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# History of Electrical Neuromodulation for Chronic Pain

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**ABSTRACT**

Electrical stimulation of the nervous system has a long history, starting in ancient Rome, progressing through the 19th century, and being applied with scientific intention since the beginning of the 20th century. In the middle of the last century, observations were made in the laboratory that stimulation of the septal area would result in profound analgesia, which led to similar stimulation being applied in patients with cancer pain. With the introduction of the Melzack-Wall gate theory, it became apparent that stimulation of the large somatosensory fibers in peripheral nerve and spinal cord might "close the gate" and inhibit chronic pain. In 1967, Wall and Sweet initiated therapeutic stimulation of peripheral nerve, and Shealy and Mortimer introduced spinal cord stimulation for chronic pain management. In 1973, Hosobuchi introduced somatosensory thalamus stimulation for treatment of denervation, and 4 years later, Richardson and Akil reported the use of periventricular stimulation for somatic pain. Along with advances in stimulation, improved patient selection has indicated both spinal and brain electrical neuromodulation for a variety of clinical types of chronic pain.

*Key Words*. Functional Neurosurgery; History; Chronic Pain; Pain; Deep Brain Stimulation; Spinal Cord Stimulation; Peripheral Vascular Disease; Angina

## Introduction

Before we begin, it would be helpful to define several terms. "Neuromodulation," as used herein, concerns electrical stimulation of the nervous system for the purpose of modulating or modifying a function, such as the perception of pain. It will not include other ways of modulating neural function such as pharmacological agents or interruption of pathways.

"Chronic pain," as used herein, is pain that lasts a long time, regardless of the etiology, and includes cancer pain as well as pain of noncancer origin (although I prefer the term "persistent pain" when both are included). It must be recognized that the physiology of each of those two types of pain is different (as is the physiology of acute pain) in that cancer pain ordinarily involves noxious stimulation of tissues or involvement of nerves, whereas chronic pain may involve pathology of particularly nerve tissue or most commonly muscle, or may not involve any identifiable tissue pathology at all. Such chronic pain is a perception rather than a sensation *per se*, but may be attenuated by the neuromodulation techniques discussed below.

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## History (see Table 1)

The dramatic effects of stimulation of the body or nervous system have long been recognized, and the use of neuromodulation has grown from those observations. Indeed, the first recorded use of neuromodulation for the treatment of pain occurred in about 15 AD, when Scribonius, after observing that gout pain had been relieved by the accidental contact with a torpedo fish, recommended torpedo fish treatment for pain in general [1]. Benjamin Franklin was an early

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**Table 1** A Timeline of Electrical Stimulation

| | | | |
|---|---|---|---|
| 15 AD | Scribonius | Torpedo fish shock used for pain treatment | [1] |
| 1774 | Benjamin Franklin | Electrical shock causes muscle contraction | [2] |
| 1780 | Galvani | Electrical contraction of frog muscle | [3] |
| 1816 | Mary Shelly | "Frankenstein" animated by electricity in novel | [4] |
| 1870 | Fritsch and Hitzig | Muscle contraction on stimulating dog motor cortex | [5] |
| 1874 | Bartholow | Muscle contraction on stimulating human motor cortex | [6] |
| 1884 | Horsley | Stimulation of encephalocele—eye movement | [7] |
| 1886 | Horsley | Motor cortex stimulation in epilepsy surgery | [7] |
| 1902 | | Electreat skin stimulation for pain and illness | |
| 1908 | Horsley and Clarke | Introduction of stereotaxis, including lab stimulation | [8] |
| 1947 | Hess and Hassler | Chronic animal stimulation | [11] |
| 1948 | Pool | Stimulation of frontal tracts for psychiatric surgery | [18] |
| 1953 | Heath | Behavior changes on deep brain stimulation | [19] |
| 1954 | Olds and Milner | Septal stimulus seeking behavior in rats | [20] |
| 1954 | Heath | Septal stimulation for pain relief | [21] |
| 1960 | Hassler and Riechert | Motor effects on brain stem stimulation in OR | [11] |
| 1964 | Spiegel and Wycis | Oculomotor localization in campotomy | [13] |
| 1965 | Alberts et al. | EEG changes on subcortical stimulation | [15] |
| 1965 | Melzack and Wall | Gate theory introduced | [24] |
| 1967 | Wall and Sweet | Analgesia on stimulation of infraorbital nerves | [26] |
| 1967 | Shealy and Mortimer | Implantable spinal cord stimulator | [28] |
| 1967 | Gol | Chronic septal stimulation for pain relief | [22] |
| 1968 | Sweet and Wepsic | Implantable peripheral nerve stimulator | [27] |
| 1968 | Medtronic | Commercial implantable stimulator | |
| 1969 | Reynolds | Analgesia on periventricular stimulation in rats | [34] |
| 1971 | Gildenberg | Spinal cord stimulation for torticollis | [29] |
| 1972 | Bechtereva | Chronic basal ganglia stimulation for Parkinson's | [23] |
| 1973 | Hosobuchi | Somatosensory thalamic stim for denervation pain | [33] |
| 1976 | Cook and Dooley | Spinal cord stimulation improvements spasticity | [30,31] |
| 1976 | Dooley | Spinal cord stimulation improves blood flow | [32] |
| 1977 | Richardson and Akil | Periventricular stimulation for pain relief | [35,36] |
| 1982 | Tasker et al. | Atlas of thalamic stimulation | [16] |
| 1985 | Augustinsson et al. | Spinal cord stimulation for peripheral vascular disease | [40] |
| 1987 | Murphy and Giles | Spinal cord stimulation for angina | [41] |
| 1996 | Hautvast et al. | Increased coronary flow on spinal cord stimulation | [42] |
| 1991 | Tsubokawa et al. | Motor cortex stimulation for pain relief | [48] |

EEG = electroencephalographic; OR = operating room.

investigator of the effect of the muscle contraction that followed electrical shock as early as 1774 [2], several years before Galvani demonstrated electrical contraction of frog muscle in 1780 [3]. Perhaps the most famous theoretical physiological use of electricity was written by Mary Shelly [4] in 1816, in her novel *Frankenstein*, which was based on scientific speculation previously published by Dr. Erasmus Darwin, Charles' grandfather.

In 1870, Fritsch and Hitzig [5] demonstrated that limb movement occurred on stimulating the motor cortex of the dog, proving the excitability of the cerebrum. Several years later, in 1874, the first documentation of electrical stimulation of the brain of an awake human was performed by Bartholow [6,7]. The patient had osteomyelitis of an area of the scalp, and the brain was exposed during debridement. Fortunately, the motor cortex was exposed, and muscle contraction was noted on faradic stimulation but not on mechanical stimulation.

The first practical use of intraoperative electrical stimulation was performed by Sir Victor Horsley, who applied stimulation of tissue within an occipital encephalocele and noted conjugate eye movements in 1884. Two years later, he used stimulation to identify the thumb cortical area for local resection in a patient with focal epilepsy [8].

The first electrical stimulator designed specifically for treatment was the Electreat, which appeared at the beginning of the 20th century. It was advertised to relieve not only pain, but every imaginable physical malady. It was battery operated and had an uncanny resemblance to later transcutaneous electrical nerve stimulation (TENS) units.

When animal stereotaxic techniques were introduced in 1908 by Horsley and Clarke [9], they simultaneously introduced stereotactically localized stimulation of deep brain structures. This was applied to humans from the first stereotactic* procedure reported in 1947 by Spiegel and

Wycis [10], and has been part of almost every functional stereotactic operation since. Although they made the pallidal and medial thalamic lesions by alcohol injection in the hope of sparing fibers *en passage*, they first stimulated to be sure that the tip of the needle was not in the internal capsule. (*The original term "stereotaxic" has been retained for use in animal experiments, but in 1973 the spelling convention for human procedures was changed to "stereotactic" [11].) Although electrical stimulation was used extensively for localization in stereotactic surgery, it is poorly documented in the literature from 1947 through the next two decades, when the custom was to visit other neurosurgeons in the operating room to learn their techniques, and the publications discussed mainly indications and results.

Hassler [12] was instrumental in suggesting that observations made on stimulation in the operating room might have some long-term implications. He had been a graduate student of Rudolph Hess in Switzerland during the late 1940s, where chronic stimulation was routinely administered via permanently implanted electrodes to awake cats. They recognized that although stimulation might produce reversible effects that were essentially the same as lesion production at the same site, changing the stimulation frequency might produce enhancement rather than inhibition.

The effects of high (inhibitory) vs low (facilitatory) stimulation frequency were not fully appreciated at that time, either in the laboratory or in the operating room. Those terms were not universally defined. Low frequency might be between 6 and 60 Hz, whereas high frequency might be between 50 and 100 Hz. There was considerable reluctance, especially in Europe, to stimulate above 50 Hz, since Riechert [13] had reported provoking a seizure in a patient by stimulating at that frequency, but others did not report such kindling.

Intraoperative stimulation became critical for electrode localization prior to lesion production. For instance, Spiegel et al. [14] made lesions in Forel's field for treatment of Parkinson's disease. They stimulated at successively deeper levels, until lateral deviation of one eye indicated that the electrode had entered the emerging oculomotor fibers. The electrode was withdrawn 2 mm and a lesion was made.

Stereotactic lesions were commonly used to treat epilepsy during the 1950s and 1960s [15], since it was recognized that a change in electroencephalogram or electrocorticogram was seen during stimulation of subcortical structures such as the thalamus or globus pallidus [16].

Tasker [17] performed an extensive stimulation study of the computerized map of the human thalamus, which he published as an atlas in 1982. He had previously worked as a graduate student with Clinton Woolsey, who had used essentially the same technique (although not computerized) to map the cortex and subcortex of animals, from 1961 to 1963 [18].

The use of stimulation as a therapeutic modality came about slowly, because during the first two decades of stereotactic surgery, there was no way to stimulate for long periods of time. Several authors inserted electrodes that had external connectors, so that stimulation might be provided but only intermittently. Perhaps the earliest was Pool [19], who stimulated frontal tracts rather than performing prefrontal lobotomy for psychosurgery as early as 1948. Heath [20] had an extensive long-term program starting in the early 1950s wherein he stimulated a variety of subcortical areas and made detailed behavioral observations.

In 1954, Olds and Milner [21] observed that rats would vigorously seek stimulation of the septal area, presumably because it provided them with great pleasure. That same year, Heath [22] theorized that, as pleasure is the opposite of pain, septal stimulation might provide pain relief. He stimulated the septum for intervals of 15 minutes daily to weekly and was able to successfully alleviate cancer pain in one patient. A decade later when better stimulators were available, Gol [23] made similar observations in several cancer patients. Shortly after, reported in 1972, Bechtereva [24] in Russia reported what may have been the first therapeutic use of stimulation in motor disorders. She provided the patient with intermittent pallidal or thalamic stimulation during outpatient visits, as implantable stimulators were not available.

In the meantime, significant advances had been made in the understanding of pain perception. The concept that provided the impetus for introducing neuromodulation for pain treatment was the introduction of Melzack and Wall's [25] landmark theory in 1965. They proposed that pain perception involves a gate that can be opened or closed depending on the balance between firing of small and large neural fibers. If large touch fibers were stimulated ("If you rub it, it feels better"), the gate would close and pain would lessen. Touch sensation transmitted by large nerves could also be simulated by applying gentle electrical stimulation to electrodes taped to the skin [26] (Electreat was

reinvented!!!) so-called transcutaneous stimulation, later called TENS (which is a misnomer).

If stimulation were gradually increased, at first a nonpainful sensation was felt (the large fibers), and later the stimulation became painful at a higher voltage (the small fibers, which have a higher threshold). Thus, the patient could control the gate by adjusting the voltage to a level where sensation but not pain was felt and provide pain relief. This concept was tested in 1967 by Wall and Sweet [27], who stimulated their own infraorbital nerves. Sweet recruited Roger Avery, an engineering colleague at Massachusettes Institute of Technology, to make an implantable stimulator, which he and Wepsic [28] used to treat chronic pain by peripheral nerve stimulation, and the field of neuromodulation for pain management was born.

At about the same time in 1967, Norman Shealy [29] at Western Reserve Medical School (later Case Western Reserve) had the idea to stimulate the large nerve fibers where they were uniquely gathered in the dorsal columns of the spinal cord. He theorized that the impulse would travel retrograde down the spinal cord to those levels at which pain sensation was entering and the gate in the dorsal root entry zone would be closed to alleviate pain. He recruited Thomas Mortimer, a graduate engineering student, to design an implantable stimulator. The first model required an external power supply connected by needles passed through the skin. Coincidentally, Mortimer had interviewed for a job at Medtronic 2 years before and contacted Norm Hagfors, one of their engineers whom he had met, to see if their cardiovascular stimulator might be adopted for dorsal column stimulation. Mortimer designed an implantable electrode that Shealy used with the Medtronic stimulator, which provided cancer pain relief for the last several months of the first patient's life.

Shealy contacted Medtronic again to improve the system. Medtronic had previously manufactured stimulators that were used for cardiovascular indications. In 1963, they produced the Barostat, which was used to stimulate the carotid sinus for the treatment of hypertension. In 1965, they had released the Angiostat, which stimulated the carotid sinus nerve for treatment of angina. The first spinal cord stimulators were modifications of those devices, with platinum electrodes originally made by Mortimer at Case Institute of Technology. Shealy's second patient used this stimulator and had relief of chronic pain for 4 years. It became commercially available through Medtronic in 1968.

The early stimulators came in two parts. The implantable portion was passive and consisted of an electrode connected to a circular wound antenna implanted subcutaneously. The external part had a battery-operated power supply and control box connected to a similar external antenna taped on the skin overlying the internal antenna. By 1981, battery technology had improved to the point where Medtronic was able to provide a fully implantable spinal cord stimulator. Avery had kept pace with Medtronic during that time, but when Roger Avery retired, that company no longer provided stimulators. A third company, Neuromed, introduced similar stimulators and continues under a different name.

In 1971, I was working at the Cleveland Clinic just down the street from where Shealy and Mortimer had introduced spinal cord stimulation, and I had used spinal cord stimulation to treat pain. I was able to obtain stimulators modified to provide frequencies of 800–1200 Hz, which were useful for the treatment of spasmodic torticollis, the first use of implanted stimulators for a motor disorder [30].

Although spinal cord stimulation was used primarily for pain, in 1976, both Cook [31] and Dooley [32] recognized improvement in spasticity in patients with multiple sclerosis who had stimulators implanted for pain of muscle spasm. In addition, Dooley [33] recognized an increase in blood flow to the extremities of patients undergoing spinal cord stimulation for pain management, an observation that was to become significant two decades later.

In 1973, shortly after the introduction of spinal cord stimulation, Hosobuchi [34] reported the successful use of chronic stimulation of the somatosensory thalamus for the treatment of denervation facial pain, anesthesia dolorosa, and the field of deep brain stimulation (DBS) was born.

It had been observed in 1969 by Reynolds [35] that stimulation of the periventricular area of rats would produce sufficiently profound analgesia that they could undergo surgery with no apparent pain. Similar stimulation was provided to patients with chronic pain by Richardson and Akil [36,37] in 1977 (Richardson had earlier worked with Heath [20] and was familiar with chronic stimulation techniques). The following year, they documented that the area was related to endorphin release [38].

Neuromodulation was being used so extensively that a symposium on safety and efficacy, sponsored by the Food and Drug Administration (FDA), was

held in 1977 [39]. The uses of stimulators for pain, movement disorders, epilepsy, cerebral palsy, and bladder control were presented. The consensus was that the use of neuromodulation for pain had been documented to be both safe and effective, but not so for the other indications [40].

It was at that time that the FDA was given the charge to regulate devices as well as drugs. They felt that the use of DBS for both motor disorders and pain management had not been sufficiently documented, and provided the three companies that made DBS systems several years to conduct studies to document their benefit. Because of the concern about conduct of such a study, the only company that provided data about pain management was Avery, but as Roger Avery retired in 1983 at just about that time and the other two companies had not complied, DBS for pain management was de-approved, as it remains today, although the recent surge in DBS activity has brought renewed interest in that field.

It was observed by Augustinsson [41] in 1985 that patients who had spinal cord stimulation for pain of peripheral vascular disease not only had pain relief but often had improvement in circulation and improvement in signs of ischemia, an observation that harkened back to Dooley's [33] earlier report. In 1987, Murphy [42] reported similar pain relief in angina. There was, however, the concern that relief of pain might make it possible for the patient to exert beyond the myocardial circulatory capacity and increase the risk of coronary artery disease. In 1996, Hautvast [43] documented that myocardial perfusion increased with spinal cord stimulation, which consequently provided considerable protection against ischemia.

Spinal cord stimulation has continued to provide a multitude of selected patients with significant relief of chronic pain. Although there have been many efforts to improve results through modification of stimulation parameters [44–47], the key to success of electrical neuromodulation, as any other pain management modality, seems to lie in patient selection [48].

In 1991, Tsubokawa [49] reported that stimulation of the motor cortex (but curiously not the sensory cortex) alleviated pain, particularly central pain. In 1995, Migita [50] used extracranial magnetic stimulation of the motor cortex to achieve that same benefit.

During the past 5 years, there has been an increasing use of DBS for motor disorders, such as dystonia or Parkinson's disease [51]. This renewed activity has precipitated renewed interest in the use of brain stimulation, with permanently deep implanted electrodes [52], and it is anticipated that DBS for management of chronic pain will again be an approved technique.

#### References


1 Stillings D. The first use of electricity for pain treatment. Medtronic Archive on Electro-Stimulation 1971.
2 Isaacson W. Benjamin Franklin: An American Life. New York: Simon & Schuster; 2003.
3 Pruel MC. A history of neuroscience from Galen to Gall. In: Greenblatt SH, Dagitf TF, Epstein MH, eds. A History of Neurosurgery. Park Ridge, IL: American Association of Neurological Surgeons; 1997:99–130.
4 Shelly M. Frankenstein. Oxford: Oxford Press; 1818.
5 Fritsch G, Hitzig E. Über die elektrische Erregbarkeit des Grosshirns. Arch Anat Physiol Wiss Med 1870;37:300–32.
6 Bartholow R. Experimental investigations into the functions of the human brain. Am J Med Sci 1874;305–13.
7 Morgan JP. The first reported case of electrical stimulation of the human brain. J Hist Med Allied Sci 1982;37:51–64.
8 Vilensky JA, Gilman S. Horsley was the first to use electrical stimulation of the human cerebral cortex intraoperatively. Surg Neurol 2002;58:425–6.
9 Horsley V, Clarke RH. The structure and functions of the cerebellum examined by a new method. Brain 1908;31:45–124.
10 Spiegel EA, Wycis HT, Marks M, Lee AS. Stereotaxic apparatus for operations on the human brain. Science 1947;106:349–50.
11 Gildenberg PL. "Stereotaxic" versus "stereotactic." Neurosurgery 1993;32:965–6.
12 Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. Brain 1960;83:337–50.
13 Riechert T. Stereotactic Brain Operations. Methods, Clinical Aspects, Indications. Bern, Stuttgart, Vienna: Hans Huber; 1980.
14 Spiegel EA, Wycis HT, Szekely EG, et al. Stimulation of Forel's field during stereotaxic operations in the human brain. Electroencephalogr Clin Neurophysiol 1964;16:537–48.
15 Crandall PH, Brown WJ, Brinza K. Stereotaxic accuracy in vivo of Talairach method in temporal lobes. Confin Neurol 1966;27:149–53.
16 Alberts WW, Feinstein B, Levin G, et al. Stereotaxic surgery for parkinsonism. Clinical results and stimulation thresholds. J Neurosurg 1965;23:174–83.

17 Tasker RR, Organ LW, Hawrylshyn PA. The Thalamus and Midbrain of Man. A Physiological Atlas Using Electrical Stimulation. Springfield, IL: Chas C Thomas; 1982.
18 Woolsey CN. Cortical localization as defined by evoked potential and electrical stimulation studies. In: Schaltenbrand G, Woolsey CN, eds. Cerebral Localization and Organization. Madison, WI: University of Wisconsin Press; 1964:17–26.
19 Pool JL. Psychosurgery in older people. J Am Geriatr Soc 1954;2:456–65.
20 Heath RG. Exploring the Mind–Brain Relationship. Baton Rouge, LA: Moran Printing, Inc.; 1996.
21 Olds J, Milner P. Positive reinforcement produced by electrical stimulation of the septal area and other regions of the rat brain. J Comp Physiol Psychol 1954;47:419–27.
22 Heath RG. Psychiatry. Annu Rev Med 1954;5:223–36.
23 Gol A. Relief of pain by electrical stimulation of the septal area. J Neurol Sci 1967;5:115–20.
24 Bechtereva NP, Bondarchuk AN, Smirnov VM. Therapeutic electrostimulations of the deep brain structures. Vopr Neirokhir 1972;1:7–12.
25 Melzack R, Wall PD. Pain mechanisms: A new theory. Science 1965;150:971–9.
26 Laitinen L. Placement of electrodes in transcutaneous stimulation for chronic pain. Neurochirurgie 1976;22:517–26.
27 Wall PD, Sweet WH. Temporary abolition of pain in man. Science 1967;155:108–9.
28 Sweet WH, Wepsic JG. Treatment of chronic pain by stimulation of fibers of primary afferent neuron. Trans Am Neurol Assoc 1968;93:103–7.
29 Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns. Preliminary clinical report. Anesth Analg (Cleve) 1967;46:489–91.
30 Gildenberg PL. Treatment of spasmodic torticollis with dorsal column stimulation. Acta Neurochir Suppl (Wien) 1977;24:65–6.
31 Cook AW. Electrical stimulation in multiple sclerosis. Hosp Pract 1976;11:51–8.
32 Dooley DM. Spinal cord stimulation. AORN J 1976;23:1209–12.
33 Dooley DM, Kasprak M. Modification of blood flow to the extremities by electrical stimulation of the nervous system. South Med J 1976;69:1309–11.
34 Hosobuchi Y, Adams JE, Rutkins B. Chronic thalamic stimulation for the control of facial anesthesia dolorosas. Arch Neurol 1973;29:158–61.
35 Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 1969;164:444–5.
36 Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. J Neurosurg 1977;47:178–83.
37 Richardson DE, Akil H. Long term results of periventricular gray self-stimulation. Neurosurgery 1977;1:199–202.
38 Akil H, Richardson DE, Hughes J, Barchas JD. Enkephalin-like material elevated in ventricular cerebrospinal fluid of pain patients after analgetic focal stimulation. Science 1978;201:463–5.
39 Gildenberg PL. Symposium on the safety and clinical efficacy of implanted neuroaugmentive devices. Appl Neurophysiol 1977;40:69–240.
40 Gildenberg PL. Neurosurgical statement on neuroaugmentive devices. Appl Neurophysiol 1977;40:69–71.
41 Augustinsson LE, Carlsson CA, Holm J, Jivegard L. Epidural electrical stimulation in severe limb ischemia. Pain relief, increased blood flow, and a possible limb-saving effect. Ann Surg 1985;202:104–10.
42 Murphy DF, Giles KE. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain 1987;28:365–8.
43 Hautvast RW, Blanksma PK, DeJongste MJ, et al. Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. Am J Cardiol 1996;77:462–7.
44 Tulgar M, Barolat G, Ketcik B. Analysis of parameters for epidural spinal cord stimulation. 1. Perception and tolerance thresholds resulting from 1,100 combinations. Stereotact Funct Neurosurg 1993;61:129–39.
45 Tulgar M, Barolat G, Ketcik B. Analysis of parameters for epidural spinal cord stimulation. 2. Usage ranges resulting from 3,000 combinations. Stereotact Funct Neurosurg 1993;61:140–5.
46 Tulgar M, He J, Barolat G, et al. Analysis of parameters for epidural spinal cord stimulation. 3. Topographical distribution of paresthesiae—A preliminary analysis of 266 combinations with contacts implanted in the midcervical and midthoracic vertebral levels. Stereotact Funct Neurosurg 1993;61:146–55.
47 Law JD. Spinal stimulation: statistical superiority of monophasic stimulation of narrowly separated, longitudinal bipoles having rostral cathodes. Appl Neurophysiol 1983;46:129–37.
48 Gildenberg PL. General principles and selection of techniques in the management of pain of benign origin. In: Gildenberg PL, Tasker RR, eds. Textbook of Stereotactic and Functional Neurosurgery. New York: McGraw-Hill; 1998:1321–36.
49 Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 1991;52:137–9.
50 Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex

in patients with central pain. Neurosurgery 1995;36:1037–9.
51 Lozano A. Deep brain stimulation: challenges to integrating stimulation technology with human neurobiology, neuroplasticity, and neural repair. J Rehabil Res Dev 2001;38:x–xix.
52 Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: A meta-analysis. J Clin Neurosci 2005;12:515–9.