Chapter 9
Anatomy of Neuromodulatory Targets: Central Nervous System and the Periphery

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Current neuromodulatory targets have advanced from the dorsal columns of the spinal cord to multiple areas of the body. This chapter describes traditional anatomic landmarks and why spinal cord stimulation leads are placed in regions that are different from dermatologic mapping. In addition, stimulation by body region and various pain conditions is introduced, explaining how neuromodulation differs in treatment from head to foot.

9.1 Central Nervous System (CNS)

A precise understanding of the three-dimensional architecture of the spine provides an important basis for neuromodulation techniques. Although the use of fluoroscopy imaging can delineate important bony structures for spinal cord stimulator (SCS) lead placement, optimal placement requires accurate inference of soft tissue structures.

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9.1.1 Spine Anatomy

The spinal cord extends from the brainstem proximally to the conus medullaris, comprised of the fibrous filum terminale and the neural cauda equina [1]. In adults, the spinal cord terminates at the caudal end of the L1 vertebral level [1]. The pia mater (innermost layer), arachnoid mater, and dura mater (outermost layer) surround the spinal cord (Fig. 9.1). The subarachnoid or intrathecal space contains cerebrospinal fluid (CSF) and is located between the pia and arachnoid mater. The choroid plexuses of the cerebral ventricles produce approximately 500 mL of CSF each day, of which 30–80 mL is located below the T11–T12 level in the subarachnoid space [1]. The subdural space, between the dura and arachnoid mater, contains minimal amounts of serous fluid [2].

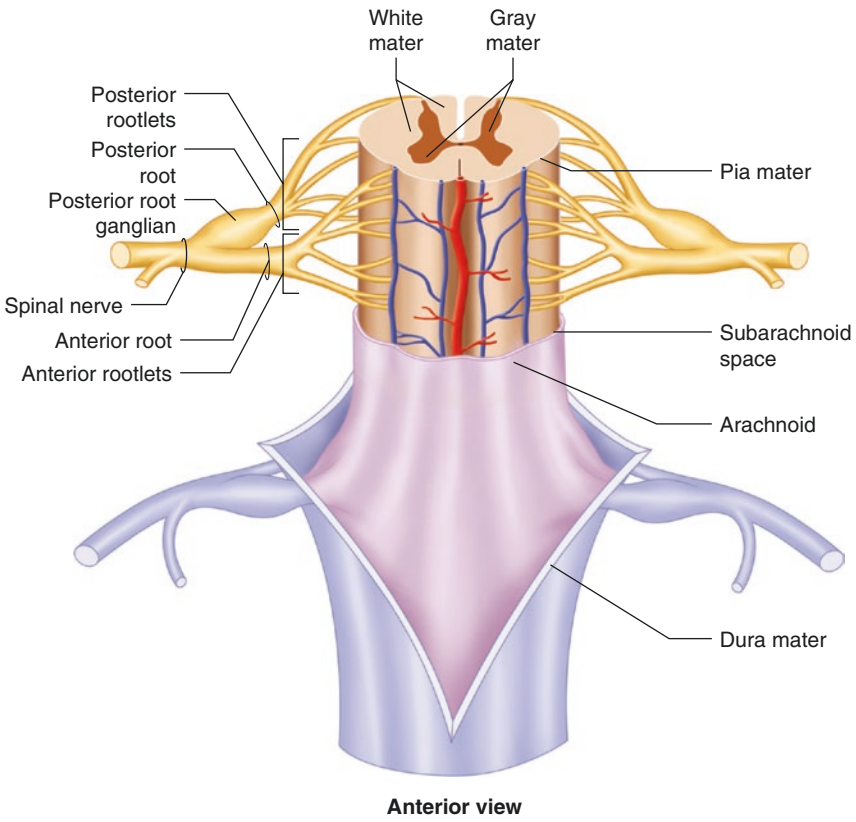

Fig. 9.1 Spinal cord meninges

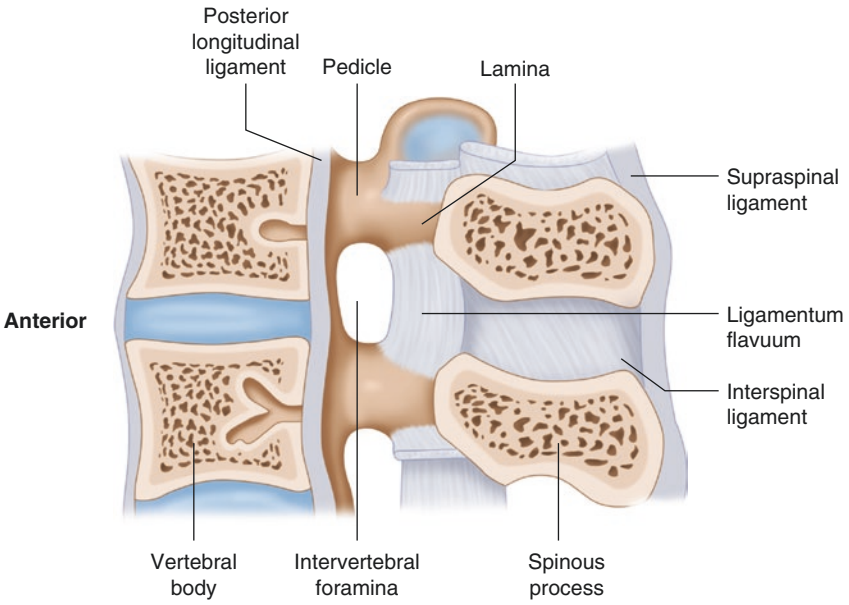

Fig. 9.2 Borders of the epidural space

The epidural space is superficial to the dura mater and extends from the foramen magnum to the sacral hiatus. The borders of the epidural space include the posterior longitudinal ligaments anteriorly, the pedicles and intervertebral foramina laterally, and the ligamentum flavum posteriorly (Fig. 9.2) [1]. In contrast to the subarachnoid space, the epidural space contains nerve roots and fat, areolar tissue, lymphatics, and blood vessels [3]. Epidural veins are situated anterolaterally within the epidural space, whereas epidural arteries are situated more laterally [2]. Though often thought of as a contiguous space, the epidural space contains meningo-vertebral ligaments that septate the epidural space into compartments of nonuniform size and shape [4]. These meningo-vertebral ligaments attach to the posterior dural sac and the ligamentum flavum or laminae, are localized to the posterior median or paramedian space, and run in a craniocaudal direction from the dural sac to the ligamentum flavum [5]. The distance between the ligamentum flavum and the dura mater is greatest (about 5–6 mm) at the L2 level. The distance decreases to 3–4 mm in the thoracic spine, and further decreases to 1.5–2 mm at C7 [2]. This variable distance between the ligamentum flavum and dura mater has important implications for SCS lead placement. Leads placed in the thoracic spine tend to exhibit higher impedance, stemming from less contact with the dura. Thus, systems placed in the thoracic spine may have a shorter battery life than those placed in the cervical spine [2]. Furthermore, the ligamentum flavum develops as a paired structure identifiable at 12 weeks gestational age, which ultimately fuses together at the midline [6]. At higher thoracic and cervical levels, midline gaps are often present from incomplete fusion of the left and right aspects of the ligament [6]. In addition,

the gaps are most often located in the inferior aspect of the intervertebral space. Consequently, above the T4 level in the thoracic spine, palpation of the ligamentum flavum through a loss-of-resistance technique may not be a reliable method for epidural needle placement. Posterior to the ligamentum flavum lay the lamina and spinous processes of the vertebral bodies or the interspinous ligament. Immediately superficial to these structures is the supraspinous ligament, which spans the vertebral spines [1]. Thus, a needle must traverse skin, subcutaneous tissue, the supraspinous ligament, interspinous ligament, and ligamentum flavum to reach the epidural space.

Most of the electrical current during SCS runs through the CSF, with negligible conductivity through the dura mater, bone, and other contents of the epidural space [7]. White matter also exhibits conductivity during SCS. Thus, the width of the subarachnoid, CSF-filled space, determines current distribution. Because the width of subarachnoid space is greatest at the T3 to T6 level, SCS lead placement in the upper thoracic spine results in the highest perception thresholds (the minimum voltage at which paresthesias are perceived from electrical stimulation). In contrast, lead placement in the cervical spine results in the lowest perception thresholds.

Perception thresholds also vary with patient position changes and with dynamic activity by altering the thickness of the dorsal CSF layer. This effectively brings neural targets closer to or further away from the electrode, causing a dynamic change in the perception threshold. In other words, patients experience overstimulation if the neural target shifts closer to the electrode, and understimulation if it shifts away. The AdaptiveStim™ technology (Medtronic; Minneapolis, MN) uses a gyroscope to detect changes in body position and automatically adjust stimulation amplitude.

9.1.2 Dorsal Column Anatomy

The dorsal column comprises nerves engaged in sensory, motor, and proprioceptive functions, and is the target of spinal cord stimulation. These ascending tracts in the dorsal column pass without decussation to the gracile and cuneate nuclei of the medulla oblongata [8]. The large myelinated fibers of the dorsal column represent the central processes of primary afferent neurons. In general, stimulation of the dorsal column large myelinated fibers is more efficacious than dorsal root stimulation, which results in segmental motor stimulation before appropriate paresthesias can be achieved [7]. Understanding the somatotopic representation of the dorsal column can optimize SCS lead placement. Lateral fibers represent more rostral dermatomes, while medial fibers represent more caudal structures [2]. This organization results from sequential entry of dorsal root fibers from a caudal to rostral direction. Therefore, at any specific level, the dorsal column contains nerves from all dermatomes distal to that level (Fig. 9.3) [8]. Thus, specific vertebral levels can be targeted to achieve desired stimulation (C5–6 for upper extremity, T10–11 for lower extremity, T6–9 for low back, and C1–4 for neck) [7]. Although any given

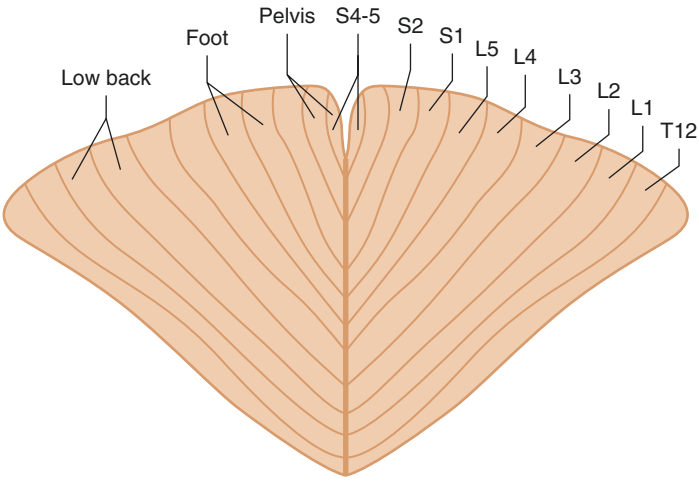

Fig. 9.3 Dorsal column somatotopic organization. Somatotopic representation of dermatomes at the level of the T11 dorsal columns [8]

spinal nerve has a vertebral entry point, the actual nerve root fibers enter the cord several segments more cranially [9]. To obtain a specific dermatomal level of stimulation, the dorsal column must be stimulated several segments above the vertebral level. Clinical neurostimulation typically recruits large myelinated fibers to a depth of 0.7 mm [9]. In addition, only about 1% of dorsal column fibers are large enough to be activated by SCS [9, 10].

9.1.3 Mechanisms of Neuromodulation

The concept of neuromodulation originated in response to Wall and Melzack's gate control theory of pain (Fig. 9.4) [11]. The concept that an imbalance between large fibers carrying innocuous input versus small fibers carrying peripheral nociceptive input laid the groundwork for the development of neuromodulation as an effective therapy for neuropathic, visceral, and nociceptive pain. Wall and Melzack's gate control theory of pain reduction described the idea of diminishing pain through selective activation of large-diameter fibers [11]. Pain signals are transmitted from nociceptors via A-delta and C-fibers, which are medium-diameter, lightly myelinated and small-diameter, nonmyelinated axons. The gate theory describes competitive input of large A-beta and smaller A-delta and C-fibers through a gate, with only one signal able to pass at a time. Thus, increasing the activity of large nerve fibers could close the gate to input from smaller pain fibers. Melzack and Wall described closing the gate to pain transmission through electrical stimulation of A-beta fibers [11].

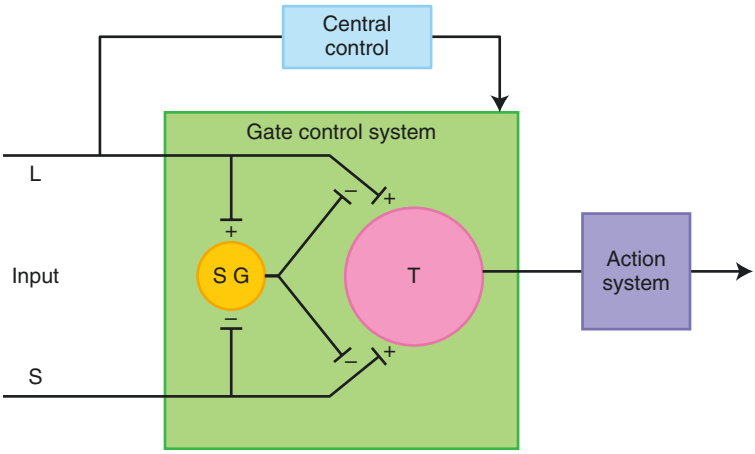

Fig. 9.4 The gate control theory of pain [11]. Large-diameter (L) and small-diameter (S) fibers project to the substantia gelatinosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. A line from the large-fiber system to the central control mechanisms represents the central control trigger. These mechanisms subsequently project back to the gate control system and the T cells project to the entry cells of the action system. + = excitation; − = inhibition

Specifically, Wall and Melzack proposed that the substantia gelatinosa functions as a modulator of afferent input, afferent patterns in the dorsal columns act as a CNS trigger for modulating properties of the gate control system, and central transmission cells in the dorsal horn activate neural mechanisms leading to response and perception [11].

Since the description of the gate control theory of pain, research has shown that additional mechanisms not described by this phenomenon are also involved in neuromodulation. This can be clinically demonstrated through continued analgesia even several hours after an SCS pulse generator is turned off [2].

Though neuromodulation has typically centered on electrical field coverage of pain regions, Foreman and Linderoth [12] have demonstrated that spinal cord stimulation affects wide dynamic range (WDR) neurons and must influence neurotransmitter levels at the spinal cord (Fig. 9.5). This graphic postulates mechanisms of action at the dorsal columns that could activate primary Aβ afferents and excite interneurons. This activation of interneurons would inhibit wide dynamic range (WDR) cells. This inhibition of WDR cells could account for the improvement of patients with neuropathic pain, peripheral vascular diseases, visceral (abdominal and pelvic) pain, and even nonanginal cardiac pain.

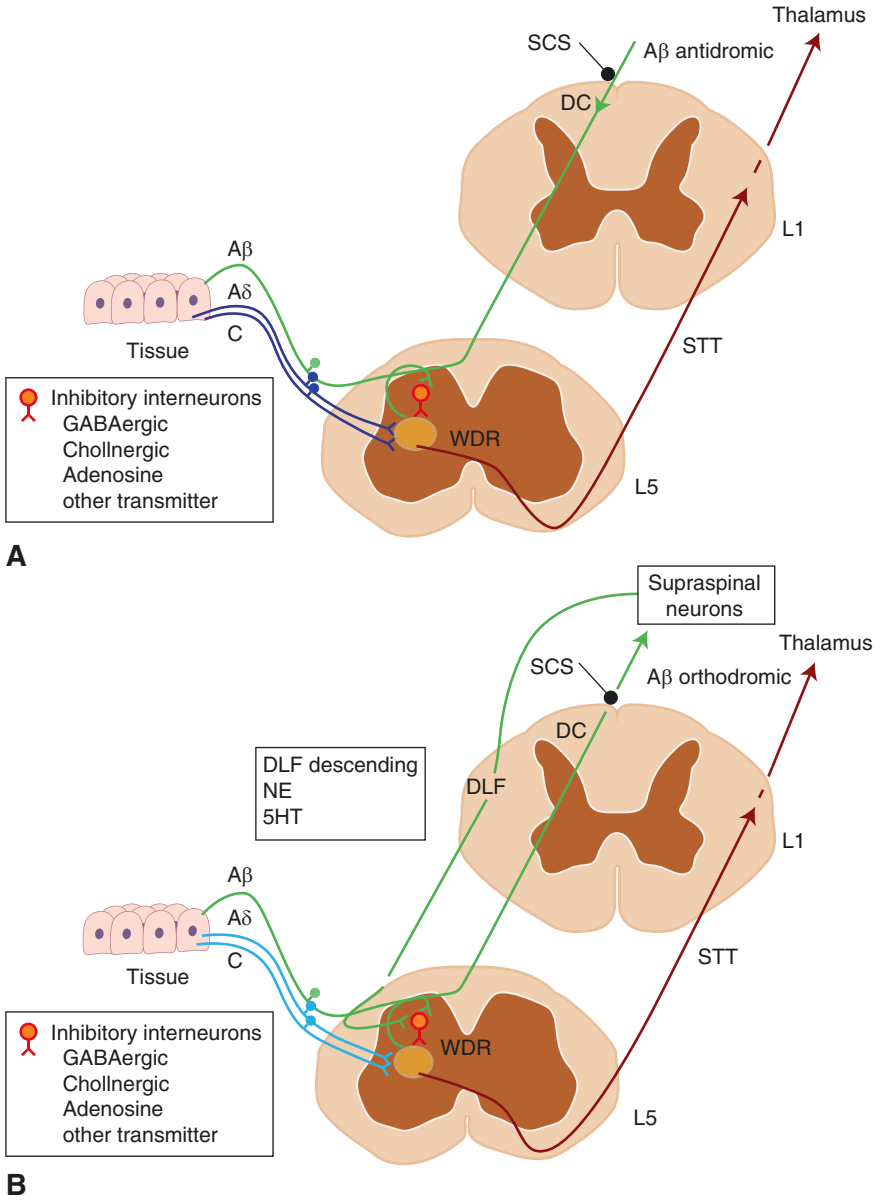

Fig. 9.5 Mechanisms of spinal cord stimulation (SCS) in neuropathic pain. SCS (*black ball at spinal segment L1*) activates dorsal columns antidromically (**a**) and orthodromically (**b**). (**a**) Antidromically transmitted action potentials activate collaterals of the primary Aβ afferents that excite interneurons (*red*). Activation of the interneurons inhibits wide dynamic range (WDR) cells. Numerous transmitters and modulators are involved in the modulation exerted by interneurons, as highlighted in the inset. The Aδ and C fibers from somatic structures (tissue) releasing glutamate and aspartate and that would excite WDR cells are inhibited, as mirrored in a decreased release of excitatory amino acids paralleled by an increase in GABA release. (**b**) Orthodromic activation of the primary afferent fibers with SCS evokes supraspinal relays (supraspinal neurons mainly in the brain stem) that transit information in descending pathways that release transmitters (DLF, dorsolateral funiculus; inset) to modulate WDR cells via segmental interneurons. Specific supraspinal relays are not shown because information about their organization is still evolving

9.2 Neuromodulatory Targets

Neuromodulation has evolved significantly in the 50 years since its initial treatment of back pain at the dorsal column by C. Norman Shealy in 1967. Spinal cord stimulation is now employed in a variety of conditions including neuropathic, ischemic, and visceral pain. Moreover, specific conditions such as postherpetic neuralgia, complex regional pain syndrome sacral and bladder pain, various headache syndromes, and even peripheral neuralgias are being increasingly treated with electrical stimulation. Specific targets and disease states are outlined in Table 9.1.

9.2.1 Spinal Cord Stimulation

Spinal cord stimulation (SCS) is the most common use of current implantable electrical stimulation systems for chronic pain management. The physiological and neuropharmacological mechanisms of action of SCS are complex and not well defined [13]. Nevertheless, SCS has been shown to be effective in treating back pain and CRPS. Newer experimental and clinical data show that SCS applied to different segments of the dorsal column elicits fundamentally different results on various target organs or parts of the body (Fig. 9.6).

Neuropathic pain caused by nerve dysfunction damage or altered nerve function is the main indication for SCS. Peripheral nerve injury, complex regional pain syndrome (CRPS) type I and II, peripheral neuropathy (idiopathic or diabetic), central neuropathic pain from stroke, or multiple sclerosis, spinal cord injury, and ischemia (cardiac as well as peripheral vascular disease) are good examples of conditions treated successfully with SCS [14].

The treatment of pain by applying electrical currents to the spinal cord, initially called dorsal column stimulation (DCS) but currently spinal cord stimulation (SCS), is delivered by electrodes over the dorsal columns of the spinal cord so as to modulate pain generation or processing. The goal of conventional SCS

Table 9.1 Targets of spinal cord stimulation

• Headache/cephalalgias
• Spinal disorders
• Angina
• Postherpetic neuralgia
• Abdominal pain
• Peripheral neuralgia/neuropathy
• Complex regional pain syndrome
• Bladder and pelvic pain

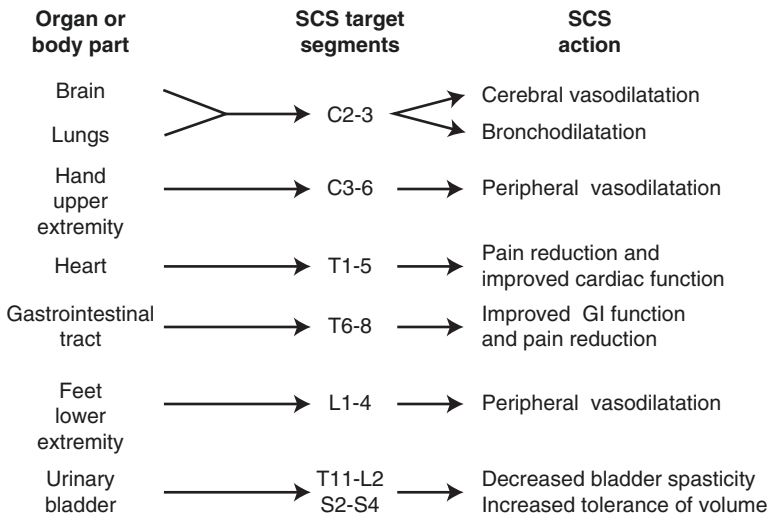

Fig. 9.6 Anatomic targets for spinal cord stimulation (SCS). This schematic diagram highlights different segments (not vertebral levels) of the spinal cord where SCS induces functional changes in target organs or body parts. Note that for the urinary bladder, T11–L2 segments modulate sympathetic control and S2–S4 segments modulate parasympathetic control [12]

(<1 kHz) is to replace the experience of pain with pleasant paresthesias targeted to the altered location [14]. Newer high-frequency (>10 kHz) stimulation devices, such as the Senza system, have become available in the United States since early 2015 [15]. The benefit to the high stimuli stimulation may include eliminating paresthesias, increasing tolerability but still providing excellent targeted pain control for patients.

Just outside of the spinal cord, dorsal root ganglion stimulation is proving to be a new region that may advance neuromodulation. A review by Krames [16] demonstrates why DRG stimulation may be an excellent target for decreasing hyperexcitability and chronic pain. Current existing devices developed by Spinal Modulation Inc. demonstrated efficacy in a multicenter, prospective trial in patients with painful regions of limb and/or trunk pain [17]. Moreover, DRG stimulation seems to prevent paresthesias due to positional changes while maintaining efficacy [18].

With emerging technology, SCS lead selection has become increasingly complex, as numerous SCS has evolved from monopolar or bipolar configurations. Complicated electrode arrays delivered either by percutaneously placed cylindrical platforms or surgically placed paddle platforms [13]. Common configurations for low back pain include two and three lead percutaneous cylindrical leads as well as paddle leads [14].

9.2.2 *Pain in the Chest: Neuromodulation for Refractory Angina*

Due to advances in modern medicine, the mortality from cardiovascular disease continues to decline. Revascularization procedures and medication have revolutionized treatment and increased survival. As a result of this, morbidity from cardiovascular disease has continued to rise.

Refractory angina (RA) has been defined as a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months [19]. Refractory angina pain can be a debilitating condition. Myocardial ischemia due to obstructive coronary disease activates both mechanical and chemical cardiac receptors. These receptors trigger the nerves which are conveying signals to the brain, where angina is ultimately 'felt'. In patients with refractory angina the high-threshold receptors in the myocardium have become low-threshold receptors. The subsequent sensitization of these receptors in the myocardium results in an altered angina threshold [19].

A variety of neuromodulatory techniques have been employed for angina. Transcutaneous electrical nerve stimulation (TENS) has been shown to be an effective method for treatment of angina, although there are technical limitations to this modality. The gel pads used to fix the electrodes to the skin can be cumbersome and have been known to cause dermatitis when used for a long period of time [20]. Patient compliance with TENS can also be a limiting consideration for this therapy.

Subcutaneous electrical nerve stimulation is an alternative to TENS and SCS. SENS electrodes are placed subcutaneously, at the side of the sternum in the area where the patient usually feels angina, and are connected to a pulse generator, which is implanted in the abdominal wall. This technique is easier and less invasive compared with SCS, thus reducing the risk of complications [21].

SCS is a proven effective therapy for RA with multiple trials supporting its use and proving its cost effectiveness [22]. It has been suggested that SCS produces its effects in refractory angina via an interaction of the following mechanisms: (1) pain reduction; (2) a reduction of sympathetic tone; (3) reduced myocardial oxygen demand; and (4) improved coronary microcirculatory blood flow, resulting in a lessening of myocardial ischemia [23].

SCS in RA patients is thought to be due to modification of the α1-adrenergic pathways leading to a sympatholytic and vasodilatory effect, which improves the microcirculation in the affected ischemic tissue [23]. Nitric oxide and calcitonin-gene-related peptide are also released, leading to vasodilation and improved microcirculation [24]. Other neurotransmitters such as acetylcholine, adenosine, and substance P are still subjects of ongoing investigations. Clinically reduced ulceration and oxygen demand have been observed in ischemic disease patients treated with SCS, which improves their pain and perfusion status significantly [25].

9.2.3 Pain in the Head: Neuromodulation for Headache Disorders

Primary headache disorders encompass a multitude of conditions that can be a source of significant disability for patients. Primary headache disorders frequently treated with neuromodulation include chronic migraine (CM), chronic tension-type headache, as well as the trigeminal autonomic cephalgias (TACs). TACs are a complex group of headache disorders that include cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA). Other peripheral conditions that may contribute to chronic headache include occipital neuralgia (ON) and supraorbital neuralgia. These conditions may exacerbate underlying primary headache conditions such as CM or TACs, but they can also be the primary source of pain as well. Neuromodulation for headache disorders is best divided into two categories: central and peripheral modalities.

9.2.3.1 Central Stimulation

Deep brain stimulation (DBS) has been in practice since the 1950s and has been used for variety of neurologic conditions including epilepsy as well as chronic pain states. Deep brain stimulation consists of the placement of electrodes through the skull and cortex to the sub-cortical structures within the brain. The purpose is to stimulate these structures and modulate their function [26]. The electrode is placed ipsilateral to the attack, except for bilateral placement for conditions affecting both sides. The most common reported side effect of DBS is ophthalmoplegia and vertigo with higher stimulation amplitudes [27]. Recent data suggests that DBS has a systems effect rather than a localized deactivation effect in the posterior hypothalamic region, and may provide further insights into the disorder itself. The literature supports the use of DBS mainly in patients with TACS, primarily those affected by cluster headaches. There are some case reports of patients also receving DBS for SUNCT and paroxysmal hemicranias, but the results have shown mixed results [28].

9.2.3.2 Peripheral Stimulation

Considerable focus has also been devoted to peripheral nerve stimulation for headache syndromes. Currently, PNS is thought to modulate central pain processing by exploiting the anatomic and functional relationship of the peripheral sensory nerves of the head and neck to affect brainstem and higher cortical pain centers [29]. The current concept of the trigeminocervical complex describes the communications between the trigeminal nerve supplying sensation to the anterior head and face and the upper cervical nerves supplying sensation to the posterior head [28]. Percutaneous

Table 9.2 Percutaneous targets for peripheral nerve stimulation (PNS)

Lead placement	Benefit
Leads placed subcutaneously at the terminal branches of afferent nerves supplying the trigeminocervical complex	Chronic migraine and chronic tension-type headache
Occipital nerve stimulation (ONS): Applying an electrode impulse over the greater, lesser, or third occipital nerves (branches of C2–C3 cervical nerve roots)	Chronic migraine, hemicrania continua, chronic cluster headache, SUNCT, and paroxysmal hemicrania
Auriculotemporal nerve stimulation: Leads placed along bilateral auriculotemporal nerves	Chronic migraine (case reports only)
Sphenopalatine ganglion (SPG) stimulation: Efferents from the SPG innervate the dura and meninges, and initiate peripheral pain mechanisms of migraine, including neurogenic inflammation and vasodilatation. The parasympathetic outflow from the superior salivatory nucleus to the SPG from there, after synapsing, to target organs of the eye and sinuses is felt to be the pathway for most of the autonomic features of cluster headache	Chronic migraine and cluster headache
Supraorbital nerve stimulation (has been combined with ONS)	Chronic cluster headache and migraine headache (case reports only)

SUNCT Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

stimulation of peripheral targets has been proven to be effective for headache syndromes are numerous (Table 9.2).

Noninvasive stimulation techniques for headache are also viable long term treatment options. The Cefaly™ device (CEFALY Technology; Belgium) is available by prescription in the USA and Europe and is the first device to use transcutaneous stimulation for targeted treatment of migraine (Fig. 9.7). The device consists of an electrode with skin adhesive placed on the forehead covering the sites of the supraorbital and supratrochlear nerves, both of which are branches of the ophthalmic nerve or the first branch of the trigeminal nerve. Biphasic rectangular impulses with an electrical mean of zero, impulse width of 250 μs, frequency of 60 Hz, and maximum intensity of 16 mA are generated with device activation. The relatively high frequency and low intensity is aimed to avoid crossing the pain threshold while still being able to activate Aβ afferents and leading to paresthesia in the distribution of the nerve and preventing the activation of Aδ and C fibers important in nociception and reducing hyperalgesia [29].

Vagal nerve stimulation (VNS) has also been a target for headache treatment. Current evidence for the use of VNS for pain indications is most robust, though still relatively limited, for the indication of chronic headaches and migraines [30]. Several noninvasive VNS (nVNS) devices are currently on the market. The NEMOS device (Cerbomed; Erlangen, Germany) provides transcutaneous VNS via the auricular branch of the vagus nerve. Its primary use has been for cluster headaches, episodic migraines, and chronic migraines. Reportable adverse events across several

Fig. 9.7 The Cefaly™ device consists of an electrode with skin adhesive placed on the forehead covering the sites of the supraorbital and supratrochlear nerves

published studies include local discomfort, skin irritation, transient muscle stiffness, and pain that resolved with NSAID treatment.

9.2.4 Pain in the Limbs: Complex Regional Pain Syndrome, Peripheral Neuropathy, and Peripheral Vascular Disease

Complex regional pain syndrome (CRPS) a neuropathic pain condition characterized by vasomotor, sudomotor, sensory, and trophic signs and symptoms. CRPS is subdivided into CRPS type 1 and type 2. The signs, symptoms, and presentation of both types are very similar. CRPS-I, classically called reflex sympathetic dystrophy, is defined by the absence of injury to a major nerve. CRPS-II, known previously as causalgia, occurs following damage to a major nerve. Patients affected by CRPS can have a significant level of disability and mental distress. Traditionally, initial treatment of CRPS has focused on multidisciplinary care including treatment with medications like opioids, anticonvulsants, and tricyclic antidepressants. Physical and occupational therapy as well as intensive psychological therapy including cognitive behavioral therapy are also pillars of CRPS treatment. An interdisciplinary treatment protocol, developed under the aegis of IASP, recommends simultaneous psychological, rehabilitative, and interventional pain management with therapeutic options determined by the patient's clinical progress. The Neuromodulation Appropriateness Consensus Committee (NACC) recommends SCS for the treatment of CRPS-I and CRPS-II with pain of at least 3 months' duration or severe, rapidly progressing disease that is not responding to more conservative measures such as physical and occupational therapy [31].

The current conceptual model for SCS supports segmental inhibition as a tenet for analgesia. Data obtained from animal studies indicate that second-order neurons and interneurons can be affected by SCS, and that spinal and supraspinal inhibitory loops may account for the major effects of SCS in neuropathic pain [32–34]. Implanting a SCS is often considered both an expensive and an invasive treatment, and satisfactory lead placement is necessary for successful treatment. The technical goal of SCS is to achieve stimulation-induced paresthesias in the anatomical distribution of the affected limb. Despite the apparent upfront cost, if the treatment is appropriate and is shown to have good outcomes, overall costs, morbidity, and chronic decreased functionality would be significantly reduced with fewer ineffective treatments and tests [35]. Krames et al. [36] have introduced the SAFE principles as a way to appropriately ordinate therapies for the treatment of chronic pain. SAFE is an acronym standing for **S**afety, **A**ppropriateness, time to **F**iscal neutrality, and **E**fficacy (Fig. 9.8) [37]. These principles help to guide pain practitioners in their decision to consider SCS for CRPS patients.

Peripheral neuropathy can also be successfully treated with neuromodulation. The prevalence of diabetes and related complications continues to rise in the United States and throughout the world. Diabetic neuropathy is common problem in longstanding diabetics. Painful diabetic neuropathy (PDN) can interfere with mobility, quality of life, and overall well being. There is good data to show that when conservative measures failure including medications fail, SCS is a reasonable alternative therapy. In several recent studies, SCS resulted in clinical and statistical improvements in pain and quality of life of patients with painful diabetic neuropathy [38, 39].

Spinal cord stimulator is approved for the treatment of critical limb ischemia in Europe, but not currently in the United States. Currently, conservative management of chronic critical limb ischemia consists of analgesics, vasodilators, and anticoagu-

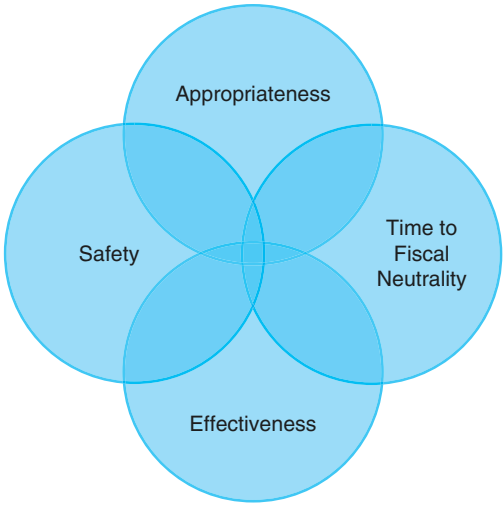

Fig. 9.8 *SAFE* analysis analyzes **S**afety, **A**ppropriateness, time to **F**iscal neutrality, and **E**fficacy [36]

lants. In those who are not surgical candidates, SCS is an alternative that may improve limb salvage. As with the therapeutic effects of SCS in CAD, it is hypothesized that SCS leads to improvement in critical limb ischemia due to vasodilation and subsequent improvement of blood flow. SCS may be a treatment option for those patients who are nonsurgical candidates and have critical limb ischemia [40]. According to the NACC, ischemia due to structural lesions (peripheral arterial occlusive disease or due to vasospasm like in Raynaud's disease) are well treated by SCS; however, venous engorgement has not been shown to respond. The NACC feels that the evidence supporting sympathectomy is very poor and recommends SCS be utilized prior to the irreversible approach of sympathectomy [31].

References

1. Miller RD. Miller's anesthesia. 8th ed. Philadelphia: Elsevier/Saunders; 2015.
2. Kreis P, Fishman S. Spinal cord stimulation: percutaneous implantation techniques. New York: Oxford University Press; 2009.
3. Boon JM, Prinsloo E, Raath RP. A paramedian approach for epidural block: an anatomic and radiologic description. Reg Anesth Pain Med. 2003;28:221–7.
4. Jiang H, Shi B, Xu S. An anatomical study of lumbar epidural catheterization. BMC Anesthesiol. 2015;15:94.
5. Shi B, Zheng X, Min S, Zhou Z, Ding Z, Jin A. The morphology and clinical significance of the dorsal meningovertebra ligaments in the cervical epidural space. Spine J. 2014;14:2733–9.
6. Yoon SP, Kim HJ, Choi YS. Anatomic variations of cervical and high thoracic ligamentum flavum. Korean J Pain. 2014;27:321–5.
7. Ramasubbu C, Flagg A 2nd, Williams K. Principles of electrical stimulation and dorsal column mapping as it relates to spinal cord stimulation: an overview. Curr Pain Headache Rep. 2013;17:315.
8. Feirabend HKP, Choufoer H, Ploeger S, Holsheimer J, Van Gool JD. Morphometry of human superficial dorsal and dorsolateral column fibres: significance to spinal cord stimulation. Brain. 2002;125:1137–49.
9. Foletti A, Durrer A, Buchser E. Neurostimulation technology for the treatment of chronic pain: a focus on spinal cord stimulation. Expert Rev Med Devices. 2007;4:201–14.
10. Yampolsky C, Hem S, Bendersky D. Dorsal column stimulator applications. Surg Neurol Int. 2012;3:S275–89.
11. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
12. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. Int Rev Neurobiol. 2012;107:87–119.
13. Kapural L. Spinal cord stimulation for intractable chronic pain. Curr Pain Headache Rep. 2014;18:406.
14. Deer T, Pope J, Hayek S, Narouze S, Patil P, Foreman R, et al. Neurostimulation for the treatment of axial back pain: a review of mechanisms, techniques, outcomes, and future advances. Neuromodulation. 2014;17:52–68.
15. U.S. Food and Drug Administration. FDA approves spinal cord stimulation system that treats pain without tingling sensation. 8 May 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm446354.htm
16. Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. Neuromodulation. 2015;18:24–32.
17. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion

neurostimulator system in the treatment of chronic pain. Neuromodulation. 2013;16:471–82; discussion 482.
18. Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. Neuromodulation. 2015;18:50–57; discussion 57.
19. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002;23:355–70.
20. Strobos MA, Coenraads PJ, De Jongste MJ, Ubels FL. Dermatitis caused by radio-frequency electromagnetic radiation. Contact Dermatitis. 2001;44:309.
21. De Decker K, Beese U, Staal MJ, Dejongste MJ. Electrical neuromodulation for patients with cardiac diseases. Neth Heart J. 2013;21:91–4.
22. Eldabe S, Thomson S, Duarte R, Brookes M, deBelder M, Raphael J, et al. The effectiveness and cost-effectiveness of spinal cord stimulation for refractory angina (RASCAL Study): a pilot randomized controlled trial. Neuromodulation. 2016;19:60–70.
23. Wu M, Linderoth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a review of experimental studies. Auton Neurosci. 2008;138:9–23.
24. Bernardini N, Neuhuber W, Reeh PW, Sauer SK. Morphological evidence for functional capsaicin receptor expression and calcitonin gene-related peptide exocytosis in isolated peripheral nerve axons of the mouse. Neuroscience. 2004;126:585–90.
25. Kinfe TM, Pintea B, Vatter H. Is spinal cord stimulation useful and safe for the treatment of chronic pain of ischemic origin? A review. Clin J Pain. 2016;32:7–13.
26. Jenkins B, Tepper SJ. Neurostimulation for primary headache disorders: part 2, review of central neurostimulators for primary headache, overall therapeutic efficacy, safety, cost, patient selection, and future research in headache neuromodulation. Headache. 2011;51:1408–18.
27. Goadsby PJ. Neurostimulation in primary headache syndromes. Expert Rev Neurother. 2007;7:1785–9.
28. Hong J, Ball PA, Fanciullo GJ. Neurostimulation for neck pain and headache. Headache. 2014;54:430–44.
29. Zhu S, Marmura MJ. Non-invasive neuromodulation for headache disorders. Curr Neurol Neurosci Rep. 2016;16:11.
30. Chakravarthy K, Chaudhry H, Williams K, Christo PJ. Review of the uses of vagal nerve stimulation in chronic pain management. Curr Pain Headache Rep. 2015;19:54.
31. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, et al. 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. 2014;17:515–50; discussion 550.
32. El-Khoury C, Hawwa N, Baliki M, Atweh SF, Jabbur SJ, Saadé NE. Attenuation of neuropathic pain by segmental and supraspinal activation of the dorsal column system in awake rats. Neuroscience. 2002;112:541–53.
33. Williams KA, Korto K, Cohen SP. Spinal cord stimulation: “neural switch” in complex regional pain syndrome type I. Pain Med. 2009;10:762–6.
34. Dubuisson D. Effect of dorsal-column stimulation on gelatinosa and marginal neurons of cat spinal cord. J Neurosurg. 1989;70:257–65.
35. Goff BJ, Naber JW, McCallin JP, Lopez EM, Guthmiller KB, Lautenschlager KA, et al. Immediate return to ambulation and improved functional capacity for rehabilitation in complex regional pain syndrome following early implantation of a spinal cord stimulation system. Case Rep Anesthesiol. 2014;2014:784021.
36. Krames E, Poree L, Deer T, Levy R. Implementing the SAFE principles for the development of pain medicine therapeutic algorithms that include neuromodulation techniques. Neuromodulation. 2009;12:104–13.

37. Poree L, Krames E, Pope J, Deer TR, Levy R, Schultz L. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. Neuromodulation. 2013;16:125–41.
38. Duarte RV, Andronis L, Lenders MW, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Qual Life Res. 2016;25:1771–7.
39. Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37:3016–24.
40. Lee S, Abd-Elsayed A. Some non-FDA approved uses for neuromodulation: a review of the evidence. Pain Pract. 2016;16:935–47.