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History of neuroaugmentative procedures

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Pain management at the beginning of the last century involved a simplistic notion that pain might invariably be controlled by obliterating all sensation. During the first half of the twentieth century, there was a transition from peripheral nerve section to interruption of central primary pain pathways to interruption of central ancillary pain systems. During the last half of the century, there was a shift in management of chronic pain from such ablation to using stimulating techniques to modulate pain perception. The history of that evolution reflects our changing concepts about the mechanisms of pain perception.

The term *neuroaugmentation* has been used experimentally to describe any process that modulates the function of the nervous system without permanently changing it, whether it is pharmacologic, stimulation, or any other experimentally introduced variable. The term has been borrowed clinically, however, to represent a specific approach to pain management, that is, the use of electric stimulation of the nervous system to modulate neural activity, such as pain perception.

For the purpose of this historical review, neuroaugmentation is defined as the use of electric stimulation of any neural structure to modify pain perception to help manage a clinically painful condition.

To review the history of neuroaugmentation for pain management, it is necessary to review those concepts and procedures that preceded and then evolved into our present treatment modalities. Although neuroaugmentation evolved from concepts about the organization of the nervous system and the stimulation techniques have proven to be clinically beneficial, there is still much to be learned about the mechanisms of neuroaugmentation.

The idea of modifying clinical pain by stimulating part of the nervous system is more complex than it seems at first blush. Pain is not a simple sensation like those defined as the primary sensations. The perception of pain is a complex phenomenon, which varies depending on the milieu in which it exists. It is subject to modification by many external and internal influences, including psychologic traits that are difficult to identify, secondary gain, psychosocial issues, and emotional factors, such as anxiety and depression. Success in alleviating clinically significant pain is subjective on the part of the patient and the physician, and measurement of success is particularly susceptible to bias resulting from the expectations of the patient, the physician, or other interested parties. These complexities also provide opportunities for management apart from treating the underlying physical etiology, among which are multimodality pain programs that may include modification of pain perception by neuroaugmentation.

To set the stage for the evolution of neuroaugmentation, let us return to the first half of the twentieth century [1,2]. The general belief about pain treatment was that pain would disappear if the proper part of the primary pain pathway were interrupted. It was thought that if a peripheral nerve were sectioned, all sensation in the distribution of that nerve would be gone and so would the pain, and probably motor function, as well. That proved not to be so, and many patients ended up with an area of total anesthesia that was still exquisitely painful, sometimes even more than before.

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Attention was directed to the primary pain pathway within the central nervous system as early as 1912, when Spiller and Martin [3] interrupted the lateral spinothalamic tract in the anterolateral spinal cord to treat pain, which provided analgesia without anesthesia or motor loss to the contralateral body below the lesion. During the next 60 years, cordotomy was the most commonly used surgical procedure for treatment of pain.

Cordotomy was made less invasive in 1963 when Mullan et al [4] used a strontium needle to lesion the high cervical spinal cord. Rosomoff et al [5] made the procedure generally available by using a radiofrequency electrode to produce the C_2 lesion. Lin and co-workers [6] approached the spinal cord through a lower cervical disk to avoid respiratory complications. Throughout the 1970s, percutaneous cervical cordotomy became the most common surgical procedure for pain management. Although many patients had pain relief, there was insufficient attention given to which patients might benefit at that time. Patients were candidates for percutaneous cervical cordotomy regardless of the etiology of the pain and what factors might influence pain perception. It was the disappointing outcomes that provided some insight into which patients benefited and what factors were associated with poor outcome. It was perhaps the opportunity to follow such patients to determine which failed to benefit that led the authors of the two largest series of percutaneous cervical cordotomy series [5,7–9] thereafter to become advocates of a conservative, generally nonsurgical, multidisciplinary approach to the management of chronic pain [10–12].

Throughout the latter half of the century, considerable attention was also given to structures within the brain and brain stem that might be targets for pain management.

In 1947, Spiegel and colleagues [13] introduced human stereotactic surgery, which was invented to insert an electrode or other probe accurately into any desired intracerebral anatomic structure to record, stimulate, or ablate it. Although the first case involved a movement disorder, their second patient was successfully treated that same year for chronic facial pain by interrupting the spinothalamic and quintothalamic tracts at the level of the mesencephalon [14,15].

Increasingly sophisticated attempts were made to alleviate severe persistent pain by interrupting pathways within the brain or brain stem with stereotactic techniques. Observations made particularly by Nashold and his colleagues [16,17] demonstrated that much better pain relief was obtained if the lesion encroached on the extralemniscal pathway rather than merely interrupting the primary pain pathway. It soon became apparent that it was possible to alleviate many types of pain by lesioning only the extralemniscal mesencephalon and not the primary pain pathway, so that pain relief without sensory loss became the goal [18].

Significant pain relief could also be obtained with lesions confined to the extralemniscal thalamus [19]. This concept was particularly important from the standpoint of pain perception, because it indicated that pain perception might be modified without interrupting primary pain pathways or inducing sensory loss.

In 1959, Noordenbos [20] postulated that this multisynaptic afferent system might be implicated when interruption of the neospinothalamic path failed to relieve chronic pain. He speculated that the same extralemniscal pathway might also be involved in modifying pain sensation. The stage was set for the introduction of the gate theory.

The gate theory

The introduction of the gate theory of pain perception by Melzack and Wall [21] in 1965 represents the most significant turning point in the approach to surgical and nonsurgical pain management and the basis for neuroaugmentation for pain management (Fig. 1). Although their paper did not present a novel experimental design, it codified and coordinated those concepts of pain perception that had been accumulating from clinical and laboratory observations particularly during the prior two decades. It took into account the four prior theories of pain perception, including physiologic specialization, central summation, patterning, and modulation of input, and included the role of psychologic or conscious factors in modifying pain perception. The single diagram in that article (see Fig. 1) represented how a host of observations and theories might account for the perception of clinical pain. Whether or not pain might be felt depended at least in part on whether a gate were open. Those factors opening the gate involve noxious stimulation, which is carried primarily through small nerve fibers. Those factors that tend to close the gate involve nonpainful stimulation, which is carried primarily through large fibers. The theory provides a concept that stimulation of the large fibers might close the gate to alleviate pain and explain why "when you rub it, it feels better."

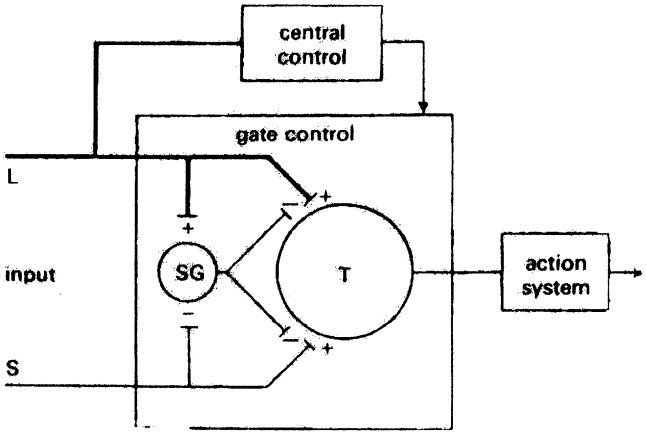

Fig. 1. The Melzack-Wall gate control theory opened new concepts of thinking about pain perception and how it might be modulated. SG = substantia gelatinosa; T = T cell; L = large fiber neuron; S = small fiber neuron. (*From* Melzack R, Wall PD. Pain mechanisms; a new theory. Science 1965;150:971–9; with permission.)

In brief summary, several concepts constitute the gate theory as elaborated in the original paper [21]:

1. T cells in the dorsal root entry zone of the spinal cord act as the pain transmission neurons. Whether or not they transmit pain information from the periphery to the spinal cord is modulated by a gating mechanism.
2. The gating mechanism is opened or closed depending on the relative activity of large neurons (low-threshold nonpain, touch, and proprioception) versus the small cells (high-threshold pain neurons).
3. The opening or closing of the gate may be further influenced by mechanisms descending from higher brain centers, which are designated as "central control." The central control mechanisms may be activated or enhanced by input from a specialized system of large and rapidly conducting nerve fibers (the "central control trigger"), represented in large part by axons ascending in the dorsal columns carrying specific information that makes it possible to identify, evaluate, localize, and modulate the input even before the main action system is activated.
4. When the gate is open, the T cells exceed threshold and conduct pain information to higher levels, where the perception of pain and the complex reaction to pain occur.
5. A preponderance of nonpain input may tip the balance toward closing the gate.

In 1968, Melzack and Casey [22] published a somewhat more complex elaboration of the gate control theory, which increased the role of cognitive control from higher centers (Fig. 2).

The most important contribution of the publication of the gate theory and its modifications was to inspire fresh thinking about how to modify pain perception toward the benefit of the patient; in turn, that led to the development of neuroaugmentative procedures for the management of pain.

One must digress at this point to define various types of clinical pain to discuss what pain may be modified by neuroaugmentation.

One of the frustrations about the literature concerning management of pain is that the type of pain under discussion is often ill defined or not defined at all. Although that has improved significantly, there have been a number of classifications of pain used by various authors, and it has only been during the past two decades that there has been a concerted effort toward a universal standard of reporting. In trying to interpret studies that have been reported and to guide my own patient selection, I have found it helpful to use the simple classification in Table 1, because each category invites a different type of management. In my simplistic system, clinical pain is divided into the three basic categories of acute pain, cancer pain, and chronic pain.

Acute pain is pain that appropriately accompanies a nociceptive stimulation, whether it is from acute tissue injury, inflammation, or disease. Management involves providing adequate analgesics and treating the underlying etiology.

The literature often defines "chronic pain" to mean pain that has persisted for a long time but

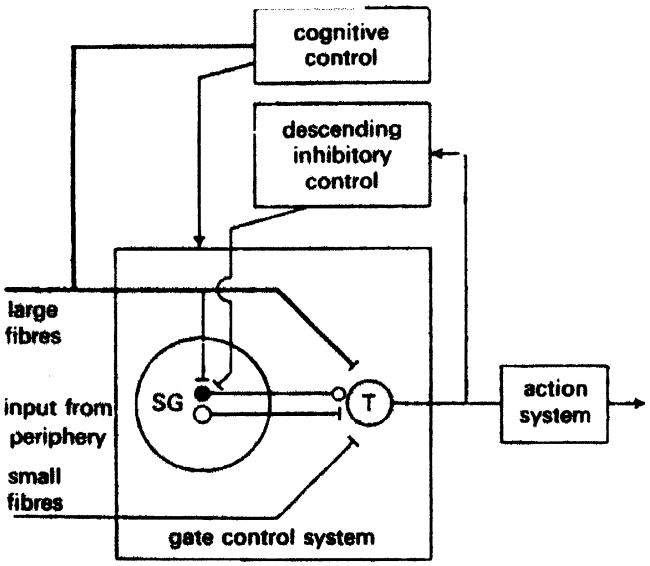

Fig. 2. A later concept of the gate control theory was presented by Melzack and Casey, with more emphasis on descending influences. SG = substantia gelatinosa; T = T cell. (*From* Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain. A new conceptual model. In: Kenshalo DR, editor. The skin senses. Springfield, IL: Charles C. Thomas; 1968. p. 423–39; with permission.)

then makes little distinction between cancer pain and pain caused by chronic conditions other than cancer, even though management is quite different in the two groups. To interpret outcome, it is necessary to make that distinction.

"Cancer pain" involves not only pain caused by direct invasion by cancer but pain secondary to treatment or complicating pathophysiology, which is most often temporally limited by the nature of the cancer. Pain management includes the use of adequate narcotics or other analgesics and sometimes ablative surgical procedures.

I prefer to reserve the term *chronic pain* for pain that has lasted a long time but does not involve cancer, which includes pain of both somatic and neuropathic origin. Chronic pain must be managed over a long term with no definitive end in sight. The original etiology is often not apparent or no longer treatable, so management is directed to alleviating as much pain as possible but also to addressing issues of rehabilitation, secondary psychologic factors, depression, family issues, and long-term disability. It is this group that most often qualifies for neuroaugmentative procedures.

Table 1
Classification of clinical pain

Usual nomenclature	Preferred nomenclature
Acute pain	Acute pain
Chronic pain, cancer	Cancer pain
Chronic pain, benign etiology	Chronic pain

Both cancer pain and chronic pain that last a long time are "persistent pain."

The stage was set to introduce neuroaugmentation for the management of chronic pain. It was established that interruption of direct pain pathways often failed over the long run. The extralemniscal pathway was somehow involved. The gate theory suggested that it or other large fiber nonpain pathways may be manipulated to close the gate to decrease T-cell firing and alleviate pain. Not all pain patients were candidates for any particular procedure. There was likely to be a subgroup of patients with chronic pain who would benefit from neuroaugmentation, but that may require that it be used as part of a more comprehensive multimodality rehabilitation-based chronic pain program.

Because neuroaugmentation is generally useful for chronic pain rather than acute pain and we have no accepted valid animal model for chronic pain, the development of neuroaugmentative

procedures has required human experimentation and clinical trial rather than a logical sequence of experimental procedures gradually and logically leading to a clinically accepted procedure.

Peripheral nerve stimulation

The first such human experimental procedure occurred in 1967, when Wall and Sweet [23,24], who were then working together in Boston, inserted needle electrodes into their own infraorbital nerves and demonstrated that electric stimulation produced analgesia throughout the distribution of those nerves. The following year, Sweet and Wepsic [25] reported successful alleviation of pain along the distribution of a peripheral nerve that was stimulated by an implanted electrode. Other reports verified successful alleviation of pain by peripheral nerve stimulation [26–28]. Despite the success of that experience, the use of peripheral nerve stimulation remains underused [24,29], partly because somatic pain is so frequently carried by more than one nerve and partly because peripheral nerve stimulation has been displaced by spinal cord stimulation.

Spinal cord stimulation

At about that same time in 1967, Shealy et al [30] took ingenious advantage of the anatomic coincidence that is apparent in the original Melzack-Wall gate theory illustration (see Fig. 1). The large fibers that may help to close the gate are contained in the dorsal columns, where they might be stimulated selectively. Shealy considered that if those fibers were stimulated above the spinal levels into which the pain information arrived via the T cells, perhaps the impulse would travel retrograde down the dorsal columns to close the gate and decrease the patient's pain perception. The concept proved to be valid, and neuroaugmentation as we know it was born. At that time, it was called "dorsal column stimulation." The original concept required that the stimulation-induced sensation blanket the area of pain, but that was soon found not to be necessary. It consequently became apparent that the stimulation affected not only the dorsal columns, but it was uncertain which structure was involved in pain relief. Indeed, pain relief could occur even if the anterior spinal cord were stimulated, so the more general term *spinal cord stimulation* became preferred [31]. Even today, there is considerable doubt as to whether the theory on which the use of spinal cord stimulation is based is actually the mechanism for its success [32]. There is evidence that pain transmission is modified by spinal cord stimulation [33]. Nevertheless, the success of spinal cord stimulation is well documented. We may be doing the right thing but for the wrong reason.

Stimulation of brain structures during the insertion of electrodes has been part of physiologic localization from the earliest days of stereotactic surgery [34]. Perhaps the first attempt to apply stimulation to permanently implanted electrodes over a prolonged period was made in Russia. There were no implantable stimulators, so the patient had to return repeatedly to the hospital to have stimulation applied to externalized electrode contacts [35]. That would not be an acceptable protocol for the general use of spinal cord stimulation.

Once there was an indication for implantation of a device that would provide controlled stimulation over a long period, there was a flurry of engineering activity. Much technology was borrowed from that of cardiac pacemakers, and Medtronic (Minneapolis, MN) consequently became involved in neurologic devices. In addition, there were several boutique companies that produced primarily or entirely neurostimulators, such as Avery. Once implantable stimulators were available, a search for additional indications also took place.

Because it was necessary to control stimulation parameters, the first implantable stimulators used for spinal cord stimulation had an external control unit that communicated by a coupled radiofrequency signal to an internalized coil attached to the stimulating electrode. That had the additional advantage in that the power source was a battery in the external device, which could be changed indefinitely. The entire implanted portion was passive, so there was no need for an implantable power supply [36]. It was another decade before a fully implantable spinal cord stimulator became available.

There was considerable concern initially about the best location for the implanted electrodes. Initially, it seemed logical to position the electrodes deep to the dura, either subarachnoid or subdural, because it was thought to be necessary to direct the current to the dorsal columns. The electrodes in that position eventually lost their effectiveness, however, as they became surrounded by fibrosis, and the impedance increased significantly [37–39]. This led to an attempt to insert the electrode within a pocket made in the dura, a so-called endodural placement, but that resulted in

similar fibrosis [37]. By that time, it had become apparent that the stimulation need not be directed specifically to the dorsal columns. Current distribution was just as effective if the electrodes were placed epidurally. The design of the original electrodes required that they be sutured in place, so it became the standard to suture the electrode array to the outer surface of the dura [36,39]. With assurance that epidural placement was preferred, it became feasible to design the electrodes so they could be inserted epidurally through a percutaneous needle [40,41].

The initial response when spinal cord stimulators became commercially available was enthusiastic. Any patient with lower body or extremity pain was considered a candidate, including all the patients who had failed low back surgery. Because of that initial enthusiasm, results of spinal cord stimulation became disappointing, as indications became less critical. In some series that employed critical follow-up in the mid-1970s, long-term success was reported in only 30% to 40% of patients [38,42,43]. As selection criteria improved, the results became more favorable by the end of the 1970s [44]. By 1985, it was estimated that more than 10,000 patients had had spinal cord stimulators implanted [45]. Satisfactory results have since been reported in a variety of pain syndromes [46–50]. A survey conducted in 1999 of academic teaching programs indicated that of the 76 programs that responded, 66 trained residents in the use of spinal cord stimulators, although the techniques varied greatly from institution to institution [51].

As spinal cord stimulation became used for various types of pain, it became apparent in the mid-1980s that certain patients with peripheral vascular disease had improvement in their circulation in the lower extremities as well as pain relief [52–54] . In one series, pain relief was obtained in 91% of patients and ulcer healing in 58% of patients [55]. Even with these impressive results in Sweden, the use of spinal cord stimulation never gained a following in the United States, perhaps because of the difference in how and when patients were referred.

This led logically to the use of spinal cord stimulation for angina [56], with equally impressive results, again, in Sweden. There was considerable concern that pain relief might mask protective angina sensation if coronary blood flow remained impaired. Careful physiologic studies, however, demonstrated significant improvement in myocardial perfusion with spinal cord stimulation [57,58], which provided a significant additional benefit. The use of spinal cord stimulation for severe angina is just now becoming used in the United States [59].

Deep brain stimulation for pain

Let us return to the middle of the twentieth century. A series of experiments involved stimulating various structures in the brain of the awake laboratory rat. It had been recognized as early as 1954 that rats responded with such positive reinforcement to stimulation of the septal area that they would neglect food and sex drives to seek septal stimulation [60]. It was demonstrated in 1960 by Heath and Mickle [61] and reported in 1967 by Gol [62] that half of the patients with severe pain subjected to similar stimulation of the septum obtained pain relief, even though they did not experience a compulsion for septal stimulation. This provided the first observations in the human being that pain perception could be modified by stimulating brain areas.

It was just about the time that spinal cord stimulation was introduced that another significant observation was made in the laboratory based on experiments involving brain stimulation in awake rats, which continued throughout the 1970s and early 1980s. Analgesic effects could be observed on stimulation of the ventrobasal complex [63,64]. In addition, supraspinal areas in the brain stem with a descending influence on pain perception were defined, including the periaqueductal gray area and nucleus raphe magnus. These pathways involve endogenous morphine-like transmitters that became identified as endorphins. Microinjection of morphine into the uppermost structures in the system caused a reduction in the response to stimulation of neurons in the pain-perceiving ventrobasal part of the thalamus [65,66]. This effect on the system could be reversed by naloxone [67] and was shown to be dependent on serotonin for descending transmission [68,69]. This experimental model suggested that pain perception in patients might be moderated by stimulation of brain stem areas, particularly the periaqueductal or periventricular gray areas involved in the effects of endorphin [70].

It had already been demonstration in patients that pain perception could be modified by stimulation of the septal area [61,62], but that had been based on experimental observations of stimulation-seeking behavior and not on a pain model. In addition, the gate control theory

suggested that a descending influence might modify pain transmission at spinal levels. The stage was set to attempt stimulation of a brain area that not only had been demonstrated to influence pain perception but involved transmitters uniquely identified with pain.

Richardson and Akil [71,72] were the first to report clinical benefit from deep brain stimulation. The target in the periaqueductal gray area planned from rat experiments produced side effects that made it impossible to stimulate regularly, but stimulation of the adjacent medial thalamus, particularly medial to the nucleus parafascicularis, yielded good relief of chronic pain at parameters that were well tolerated. These observations were soon duplicated and extended by others who popularized the use of such neuroaugmentation, such as Gybels and Cosyns [73], Lazorthes [74], and Hosobuchi et al [75].

I must digress to share a unique double-blind experiment that demonstrated to me the effectiveness of such deep brain stimulation. I visited Richardson in 1978 to learn his technique and targets and to see patients first hand to decide whether to attempt this new procedure. The patient whose surgery I witnessed had severe cancer pain. The electrode was inserted stereotactically, and a test stimulation was applied with a battery-operated screening unit similar to those subsequently used in the operating room to test for spinal cord stimulation. Even though the patient and the surgeon (and the visitor) thought stimulation was being applied, the patient had no pain relief but also reported no sensation even when the voltage was turned to maximum. Richardson retrieved a back-up test stimulator from his locker, returned to the operating room without saying a word, connected it to the electrode leads, and, without the patient knowing, began to raise the voltage slowly. The patient suddenly and excitedly announced, "Hey, my pain is gone!"

A second type of deep brain stimulation for pain was based on a different concept and involved a different type of pain. In 1973, Hosobuchi et al [76] had reported relief of anesthesia dolorosa by deep brain stimulation of the ventroposterior medial (VPM)–ventroposterior lateral (VPL) somatosensory thalamus, essentially inserting facial sensation into the area that had been deprived by peripheral denervation. Hosobuchi [77] continued to use stimulation of the somatosensory thalamus for treatment of various types of denervation pain.

There is a third origin of deep brain stimulation for pain that has historical significance. In 1973, Mazars et al [78] reported the use of intermittent ventrobasal thalamic stimulation for analgesia for treating central and deafferentation pain (although it was suggested that the first patient was actually treated as early as 1961 [79]). The theoretic basis was the hope of activation of a multisynaptic inhibitory pathway to the medial thalamus, but subsequent laboratory investigation failed to elucidate the precise mechanism.

There are several ways one might assign priority for initiation of deep brain stimulation for pain management. The earliest use of deep brain stimulation for pain management may have begun with Heath and Mickle [61] in 1960, based on the drive for experimental self-stimulation of the septum. Mazars et al [78] employed deep brain stimulation in 1961 (but did not report on it until 1973 [79]), based on the concept of inhibition derived from stimulation of the ventrobasal thalamus. Hosobuchi et at [76] used deep brain stimulation in 1973, based on stimulation of somatosensory thalamus for denervation pain. Finally, in 1977, Richardson and Akil [71,72] employed periaqueductal gray stimulation based on laboratory evidence of an endorphin-related descending inhibitory system.

During the late 1970s and through the early 1980s, when the use of deep brain stimulation for pain was evolving, there was also an evolution in pain management in general. It was increasingly recognized that cancer pain and chronic pain of noncancer origin invited different management. Cancer pain was treated more aggressively with narcotics, and ablative procedures continued to develop. Management of chronic pain included more and more those factors that increased disability and made pain worse, with comprehensive rehabilitative-oriented pain programs [11,80].

The concept of evaluation of pain management modalities also became more scientific, which followed the general philosophy about clinical trials in general. Because chronic pain is affected by so many subjective variables, it has been particularly difficult to document the success of any modality.

At the time that deep brain stimulation for pain management was introduced, there were three major companies in the United States manufacturing implantable stimulators that could be used. It was also about that time that the US Food and Drug Administration (FDA) began to require approval for implanted devices, such as deep brain or spinal cord stimulators. Because such implanted

deep brain stimulators were already in clinical use, approval was grandfathered. For approval to continue, however, the manufacturers were required to submit sufficient data to demonstrate efficacy and safety within several years. As I understand from my activity with committees concerned with drugs and devices at that time, the only company that submitted data was one that closed shortly thereafter on the retirement of its founder. One other company changed ownership at about the same time. The protocol to establish efficacy for such a nebulous and difficult-to-define indication as chronic pain would have been difficult and expensive to establish, results would have been uncertain, a less invasive option of spinal cord stimulation was available for most patients, and it is doubtful that the market in a changing environment would have justified the high cost of such an uncertain study. Consequently, the data were not submitted, and the use of deep brain stimulation for pain management was "deapproved" [81]. (It was almost 15 years later that the FDA approved the use of deep brain stimulation for movement disorders, even though the implantable device is essentially the same).

Motor cortex stimulation

There is one final neuroaugmentative procedure for pain that was introduced as recently as 1991 and warrants mention. At that time, Tsubokawa et al [82] introduced motor cortex stimulation for management of central deafferentation pain. Tsubokawa's interest began with laboratory experiments several years earlier in which he characterized abnormal thalamic activity after a central deafferentation lesion and compared it with cortical recordings from patients similarly afflicted [83]. His initial thought was to stimulate the somatosensory cortex to supply the missing sensory input, but he soon realized empirically that stimulation applied to the precentral motor cortex rather than the postcentral gyrus was more effective in alleviating the pain that followed thalamic stroke [82,84]. This observation has been documented by a number of other authors, so that motor cortex stimulation by use of an implanted stimulator has become an accepted procedure not only for central deafferentation pain but for neurogenic pain as well [85].

Neuroaugmentation continues to evolve. As we learn more about pain perception, additional opportunities will present themselves. In 1978, I commented that the engineers can provide us with any stimulation parameters we want. We only have to know where to put the electrode and what to ask for [36]. That situation continues to exist.

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