Peripheral Nerve Stimulation

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Introduction

In 1967, Wall and Sweet reported the first clinical use of peripheral nerve stimulation (PNS) in the treatment of neuropathic pain. Their hypothesis stemmed from the recently advanced gate control theory of pain perception, namely, that stimulation of large-diameter cutaneous nerves could saturate the transmission of pain impulses by smaller nerve fibers, mitigating the central perception of pain [1, 2]. They applied a square wave of 0.1 msec pulse width at 100 Hz of increasing voltage until paresthesias and/or hypesthesia was produced in the receptive field of the nerve in question. Remarkably, prior to treating patients, the authors tested the technique on themselves by placing needle electrodes near their own infraorbital nerves and described the sensation as "not unpleasant and always tolerable for an indefinite period of time" [1]. In the decades since, peripheral nerve stimulation has become an important tool for the treatment of a variety of disorders including neuropathic pain, visceral referred pain, musculoskeletal pain, and chronic refractory pain [3]. In this in this chapter, we discuss the biology of peripheral nerves with respect to the somatosensory system, biophysics of peripheral nerve stimulation, and the use of PNS for the treatment of neuropathic pain.

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The Physiology of the Somatosensory Peripheral Nervous System

In the somatosensory system, information from peripheral cutaneous receptors is converted into electrophysiologic signals that are processed and subsequently transmitted to the central nervous system (CNS) [4]. Somatic sensations are broadly categorized into several distinct modalities. Exteroception is the response of direct interaction with the external world through the sense of touch (including the sensation of contact, pressure, stroking, motion, and vibration), thermal perception, and pain or nociception. Proprioception is the sense of joint and limb position and movement transmitted through receptors in skeletal muscle, joint capsules, and skin. Interoception is a mostly unconscious perception of the major organs and their internal state through receptors in the viscera. Afferent, or sensory, nerve fibers can be categorized by the information they relay to the CNS as either general or specialized and either somatic or visceral [5]. General somatic afferent (GSA) fibers transmit information from exteroceptive

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and proprioceptive receptors. General visceral afferent (GVA) fibers transmit information of interoception and visceral pain. Special somatic afferents (SSA) transmit visual, auditory, and vestibular sensory input. Special visceral afferents (SVA) transmit taste and smell. General somatic afferent information from the trunk and peripheral extremities is transmitted to the CNS via nerve fibers of dorsal root ganglion neurons. Individual neurons in each ganglion are specialized to respond to specific stimuli through differences in morphology and molecular expression at the dendrite [4]. General visceral afferent, SSA, and SVA modalities are mainly transmitted through the cranial nerves of the brain stem.

Dorsal root ganglion neurons originate from neural crest cells [4]. These are pseudo-unipolar neurons that carry primary afferent fibers. The proximal terminal of the neuron synapses with neurons of the CNS in the dorsal horn of the spinal cord. The dorsal horn is divided into functional layers of gray matter termed the laminae of Rexed 1–10, from superficial to deep [6, 7]. Of note, the major nociceptive primary afferents terminate on Rexed laminae I and II [8]. The distal termination of the nerve ends in a specialized receptor type or exists as a free nerve ending that determines the receptive field to which it is tuned and in response to which an action potential is generated. These neurons are bundled in fascicles and joined by efferent motor axons to form a peripheral nerve that travels to a specific anatomical part of the body, defining a sensory dermatome and muscular myotome. The nerve fibers are classified into functional groups by their degree of myelination and diameter, which both influence nerve conduction velocity. Large-diameter axons conduct action potentials more rapidly due to lower internal (longitudinal) resistance. The myelin sheath of a Schwann cell around an axon increases conduction velocity through a process termed saltatory conduction. Group A fibers are the most heavily myelinated, group B fibers are moderately myelinated, and group C fibers are unmyelinated.

Aα, Aβ, and Aγ fibers are large-diameter myelinated fibers that convey sensations of touch and proprioception transduced by cutaneous, subcutaneous, muscle, and skeletal mechanoreceptors. These fibers range in diameter from 6 to 20 μm with conduction velocities ranging from 36 to 120 m/s [4]. Slower smaller-diameter axons that are lightly myelinated or unmyelinated (Aδ and C fibers, respectively) transmit information from chemoreceptors, thermal receptors, and nociceptors. Aδ fibers have a diameter of 1–6 μm and conduction velocities of 4–36 m/s, whereas C fibers have a diameter of 0.2–1.5 μm and conduction velocities ranging from 0.2 to 2.0 m/s. Therefore, the somatosensory system transmits different types of information to the CNS at different rates and temporal resolution. Due to its faster conduction velocity, multiple impulses can be transmitted by an Aδ fiber in the same time a type C fiber transmits the initial stimuli. Consequently, Aδ fibers transmit sensations perceived as pain faster than the type C fibers and can respond to changes in stimuli more rapidly [9]. Nociceptors innervated by Aδ fibers respond to stimuli perceived as sharp, whereas C fibers transmit a dull, burning pain that is diffusely localized.

Properties of peripheral nerves can be measured using cutaneous stimulating and recording electrodes placed both proximally and distally along the course of a peripheral nerve. By stimulating a cutaneous sensory nerve with a distally placed electrode, a proximally placed electrode can measure the resulting compound action potential, a summation of action potentials from each axon within the nerve. An increase in stimulation will result in recruitment of a larger number of axons, and those with the largest diameter are recruited first due to their lower electrical resistance. Therefore, lower stimulation intensities are perceived as tingling through the activation of Aβ fibers while increased stimulation results in pain through the activation of Aδ and C fibers [4].

Theories of Pain Perception

Although significant research has been dedicated to elucidating the mechanisms that underlie pain perception, its physiological basis remains unclear. Most frameworks that have been proposed describe a series of observations about

nociception but fail to adequately account for the multidimensionality and complexity inherent in the experience of pain. In this section, we briefly outline three influential theories of pain perception including (1) the specificity (labeled line) theory, (2) the intensity theory, and (3) the gate control theory. Later, we will focus on the latter, which inspired the development of modern PNS for the treatment of neuropathic pain.

Specificity Theory of Pain Perception

The fundamental tenet of the specificity (labeled line) theory is that each sensory modality has specific specialized receptor end organs and their associated primary afferent sensory fibers that are sensitive to a particular stimulus (or family of stimuli) [10, 11]. Non-noxious mechanical stimuli, for example, are encoded by low threshold mechanoreceptors which project through dedicated afferent fibers to mechanoreceptive neurons in the spinal cord and the brainstem and from there to higher-order "mechanoreceptive" brain regions [11]. Similarly, noxious stimuli activate a nociceptor, which projects through dedicated pain conducting afferent fibers to higher-order pain centers. Such a theory was rooted in a belief that the brain, contrary to the prevailing idea of much of the eighteenth century, is not a "common sensorium," but rather a heterogeneous structure in which nerves with specialized functions convey a perceived stimulus from a sensory organ to a *dedicated* brain region for its perceptual experience [10–12].

The specificity theory of pain perception found validation in the discovery of specific, cutaneous touch receptors including Pacinian corpuscles (1835), Meissner's corpuscles (1853), Merkel's discs (1875), and Ruffini's end organs (1893) [11, 13–15]. These appeared to provide evidence that specific sensory qualities were encoded by dedicated nerve fibers. Moreover, in a series of experiments between 1854 and 1859, Schiff and Woroschiloff identified specific pathways for pain and temperature transmission within the spinal cord (anterolateral pathway) distinct from the posterior columns (for tactile sensation) [12]. This provided further corroboration that various sensory qualities were conducted by dedicated fiber tracts. Through the early twentieth century, validity for the specificity theory in explaining pain perception appeared to grow with the discovery of myelinated fibers (that responded to mechanical noxious stimuli) and unmyelinated nerve fibers (that responded to chemical nociceptive stimuli) [11, 16, 17]. Indeed, it was the prevailing theory of pain perception until the promulgation of the gate control theory by Melzack and Wall in 1965, described below [2].

Intensity and Pattern Theory of Pain Perception

A less popular theory that coexisted with the specificity theory was the intensity theory. In its simplest form, its foundational idea was that pain occurs in any sensory system when sufficient intensity is reached through repeated stimulation, rather than by virtue of the stimulus itself [11, 18]. An early nineteenth century experiment appeared to corroborate this theory by demonstrating that repeated subthreshold tactile stimulation (below the threshold for tactile perception) produced pain in patients with syphilis (with degenerated dorsal columns) [18]. This was interpreted to indicate that repeated subthreshold stimuli were summated in the spinal cord (or elsewhere in the nervous system) to produce the sensation of pain. A self-evident, major shortcoming of this theory is that outside of special circumstances (such as patients with syphilis) it failed to explain the myriad ways in which single (non-summated) stimuli could also elicit pain in animal and human subjects. The theory was occasionally expanded and referred to as the pattern theory – a concept of pain perception in which the experience of pain depended not only on the intensity of the stimulus but also on the specific pattern of neural firing that it elicited within peripheral nerves encoding its transmission [11, 18–20]. Due to a lack of experimental evidence, the theory quickly fell out of favor, especially with the introduction of the gate control theory.

Gate Control Theory of Pain Perception

At its core, the gate control theory was an attempt to bridge the gap between two dominant theories of its era – the "specificity" and the "intensity" theories of pain perception – by delineating a framework derived from aspects of both and based on the then available electrophysiological data [2]. While the specificity theory proposed the presence of dedicated pathways for each somatosensory modality, the intensity theory stated that any sensation could be elicited by producing a specific pattern of neuronal activity within the peripheral nerves. Within this context, the gate control theory accepted that there were at least two fiber types – small fibers (Aδ and C that mediated primarily pain) and touch fibers (Aα and Aβ that mediated primarily touch) [11]. In fact, the difference in small and large fiber inputs played an important role in the elaboration of the theory. It had been demonstrated that large fibers traversed deeper Rexed laminae of the dorsal horn, prior to curving rostrally to enter the substantia gelatinosa (SG), contained in Rexed laminae II, from the ventral side. Small diameter afferents, on the other hand, entered the SG directly from the dorsal side. Moreover, high-frequency stimulation of the large-diameter sensory fibers appeared to enhance negative potentials measured at the dorsal root ganglia, while similar stimulation of small sensory afferents enhanced positive dorsal root potentials [11, 21, 22]. In distilling these complex electrophysiological findings into a unified theory of pain perception, Melzack and Wall assumed that both large and small fibers projected to a common cell population that was termed the "transmission" (or T) cell, which projected to the forebrain for the conscious perception of pain [2]. The output of the T cells was modulated by the balance between small and large fiber input. Selective activation of large fibers was assumed to reduce the net input to T cells, by inhibiting (or closing) a presynaptic gate located in the SG. Conversely, small fiber activity facilitated (or opened) the gate, thereby increasing T cell input. Pain is perceived when T cell output reaches an internal threshold. This occurs when small fiber activation of the T cell overcomes large fiber inhibition.

The fundamental predictions of this seminal theory, namely, that stimulation of large-diameter fibers should close the gate by reducing activity in T cells and thereby diminish pain perception, spurred exploration into peripheral nerve stimulation. In 1967, Wall and Sweet reported on their outcomes from high-frequency, transcutaneous electrical nerve stimulation (TENS) in eight pain patients, four of whom had peripheral nerve damage [1, 2, 23, 24]. In all patients, the stimulation of large-diameter afferents was analgesic. Interestingly, patients with peripheral nerve damage experienced a longer duration of relief after cessation of stimulation than patients without nerve damage. The rationale for the abolition of pain was thought to be the selective Aα and Aβ fiber stimulation, while the reappearance of pain was thought to arise from a gradual reopening of the gate by ongoing small fiber activity. Furthermore, because patients with peripheral nerve damage presumably had fewer preserved small fibers (Aδ and C), the duration of relief following stimulation cessation was longer (or time to reappearance of pain was greater) [21].

Electrical Nerve Stimulation

Nerves transmit cutaneous information by means of propagation of action potentials [25]. When a stimulus sufficiently depolarizes an axon from its resting membrane potential, an action potential is propagated along its long axis. The resting potential across a membrane selectively permeable to a single ion is modeled by the Nernst equation, which was subsequently expanded in by the Goldman equation for the dominant ions influencing the resting potential of the neuron [25–28]. Electrical conduction along an axon is modeled as a series of parallel RC circuits, mathematically modeled by the cable equation [29]. Based on this work, the threshold amplitude for depolarization of myelinated nerves is expected to increase based on electrode distance to the fiber and decrease based on stimulus pulse duration and fiber diam-

eter [29]. This is the basis of the differential activation of recruitment of different cell and axon types, enabling therapeutic PNS.

Paresthesia-Free Stimulation

PNS, like spinal cord stimulation (SCS), has shown great clinical success in recent decades. It has the advantage of being targeted to specific peripheral nerve distributions, with little to no side effects. The stimulation patterns used in PNS, however, have historically predominantly relied on the production of paresthesias, which, based on Melzack and Wall's gate control theory of pain perception, are necessary for analgesia [2]. Until recently, the pattern of stimulation used in PNS (similar to SCS) has been composed of pulse waves at a frequency of 40–50 Hz, a pulse width between 300 and 500 μs, and a peak amplitude between 2 and 4 mA [3, 30, 31]. This paresthesia-generating pattern is known as "tonic" stimulation. In recent years, it has become increasingly clear that paresthesias are not necessary for pain relief in SCS. Effective pain relief in SCS has also been demonstrated with systems delivering pulses in short bursts or continuously but in much higher frequencies, both of which operate without the generation of paresthesias [3, 30]. Such paresthesia-free stimulation is becoming increasingly utilized in PNS, although clinical outcomes data remain limited.

Burst Stimulation

Burst stimulation consists of small bursts of pulses rather than continuous streams of pulses. More specifically, the pulses are delivered in a series of five 1000 μs pulses at a frequency of 500 Hz, with an interspike interval of 1000 μs, and spike trains repeated at a frequency of 40 Hz [30, 32]. The mechanisms by which burst stimulation achieves paresthesia-free stimulation are unknown but are believed to arise through modified neuronal firing. In rodents, increasing the number of pulses in a burst, or their pulse width, led to greater reductions in the firing rate of neurons within the dorsal horn from their baseline [33, 34]. This was especially true for wide dynamic range (WDR) neurons, which appear to function as the T cells (from the gate control theory), and may alter neural transmission from the thalamus to the anterior cingulate cortex and influence the perception of pain [3]. Burst stimulation also appears to differ from tonic stimulation in its effect on dorsal column nuclei (in particular, the gracile nucleus). Tonic stimulation appears to significantly increase spontaneous activity of gracile nucleus neurons (by 20%), compared to no significant change during burst stimulation [30, 33, 34]. Because the gracile nucleus is the tactile sensory receiving area for much of the information ascending within the dorsal columns, this also supports why tonic stimulation results in paresthesias, compared to burst stimulation which does not.

High-Frequency Stimulation

High-frequency (HF) stimulation is a more recent alternative to burst stimulation for the induction of paresthesia-free stimulation. HF stimulation involves the use of kilohertz range tonic stimulation (up to 10 kHz) and has shown success in spinal cord stimulation [30]. Its mechanism of action appears to be a rapid and reversible conduction block of neural activity by inactivation of sodium channels along several nodes of Ranvier [30, 35–40]. HF stimulation appears to *block* paresthesias by inhibiting large-diameter fibers from generating action potentials. Nerve fibers that are greater than 15–18 μm shut down at 4 kHz and those that are smaller (8–9 μm) shut down at frequencies of around 8 kHz [30, 36, 37]. Medium fibers that reduce WDR signaling are activated instead by HF stimulation, which leads to decreased pain stimulus conduction. Indeed, the mechanisms through which HF stimulation mitigates pain may be more complex. Although the effect of pulse rate has not been systematically evaluated, it appears that beyond a certain threshold, pain relief may not be significantly different with further increases in stimulation frequency [30]. For example, in a recent randomized, multicenter, double-blind, crossover clinical study of SCS, 1

kHz stimulation was compared with 10 kHz stimulation and demonstrated no observable differences in clinical outcomes [3, 30, 41]. Future work is necessary to evaluate the role of HF patterns for PNS.

Devices Used for Peripheral Nerve Stimulation

Starting with Wall and Sweet in the 1960s, externalized wire electrodes were percutaneously placed adjacent to nerves but the adoption of this technique was greatly limited by lack of commercialized equipment [1, 42]. By the 1970s and 1980s, implantable cuff-shaped electrodes which were later supplanted by button-shaped and paddle electrodes were used in a number of clinical studies, demonstrating greater than 50% pain relief for some patients [42]. These procedures subsequently fell out of favor and were replaced by a growing interest in SCS, which avoided the challenges at that time of surgical nerve exposure, electrode positioning, and generation of fibrosis around the nerve and electrodes. In 1999, the use of percutaneous SCS leads for PNS described by Weiner and Reed greatly renewed interest in PNS for a variety of pain disorders [43]. Despite growing evidence supporting PNS, the surgical placement of commonly used SCS systems for PNS generally remains "off-label." These companies offer several different features and capabilities on their platform, allowing the surgeon to select an implant that best matches the patient's goals for therapy. These considerations include battery size and recharging ability, whole-body MRI compatibility, the ability implant 1–4 leads with up to 32 active contacts, choice of programing waveforms, and programming interface [44–47]. Each company offers either paddle or percutaneous lead configurations, the latter more commonly used for PNS [42]. Recently, percutaneously inserted electrodes powered by an external, transcutaneous transmitter and battery pack have been introduced by several companies. Examples include the Freedom Stimulator by Stimwave, StimRouter by Bioness, and the SPRINT PNS System by SPR Therapeutics. These stimulator systems have FDA approval for PNS throughout the body but not for craniofacial nerve stimulation at time of publication. This style of stimulator is particularly amenable for placement for and treatment of intercostal nerve pain, shoulder pain, and extremity pain along a specific peripheral nerve distribution [48–52].

Patient Selection

Peripheral nerve stimulation is generally regarded as second-line treatment for chronic pain disorders ranging from localized neuralgias, complex regional pain syndrome, post-traumatic pain, postherpetic pain, and postoperative pain throughout the body [53]. Patients should be co-managed with a pain specialist and keep a pain diary to track their visual analog scores (VAS) for pain. A large portion of the initial patient encounter should be focused on managing expectations and emphasizing that PNS is only one component of a comprehensive pain plan. Pain psychology evaluation is also advised for patients considering implantation of a stimulator [54]. Responses to local blocks or TENS treatment have not predicted how patients respond to PNS [42, 55]. As such, a trial period using externalized leads is first completed before a permanent implant is considered. As a general guide, patients should have a 50% reduction in their VAS scores noted in their diary and reasonable expectations for treatment with a permanent implant. Some of the transcutaneous powered systems described above have options for permanent implantation in one stage, with a second operation reserved for removal if necessary. The duration of a trial varies between institutions, with some concern that short duration trials do not adequately account for early placebo effect. Still, no systematic benefits of longer trial periods have been reported.

Surgical Technique

Placement of a SCS for PNS can be performed as an outpatient procedure [53]. It is important to map and mark the region of the patient's pain prior

to the start of the procedure. Conscious sedation is used for trial placement while general anesthesia is used for permanent implantation. Patient positioning depends on the targeted nerve(s). Ultrasound can be helpful to identify the target nerve or its associated neurovascular bundle [52]. Once the nerve or the region of interest is identified, a small stab incision is made just proximal to the pain region along the course of the nerve. Minimal to no local anesthetic is used to avoid an inadvertent nerve block which will eliminate the utility of intraoperative testing (if planned) or postoperative device programming. Under fluoroscopic guidance, a Tuohy needle is passed subcutaneously along the course of the nerve above deep fascia. A percutaneous lead is introduced through the Tuohy needle which is then removed. It can be useful at this point to awaken the patient and apply paresthesia-inducing stimulation to ensure adequate coverage and make any lead position adjustments as necessary. Fluoroscopy is used to ensure the lead does not migrate while using the Tuohy and to document final lead position. The externalized lead is secured to the skin with suture and sterile dressings. In recovery, the leads are connected to an external generator and initially programmed to provide paresthesia in the distribution of pain without motor contractions. The Neurostimulation Appropriateness Consensus Committee recommends the use of prophylactic antibiotics for no longer than 24 hours after surgery, but studies suggest benefit in using antibiotics during the trial setting for the reduction of permanent implant infection [56, 57].

Patients are informed to keep a daily pain diary to log their VAS. The patient is seen in clinic after 1–2 weeks, during which time stimulation parameters are adjusted. The electrodes are removed in the office and if the patient responds well to PNS and wishes to proceed, permanent implantation is scheduled in a few weeks to allow for wound healing. Images obtained for the trial in addition to insight gained from programming during the trial period guide permanent electrode placement. General anesthesia is recommended mainly due to the pain from tunneling subcutaneous extension cables and placement of the pulse generator. Once the stimulation leads are placed, they should be secured to the fascia and excess cabling should be used to create a strain relief loop. Implantable stimulators are commonly placed in subcutaneous infraclavicular pocket or in the gluteal region below the belt line but above the ischial tuberosity. Each manufacture has guidelines on the acceptable depth of implantation. Lead impedances are interrogated in the OR prior to skin closure. The device is turned on in the recovery area and programmed to settings that provided the best overall pain relief with minimal side effects during the trial period.

Trigeminal Nerve Stimulation for Pain

Peripheral nerve stimulation is a useful alternative option for treating craniofacial pain refractory to pharmacological therapy that is not appropriate for traditional surgical procedures such as microvascular decompression and/or percutaneous trigeminal rhizotomy procedures. PNS for facial pain is addressed briefly in Chap. 32, but discussed in greater detail here. Since the experiments by Wall and Sweet, stimulation of peripheral branches of the trigeminal nerve has been well demonstrated to mitigate certain types of facial pain. Neuropathic and postherpetic neuralgia pain have been the most commonly studied [58–63]. Furthermore, trigeminal nerve stimulation (TNS) has also shown some promise for the treatment of refractory headache disorders [64, 65].

In a case series of TNS published in 2015, 15 out of 35 patients with intractable craniofacial pain trialed with stimulation proceeded to permanent implantation [58]. In this study, indications for peripheral trigeminal branch stimulation included trigeminal neuralgia, trigeminal neuropathic pain, trigeminal deafferentation pain, postherpetic neuralgia, and headache. After a minimum follow-up length of 15 months, 73% of these patients reported "worthwhile" pain relief. Though there were no serious side effects, seven patients underwent 12 revision surgeries related to hardware complications including three total explants. The authors noted that the lancinating pain characteristic of trigeminal neuralgia type 1

did not respond well to neurostimulation and should be managed by traditional treatment options. In addition, stimulation of the mandibular branch for temporomandibular joint was attempted in this study but was not found to be beneficial. Stimulation parameters appear to be patient dependent, as noted in a case series of six patients treated with PNS to the trigeminal nerve, that were programmed with pulse widths from 210 to 450 μsec and frequencies between 16 and 80 Hz [66]. Peripheral nerve stimulation systems implanted for the treatment of ophthalmic postherpetic neuralgia were programmed with similar parameter ranges [61]. Amplitude of stimulation influenced the intensity of the paresthesias elicited by stimulation and was titrated to comfort.

For trigeminal nerve stimulation, a percutaneous SCS lead is placed adjacent to the targeted nerve branch. The patient is positioned supine on the operating table with head turned toward the unaffected side. A small stab incision is made on the lateral side of the face, commonly just anterior the tragus where minimal local anesthetic is injected. To target the supraorbital or infraorbital nerves, the distal tip of a four- or eight-contact percutaneous lead is placed 1 cm away from the orbital rim and medially past the mid-pupillary line (Fig. 14.1). For the mandibular branch, the needle is directed toward the chin. In recovery, the leads are connected to an external generator and initially programmed to provide paresthesia in the distribution of pain without producing facial muscle contraction. Imaging and insight gained from programming during the trial period guide permanent electrode placement. The leads are tunneled behind the ear and secured both at the insertion sites and to the temporalis fascia. Extension cables are tunneled behind the ear and over the clavicle and connected to the pulse generator, placed in an infraclavicular pocket.

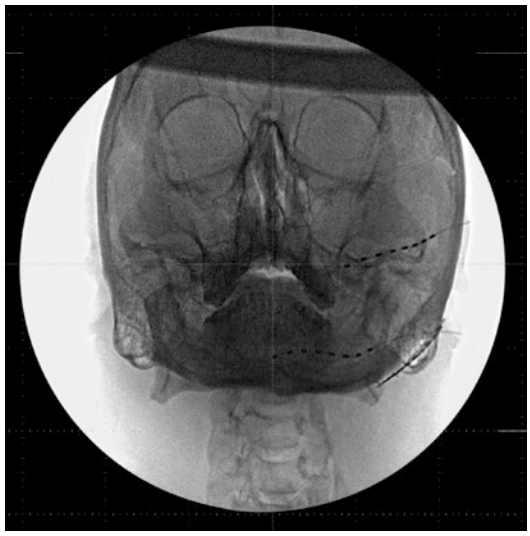

Fig. 14.1 Intraoperative x-ray for placement of leads for infraorbital and mandibular nerve stimulation

Greater and Lesser Occipital Nerve Stimulation for Pain

One of the more common uses of PNS is for the treatment of occipital neuralgia (ON) and related headache disorders. In 1999, Weiner and Reed described percutaneous lead placement for the treatment of intractable ON [43]. They demonstrated that pain relief could be achieved by placing the electrode in proximity to the nerve rather than directly on the nerve with paddle electrodes or cuff electrodes. Their technique was widely adopted and cuff electrodes have largely been abandoned in PNS for the treatment of pain [42].

A number of published case series show excellent results with ONS for the treatment of medically refractory ON, with improvement estimated to be as high as 60–90% [43, 59, 67–71]. One of the larger prospective studies followed 11 patients with occipital headaches over a 12-week period. Following ONS, 64% of patients reported a decreased headache frequency and 91% of patients reduced their medication use [72]. Interestingly, ONS has also been shown to improve pain associated with disorders of the trigeminal nerve, such as cluster headache, which is considered a trigeminal autonomic cephalalgia [73–75]. In a pilot study, ONS reduced the average number of weekly cluster headache attacks by about 80% in eight patients with drug-resistant chronic cluster headache [75].

A large interest in using ONS for the treatment of chronic migraines lead to several large

trials, with a meta-analysis of five randomized controlled trials (total $n = 402$) concluding that ONS reduced mean severe headache frequency by 2.59 days per month after 3 months in comparison to patients undergoing sham stimulation [76]. The Precision Implantable Stimulator for Migraine (PRISM) study compared active bilateral stimulation (stimulation parameters: 250 μs, 60 Hz, 0–12.7 mA) to sham stimulation in 139 out of 179 screened patients with episodic or chronic migraine. Twelve weeks after implantation, patients treated with ONS did not report a statistically significant difference in daily frequency of migraine compared to those treated with sham stimulation, based on daily pain diary entries [77]. The authors hypothesized that the lack of efficacy was due do the heterogenous character of headaches despite using definitions defined in the 2004 International Classification of Headache Disorders. In the Occipital Nerve Stimulation for the Treatment of Chronic Migraine Headache (ONSTIM) study, three-month responder rates were 39% for patients in the adjustable stimulation group, 6% in the sham stimulation group, and 0% for those in the medical management group [78]. A responder was defined as someone who achieved a 50% or greater reduction in number of headache days per month or a three-point or greater reduction in average overall pain *intensity* compared to baseline. In a multicenter study of 157 patients (Clinicaltrials.gov NCT00615342), there was no significant difference between active and control groups with regard to number of responders reaching a 50% reduction in mean daily (VAS) at 12 weeks, but there were significant reductions in pain intensity, headache days, and migraine-related disability [79]. The authors published a 52-week update which reported continued efficacy of ONS for chronic migraine, with intention-to-treat analysis showing a 50% reduction in headache days and/or pain intensity in 48% of patients [80].

The technique for occipital nerve lead implantation is similar to that of TNS and can be performed with the patient in either prone or lateral position. Percutaneous electrodes are introduced at the midline and directed laterally above the nuchal fascia (Fig. 14.2). Eight-contact percutaneous leads span a length long enough to have electrode contacts perpendicularly cross both the greater and lesser occipital nerves. To ensure the distal electrode tip does not pierce the scalp, the hair on the back of the head can be clipped. With the patient prone, the stimulator battery can be easily placed in the gluteal position whereas lateral positioning allows for infraclavicular placement. Surprisingly, in the NCT00615342 study referenced above, 70% of patients experienced an adverse event, totaling 209 with 183 of these device/procedure related [80]. In fact, lead migration or dislodgement appeared to be a common adverse effect associated with implanted ONS, with randomized trials demonstrating an incidence rate of 10–24% [35, 43, 68, 69, 76]. The authors of one series suggest the use of paddle-type leads instead of cylindrical leads to reduce the occurrence of lead migration [69]. Yet others report similar rates of migration with paddle electrodes [75]. Other variations in technique include open placement of a cylindrical electrode, a greater number of strain relief coils with lead cabling, and varying pulse generator placement from a gluteal to infraclavicular location [78, 81]. Infection rates vary from 4% to 30% based on follow-up ranging from 2 months to 6 years [76].

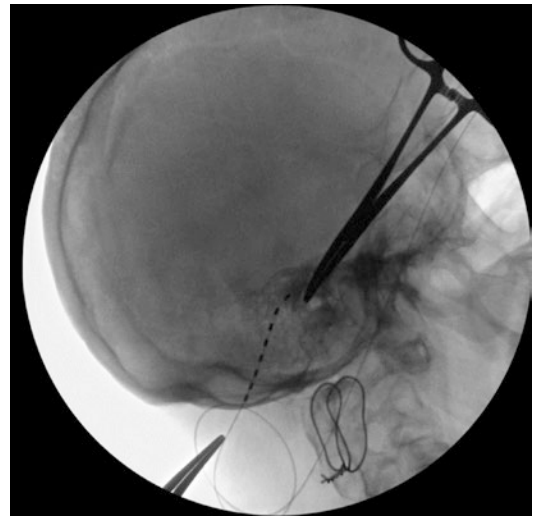

Fig. 14.2 Intraoperative x-ray for placement of lead for unilateral occipital nerve stimulation

Peripheral Nerve Stimulation for Postamputation Pain

Amputation can lead to chronic neuropathic pain that responds poorly to medication and frequently leads to opioid dependence [82–86]. Two types of chronic pain may occur after amputation: phantom limb pain (PLP) and residual limb pain (RLP). Up to 70–80% of patients experience either PLP, RLP, or both [87, 88]. For many amputees, the pain following amputation can impact activities of daily living more than the loss of the limb itself [89–91]. Additionally, poor management of RLP limits the use of prostheses, further impairing function in these patients. Therefore, PNS is an appealing treatment for these conditions. In a study of 16 patients with PLP and/or RLP, 14 patients responded to stimulation with ≥75% paresthesia coverage [92]. Nine of these patients completed a two-week home trial with a percutaneous PNS system and reported a 56 ± 26% reduction in pain at the end of the trial period [92]. In this study, the surgeons used ultrasound to guide percutaneous placement of a monopolar lead near the femoral or sciatic nerve and used stimulation to further validate proximity to the nerve while avoiding local cutaneous stimulation [92]. Once the patient reported limb paresthesia without cutaneous spread, the monopolar lead was replaced with the stimulating electrode, at a depth 0.5–2.0 cm shallower than the monopolar lead. In a pilot trial, using a cuff electrode wrapped around the sciatic or tibial nerve to deliver 10 kHz stimulation, seven patients with postamputation pain experienced a 75% reduction in pain at the three-month endpoint [93].

Peripheral Nerve Field Stimulation

Peripheral nerve stimulation differs in principle from peripheral nerve field stimulation (PNFS) [48]. Peripheral nerve stimulation refers to stimulation of a targeted nerve by an electrode implanted in its proximity. Its mechanism of therapeutic benefit is attributed to direct stimulation of the nerve. Consequently, the patient's pain must be attributed to a specific nerve and the surgeon needs to have a working knowledge of the nerve's anatomical course for proper electrode placement. Conversely, PNFS refers to the placement of subcutaneous electrodes in the region of the patient's pain, thus benefiting patients who have symptoms that may be less well localized [94]. For PNFS, the depth at which the electrode is implanted is critical as a shallow placement can result in stimulation that is perceived as a burning sensation and may lead to skin erosion, whereas insertion that is too deep may trigger muscle contractions. To program PNFS, frequencies between 20 and 50 Hz and pulse widths of 90–250 μsec are best tolerated, with higher settings of either parameter resulting in burning or pinching sensations [94]. For well-placed electrodes, intensities between 1.5 and 2 mA can provide patients with pain relief. PNFS has been used for the treatment of complex regional pain syndrome, neuralgias, post-traumatic pain, and postoperative pain throughout the body [94]. In a study of 100 patients who underwent PNFS for treatment of chronic craniofacial, thorax, lumbosacral, abdominal, pelvic, and groin pain, 72% of patients demonstrated a reduction in analgesic use after surgery and a mean pain reduction of 36% [95]. Although the procedures are similar and use the same implantable hardware, insurance reimbursement and authorization may be more challenging for PNFS than for PNS in the United States [9].

Brain Correlates of Peripheral Nerve Stimulation

As described earlier in this chapter, peripheral nerve stimulation in its earliest use was grounded on the gate control theory of pain perception, in which a non-noxious stimulus interferes with the transmission of pain-related sensory input [21, 96]. Mounting evidence indicates that at least a part of the pain alleviation may stem from central neuromodulation [96]. This may occur on two different timescales – acutely from alterations in network activity between the peripheral and central nervous system and chronically from an integration of modulated neural activity in the

nervous system. Chronic stimulation results in adaptive changes in the brain and contributes to the therapeutic effect of peripheral nerve stimulation [94, 97]. Data regarding central neuromodulation following PNS are limited to functional neuroimaging studies. Most studies that describe the central effects of PNS are from vagus nerve stimulation (VNS) for epilepsy and depression [98–100]. Other peripheral nerve stimulation paradigms in which the brain correlates have been studied include trigeminal nerve stimulation for neuropathic trigeminal pain, occipital nerve stimulation for headaches and occipital neuralgia, and sacral nerve stimulation (SNS) for urinary and fecal incontinence or detrusor hyperactivity [75, 101, 102]. In this section, we briefly highlight brain correlates of VNS and SNS, which may be reflective of patterns of central neuromodulation in response to PNS that will need to be explored further to truly understand the mechanisms by which PNS exerts its effects.

Unlike most PNS, VNS is unique in that the vagus nerve carries sensory afferents belonging to different categories that synapse on the nucleus of the solitary tract (NTS), the dorsal motor nucleus of the vagus nerve, and others [96, 97, 99]. Because the NTS in turn projects diffusely to the reticular formation, hypothalamus, thalamus, and other cortical and subcortical structures, functional neuroimaging studies implicate a major role for the thalamus and limbic structures in the mechanisms of action of VNS [96]. Increased regional cerebral blood flow (rCBF) on positron emission tomography (PET) has been described in regions of the bilateral, anterior thalami, the cingulate gyrus, hypothalamic, and the postcentral gyrus in the acute phase in patients implanted with VNS for epilepsy, for instance [96]. In contrast, single photon emission computed tomography (SPECT) studies suggest that after chronic VNS (at least 6 months of stimulation), there is a general trend toward thalamic and limbic inhibition [96, 99, 100, 102, 103]. This trend of initial increased activity but delayed depression readily explains the efficacy of VNS in the treatment of epilepsy. The thalamus supplies excitatory glutamatergic input to the cortex. The depression that occurs over the long term may not only decrease seizures of limbic origin but may also enable the thalamus to serve as a gating structure for secondary generalization of limbic seizures to the rest of the cortex [96, 103].

VNS is hypothesized to affect clinical depression due to connectivity of the NTS to several regions implicated in the pathogenesis of depression including the prefrontal cortex, cingulate cortex, amygdala, hippocampus, thalamus, and basal forebrain [96, 100, 102, 104, 105]. While mechanisms by which VNS modulates network activity are largely unknown for patients with depression, functional neuroimaging studies definitively indicate that on both acute and chronic timescales they are central to its neuromodulatory effects.

Sacral nerve stimulation differs from vagus nerve stimulation because vagus nerve nuclei are directly located in the brain stem. As such, sacral stimulation can serve as a paradigm to understand how peripheral nerve stimulation modulates targets that are not directly connected within the central nervous system. Chronic stimulation of the sacral S3 nerve is used for urge incontinence and for medically refractory bladder hyperactivity. The urge during bladder distension may involve the periaqueductal gray, anterior cingulate gyrus, insula, thalamus, and cerebellum [96, 106, 107]. In functional imaging studies, in patients implanted with SNS, acute SNS has been found to lead to decreased rCBS in the medial cerebellum, insula, and orbitofrontal cortex [96, 106–109]. After chronic SNS, there is a decreased rCBF in the middle cingulate gyrus, the dorsolateral prefrontal cortex, the thalamus, and the cerebellum, among others. In particular, the difference between the acute and chronic states appears to involve the premotor and the cerebellar regions. This indicates that acute SNS alters structures involved in sensorimotor learning (premotor cortex and cerebellum), while chronic SNS leads to these regions becoming less active while regions involved in central control of micturition becoming more active [96, 106–109].

These two paradigms allow us to conclude that pathologies affect multiple brain structures both primarily and secondarily. Appropriately targeted peripheral nerve stimulation appears to

achieve therapeutic benefits by acutely altering the relative valence of the various brain structures involved through modulating variables such as rCBF. Through chronic stimulation, brain regions appear to develop adaptive strategies that help provide sustained relief. More work is necessary to elucidate the mechanisms by which central neuromodulation relates to PNS, which may ultimately lead to optimized therapies.

Peripheral Nerve Stimulation for Epilepsy and Depression

Concerningly, as many as 20–30% of patients with epilepsy will develop drug-resistant epilepsy and thus remain at risk for seizure-related injury [110]. Similarly, major depressive disorder can become a chronic illness for many patients who become refractory to multiple antidepressant medications [111, 112]. As such, vagus nerve stimulation (VNS) and trigeminal nerve stimulation (TNS) are being studied as treatment adjuncts.

VNS is a neuromodulatory treatment that was approved by the FDA in 1997 as an adjunctive therapy for epilepsy in adults over 12 years of age with partial onset seizures [110]. Treatment consists of chronic intermittent electrical stimulation of the left vagus nerve by a cuff electrode connected to an implanted programmable pulse generator (neurocybernetic prosthesis, Cyberonics, Inc., Houston, TX, USA). Following the observation that stimulation of the vagus nerve of dogs demonstrated an anticonvulsive effect, the first human patients were implanted in 1988 as part of two initial pilot studies [113, 114]. Since then, several controlled studies have demonstrated both short- and long-term improvement in seizure control. A recent review, including both adult and pediatric patients, demonstrated that approximately 60% of individuals receiving VNS have 50% or greater reduction in seizure frequency [110]. As such, VNS has been widely adopted as a treatment of epilepsy and an estimated 100,000 VNS devices have been implanted worldwide as of 2014 [115].

Although VNS was not originally intended for treatment of depression, Elger et al. noted improvement in mood, independent of effects on seizure activity, in patients who received VNS for treatment of drug-resistant epilepsy [116]. Rush et al. conducted the first trial that systematically examined the short-term efficacy (10 weeks) of VNS in 30 patients with major depressive episodes and found that 40% of patients responded favorably (greater than or equal to 50% reduction in baseline 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) to VNS therapy [117]. Likewise, when patients receive long-term treatment (greater than 12 months), studies show that as many as two-thirds of patients respond favorably to VNS therapy [118–120]. However, though VNS received FDA approval in 2005 for the treatment of depression, multiple systemic review studies have concluded that more research, particularly in the form of randomized control studies, are needed to convincingly establish the safety and efficacy of this therapy for the treatment of depression [118, 121].

The ability to neuromodulate brain activity via stimulation of the vagus nerve inspired clinicians and scientists to investigate the therapeutic potential of other cranial nerves, such as the trigeminal nerve. In contrast to the vagus nerve, the trigeminal nerve is located more superficially and is not associated with the adverse autonomic effects potentially seen with VNS [122]. In their animal model study, Fanselow et al. demonstrated that TNS can cause cortical and thalamic desynchronization, resulting in a decrease in the number of seizures in awake rats [123]. Based on this work, DeGiorgio and colleagues evaluated the feasibility of external TNS (eTNS) in adults with drug-resistant epilepsy in a series of early-phase clinical studies [124–126]. Positive results from these studies led this same group to conduct the first double-blind randomized active-control trial of eTNS in 50 patients with drug-resistant epilepsy. Although the responder rate (defined as greater than 50% reduction in seizure frequency) was not statistically significant between the treatment group and controls, 40.5% of the 25 patients that received eTNS responded to treatment upon evaluation at 18 weeks. Similar to findings in VNS studies, the authors also noted significant improvement in

mood, independent of changes in seizure frequency, in those receiving eTNS compared with the control group [116, 127]. Although not FDA approved, recent analyses have observed a significant improvement in both quality of life and mood in those using eTNS, as well as a retention rates that are comparable to commonly prescribed antiepileptic drugs [128, 129].

Considering the known anatomical connections of the trigeminal nerve to structures associated with mood and regulation and the known effects of VNS on both epilepsy and mood, Drs. Cook and Schrader conducted the first proof-of-concept trial of eTNS in 11 adults with unipolar major depressive disorder [130]. Nightly stimulation of the V1 branch was well-tolerated over an 8-week period and resulted in significant improvement in $HDRS_{28}$, which decreased from a score of 28.0 (s.d. = 6.9) to 14.4 (s.d. = 6.5), as well as significant improvement in quality of life [131]. Promising results ultimately motivated randomized, double-blind, sham-controlled clinical trials, in which patients underwent 10 daily 30-minute eTNS sessions for major depressive disorder. Both of these trials demonstrated positive effects of TNS in improving depressive symptoms, with a mean reduction in $HDRS_{28}$ of up to 36.15% [132, 133]. Further studies are currently underway to help establish TNS for depression, including investigation of subcutaneous TNS as an alternative technique [122].

Conclusion

PNS is not a new field, but still evolving likely in large part due to limited regulatory approval for this approach. The biophysical underpinning relies on differential modulation of peripheral nerve fibers of different sizes which convey different aspects of peripheral sensation. Successful applications have been detailed in facial, truncal, and extremity pain suggesting PNS as a useful option for peripheral neuromodulation and treatment for chronic pain. While work to date has largely focused on treatment of chronic pain, there is increasing interest in the role of peripheral neuromodulation to access and modulate the central nervous system in other neurological and psychiatric disorders, such as epilepsy and depression.

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