al.* successfully developed a method to implant an electrode along the dorsal root ganglion and deliver electrical field stimulation in their freely moving *in vivo* rat model.⁴ This is an accomplishment in itself as the implantation of an electrode through the neural foramen without trauma or migration is challenging even with larger anatomical dimensions in humans.⁵ The authors observed that multilevel and single ganglion stimulation produced analgesia in their nerve injury and knee osteoarthritis models. Both models demonstrated that traditional spinal cord stimulation produced equal or greater analgesia than dorsal root ganglion stimulation, which is contrast to industry-sponsored clinical trials.⁶

In the discussion, the authors stated that it was “unexpected” that fourth lumbar (L4) but not L3 dorsal root ganglion stimulation, which provides greater innervation to the knee in humans, produced analgesia in knee osteoarthritis during weightbearing; however, a previous moniodoacetate model of knee osteoarthritis in rats described L4 as the primary sensory contributor.⁷ Nevertheless, it is not entirely clear why L4 but not L3 dorsal root ganglion stimulation resulted in analgesia, but one explanation is that stimulation of the adjacent segment occurred, which may be more likely given the smaller distances in rodents. Although the exact mechanistic basis for adjacent dorsal root ganglion stimulation remains unknown, this phenomenon has been noted in clinical settings and computational models whereby the electrical field of single dorsal root ganglion stimulation has been observed to encompass adjacent levels.⁸ Clinical reports have even suggested that stimulation of an adjacent dorsal root ganglion provides greater pain relief than stimulation of the primary-diseased dorsal root ganglion in postherpetic neuralgia.⁹ However, an equally likely and more elegant explanation is that L4 dorsal root ganglion field stimulation in this model may have encompassed the lateral aspect of the spinal cord, as dorsal root ganglion location and size vary throughout the spine. Perhaps anticipating this criticism, the authors accurately describe their model as dorsal root ganglion “field” stimulation to acknowledge the possible delivery of electricity to adjacent structures.

Another obstacle in developing electrodes for dorsal root ganglion placement is the inverse correlation between miniaturization and durability. Whereas some of the reflexive behavioral findings in this study suggest that placement of multiple dorsal root ganglion electrodes increases analgesia, technical, practical (*e.g.*, costs), and safety considerations must be taken into account when translating findings to patients, especially since their operant behavior assessments (*e.g.*, conditioned place preference and incapacitance) did not support

multilead placement. Since their model involved open surgery with screw fixation of the electrode to the transverse process, it is unlikely to serve as a tool for understanding infection or migration in the clinical setting, wherein these devices are placed percutaneously without fixation to bone.

The observed benefit of dorsal root ganglion stimulation and traditional spinal cord stimulation in nociceptive knee osteoarthritis is in stark contrast to the commonly held belief that electrical stimulation is primarily effective for neuropathic pain conditions. The implications of these findings are striking since knee osteoarthritis is one of the leading causes of disability worldwide, and treatment options are limited.¹⁰ Currently, total knee replacement is widely considered a standard treatment for refractory cases, but dorsal root ganglion stimulation could someday serve as an alternative if relative costs, safety, and outcomes so dictate. Although uncontrolled studies examining spinal cord stimulation for nonneuropathic conditions such as chronic pelvic and abdominal pain demonstrate benefit, support for neuropathic conditions is more robust, as evidenced by the greater benefit observed for radicular pain compared to axial, nociceptive back pain.¹¹

The authors also demonstrated the utility of dorsal root ganglion stimulation and spinal cord stimulation for nociceptive pain in normal uninjured rats subjected to noxious stimuli. Although they posited that impulse filtering at the sensory neuron T-junction in the dorsal root ganglion can account for neuropathic and nociceptive analgesia with dorsal root ganglion stimulation,¹² the mechanisms of spinal cord stimulation-induced analgesia in nociceptive pain remain unclear. However, these findings raise questions about our current pain classification system, as the differences between nociceptive and neuropathic pain (*e.g.*, absence of transduction for neuropathic pain, neuroma formation, and deafferentation pain) pale in comparison to the similarities (*e.g.*, utilization of the same ascending pathways and inhibitory systems, large affective component, presence of peripheral and central sensitization). Thus, many experts view different types of pain as points on a continuum rather than discrete categories, similar to popular paradigms for headaches, hypertension, diabetes, and other medical conditions, which could have implications for neuromodulation research. Modifying our thought paradigm to reflect a pain continuum may reveal conditions classically associated with nociceptive pain that display neuropathic features amenable to neurostimulation.

This study also highlights the importance of preclinical research. For example, the influence of neuromodulation on normal sensory function found in this study, which may improve our understanding of mechanisms and serve as a basis for studies involving preemptive neuromodulation for high-risk surgeries, necessitates further investigation in animals since the implantation of these devices in asymptomatic humans is unethical.

In summary, Yu *et al.* describe the development of an animal model of dorsal root ganglion stimulation and spinal

cord stimulation for nociceptive and neuropathic pain that can serve as the foundation for future mechanistic discovery. Their work has opened the door for further investigation into the role of neuromodulation in nociceptive and inflammatory pain conditions. Future studies may apply this model to investigate waveform parameters, electrophysiologic characteristics of dorsal root ganglion stimulation, and the effects of neurostimulation on neurogenic inflammation.

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Competing Interests

Dr. Cohen has served as a consultant to Abbott (Chicago, Illinois) in the past 3 yr on the topic of radiofrequency ablation and currently is a consultant to SPR Therapeutics (Cleveland, Ohio), which is involved in peripheral nerve stimulation. He also serves as a consultant for Scilex (San Diego, California) and Persica (Kent, United Kingdom). Dr. Sivanesan declares no competing interests.

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