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Neurotechnology for Pain

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Abstract

Neurotechnologies for treating pain rely on electrical stimulation of the central or peripheral nervous system to disrupt or block pain signaling and have been commercialized to treat a variety of pain conditions. While their adoption is accelerating, neurotechnologies are still frequently viewed as a last resort, after many other treatment options have been explored. We review the pain conditions commonly treated with electrical stimulation, as well as the specific neurotechnologies used for treating those conditions. We identify barriers to adoption, including a limited understanding of mechanisms of action, inconsistent efficacy across patients, and challenges related to selectivity of stimulation and off-target side effects. We describe design improvements that have recently been implemented, as well as some cutting-edge technologies that may address the limitations of existing neurotechnologies. Addressing these challenges will accelerate adoption and change neurotechnologies from last-line to first-line treatments for people living with chronic pain.

Contents

1. INTRODUCTION

As early as 2,000 years ago, physicians recognized the power of electrical stimulation to relieve pain. Scribonius Largus, physician to at least one Roman emperor, first documented the analgesic effects of the torpedo fish, a ray with the ability to generate electrical discharges, for treating headache and gout (1, 2). As is still often the case, Scribonius had little or no understanding of the underlying mechanisms of pain relief, but the therapeutic effects of this electrical intervention were clear.

Since the 1960s, the development of neurotechnologies to treat pain has rapidly accelerated, from the first clinical implantation of spinal cord stimulators to today's multibillion-dollar industry that includes a wide portfolio of devices and neural targets (3). While there are still many aspects of the effects of neurostimulation that we do not understand, our knowledge base and available neuroscience techniques continue to grow, facilitating development of new therapies and optimization of existing approaches.

In this review, we aim to describe the various electrical interventions that have been developed to treat pain, as well as to explain what is currently understood about the mechanisms of these interventions. Furthermore, we describe some of the exciting recent innovations to improve the clinical efficacy of these technologies. First, we provide an overview of the main pain conditions that have been targeted with neurostimulation. Next, we describe existing neurostimulation technologies, their indications, and their limitations. Finally, we discuss some of the important recent innovations to improve the efficacy, precision, and clinical adoption of neurostimulation

technologies for pain. We intentionally omit an in-depth review of the neurobiology of pain, as many comprehensive reviews of that topic exist (4–6).

1.1. Overview of Pain and Pathological Pain Conditions

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential damage" (7, p. 1976). This definition highlights several key aspects to consider when designing neurotechnologies to treat pain. First, pain normally serves a critical evolutionary purpose by alerting us to potential or actual tissue damage and facilitating a behavioral response. Under normal circumstances, pain provides a corrective signal to avoid dangerous or damaging activities or environments. In cases where genetic mutations cause people to be insensate to pain, case studies describe self-injurious and dangerous behaviors resulting in skin wounds, painless bone fractures, and self-amputation of the tip of the tongue (8). A second important aspect of pain highlighted in the IASP definition is that it can also resemble the experience of tissue damage. While normal pain serves an important role, pain can also be pathological, serving no specific purpose in maintaining health. Pathological pain is the primary target for neurotechnologies, although this is an umbrella term encompassing many different types of pain. Nociceptive pain arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors; neuropathic pain is caused by a lesion or disease of the somatosensory system; and nociplastic pain arises from altered nociception despite no clear evidence of actual or threatened tissue damage. A third important aspect of pain is that it is both a sensory and an emotional experience. Chronic pain can cause both anxiety and depression, and, in a vicious circle, depression and anxiety can exacerbate the perception of pain (9). Furthermore, the experience of pain is subjective, and similar levels of tissue damage or neuropathy will not produce the same experience of pain in two different people. Treating the tissue damage associated with pain (e.g., via surgical intervention) may not always produce pain relief, and because of the strong emotional component associated with pain, interventions such as psychotherapy may help break the cycle of chronic pain (10). Still, over the past two decades, neuromodulatory approaches have gained traction, with clinical evidence supporting their use for the treatment of a variety of pain conditions. Below, we briefly describe some of these pain conditions (**Figure 1**), their clinical presentation, their incidence, and nonneuromodulatory approaches to treat them. We also provide references to more comprehensive reviews of each pain condition, where available.

1.2. Chronic Pain Conditions Targeted by Neurostimulation

As the clinical use of neuromodulation has accelerated, an expanding array of pain conditions have been targeted with electrical stimulation. These conditions span the various types of pain (i.e., nociceptive, neuropathic, and neuroplastic), and in total, they affect millions of people worldwide. Below, we describe the primary pain conditions that have been targeted with neurostimulation, including information about their prevalence, causes, and existing nonneurostimulation approaches to their treatment.

1.2.1. Low back pain. Low back pain (LBP) encompasses multiple different clinical conditions and presentations, including axial lumbosacral pain (i.e., pain experienced near or in the spine at the low back), radicular pain (i.e., pain that radiates out into the extremities as a result of impingement or irritation of the spinal nerves or dorsal root ganglia), and referred pain (i.e., pain associated with the low back that spreads to other regions of the body along nondermatomal patterns) (11). LBP is one of the most common reasons for doctor visits, and up to 65–80% of

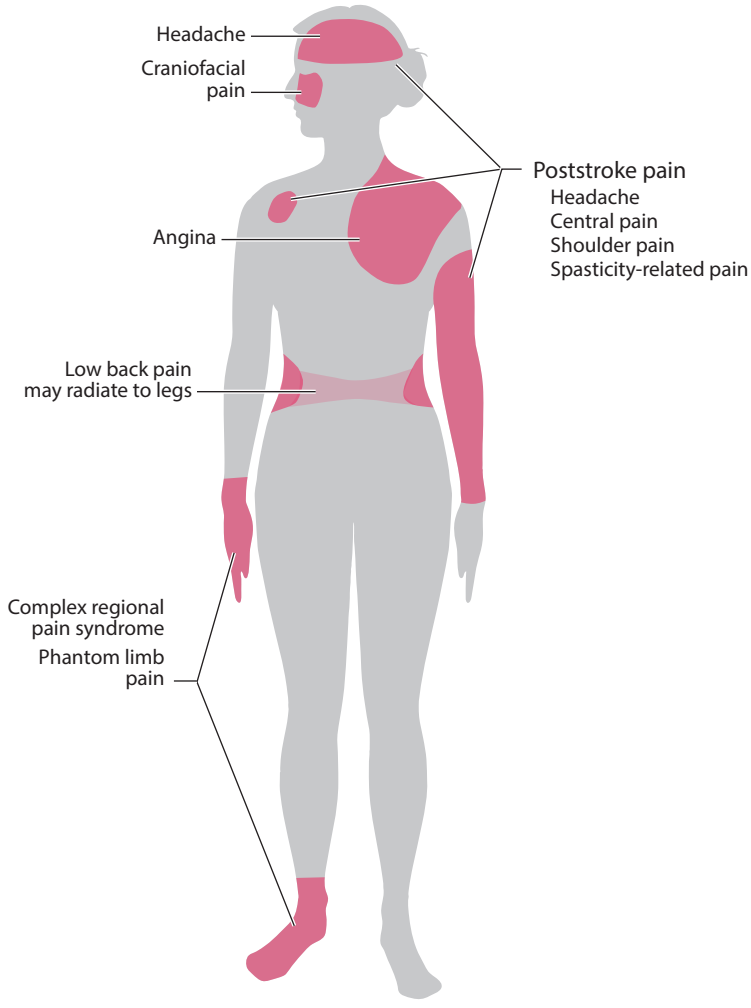

Figure 1

Pain conditions commonly treated with neurotechnologies. Electrical stimulation can be delivered at the brain, spinal cord, or peripheral nerves, depending on the specific neurobiology of each pain condition.

adults will experience LBP at some point, with approximately 10% of these cases developing into persistent chronic pain. A variety of tissues and conditions can be associated with LBP, including inflamed muscle, tendon, and fascia near the spine; spine arthritis; herniation of the intervertebral discs; and spinal stenosis (i.e., narrowing of the spinal canal that causes impingement of the spinal cord and nerves). Additionally, post laminectomy syndrome can occur in up to 10–40% of people who undergo surgeries in which a portion of the bony lamina is removed from the dorsal spine. First-line treatments for LBP typically include pharmaceuticals, such as nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxers, anticonvulsants (e.g., gabapentin), and opioids (11). Physical therapy, psychological treatment, steroidal injections, nerve blocks, and radioablative procedures are common (11). There are also various surgical interventions, such as nerve decompression and spinal fusion (12, 13). While each of these approaches may be effective for a subset of patients, chronic LBP remains a common and costly problem.

1.2.2. Complex regional pain syndrome. Complex regional pain syndrome (CRPS) is an often-severe inflammatory condition of the extremities that typically presents with hyperalgesia (i.e., an increased sensitivity to pain) and allodynia (i.e., pain from a stimulus that would not normally be painful) (14). CRPS affects approximately 1.2% of people, and the condition is often extremely disruptive to quality of life with poor treatment outcomes (14). The underlying causes and mechanisms of CRPS are not fully understood, but the condition typically develops after an injury to the extremities, such as a fracture or sprain, surgical intervention, or other clinical conditions (e.g., carpal tunnel syndrome). There is typically an acute phase of the condition in which redness, swelling, pain, and warmth develop in the affected limb. During the chronic phase of CRPS, the limb becomes cold, hair growth slows, nails become brittle, and muscles atrophy. There is evidence of a psychological association with the development of CRPS, and there may also be a genetic predisposition. Multiple studies have suggested that women are more likely than men to develop CRPS (15, 16). Treatment options for this condition are limited and typically focus on alleviating symptoms with medications, such as anticonvulsants (e.g., gabapentin), anti-inflammatory drugs (e.g., NSAIDs), and sympathetic nerve blocks (14). Physical, occupational, and psychological therapies are also recommended to treat CRPS (14).

1.2.3. Chronic headache and craniofacial pain. Headache and craniofacial pain are conditions that respectively affect up to 10% and 22% of adults in the USA (17). While these conditions are not always linked, there is an elevated rate of headache in people with temporomandibular joint disorders (TMD), and both conditions are associated with sensitization of the trigeminal ganglion (18). Chronic headache includes multiple classifications, such as migraine, cluster headache, occipital neuralgia, and hemicrania continua, and symptoms may also include nausea, visual and auditory sensitivity, and cutaneous allodynia (19). Chronic craniofacial pain conditions include TMD, trigeminal neuralgia, and posttraumatic trigeminal neuropathy. In these conditions, pain can be accompanied by numbness, burning, excessive tear formation, and eye redness (20). Treatment approaches depend on the diagnosis but may include pharmaceuticals (e.g., NSAIDs, migraine-specific agents such as triptans), lifestyle and dietary changes (e.g., exercise and hydration), injections (e.g., botulinum toxin), and psychotherapy (19). Despite these treatments, the American Headache Society consensus statement on the treatment of migraines recommends establishing realistic expectations including modest goals, such as a "50% reduction in frequency of days with headache" (19).

1.2.4. Phantom limb pain. Beyond the functional impairments that occur with limb amputation, one of the most debilitating aspects of limb loss is the development of phantom limb pain (PLP). Of the nearly 200,000 people who undergo an amputation each year, up to 85% of them will develop PLP (21, 22). PLP is defined by painful sensations that appear to emanate from the missing limb and can be either sporadic or constant. People often describe PLP as stabbing, burning, cramping, throbbing, or shooting pain. Pharmaceutical treatments for PLP are largely ineffective, and the only drug recommended in a recent consensus review was amitriptyline, a drug for nerve pain (23). This study also recommended nonpharmacological treatments, such as cognitive behavioral therapy and use of a functional prosthesis to reduce PLP. Surgical approaches, such as ligation of the peripheral nerve in the residual limb and lesioning of the dorsal root entry zone, where primary sensory neurons enter the spinal cord, have demonstrated efficacy in some cases (24).

1.2.5. Poststroke pain. Stroke is one of the most common causes of disability, affecting 13.7 million people each year (25). Pain is a major and common complication of stroke. Up to 50% of stroke survivors experience pain, and people who develop new chronic pain after a stroke

are more likely to experience cognitive decline, functional dependence, and depression (26, 27). Pain conditions associated with stroke include both nociceptive and neuropathic conditions. The hemiparesis that commonly results from stroke can cause weakening of the muscles of the shoulder girdle as well as laxity and painful subluxation of the shoulder joint (28). Stroke also often causes spasticity in the upper limb which is sometimes associated with pain. The origin of spasticity-related pain is somewhat unclear, but it may be related to abnormal muscle loading, as well as atrophy and fibrosis in the muscles. Central poststroke pain accounts for up to one-third of post-stroke pain cases. It often presents as nearly constant burning, aching, freezing, or squeezing, and typically includes allodynia and/or hyperalgesia (28). Central pain is frequently associated with strokes that affect the thalamus and spinothalamic tracts, although people with cortical and brainstem strokes can also develop central poststroke pain. Poststroke chronic headache is also commonly reported, although the incidence and pathophysiology are less well understood than for other poststroke pain conditions.

Treatment of poststroke pain depends on the specific type of pain (29). For people with shoulder pain, devices to stabilize the joint (e.g., shoulder orthoses) can be effective. For spasticity-related pain, treatments that address the spasticity (e.g., botulinum toxin injections), can help reduce pain (29). For neuropathic pain conditions (e.g., central poststroke pain and headache), treatments are similar to those for other neuropathic pain conditions, including prescription of antidepressants, anticonvulsants, and psychotherapy (29).

1.2.6. Angina. Angina pectoris is chest pain that can occur unpredictably (known as unstable angina) or be associated with exertion and relieved by rest (known as stable angina) (30). Unstable angina is an acute condition that is not typically a target for neuromodulation therapies. Stable angina is a chronic and disruptive pain condition often associated with coronary artery disease and insufficient oxygen supply to the heart. There are approximately 10 million cases of stable angina in the USA, with more than 500,000 new cases annually (30). Treatment for angina typically focuses on improving cardiac function via lifestyle changes (e.g., diet and exercise) and pharmacologic therapies (e.g., antiplatelet agents, β-blockers, statins, and aspirin) (30). For severe cases, surgical interventions (e.g., coronary revascularization) may be effective.

2. EXISTING NEUROTECHNOLOGIES FOR PAIN

The pain conditions described above affect many parts of the body, each with its own unique neurobiology and neural anatomy. As such, existing neurotechnologies (**Figure 2**) rely on a variety of approaches to deliver stimulation to multiple locations throughout the central and peripheral nervous system. In this section, we describe these existing technologies, along with the pain conditions they currently treat and some of the benefits and challenges of each approach.

2.1. Spinal Cord Stimulation

Spinal cord stimulation (SCS) is one of the most common forms of neurostimulation to treat chronic pain. SCS is approved by the US Food and Drug Administration (FDA) with a primary indication for neuropathic trunk and limb pain that is refractory to conventional medical management (e.g., failed back surgery syndrome, CRPS) (31, 32). SCS has also proven effective for visceral pain (e.g., refractory angina, peripheral vascular disease) (33). It has been estimated that as many as 50,000 systems are implanted annually, and demand continues to grow (34).

SCS typically involves a two-stage implantation procedure. The first stage is a short-duration trial phase (e.g., 3–10 days) in which an array of electrodes is temporarily implanted at a few spinal levels rostral to the spinal nerves that innervate the affected regions (e.g., lower thoracic spine

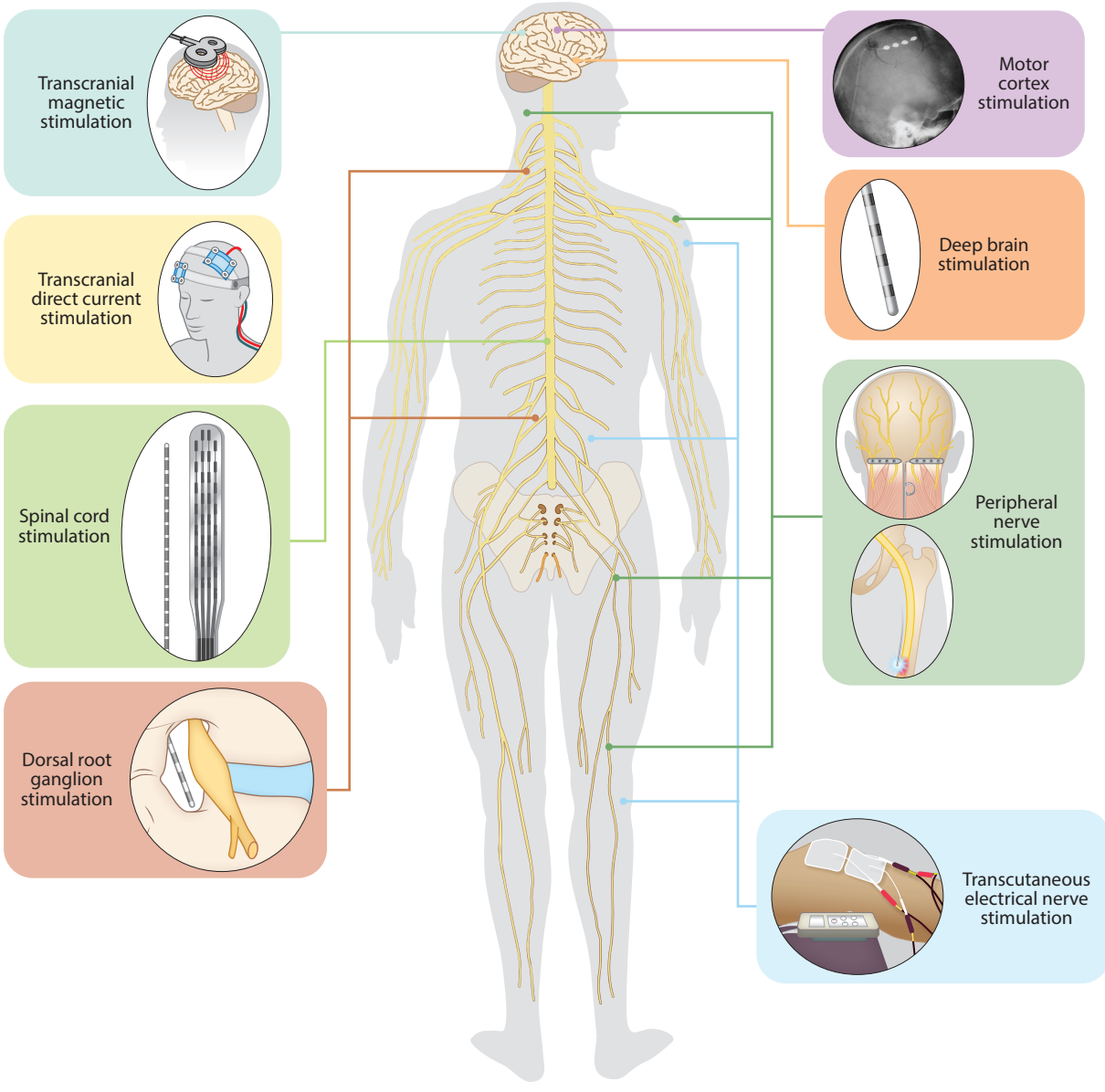

Figure 2

Existing neurotechnologies for treating pain. These devices deliver electrical stimulation at multiple locations throughout the central and peripheral nervous system and span the spectrum of invasiveness. To target the brain, technologies include deep brain stimulation, motor cortex stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. Spinal cord and dorsal root ganglion stimulation are commonly used to treat pain conditions in the limbs and trunk. Peripheral nerve stimulation can also be used for limb pain, as well as for head and facial pain. Transcutaneous electrical nerve stimulation is used to target peripheral nerves via a noninvasive approach with devices that are available over the counter. Motor cortex stimulation image used with permission from Reference 152 (CC BY-NC 4.0).

levels for lower-limb and/or back pain, cervical spine levels for upper-limb pain) and connected to an external stimulator. This procedure can be performed on an outpatient basis, under either local or general anesthesia, with cylindrical electrode arrays implanted through a needle. The goal of this trial phase is to determine the likelihood that a patient will receive sufficient pain relief from SCS. Several stimulation parameters (e.g., pulse amplitude, pulse frequency, pulse width) can be adjusted during the trial phase to maximize pain relief. If the patient receives sufficient pain relief (e.g., $\geq$50% reduction in pain intensity as measured on the visual analog scale), the patient can proceed to the second phase, in which an array of electrodes is permanently implanted and connected to an implantable pulse generator (IPG).

SCS can utilize either cylindrical electrodes that can be percutaneously implanted with a Tuohy needle or paddle-style electrode arrays. The paddle electrode arrays require a laminotomy to make space for insertion of the electrode array and therefore must be implanted by a surgeon, while cylindrical leads are sometimes implanted by nonsurgeon physicians with expertise in pain medicine (e.g., anesthesiologists, physiatrists). Paddle arrays have potential advantages over cylindrical leads, because they can be fixed to bone or connective tissue at the base of the lead body and are less prone to migration than cylindrical leads. Paddle arrays are also insulated on the back side and therefore provide more unidirectional stimulation toward the spinal cord, whereas cylindrical leads have circumferential contacts that allow current to flow in all directions from the lead. Paddle arrays also can have multiple columns of electrodes that provide additional flexibility to increase stimulation selectivity. While these advantages have demonstrated increased success over percutaneous electrodes, they come at the cost of increased invasiveness (35).

Conventional SCS utilizes tonic stimulation that generates perceptible paresthesias (e.g., electrical buzzing sensations), and parameters are selected to provide maximum overlap of the stimulation-induced paresthesias with the patient's pain areas (36). Empirical data suggest that sufficient pain–paresthesia overlap increases the likelihood that a patient will experience pain relief. The putative mechanism of this approach is feed-forward inhibition via the gate-control theory of pain (37). While stimulation-induced paresthesias occur effectively instantaneously, it can take minutes to several hours for stimulation-induced pain relief to occur. Therefore, the stimulation-induced paresthesias are used as a surrogate signal to test a large number of stimulation parameters within a typical clinical visit (38).

Although SCS has been widely available for the last several decades, and despite dramatic improvements in lead design and the capabilities of the IPGs, outcomes for SCS remain highly variable and efficacy often declines over time (39, 40). In response to these limited outcomes, several new forms of SCS have emerged over the last 5–10 years, such as kilohertz-frequency, burst, and closed-loop SCS. There also continue to be several advances in lead design and IPG capabilities (see Section 4, below).

2.2. Dorsal Root Ganglion Stimulation

Despite the overall success of SCS, the approach has faced challenges in targeting focal pain in specific areas, such as the groin and knee, due to current shunting within the cerebrospinal fluid (CSF), variations in stimulation intensity due to postural changes, and lead migration (41). Dorsal root ganglion stimulation (DRGS) is an alternative to SCS that involves percutaneous implantation of a four-electrode cylindrical lead in the epidural space along the dorsal side of the dorsal root ganglion (DRG) (42, 43). The DRG contains the cell bodies of sensory neurons and plays a key role in the development and maintenance of chronic pain (44). A single DRG receives sensory information from a discrete region of the body. Because the stimulating electrodes are placed close to the DRG, DRGS was developed to provide more focal stimulation to dermatomes that are difficult to target with SCS (42). Furthermore, because of the proximity of the electrodes to

the target, clinical DRGS typically utilizes lower stimulation amplitudes (≤1 mA) than SCS. The smaller epidural space in the neural foramen surrounding the DRG may also improve lead stability and reduce postural variation in stimulation intensity (42). A large multicenter study demonstrated superior success rates of DRGS relative to SCS (81% versus 56%) for treating chronic intractable pain of the lower limbs in adults with CRPS (42). DRGS has also shown promise in treating other pain etiologies that affect primarily the hands, feet, and groin, such as painful diabetic neuropathy, PLP, and groin pain (45–47).

2.3. Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) to treat pain has developed alongside SCS, with the first studies reporting pain relief in 1967 (48) and the first implanted devices in 1976 (49). Because of the challenges associated with SCS for pain in the hands and feet, PNS is an attractive alternative for some pain conditions. Additionally, for pain conditions affecting the head and face, SCS is not a viable option because the nerves innervating these regions exit the central nervous system at or near the top of the spinal cord. PNS is believed to engage the same gating mechanisms as SCS and DRGS by activating Aβ tactile afferents to gate C-fiber transmission of pain signals (50). Modern PNS electrodes are typically cylindrical with one or more circumferential contacts. The devices are inserted through a needle under ultrasound guidance, and the procedures are often performed in an outpatient setting, although some devices are also placed via an open surgical approach or may be used temporarily for postoperative pain. Because peripheral nerves stretch and move as the limbs change position, the most common complication of PNS is lead migration (50, 51). To avoid spanning joints and reduce the likelihood of migration, PNS systems typically include a small IPG that can be placed near the electrode. The particular nerve target varies according to the location of pain, but PNS is most commonly used for shoulder, knee, back, pelvic, and facial pain. Multiple systematic reviews have found evidence for the efficacy of PNS for treating refractory neuropathic pain, pelvic pain, and headaches (52–54).

2.4. Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is one of the most widely used electrical stimulation techniques for treating pain. TENS is believed to act through the same mechanisms as PNS, although it relies on patch electrodes adhered to the skin surface and does not require any device implantation. The primary advantages of this approach are its low risk and low cost. TENS devices can be purchased over the counter and typically cost less than US$100. For some users, TENS provides a great deal of pain relief, although systematic reviews have questioned the evidence for efficacy and suggest that bias and the placebo effect may play a major role in TENS adoption (55). The efficacy of TENS is likely limited by several factors. First, because stimulation is delivered transcutaneously, it is possible to target only relatively superficial nerves without relying on high stimulation amplitudes that could also cause pain. Second, efficacy is highly dependent on placement of the electrodes over the appropriate region of the body. Nonexpert users may find it challenging to consistently place electrodes in the same location from day to day. Still, TENS remains an attractive option for patients who may not be interested in or eligible for the more invasive surgical procedures involved in other neuromodulatory interventions.

2.5. Deep Brain Stimulation

Although deep brain stimulation (DBS) is a popular therapy to treat movement disorders (56), it was originally developed to treat chronic pain (57). DBS involves the implantation of one

or more annular electrode arrays to target deep structures within the brain (57–59). Major complications are uncommon but include hemorrhage (1–2%), seizures, and infection (3–5%). Hardware-related complications, such as lead fracture, lead malfunction, and lead migration, are more common (60, 61).

DBS has been utilized to treat many refractory pain conditions, such as poststroke pain, peripheral neuropathy, PLP, failed back surgery syndrome, and headache (58, 62). The number of patients treated with DBS has progressively declined as a result of improvements in other treatment modalities, poor results of multicenter clinical trials, and the lack of approval to treat chronic pain in many countries (62–64). However, in the USA, FDA approval of DBS for essential tremor in 1997 and Parkinson's disease in 2002 made DBS devices available for off-label use to treat pain (57). The most common anatomical targets of DBS are the periaqueductal gray (PAG) and periventricular gray (PVG) regions to treat nociceptive pain and the ventroposterolateral/ventroposteromedial (VPL/VPM) thalamus to treat neuropathic pain (59). The exact mechanisms of DBS-induced analgesia are unknown, but analgesia from PAG/PVG DBS is believed to be mediated partly by the release of endogenous opioids (65, 66), while analgesia from VPL/VPM DBS may be related to the antidromic activation of primary afferents leading to regulation of activity in the dorsal horn of the spinal cord, consistent with the gate-control theory of pain (67–70). Because pain is multidimensional and includes sensory, cognitive, and affective domains (71), some DBS trials have targeted the neural circuitry related to the affective component of pain, which reflects the anxiety, depression, and fear associated with chronic pain (72, 73).

2.6. Motor Cortex Stimulation

Motor cortex stimulation (MCS) is another intracranial technique to treat chronic pain (57, 63). Although the analgesic mechanisms of MCS are not well understood, the rationale behind its development was an experimentally observed decrease in deafferentation-related hyperactivity in the thalamus during MCS (74). Over the past few decades, several reports have described the use of MCS to treat a variety of pain disorders; most of these studies focused on treating poststroke and trigeminal neuropathic pain. Systematic reviews have demonstrated substantial variability in the efficacy of MCS (75, 76). Furthermore, because MCS does not produce paresthesias, it is possible to investigate the efficacy of MCS with controlled studies. Recent multicenter randomized controlled trials have shown mixed results and limited efficacy during the blinded phase (63, 77, 78).

During the implantation procedure for MCS, magnetic resonance imaging (MRI) and electrophysiological recordings are used to determine the location of the motor cortex (57). Next, the dura is exposed and electrode arrays are implanted epidurally. Motor threshold testing is often performed to evoke motor responses (i.e., muscle twitches or electromyogram activity) in the painful regions (79). Paddle leads, developed for SCS, are typically used off-label for MCS. After implantation, a trial period of ~5–10 days can be conducted via externalized extensions (80). MCS does not induce paresthesias, and it may take time for patients to appreciate the analgesic effect of each new stimulation setting. If the patient receives sufficient pain relief during the trial period, the system can be internalized as in other staged neurostimulation procedures. Complications of MCS include hardware-related problems, infection (which may require revision or removal of part or the entire system), and hemorrhage. Seizures have also been reported during MCS programming and during active stimulation (59, 81, 82).

2.7. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) utilizes the principle of electromagnetic induction to noninvasively modulate activity in the brain. A single TMS pulse involves a short-lasting

current applied through a coil that generates a time-varying electromagnetic field perpendicular to the transducing coil, which is placed tangentially to the head (83). The magnetic field is not attenuated by the tissues surrounding the brain, and it induces a phasic electric field in the target tissue. These electric field effects can either generate action potentials in the target neurons or produce subthreshold polarization that can affect ongoing endogenous activity. The neuromodulatory effects of TMS depend on several variables, such as the orientation of the coil, anatomy of the target, stimulation frequency, and number of sessions. Computational modeling research suggests that the primary target of TMS is axonal terminals in the cortical gyri (84). The clinical efficacy of TMS relies on applying repetitive pulses to a specific brain region. In Europe, TMS is approved for depression, schizophrenia, and chronic pain (63). In the USA, TMS is approved for treating depression, migraines to abort aura, and obsessive–compulsive disorder, while its use for pain is considered investigational. While there is conflicting evidence regarding its efficacy, TMS targeting the primary motor cortex or the dorsolateral prefrontal cortex has been recommended for treating various pain conditions (85–87).

2.8. Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is another technique to noninvasively modulate brain activity. tDCS delivers low-intensity current to the cortex through two or more electrodes placed on the scalp (88). Due to attenuation of the applied current, the primary mechanism of tDCS is assumed to be subthreshold modulation that may involve long-term potentiation and/or depression at the synaptic level. The direct neuromodulatory effects of tDCS are polarity dependent, with enhanced excitatory effects near the anode and enhanced inhibitory effects near the cathode. In Europe, tDCS is approved for treatment of pain and depression (63). In the USA, it is used off-label for treating pain and other indications, such as depression and fatigue. For chronic pain, there is low-quality evidence, based on multiple randomized trials, that tDCS is more effective than sham or no treatment (86).

3. CHALLENGES WITH EXISTING NEUROMODULATORY THERAPIES

While existing neuromodulatory treatments provide pain relief for many people who have responded poorly to traditional interventions, these techniques have several unaddressed limitations. Currently, neuromodulation remains a last-line treatment after patients have already undergone multiple failed rounds of pharmaceuticals, surgery, and other procedures. Additionally, the complexity and high cost of neuromodulation therapies have led to major disparities in access to these technologies, with racial and socioeconomic factors highly associated with their usage (89, 90). If neuromodulation is to be adopted as a first-line replacement for existing therapies, these limitations should be addressed.

3.1. Limited Understanding of Mechanisms of Action

Since the initial description of the gate-control theory of pain by Melzack & Wall (91) in 1965, this theory has guided much of our understanding of the mechanisms of action of neuromodulation in treating pain. The primary mechanistic hypothesis driving the original development of SCS in the late 1960s was that activation of Aβ-fibers causes inhibition of C-fibers that carry information about pain to the brain (3). This hypothesis has further supported the development of other neurostimulation strategies and neural targets, including TENS, PNS, and DRGS. While there is strong evidence in support of the gate-control theory, this model of pain is limited

and ignores other important pathways by which neuromodulatory technologies can reduce pain. In fact, Melzack (92) later suggested an expansion of the gate-control theory model, known as the neuromatrix, which aims to explain the multifaceted nature of pain and how pain can arise without any obvious damage to the body. Indeed, multiple studies have demonstrated that, beyond activation of Aβ afferents, SCS has broad effects on the autonomic nervous system that can alter blood flow and heart rate (93, 94) and may also alter neuronal gene expression and the behavior of nonneuronal cells such as microglia (95, 96).

Often, with neuromodulatory therapies, mechanistic understanding lags behind development of the treatment. Still, the clinical benefit of many of these devices is undeniable, so there is strong justification for continued development and deployment before we have a complete understanding of the mechanisms of action. However, a problem arises if we continue that development without eventually also building a strong mechanistic understanding. A deep understanding of the mechanisms of action can lead to optimization of the therapy, making it both more effective and more consistent across patients.

3.2. Limited or Inconsistent Efficacy

For many randomized controlled trials that measure the efficacy of neuromodulatory therapies for treating pain, the primary gauge of success is a ≥50% reduction in pain relief in ≥50% of patients (34, 97). To be sure, for many patients with chronic pain, a 50% reduction can be life-altering. However, it is important to note that for a neuromodulatory therapy that was deemed successful, it is possible that no subject received complete pain relief and that almost half of the enrolled subjects may have had little to no pain relief. Furthermore, multiple longitudinal studies have shown that efficacy decreases over time (39, 40). It is likely that our lack of understanding of the mechanisms of action is a primary reason for this decline in efficacy. If we can better understand the disease states that result in chronic pain, as well as the ways in which electrical stimulation produces analgesia, we may be able to design more effective and more consistent therapies.

3.3. Limited Selectivity and Off-Target Effects

As with many medical interventions, off-target side effects can limit the efficacy of neuromodulation therapies for pain. For many neuromodulation techniques, electrical stimulation evokes a buzzing sensation, called paresthesia (98, 99). While some people find these paresthesias to be pleasant, many report them as noxious or disruptive, and they are frequently a limiting factor in adoption of neuromodulation. Other common side effects include uncomfortable recruitment of muscles (e.g., activation of paraspinal muscles with thoracic SCS) and motor and cognitive effects (e.g., with DBS) (100). Neuromodulatory electrical stimulation often involves milliamp currents driven through electrodes with relatively large surface areas. For example, SCS typically involves stimulation currents in the range of 1–10 mA via electrodes with a surface area of 6–12 mm^2 (101, 102). With TENS, stimulation currents and electrode surface areas can be more than an order of magnitude higher (103, 104). As a result, stimulation often activates large populations of neurons, with selectivity governed primarily by proximity of the neurons to the stimulating electrode, and large myelinated neurons (e.g., Aα- and Aβ-fibers) responding at lower amplitudes than small and unmyelinated neurons (e.g., Aδ- and C-fibers). Stimulation systems have undergone incremental improvements over time, primarily by increasing the number and density of electrode contacts, by using stimulators that are current- rather than voltage-controlled, and by including multiple current sources so that multipolar combinations of cathodes and anodes can be used to more precisely direct the flow of current (105, 106). Still, the process of tuning stimulation is usually manual and time intensive, with the health care provider slowly adjusting stimulation parameters

and waiting to observe efficacy and side effects (107). For some neuromodulation techniques, the onset of both efficacy and side effects can take hours to days (102, 108, 109), making the process even more challenging. These challenges limit the adoption of neuromodulatory techniques for pain.

4. EMERGING TECHNOLOGICAL INNOVATIONS

Several important recent technological advances are helping to improve the efficacy of neuromodulatory therapies for pain. These advances (**Figure 3**) include new waveform paradigms, electrode designs, improved stimulator capabilities, and closed-loop stimulation. Due to the widespread clinical use of SCS, many of these innovations were first performed with these devices, although the improvements are often applicable to other approaches as well.

4.1. Waveforms

Traditional neurostimulation for pain therapies, such as SCS and PNS, have utilized moderate frequencies (e.g., 20–60 Hz) with the goal of targeting large-diameter cutaneous (i.e., nonnociceptive) afferents to produce paresthetic coverage of the painful regions of the body. However, over the last several years, paresthesia-free SCS paradigms have gained popularity because of two potential advantages over paresthesia-based approaches. First, clinical data suggest that these paresthesia-free paradigms may provide improved pain relief over paresthesia-based approaches. Second, stimulation-induced paresthesias can disturb sleep, be experienced as excessive or uncomfortable, and vary with body position, so paresthesia-free approaches may have fewer side effects (110). It can be challenging, however, to explore the stimulation parameter space with these paresthesia-free approaches because stimulation-induced pain relief may take several hours. Therefore, to more efficiently explore the stimulation parameter space, several forms of paresthesia-free SCS utilize paresthesia mapping like conventional SCS. Below, we describe the various novel waveforms that have recently been implemented to improve the efficacy of pain relief with neuromodulation technologies.

4.1.1. Burst SCS. Burst SCS is a paresthesia-free paradigm that delivers intermittent bursts of electrical pulses (e.g., five pulses at 500 Hz, delivered 40 times per second) to mimic bursting within the thalamus. Burst SCS was approved by the FDA in 2016 following a clinical trial demonstrating superior efficacy relative to conventional SCS (i.e., 60% versus 51% success rate) (111). Preliminary evidence suggests that burst SCS may be able to engage both the lateral and medial pain pathways in the spinal cord, in contrast to conventional SCS, which may engage only the lateral pain pathway (112, 113).

4.1.2. High-frequency stimulation. Kilohertz-frequency SCS is another paresthesia-free paradigm that delivers stimulus pulses at a frequency of 1 kHz or higher (114). In 2015, the FDA approved a form of SCS that applies stimulation at a pulse frequency of 10 kHz that provided dramatic pain relief (~80%) without generating paresthesias (114). This research was motivated partly by prior studies demonstrating the ability of 10-kHz stimuli to block action potential conduction in the peripheral nervous system (115). Therefore, it may be possible to block the conduction of pain signals to the brain using these frequencies in SCS. However, according to computational modeling, preclinical, and clinical studies, clinical implementation of 10-kHz SCS utilizes stimulation amplitudes that are likely below the amplitudes necessary to generate conduction block (116–118). Although the mechanisms of kilohertz frequency SCS are still unknown, research has demonstrated its potential ability to selectively increase activity in inhibitory interneurons in the dorsal horn, decrease output from lamina I nociceptive-specific neurons, and

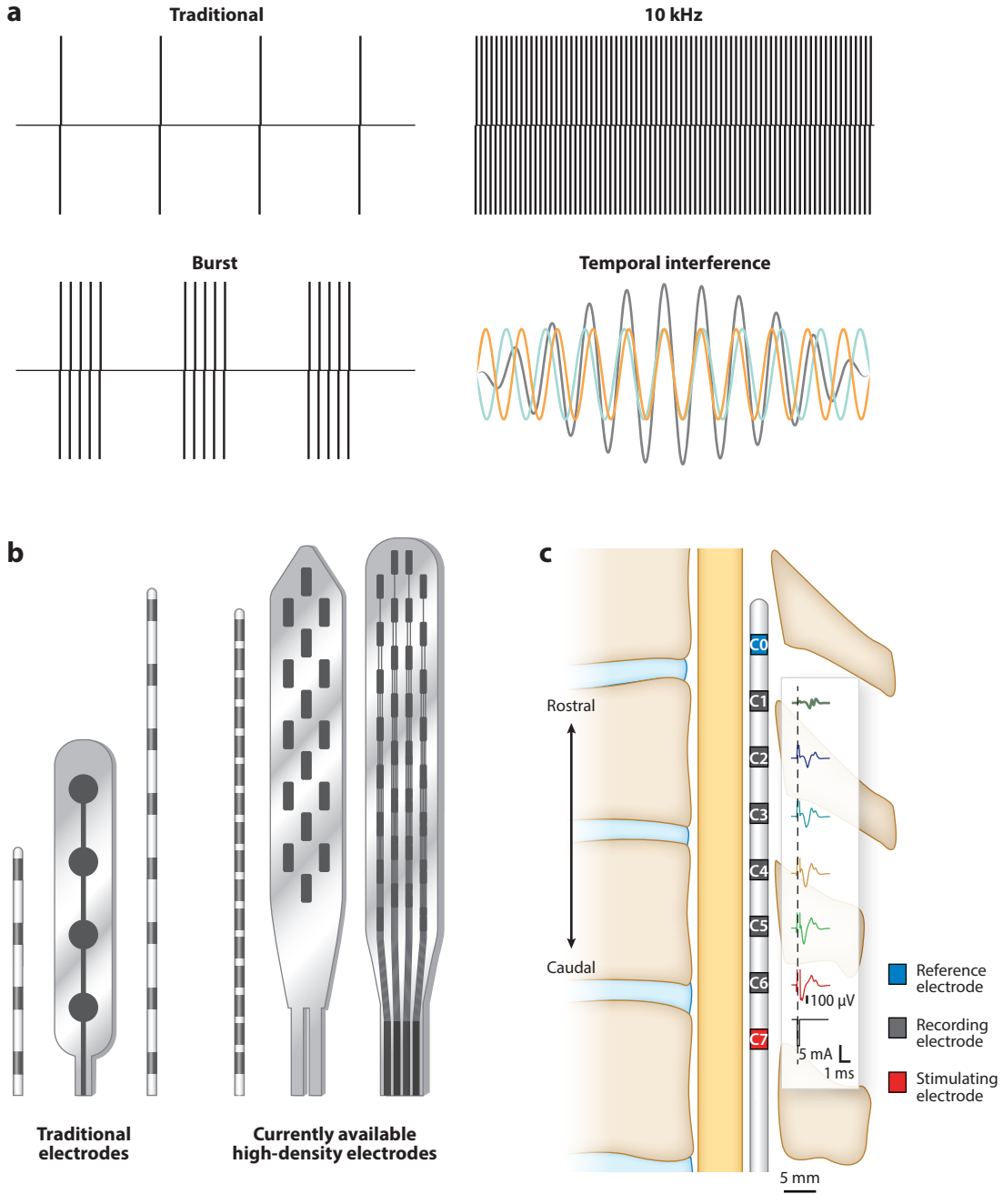

Figure 3

Emerging technological innovations for treatment of pain. (*a*) Multiple novel stimulation waveforms have been developed to improve the efficacy of stimulation, including high-frequency (e.g., 10 kHz), burst, and temporal interference. (*b*) Modern spinal cord stimulation (SCS) devices include a higher density and number of electrodes, enabling improved stimulation selectivity. (*c*) Recording the responses evoked by stimulation allows for closed-loop control to modulate stimulation parameters in response to changes in the position of the spinal cord, as can occur during postural shifts (e.g., from sitting to standing), respiration, coughing, and so forth.

produce excitability changes from tissue heating due to the increased power deposited during stimulation at these high frequencies (112, 119). In addition to SCS, another commercial system is being explored that utilizes 5–10-kHz stimulation applied via a cuff electrode in the peripheral nervous system to treat postamputation pain (120), though this system may leverage the blocking effects of kilohertz-frequency stimulation. Similar approaches are also under development for other indications such as osteoarthritis (121).

4.1.3. Direct current or low-frequency stimulation. Conventional forms of neurostimulation rely on short-duration electrical pulses that directly or indirectly activate inhibitory cells in the central nervous system to decrease pain. Except for high-frequency PNS, none of these conventional forms of stimulation can mimic the effects of local anesthetics in directly blocking the propagation of pain-related signals from the periphery to the central nervous system. For decades, direct current (DC) has been employed to inhibit the propagation of action potentials along axons (122), but because long-term DC causes tissue damage and electrode degradation, this approach has not been pursued for clinical applications (123). However, recent technological developments have demonstrated the possibility of using DC for chronic pain management. Investigators have explored the use of high-capacitance electrode materials (e.g., activated carbon or platinum black) to provide charge-balanced DC block along with cycling between multiple high-capacitance electrodes placed longitudinally along a nerve (124). A second approach uses a separate nerve interface electrode in which the electrode is physically separated from the surrounding biological tissue (e.g., using a column of electrolyte) to keep any toxic electrochemical products (e.g., concentrated hydroxide ions, reactive oxygen species) from reaching the nerve or other biological tissue (123). A third approach applies alternating current through an isolated fluid network and rectifies the resulting ionic current through a series of valve actuations (125). A fourth technology utilizes slow ascending and descending current ramps connected by two plateau phases with a period of ~12 s that is viewed by the target neurons as DC (126).

4.1.4. Interferential stimulation. With all neurostimulation approaches, it is important to selectively stimulate target neurons while avoiding off-target activation effects that could produce side effects and decrease efficacy. Unfortunately, the physical laws governing the penetration of electromagnetic radiation within biological tissues preclude the ability to manipulate activity in deep neural structures without performing invasive surgical procedures. One approach, termed interferential or temporal interference stimulation, uses two (or more) electrode pairs to noninvasively stimulate deep neural structures by applying high-frequency (>1-kHz) currents with a small-frequency offset (127, 128). In theory, superposition of these high-frequency fields would result in a low-frequency amplitude modulation to activate neurons within a certain region of space. Although this approach has been around since the 1950s, it has recently gained renewed interest. However, prior research has demonstrated limited clinical success using interferential stimulation for treating pain and other clinical applications. Furthermore, recent studies have demonstrated that interferential stimulation may affect off-target structures, and it may be infeasible to achieve the desired field strengths to elicit activation in deep neural structures (127, 129, 130).

4.1.5. Glial cell modulation. Historically, the nonneuronal effects of neurostimulation have largely been ignored, except in the context of the foreign-body response to implanted electrodes. SCS is commonly applied at lower thoracic spine levels, where it has been estimated that there are more than 10 times as many glial cells as neurons (131). This high density of glial cells near the putative neural targets of SCS means that the applied potential fields could modulate the activity of the surrounding glial cells. Differential target multiplexed (DTM) SCS was developed to concurrently drive both neuronal and glial mechanisms of pain relief by concurrently delivering

a low-frequency (~50-Hz) waveform and a high-frequency (~300–1,200-Hz) waveform (132). In a prospective randomized controlled trial, DTM SCS demonstrated superior response rates relative to traditional SCS (80% versus 51%) in patients with chronic LBP and leg pain at 12-month follow-up (132). A preclinical study also demonstrated that astrocytes may be an important component of pain gating in the spinal cord (133). These results suggest that simultaneously modulating the neuronal and glial components of pain may lead to greater pain relief than modulating the neural component alone.

4.2. Electrode Designs

Electrode design has been another major area of development for neuromodulation therapies. By increasing the number of electrode contacts and minimizing the invasiveness of their implantation, multiple efforts have aimed to improve the outcomes of neuromodulation therapies for pain.

4.2.1. High-density electrode arrays. The success of neurostimulation therapies for chronic pain management relies on the ability to selectively stimulate target neural structures. Therefore, several technological advances have focused on increasing the number and density of contacts on electrode arrays. Theoretically, a higher electrode count allows the user to have better control over the shape of the applied potential fields to achieve better stimulation selectivity by strategic selection of the cathodes and anodes used to apply the stimulation. For several years, clinical SCS and DBS systems consisted of four electrodes (36). However, clinical electrode arrays now have 8–32 electrodes, including paddle arrays with up to five columns of electrodes (33, 38). Investigational SCS devices with 60 electrodes are also being developed (134). To achieve an even higher degree of selectivity in PNS, studies have utilized high-contact cuff electrodes or penetrating electrode arrays that are surgically inserted into the epineurium or through fascicles (135). However, there are likely to be diminishing returns as contacts become smaller and more densely packed. Not only does a higher electrode count dramatically increase the complexity of stimulator programming, but also stimulation is filtered by the surrounding biological tissue (e.g., CSF), which may limit selectivity. Additionally, as electrodes get smaller, for a given set of stimulus parameters, the impedance and charge density increase, leading to a need for stimulators with higher compliance voltage and increasing the likelihood of electrode and tissue damage.

4.2.2. Segmented lead designs. Like SCS, conventional DBS systems included only four annular electrodes. However, current DBS systems include arrays with 4–16 electrodes (106). Furthermore, some of these systems include segmented or directional electrodes in which the individual contacts span only a portion (e.g., 120°) of the lead circumference. These segmented electrodes may improve the ability to focus stimulation toward the brain area believed to be responsible for therapeutic benefit and avoid brain areas associated with unwanted side effects (136).

4.2.3. Injectable electrodes. Due to the limitations of noninvasive stimulation strategies, implantable neural stimulation electrodes are commonly used to provide more selective activation of neural targets. Approaches that reduce the degree of invasiveness associated with implantable electrodes are being developed. In one of these approaches, a needle-delivered electrode is injected near neural structures under image guidance, and power is then delivered to the device transcutaneously (137). Another approach uses fluidic channels embedded in a flexible paddle that can be rolled up to fit through a needle and expanded after implantation to achieve coverage similar to that of existing devices that require open surgery for insertion (138). This type of approach could be less invasive, more robust, and more cost effective and may help increase the adoption of neuromodulation therapies.

4.2.4. Absorbable local cooling. The controlled application of electrical, pharmacological, optical, mechanical, or thermal stimuli can produce local and reversible blocking of neural signals. Because ion channel kinetics are sensitive to temperature, cooling provides a method to achieve rapid and reversible nerve block. One approach to leverage this blocking action has been the development of a combined evaporative microfluidic cooling and temperature sensing system that enables the delivery of focused, minimally invasive cooling with real-time temperature feedback control (139). This device is constructed with water-soluble, biocompatible materials that lead to dissolution of the cooling system after the healing process is completed, obviating the need for extraction surgery.

4.3. Implantable Pulse Generators

IPGs have been dramatically improved over the last several years. The technologies associated with neurostimulation therapies like SCS and DBS are expensive and involve invasive procedures. Therefore, significant research has focused on improving the efficacy and lifetime of IPGs to help reduce the costs and risks associated with these therapies.

4.3.1. Voltage versus current regulation. Most early clinical neurostimulation systems used voltage-controlled stimulation, in which the system regulates the voltage of the stimulus pulse and the corresponding electrode current is dependent on the electrode impedance (38, 106). In clinical applications, large impedance variations can affect the extracellular potentials generated within the target neural tissue and may require adjusting the stimulation parameters to improve pain relief. Instead, most modern clinical neurostimulation systems utilize current-controlled stimulation, in which the device controls the output current throughout the duration of the stimulus pulse and adjusts the output voltage to maintain a controlled current (33, 106). Therefore, the amplitude of the injected current is independent of electrode impedance. Thus, current-controlled stimulation may produce more stable extracellular potentials and may maintain a more constant physiologic response during treatment.

4.3.2. Multiple-source systems. Most neurostimulation systems use a single current source to drive stimulation. In these systems, individual electrodes can be assigned only as a cathode, an anode, or inactive. While the user can select complex stimulation configurations, if multiple cathodic or anodic electrodes are grouped together, the division of current between them will be dependent on their relative impedances in a way that is difficult to predict or control. To achieve stimulation via multiple independent electrodes, stimulation trains must be scheduled with the output of the single current source switched to different electrodes at different times. However, some newer stimulators have multiple independent current sources, giving them the ability to precisely partition the applied current across the desired active electrodes with increased flexibility in shaping the applied potential fields (38). This flexibility is believed to improve the ability to target the desired areas within the nervous system.

4.3.3. Reduced invasiveness. Several technological advances have helped reduce the invasiveness of neurostimulation technologies by reducing the footprint of the IPG and the number of implanted components. Rechargeable systems have improved battery longevity (9–25 years) in comparison to nonrechargeable stimulators and allow for a significant reduction in the size of the IPG and decreases in the cost and potential risk of discomfort and infection at the implant site (41). Furthermore, these rechargeable systems have enabled stimulation approaches with higher-energy demands (e.g., kilohertz-frequency and closed-loop SCS) that would dramatically decrease the lifetime of a nonrechargeable system. However, it is also important to recognize that

some patients may prefer nonrechargeable systems due to the additional burden associated with frequent charging of rechargeable systems.

Researchers have developed wireless SCS and PNS systems that include a passive electrode array containing a microprocessor receiver and an antenna. The electrode array and receiving antenna are implanted near the target tissue. The patient wears an external transmitting antenna and pulse generator that transcutaneously transmit stimulation parameters and power to the implanted electrode array (140).

4.3.4. Magnetic resonance imaging compatibility. Patients with chronic pain frequently have comorbidities that require diagnostic imaging. MRI is considered the gold standard for clinical evaluation and diagnosis of many disease states, including chronic pain. It has been estimated that >80% of SCS patients will need at least one MRI within a year after implantation of their SCS system (141). However, due to potential interaction between the MRI and the implanted neurostimulation system, patients have historically been excluded from MRI or the device must be explanted so the patient can undergo imaging. In the last several years there have been significant improvements in MRI compatibility, and several clinical systems are MRI conditionally safe (142). These developments have played a major role in increasing access to implantable neuromodulation systems.

4.3.5. Multiwave platforms. Neurostimulation systems are more robust than ever before, and the newest implantable stimulators can apply a wide range of pulse amplitudes, pulse widths, pulse frequencies, pulse patterns, and stimulation configurations. As discussed above, several different waveform paradigms (e.g., burst, kilohertz-frequency SCS) are now used in the clinic and demonstrate superior efficacy to conventional SCS. New stimulators can implement one or more of these paradigms and can also vary the duty cycle of stimulation, with the device either turned on continuously or cycled on and off for brief periods of time (e.g., 30 s on followed by 90 s off) (143). Duty cycling can provide significant pain relief while increasing battery life and/or decreasing the need to recharge the system. These systems can also be programmed with several stimulation programs (~4–16 programs at a time) that the patient can select (144). Multiple paradigms can be interleaved and/or applied simultaneously to target different types of pain and/or painful areas.

4.4. Closed-Loop Stimulation

Neuromodulatory stimulation systems are typically operated in an open-loop manner. Patients can provide critical feedback with regard to stimulation-induced paresthesias, pain relief, and discomfort to help select efficacious stimulation parameters. However, once the optimal stimulation parameters are determined, they are largely left unchanged.

With regard to SCS, stimulation efficacy can vary due to movement of the spinal cord that occurs with changes in body position, respiration, coughing, and heartbeat. Studies suggest that, with changes in body position, the thoracic spinal cord can move ~2–3 mm in the anterior–posterior direction within the thecal sac (145). This movement causes a substantial change in the distance between the stimulating electrodes and the neural target and can lead to either under- or overstimulation. Therefore, a given set of stimulation parameters can be efficacious in one body position but lead to discomfort or poor pain relief in another position. This movement can also prevent patients from participating in activities of daily living, such as driving. To reduce the potential deleterious effects of movement of the spinal cord, one commercial system utilizes a three-axis accelerometer inside the IPG to estimate the body position of the patient. Effective and comfortable stimulation parameters can be determined for multiple body positions (e.g., sitting, standing, supine) and stored within the IPG. Then, when the patient assumes a given

body position, the system automatically switches to the appropriate predetermined program (110, 146). Another clinical system uses electrodes on the implanted SCS electrode array to record evoked compound action potentials (ECAPs) generated in the spinal cord during SCS (147). ECAPs provide a quantitative measure of neural recruitment during SCS, and their amplitude is used as a control signal to continuously adjust stimulation parameters in real time. To implement this closed-loop approach, the user defines a reference ECAP amplitude range evoked during comfortable and effective stimulation parameters. The IPG then utilizes a feedback controller to continuously adjust stimulation amplitude so that the recorded ECAP amplitude stays within a therapeutic window. The therapeutic efficacy of this approach was demonstrated in a large, pivotal multicenter trial that helped lead to FDA approval of the device in 2022 (147).

Closed-loop approaches for DBS and other neuromodulatory devices are also under active development. Closed-loop responsive brain stimulation has been utilized in the treatment of epilepsy with a device that includes a cranially implanted neurostimulator connected to depth and/or subdural cortical strip electrodes placed at the seizure focus and applies stimulation when abnormal activity is detected in the electrocorticogram (148). Other DBS systems that can provide both stimulation and sensing are being explored for a variety of neurological disorders, such as movement disorders and chronic pain (149). These systems can sense local field potentials and perform spectral analysis of the signals to provide real-time adjustment of the applied stimulation. Other closed-loop DBS approaches utilized control signals based on neurochemical sensing and signals from wearable sensors (150, 151).

5. CONCLUSIONS

Neurotechnologies provide important opportunities to treat a variety of intractable pain conditions. Despite their widespread and accelerating adoption for the treatment of pain, these devices often remain last-line approaches, after patients have undergone multiple other treatments and have experienced years of debilitating pain. Our limited understanding of the mechanisms of action of electrical stimulation impedes our ability to optimize existing therapies and slows the development of new approaches. Importantly, though, multiple new technologies are in development or have recently been translated that aim to improve the efficacy and reduce the invasiveness of neurotechnologies for pain. While a deeper understanding of their underlying mechanisms must be a focus of scientific research, these improvements are likely to increase adoption of these promising technologies for the treatment of pain.

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LITERATURE CITED

1. Francis J, Dingley J. 2015. Electroanaesthesia—from torpedo fish to TENS. *Anaesthesia* 70(1):93–103
2. Cambiaghi M, Sconocchia S. 2018. Scribonius Largus (probably before 1 CE–after 48 CE). *J. Neurol.* 265(10):2466–68
3. Shealy CN, Mortimer JT, Reswick JB. 1967. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth. Analg.* 46(4):489–91

4. Mertens P, Blond S, David R, Rigoard P. 2015. Anatomy, physiology and neurobiology of the nociception: a focus on low back pain (part A). *Neurochirurgie* 61(Suppl. 1):S22–34
5. Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. 2018. When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain* 159(12):2421–36
6. Fenton BW, Shih E, Zolton J. 2015. The neurobiology of pain perception in normal and persistent pain. *Pain Manag.* 5(4):297–317
7. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, et al. 2020. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 161(9):1976–82
8. Woods CG, Babiker MOE, Horrocks I, Tolmie J, Kurth I. 2015. The phenotype of congenital insensitivity to pain due to the $Na_V1.9$ variant p.L811P. *Eur. J. Hum. Genet.* 23(5):561–63
9. Woo AK. 2010. Depression and anxiety in pain. *Rev. Pain* 4(1):8–12
10. Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, et al. 1998. Complex regional pain syndromes: guidelines for therapy. *Clin. J. Pain* 14(2):155–66
11. Urits I, Burshtein A, Sharma M, Testa L, Gold PA, et al. 2019. Low back pain, a comprehensive review: pathophysiology, diagnosis, and treatment. *Curr. Pain Headache Rep.* 23(3):23
12. Baliga S, Treon K, Craig NJA. 2015. Low back pain: current surgical approaches. *Asian Spine J.* 9(4):645–57
13. Jacobs WCH, Rubinstein SM, Willems PC, Moojen WA, Pellisé F, et al. 2013. The evidence on surgical interventions for low back disorders, an overview of systematic reviews. *Eur. Spine J.* 22(9):1936–49
14. Taylor SS, Noor N, Urits I, Paladini A, Sadhu MS, et al. 2021. Complex regional pain syndrome: a comprehensive review. *Pain Ther.* 10(2):875–92
15. Kim H, Lee CH, Kim SH, Kim YD. 2018. Epidemiology of complex regional pain syndrome in Korea: an electronic population health data study. *PLOS ONE* 13(6):e0198147
16. Ott S, Maihöfner C. 2018. Signs and symptoms in 1,043 patients with complex regional pain syndrome. *J. Pain* 19(6):599–611
17. Bender SD. 2014. Orofacial pain and headache: a review and look at the commonalities topical collection on uncommon headache syndromes. *Curr. Pain Headache Rep.* 18(3):400
18. Yap AUJ, Chua EK, Hoe JKE. 2002. Clinical TMD, pain-related disability and psychological status of TMD patients. *J. Oral Rehabil.* 29(4):374–80
19. Ailani J, Burch RC, Robbins MS. 2021. The American Headache Society Consensus Statement: update on integrating new migraine treatments into clinical practice. *Headache* 61(7):1021–39
20. Van Deun L, De Witte M, Goessens T, Halewyck S, Ketelaer MC, et al. 2020. Facial pain: a comprehensive review and proposal for a pragmatic diagnostic approach. *Eur. Neurol.* 83(1):5–16
21. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. 2008. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch. Phys. Med. Rehabil.* 89(3):422–29
22. Hsu E, Cohen SP. 2013. Postamputation pain: epidemiology, mechanisms, and treatment. *J. Pain Res.* 6:121–36
23. Limakatso K, Parker R. 2021. Treatment recommendations for phantom limb pain in people with amputations: an expert consensus Delphi study. *PM&R* 13(11):1216–26
24. Awad A, Forbes J, Jermakowicz W, Eli I, Blumenkopf B, Konrad P. 2013. Experience with 25 years of dorsal root entry zone lesioning at a single institution. *Surg. Neurol. Int.* 4(1):64
25. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, et al. 2019. Ischaemic stroke. *Nat. Rev. Dis. Primers* 5(1):70
26. Lundström E, Smits A, Terént A, Borg J. 2009. Risk factors for stroke-related pain 1 year after first-ever stroke. *Eur. J. Neurol.* 16(2):188–93
27. O'Donnell MJ, Diener HC, Sacco RL, Panju AA, Vinisko R, Yusuf S. 2013. Chronic pain syndromes after ischemic stroke: PRoFESS trial. *Stroke* 44(5):1238–43
28. Harrison RA, Field TS. 2015. Post stroke pain: identification, assessment, and therapy. *Cerebrovasc. Dis.* 39(3/4):190–201
29. Plecash AR, Chebini A, Ip A, Lai JJ, Mattar AA, et al. 2019. Updates in the treatment of post-stroke pain. *Curr. Neurol. Neurosci. Rep.* 19(11):86
30. Kloner RA, Chaitman B. 2017. Angina and its management. *J. Cardiovasc. Pharmacol. Ther.* 22(3):199–209

31. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, et al. 2000. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N. Engl. J. Med.* 343(9):618–24
32. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, et al. 2008. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 63(4):762–70
33. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, et al. 2014. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. *Neuromodulation* 17(6):515–50
34. Sdrulla AD, Guan Y, Raja SN. 2018. Spinal cord stimulation: clinical efficacy and potential mechanisms. *Pain Pract*. 18(8):1048–67
35. North RB, Kidd DH, Petrucci L, Dorsi MJ. 2005. Spinal cord stimulation electrode design: a prospective, randomized, controlled trial comparing percutaneous with laminectomy electrodes. Part II. Clinical outcomes. *Neurosurgery* 57(5):990–95
36. North RB, Ewend MG, Lawton MT, Piantadosi S. 1991. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. *Pain* 44(2):119–30
37. Guan Y. 2012. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. *Curr. Pain Headache Rep.* 16(3):217–25
38. Moffitt MA, Lee DC, Bradley K. 2009. Spinal cord stimulation: engineering approaches to clinical and physiological challenges. In *Implantable Neural Prostheses 1*, ed. E Greenbaum, D Zhou, pp. 155–94. New York: Springer
39. Geurts JW, Smits H, Kemler MA, Brunner F, Kessels AGH, van Kleef M. 2013. Spinal cord stimulation for complex regional pain syndrome type. I. A prospective cohort study with long-term follow-up. *Neuromodulation* 16(6):523–29
40. Aló KM, Redko V, Charnov J. 2002. Four year follow-up of dual electrode spinal cord stimulation for chronic pain. *Neuromodulation* 5(2):79–88
41. Kumar K, Caraway DL, Rizvi S, Bishop S. 2014. Current challenges in spinal cord stimulation. *Neuromodulation* 17(Suppl. 1):22–35
42. Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, et al. 2017. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 158(4):669–81
43. Graham RD, Sankarasubramanian V, Lempka SF. 2022. Dorsal root ganglion stimulation for chronic pain: hypothesized mechanisms of action. *J. Pain* 23(2):196–211
44. Krames ES. 2014. The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Med*. 15(10):1669–85
45. Eldabe S, Burger K, Moser H, Klase D, Schu S, et al. 2015. Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). *Neuromodulation* 18(7):610–16
46. Eldabe S, Espinet A, Wahlstedt A, Kang P, Liem L, et al. 2018. Retrospective case series on the treatment of painful diabetic peripheral neuropathy with dorsal root ganglion stimulation. *Neuromodulation* 21(8):787–92
47. Morgalla MH, Bolat A, Fortunato M, Lepski G, Chander BS. 2017. Dorsal root ganglion stimulation used for the treatment of chronic neuropathic pain in the groin: a single-center study with long-term prospective results in 34 cases. *Neuromodulation* 20(8):753–60
48. Wall PD, Sweet WH. 1967. Temporary abolition of pain in man. *Science* 155(3758):108–9
49. Campbell JN, Long DM. 1976. Peripheral nerve stimulation in the treatment of intractable pain. *J. Neurosurg.* 45(6):692–99
50. Kaye AD, Ridgell S, Alpaugh ES, Mouhaffel A, Kaye AJ, et al. 2021. Peripheral nerve stimulation: a review of techniques and clinical efficacy. *Pain Ther*. 10(2):961–72
51. Novak CB, Mehdian H, von Schroeder HP. 2012. Laxity of the ulnar nerve during elbow flexion and extension. *J. Hand Surg.* 37(6):1163–67
52. Helm S, Shirsat N, Calodney A, Abd-Elsayed A, Kloth D, et al. 2021. Peripheral nerve stimulation for chronic pain: a systematic review of effectiveness and safety. *Pain Ther*. 10(2):985–1002
53. Chen YF, Bramley G, Unwin G, Hanu-Cernat D, Dretzke J, et al. 2015. Occipital nerve stimulation for chronic migraine—a systematic review and meta-analysis. *PLOS ONE* 10(3):e0116786

54. Gaziev G, Topazio L, Iacovelli V, Asimakopoulos A, Di Santo A, et al. 2013. Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. *BMC Urol.* 13:61
55. Johnson MI, Paley CA, Howe TE, Sluka KA. 2015. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst. Rev.* 2015(6):CD006142
56. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, et al. 2019. Deep brain stimulation: current challenges and future directions. *Nat. Rev. Neurol.* 15(3):148–60
57. Lempka SF, Machado A. 2014. Deep brain and motor cortex stimulation for head and face pain. In *Interventional Management of Head and Face Pain: Nerve Blocks and Beyond*, ed. SN Narouze, pp. 141–49. New York: Springer
58. Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, et al. 2005. Deep brain stimulation for pain relief: a meta-analysis. *J. Clin. Neurosci.* 12(5):515–19
59. Levy R, Deer TR, Henderson J. 2010. Intracranial neurostimulation for pain control: a review. *Pain Phys.* 13:157–65
60. Hamani C, Lozano AM. 2006. Hardware-related complications of deep brain stimulation: a review of the published literature. *Stereotact. Funct. Neurosurg.* 84(5/6):248–51
61. Levy R, Deer TR, Henderson J. 2010. Intracranial neurostimulation for pain control: a review. *Pain Phys.* 13:157–65
62. Coffey RJ. 2001. Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. *Pain Med.* 2(3):183–92
63. Knotkova H, Hamani C, Sivanesan E, Le Beuffe FME, Moon JY, et al. 2021. Neuromodulation for chronic pain. *Lancet* 397:2111–24
64. Fontaine D, Lazorthes Y, Mertens P, Blond S, Géraud G, et al. 2010. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. *J. Headache Pain* 11(1):23–31
65. Hosobuchi Y, Adams JE, Linchitz R. 1977. Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. *Science* 197(4299):183–86
66. Hosobuchi Y, Rossier J, Bloom F, Guillemin R. 1979. Stimulation of human periaqueductal gray for pain relief increases immunoreactive β-endorphin in ventricular fluid. *Science* 203(4377):279–81
67. Benabid AL, Henriksen SJ, Mcginty JF, Bloom FE. 1983. Thalamic nucleus ventro-postero-lateralis inhibits nucleus parafascicularis response to noxious stimuli through a non-opioid pathway. *Brain Res.* 280:217–31
68. Gerhart KD, Yezierski RP, Fang ZR, Willis WD. 1983. Inhibition of primate spinothalamic tract neurons by stimulation in ventral posterior lateral (VPLc) thalamic nucleus: possible mechanisms. *J. Neurophysiol.* 49(2):406–23
69. Tsubokawa T, Yamamoto JT, Katayama Y, Iirayama T, Sibuya H. 1984. Thalamic relay nucleus stimulation for relief of intractable pain. Clinical results and β-endorphin immunoreactivity in the cerebrospinal fluid. *Pain* 18:115–26
70. Young RF, Bach FW, van Norman AS, Yaksh TL. 1993. Release of β-endorphin and methionine-enkephalin into cerebrospinal fluid during deep brain stimulation for chronic pain: effects of stimulation locus and site of sampling. *J. Neurosurg.* 79:816–25
71. Talbot K, Madden VJ, Jones SL, Moseley GL. 2019. The sensory and affective components of pain: Are they differentially modifiable dimensions or inseparable aspects of a unitary experience? A systematic review. *Br. J. Anaesth.* 123(2):e263–72
72. Galafassi GZ, Simm Pires de Aguiar PH, Simm RF, Franceschini PR, Filho MP, et al. 2021. Neuromodulation for medically refractory neuropathic pain: spinal cord stimulation, deep brain stimulation, motor cortex stimulation, and posterior insula stimulation. *World Neurosurg.* 146:246–60
73. Lempka SF, Malone DA, Hu B, Baker KB, Wyant A, et al. 2017. Randomized clinical trial of deep brain stimulation for poststroke pain. *Ann. Neurol.* 81(5):653–63
74. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. 1991. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir. Suppl.* 52:137–39
75. Parravano DC, Ciampi DA, Fonoff ET, Monaco B, Navarro J, et al. 2019. Quality of life after motor cortex stimulation: clinical results and systematic review of the literature. *Clin. Neurosurg.* 84(2):451–56

76. Sachs AJ, Babu H, Su YF, Miller KJ, Henderson JM. 2014. Lack of efficacy of motor cortex stimulation for the treatment of neuropathic pain in 14 patients. *Neuromodulation* 17(4):303–11
77. Lefaucheur JP, Drouot X, Cunin P, Bruckert R, Lepetit H, et al. 2009. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain* 132(6):1463–71
78. Radic JAE, Beauprie I, Chiasson P, Kiss ZHT, Brownstone RM. 2015. Motor cortex stimulation for neuropathic pain: a randomized cross-over trial. *Can. J. Neurol. Sci.* 42(6):401–9
79. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ. 2000. Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. *Pain* 84:431–37
80. Machado A, Azmi H, Rezai AR. 2007. Motor cortex stimulation for refractory benign pain. *Clin. Neurosurg.* 54:70–77
81. Fontaine D, Hamani C, Lozano A. 2009. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. *J. Neurosurg.* 110(2):251–56
82. Henderson JM, Heit G, Fisher RS. 2010. Recurrent seizures related to motor cortex stimulator programming. *Neuromodulation* 13(1):37–43
83. Siebner HR, Funke K, Aberra AS, Antal A, Bestmann S, et al. 2022. Transcranial magnetic stimulation of the brain: What is stimulated? A consensus and critical position paper. *Clin. Neurophysiol.* 140:59–97
84. Aberra AS, Wang B, Grill WM, Peterchev AV. 2020. Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. *Brain Stimul.* 13:175–89
85. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, et al. 2020. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin. Neurophysiol.* 131(2):474–528
86. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. 2018. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst. Rev.* 4(8):CD008208
87. Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, et al. 2016. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur. J. Neurol.* 23(10):1489–99
88. Truong DQ, Bikson M. 2018. Physics of transcranial direct current stimulation devices and their history. *J. ECT* 34(3):137–43
89. Jones MR, Orhurhu V, O'Gara B, Brovman EY, Rao N, et al. 2021. Racial and socioeconomic disparities in spinal cord stimulation among the Medicare population. *Neuromodulation* 24(3):434–40
90. Lad SP, Kalanithi PS, Arrigo RT, Patil CG, Nathan JK, et al. 2010. A socioeconomic survey of spinal cord stimulation (SCS) surgery. *Neuromodulation* 13(4):265–69
91. Melzack R, Wall PD. 1965. Pain mechanisms: a new theory. *Science* 150(3699):971–79
92. Melzack R. 2001. Pain and the neuromatrix in the brain. *J. Dent. Educ.* 65(12):1378–82
93. Goudman L, De Smedt A, Louis F, Stalmans V, Linderoth B, et al. 2022. The link between spinal cord stimulation and the parasympathetic nervous system in patients with failed back surgery syndrome. *Neuromodulation* 25(1):128–36
94. Olgin JE, Takahashi T, Wilson E, Vereckei A, Steinberg H, Zipes DP. 2002. Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. *J. Cardiovasc. Electrophysiol.* 13(5):475–81
95. Shu B, He SQ, Guan Y. 2020. Spinal cord stimulation enhances microglial activation in the spinal cord of nerve-injured rats. *Neurosci. Bull.* 36(12):1441–53
96. Tilley DM, Cedeño DL, Kelley CA, Benyamin R, Vallejo R. 2016. Spinal cord stimulation modulates gene expression in the spinal cord of an animal model of peripheral nerve injury. *Reg. Anesth. Pain Med.* 41(6):750–56
97. Forouzanfar T, Weber WEJ, Kemler M, Van Kleef M. 2003. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin. J. Pain* 19(5):281–85
98. Wang J, Chen Z. 2019. Neuromodulation for pain management. In *Neural Interface: Frontiers and Applications*, ed. X Zheng, pp. 207–23. Berlin: Springer
99. North R, Shipley J. 2007. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. *Pain Med.* 8(Suppl. 4):200–75
100. Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, et al. 2013. Neuromodulation of chronic headaches: position statement from the European Headache Federation. *J. Headache Pain* 14(1):86

101. Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderoth B. 2016. Parameters of spinal cord stimulation and their role in electrical charge delivery: a review. *Neuromodulation* 19(4):373–84
102. Sheldon B, Staudt MD, Williams L, Harland TA, Pilitsis JG. 2021. Spinal cord stimulation programming: a crash course. *Neurosurg. Rev.* 44(2):709–20
103. Chesterton LS, Barlas P, Foster NE, Lundeberg T, Wright CC, Baxter GD. 2002. Sensory stimulation (TENS): effects of parameter manipulation on mechanical pain thresholds in healthy human subjects. *Pain* 99(1/2):253–62
104. Bjordal JM, Johnson MI, Ljunggreen AE. 2003. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur. J. Pain* 7(2):181–88
105. Lempka SF, Patil PG. 2018. Innovations in spinal cord stimulation for pain. *Curr. Opin. Biomed. Eng.* 8:51–60
106. Amon A, Alesch F. 2017. Systems for deep brain stimulation: review of technical features. *J. Neural Transm.* 124(9):1083–91
107. Meuwissen KPV, Gu JW, Zhang TC, Joosten EAJ. 2018. Burst spinal cord stimulation in peripherally injured chronic neuropathic rats: a delayed effect. *Pain Pract.* 18(8):988–96
108. Koetsier E, Franken G, Debets J, van Kuijk SMJ, Linderoth B, et al. 2020. Dorsal root ganglion stimulation in experimental painful diabetic polyneuropathy: delayed wash-out of pain relief after low-frequency (1 Hz) stimulation. *Neuromodulation* 23(2):177–84
109. Arle JE, Mei L, Carlson KW. 2020. Fiber threshold accommodation as a mechanism of burst and high-frequency spinal cord stimulation. *Neuromodulation* 23(5):582–93
110. Ross E, Abejõn D. 2014. Improving patient experience with spinal cord stimulation: implications of position-related changes in neurostimulation. *Neuromodulation* 17(Suppl. 1):36–41
111. Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, et al. 2018. Success Using Neuromodulation With BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. *Neuromodulation* 21(1):56–66
112. Linderoth B, Foreman RD. 2017. Conventional and novel spinal stimulation algorithms: hypothetical mechanisms of action and comments on outcomes. *Neuromodulation* 20(6):525–33
113. de Ridder D, Vanneste S. 2016. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation* 19(1):47–59
114. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, et al. 2015. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain. *Anesthesiology* 123(4):851–60
115. Kilgore KL, Bhadra N. 2014. Reversible nerve conduction block using kilohertz frequency alternating current. *Neuromodulation* 17(3):242–54
116. Lempka SF, McIntyre CC, Kilgore KL, Machado AG. 2015. Computational analysis of kilohertz frequency spinal cord stimulation for chronic pain management. *Anesthesiology* 122(6):1362–76
117. Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. 2014. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. *Neuromodulation* 17(3):226–34
118. Crosby ND, Janik JJ, Grill WM. 2017. Modulation of activity and conduction in single dorsal column axons by kilohertz-frequency spinal cord stimulation. *J. Neurophysiol.* 117(1):136–47
119. Zannou AL, Khadka N, Truong DQ, Zhang T, Esteller R, et al. 2019. Temperature increases by kilohertz frequency spinal cord stimulation. *Brain Stimul.* 12(1):62–72
120. Kapural L, Shah NS, Fang ZP, Mekhail N. 2022. Multicenter, double-blinded, randomized, active–sham controlled clinical study design to assess the safety and effectiveness of a novel high frequency electric nerve block system in the treatment of post-amputation pain (the QUEST study). *J. Pain Res.* 15:1623–31
121. Dewberry LS, Dru A, Gravenstine M, Nguyen B, Anderson J, et al. 2021. Partial high frequency nerve block decreases neuropathic signaling following chronic sciatic nerve constriction injury. *J. Neural Eng.* 18:026009
122. Bhadra N, Kilgore KL. 2004. Direct current electrical conduction block of peripheral nerve. *IEEE Trans. Neural Syst. Rehabil. Eng.* 12(3):313–24

123. Ackermann DM, Bhadra N, Foldes EL, Kilgore KL. 2011. Separated interface nerve electrode prevents direct current induced nerve damage. *J. Neurosci. Methods* 201(1):173–76
124. Vrabec T, Bhadra N, van Acker G, Bhadra N, Kilgore K. 2017. Continuous direct current nerve block using multi contact high capacitance electrodes. *IEEE Trans. Neural Syst. Rehabil. Eng.* 25(6):517–29
125. Aplin FP, Fridman GY. 2019. Implantable direct current neural modulation: theory, feasibility, and efficacy. *Front. Neurosci.* 13:379
126. Jones MG, Rogers ER, Harris JP, Sullivan A, Ackermann DM, et al. 2021. Neuromodulation using ultra low frequency current waveform reversibly blocks axonal conduction and chronic pain. *Sci. Transl. Med.* 13:9890
127. Mirzakhalili E, Barra B, Capogrosso M, Lempka SF. 2020. Biophysics of temporal interference stimulation. *Cell Syst.* 11(6):557–72.e5
128. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, et al. 2017. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 169(6):1029–41.e16
129. Rampersad S, Roig-Solvas B, Yarossi M, Kulkarni PP, Santarnecchi E, et al. 2019. Prospects for transcranial temporal interference stimulation in humans: a computational study. *NeuroImage* 202:116124
130. Howell B, McIntyre CC. 2021. Feasibility of interferential and pulsed transcranial electrical stimulation for neuromodulation at the human scale. *Neuromodulation* 24(5):843–53
131. Ruiz-Sauri A, Orduña-Valls JM, Blasco-Serra A, Tornero-Tornero C, Cedeño DL, et al. 2019. Glia to neuron ratio in the posterior aspect of the human spinal cord at thoracic segments relevant to spinal cord stimulation. *J. Anat.* 235(5):997–1006
132. Fishman M, Cordner H, Justiz R, Provenzano D, Merrell C, et al. 2021. Twelve-month results from multicenter, open-label, randomized controlled clinical trial comparing differential target multiplexed spinal cord stimulation and traditional spinal cord stimulation in subjects with chronic intractable back pain and leg pain. *Pain Pract.* 21(8):912–23
133. Xu Q, Ford NC, He S, Huang Q, Anderson M, et al. 2021. Astrocytes contribute to pain gating in the spinal cord. *Sci. Adv.* 7(45):eabi6287
134. Telkes I, Hadanny A, DiMarzio M, Chitnis G, Paniccioli S, et al. 2022. High-resolution spinal motor mapping using thoracic spinal cord stimulation in patients with chronic pain. *Neurosurgery* 91(3):459–69
135. Raspopovic S, Capogrosso M, Petrini FM, Bonizzato M, Rigosa J, et al. 2014. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci. Transl. Med.* 122:222ra19
136. Fiorella Contarino M, Bour LJ, Verhagen R, Lourens MAJ, de Bie RMA, et al. 2014. Directional steering: a novel approach to deep brain stimulation. *Neurology* 83:1163–69
137. Trevathan JK, Baumgart IW, Nicolai EN, Gosink BA, Asp AJ, et al. 2019. An injectable neural stimulation electrode made from an in-body curing polymer/metal composite. *Adv. Healthc. Mater.* 8(23):e1900892
138. Woodington BJ, Curto VF, Yu Y-L, Martínez-Domínguez H, Coles L, et al. 2021. Electronics with shape actuation for minimally invasive spinal cord stimulation. *Sci. Adv.* 7(26):eabg7833
139. Reeder JT, Xie Z, Yang Q, Seo M-H, Yan Y, et al. 2022. Soft, bioresorbable coolers for reversible conduction block of peripheral nerves. *Science* 377:109–15
140. Tyler Perryman L, Speck B, Montes Garcia C, Rashbaum R. 2012. Injectable spinal cord stimulator system: pilot study. *Tech. Reg. Anesth. Pain Manag.* 16(2):102–5
141. Desai MJ, Hargens LM, Breitenfeldt MD, Doth AH, Ryan MP, et al. 2015. The rate of magnetic resonance imaging in patients with spinal cord stimulation. *Spine* 40(9):e531–37
142. Rubino S, Adepoju A, Kumar V, Prusik J, Murphy N, et al. 2016. MRI conditionality in patients with spinal cord stimulation devices. *Stereotact. Funct. Neurosurg.* 94(4):254–58
143. Deer TR, Patterson DG, Baksh J, Pope JE, Mehta P, et al. 2021. Novel intermittent dosing burst paradigm in spinal cord stimulation. *Neuromodulation* 24(3):566–73
144. Metzger CS, Hammond MB, Pyles ST, Washabaugh EP, Waghmarae R, et al. 2020. Pain relief outcomes using an SCS device capable of delivering combination therapy with advanced waveforms and field shapes. *Expert Rev. Med. Devices* 17(9):951–57
145. Holsheimer J, den Boer JA, Struijk JJ, Rozeboom AR. 1994. MR assessment of the normal position of the spinal cord in the spinal canal. *Am. J. Neuroradiol.* 15(5):951–59

146. Davies C, Komoroski C, Roy L. 2018. Evaluation of an innovative spinal cord stimulator platform for the treatment of chronic pain. *Pain Manag*. 8(3):167–74
147. Mekhail N, Levy RM, Deer TR, Kapural L, Li S, et al. 2020. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol*. 19(2):123–34
148. Nair DR, Morrell MJ, Skarpaas TL, Murro AM, Park YD, et al. 2020. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology* 95(9):e1244–56
149. Prosky J, Cagle J, Sellers KK, Gilron R, de Hemptinne C, et al. 2021. Practical closed-loop strategies for deep brain stimulation: lessons from chronic pain. *Front. Neurosci.* 15:762097
150. Price JB, Rusheen AE, Barath AS, Rojas Cabrera JM, Shin H, et al. 2020. Clinical applications of neurochemical and electrophysiological measurements for closed-loop neurostimulation. *Neurosurg. Focus* 49(1):e6
151. Cernera S, Alcantara JD, Opri E, Cagle JN, Eisinger RS, et al. 2021. Wearable sensor–driven responsive deep brain stimulation for essential tremor. *Brain Stimul*. 14(6):1434–43
152. Fagundes-Pereyra WJ, Teixeira MJ, Reyns N, Touzet G, Dantas S, et al. 2010. Motor cortex electric stimulation for the treatment of neuropathic pain. *Arq. Neuropsiquiatr*. 68(*6*):923–29