Deep brain stimulation for the treatment of various chronic pain syndromes

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Object. Electrical intracerebral stimulation (also referred to as deep brain stimulation [DBS]) is a tool for the treatment of chronic pain states that do not respond to less invasive or conservative treatment options. Careful patient selection, accurate target localization, and identification with intraoperative neurophysiological techniques and blinded test evaluation are the key requirements for success and good long-term results. The authors present their experience with DBS for the treatment of various chronic pain syndromes.

Methods. In this study 56 patients with different forms of neuropathic and mixed nociceptive/neuropathic pain syndromes were treated with DBS according to a rigorous protocol. The postoperative follow-up duration ranged from 1 to 8 years, with a mean of 3.5 years. Electrodes were implanted in the somatosensory thalamus and the periventricular gray region. Before implantation of the stimulation device, a double-blinded evaluation was carefully performed to test the effect of each electrode on its own as well as combined stimulation with different parameter settings.

The best long-term results were attained in patients with chronic low-back and leg pain, for example, in so-called failed-back surgery syndrome. Patients with neuropathic pain of peripheral origin (such as complex regional pain syndrome Type II) also responded well to DBS. Disappointing results were documented in patients with central pain syndromes, such as pain due to spinal cord injury and poststroke pain. Possible reasons for the therapeutic failures are discussed; these include central reorganization and neuroplastic changes of the pain-transmitting pathways and pain modulation centers after brain and spinal cord lesions.

Conclusions. The authors found that, in carefully selected patients with chronic pain syndromes, DBS can be helpful and can add to the quality of life.

KEY WORDS • chronic pain • deep brain stimulation • neuromodulation •
periventricular gray region • somatosensory cortex • thalamus

THE treatment of chronic pain syndromes includes pharmacological, physiotherapeutic, and invasive methods and techniques. One of the invasive methods is the stimulation of deep brain areas like the thalamus or the periventricular region with implanted electrodes. Because of its invasiveness and the risks associated with DBS, it is restricted to a selected group of patients in whom conservative treatment of chronic pain syndromes has been ineffective. The technique of DBS has been used since the 1950s, and experience regarding the indications and long-term results has been gained at different centers worldwide. To date more than 450 cases have been reported in the literature, and long-term results with a follow-up period of more than 15 years have also been documented.^{6,8,10,23,24,40,43,56}

In this series we demonstrate our results in 56 patients

with different chronic pain syndromes. A review of the current literature is included in the *Discussion*. The patients in this series underwent a rigorous selection and testing protocol, including a double-blinded evaluation during the testing trial, and an intensity-dependent test stimulation. The results are presented in relation to clinical diagnoses.

Clinical Material and Methods

Patient Selection

Fifty-six patients were enrolled in the study between 1991 and 2001. Almost all (54) suffered from neuropathic or mixed nociceptive/neuropathic pain; only two patients suffered from mainly nociceptive pain (Table 1). The study protocol was approved by the ethics committee of the medical faculty of the University of Heidelberg. The protocol was in compliance with the Helsinki declarations of human rights and the data protection laws. All patients were informed about and consented to the DBS procedure.

Patients were considered for DBS after pharmacological and other conservative treatment regimens had failed.

Abbreviations used in this paper: CRPS II = complex regional pain syndrome Type II; DBS = deep brain stimulation; FBSS = failed-back surgery syndrome; IPG = implantable pulse generator; PAG = periaqueductal gray region; PVG = periventricular gray region; SCS = spinal cord stimulation; VAS = visual analog scale; VPL = ventral posterior lateral nucleus; VPM = ventral posterior medial nucleus.

TABLE 1

Overview of data in 56 patients in whom an IPG was placed for refractory pain*

Pain Syndrome	No. of Patients	Mean FU (yrs)	No. w/ IPG
FBSS	13	3.5	11
CRPS II	6	4.9	4
dysesthesia dolorosa	6	3.0	5
phantom-limb pain	4	2.8	3
central pain			
spinal cord injury	12	3.5	5
poststroke	11	1 + 2.5†	2
postherpetic neuralgia	2	5.5	1
nociceptive pain	2	1	1

* .FU = follow-up.

† Only known in two patients; see Table 7.

This explains the low number considered for DBS, despite the fact that more than 2500 patients with chronic pain were seen in our pain clinic during the same time. The 56 patients included in this study were referred from other pain specialists or pain clinics. All patients were treated with nonopioid, opiate, tricyclic antidepressant, and/or anticonvulsant medications in sufficient doses over a long enough time for improvement to occur (at least 3 months for the different substances once they reached sufficient levels after a titrating phase).

Most patients with neuropathic pain of peripheral origin had previously been treated with transcutaneous electrical nerve stimulation or SCS, which either failed or were insufficient due to high stimulation intensities. All patients underwent a psychological interview conducted by an experienced neuropsychologist and most (after 1996) were screened using the questionnaire of the German chapter of the International Association for the Study of Pain, including a VAS,⁴⁷ a verbal rating scale, the pain disability index,⁵² the Short Form-36 Health Survey,⁵⁷ a modified Minnesota Multiphasic Personality Inventory,³⁵ a pain experience measure,¹⁴ the Beck Depression Inventory,⁵ and other measures, including a pain diary. A finding of depression was considered to be a consequence of the chronic pain state and not a contraindication for implanting electrodes.¹³

Surgical Technique

Each patient underwent implantation of two leads (PVG and lateral somatosensory thalamus [VPL or VPM]). Lead implantation was performed after induction of local anesthesia with intravenous analgesedation (remifentanyl and propofol) during frame placement. This analgesedation was stopped during the imaging procedure. A stereotactic frame (Leksell Stereotactic System; Elekta AB, and Zamorano-Dujovny localizing unit; Fischer-Leibinger GmbH) was aligned parallel to the orbitomeatal line to be as parallel as possible to the intercommissural line. Target localization was performed using magnetic resonance imaging only (sagittal T₁-weighted images to determine the midline, demonstrating the anterior and posterior commissures; and a three-dimensional T₁-weighted sequence for target localization).

The coordinates for the lateral somatosensory thalamus were as follows: Y = 3 to 5 mm anterior to the posterior

FIG. 1. Intraoperative microelectrode recording showing neuronal activity in the VPL in a 62-year-old woman with chronic pain due to a conus syndrome.

commissure; Z = 0 to -2 mm below the intercommissural line; and X = 10 to 12 mm lateral to the midline for facial pain, 12 to 15 mm for pain in the upper extremity, and 15 to 18 mm for pain in the lower extremity (corrections had to be made according to the width of the third ventricle).

The coordinates for PVG were as follows: Y = 2 to 3 mm anterior to the posterior commissure; Z = 2 mm above to 2 mm below the intercommissural line; and X = 2 mm lateral to the wall of the third ventricle.

A 14-mm precoronal bur hole was created 2 cm lateral to the midline to affix either the bur hole cap provided by Medtronic or the one provided by Image Guided Neurologics. Both leads for long-term stimulation (model 3387; Medtronic, Inc.) were placed through the same bur hole.

Target refinement was performed using intraoperative microelectrode recordings (Figs. 1 and 2) as well as micro- and macrostimulation. Intraoperative microrecordings were performed for many years with custom-made bipolar concentric tungsten electrodes, and in recent times with commercially available microelectrodes with diameters of 0.5 and 0.9 mm (inomed Medizintechnik GmbH). Several recording systems and kinds of software were used over the years (most recently Leadpoint; Medtronic, Inc.).

FIG. 2. Intraoperative microelectrode recording showing neuronal activity in the VPL of a 58-year-old man with chronic pain due to paraplegia after spinal cord injury.

Stimulation in the PVG created a feeling of warmth, floating, and dizziness at the threshold stimulation with frequencies of 50 Hz and a pulse width of 210 μ sec. At higher intensities, anxiety or even panic was reported by the patients. Below the intercommissural line, diplopia, gaze deviation, or gaze paralysis could be elicited. More posteriorly, paresthesias in the contralateral body without somatotopy were reported occasionally; these were most likely caused by the spread of current to the medial lemniscus. A reproducible elevation of blood pressure and heart rate at threshold stimulation in the PVG was helpful for intraoperative target localization.⁶¹ Interestingly, these effects faded with long-term stimulation. In some cases, pain could be evoked by stimulation, and it was similar to the patients' original pain; however, this occurred more often in the lateral thalamus.

Stimulation of the lateral, somatosensory thalamus elicited paresthesias in different body areas according to the laterality of the implanted lead. Especially in patients with large areas of deafferentation (that is, paraplegia), cells in the representation of the anesthetic body part had no receptive fields.²⁸ In other patients, a distortion of the receptive and projection fields (that is, face instead of the amputated arm 16 mm lateral) was found as described by Lenz et al.²⁵

Suprathreshold stimulation was reported to be painful by the patients, especially in those with thalamic pain. In one of our patients with phantom-limb pain, just placing the macroelectrode lead caused immense pain in the phantom. Dystonic movements of the extremities were caused by the spread of high-intensity stimulation to the internal capsule.

After placing the leads into the intended targets, both wires were connected to external extension leads for consecutive testing. To minimize the risk of infection, these extension wires were externalized in the temporal area in front of the ear, away from the planned placement of the permanent extensions.

Postoperative Testing Trial

Patients underwent a test trial period for approximately 7 days while receiving antibiotic treatment. Double-blinded test stimulation was performed. Both leads were tested separately and in combination after the optimal electrode contacts were determined by single-lead testing. After determination of the threshold for experiencing any stimulation-induced effects (paresthesias in somatosensory thalamus; floating, dizziness, and/or panic in PVG), testing was conducted with subthreshold stimulation (0.5–1 V below threshold), half of the intensity of subthreshold stimulation, and placebo stimulation (intensity set to zero). The patient as well as the evaluating physician and the nurse who recorded the VAS score was unaware of the stimulator settings. At least a 50% pain reduction, documented with the VAS, was mandatory for the decision to proceed with permanent implantation (internalization) of the IPG. There also had to be a marked decrease in the use of pain medication and an increase in activities of daily living. No narcotic use was allowed during the test trial. In some cases a preoperative opioid withdrawal had to be completed. Nonsteroidal antiinflammatory drugs, tricyclic antidepressants, and clonidine (especially after withdraw-

TABLE 2
Results of combined stimulation for the treatment of FBSS in 13 patients*

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	48, M	VPL/PVG	PVG	5	75–100
2	66, M	VPL/PVG	NA	NA	0
3	61, M	VPL/PVG	VPL/PVG	0.5	0
4	48, F	VPL/PVG	VPL	3	75–100
5	67, F	VPL/PVG	PVG	6	25–50
6	67, M	VPL/PVG	VPL/PVG	4	75–100
7	44, M	VPL/PVG	VPL/PVG	4	50–75
8	58, M	VPL/PVG	NA	NA	0
9	36, M	VPL/PVG	VPL/PVG	2	50–75
10	72, F	VPL/PVG	VPL/PVG	2	50–75
11	42, F	VPL/PVG	VPL/PVG	2	50–75
12	71, M	VPL/PVG	VPL/PVG	2	50–75
13†	37, F	VPL/PVG	PVG	8	75–100

* The mean follow-up duration was 3.5 years. Pain relief is described as reduction of subjective pain intensity measured according to the VAS. Abbreviation: NA = not applicable.

† Radicular pain was treated with SCS.

al of narcotics) were tolerated during the testing. Finally, the decision to remove one lead or both, or the internalization of the system, was discussed with the patient and his or her relatives.

Internalization of the extension and the stimulating device (one or two Itrel 2 or 3 IPGs [Medtronic, Inc.] for single or dual stimulation; the two-channel Synergy IPG cannot be used due to the different frequency settings) was performed after a magnetic resonance image confirmed correct electrode positioning.

Results

The data in our 56 patients are presented with respect to different pain origins (Table 1). These groups are discussed in detail in the following sections.

Failed-Back Surgery Syndrome

The best long-term results were seen in patients with FBSS (Table 2). This term describes chronic low-back and also radicular pain of the lower extremities after one or more operations in the lumbar spine—for example, herniated vertebral disc, lumbar stenosis, spondylolisthesis, and spondylolysis. Despite the availability of numerous other options, such as SCS and intrathecal opioids, DBS was performed in patients with combined low-back and radicular pain. In our experience, SCS only relieves the radicular component of the patients' pain, whereas intrathecal opioids are better for relief of the low-back component. Considering the long-term side effects of intrathecal opioids, we believe that DBS is an alternative treatment option for patients who do not respond to other conservative or less invasive procedures. Whereas PVG stimulation is recommended for low-back pain, VPL stimulation improves mainly the radicular neuropathic pain component. The favorable results in this patient group have been confirmed by other authors.⁵⁸

Neuropathic Pain of Peripheral Origin

Patients with peripheral neuropathic pain (also known

TABLE 3

*Results of combined stimulation for the treatment of CRPS II in six patients**

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	51, M	VPL/PVG	NA	NA	0
2	50, F	VPL/PVG	VPL/PVG	4	75–100
3	59, M	VPL/PVG	VPL/PVG	2	50–75
4	35, M	VPL/PVG	VPL/PVG	8	75–100
5	41, F	VPL/PVG	NA	NA	0
6	53, M	VPL/PVG	VPL/PVG	5.5	50–75

* The mean follow-up duration was 4.9 years. For definition of pain relief, see Table 2.

as CRPS II) responded very well to DBS. In treating this condition, one usually has to deal with a rather circumscribed area of pain. Most of our patients were treated first with SCS but suffered complications or needed very high current intensities, which made IPG replacements necessary after very short intervals (Table 3).

Dysesthesia Dolorosa

Another fairly good indication is the treatment of patients with trigeminal neuropathic pain and/or dysesthesia dolorosa. In those patients, our results with Gasserian stimulation were disappointing, mainly because of side effects (motor activation and lead migration). An alternative however, might be stimulation of the motor cortex (Table 4).

Phantom-Limb Pain

Phantom-limb pain as a primary peripheral neuropathic pain with secondary central changes is considered a rather good indication for using this procedure because of the well-circumscribed pain (Table 5). In this series, however, we had rather mixed results, as have other authors.^{7,9,50,54}

Central Pain Syndromes

Spinal Cord Injury. The results in patients with central pain syndromes were less favorable. In cases of central pain due to spinal cord lesions, patients respond less after complete deafferentation and diffuse infralesional pain (also called central dysesthesia syndrome or below-level pain).⁴⁸ Usually the lead in the lateral somatosensory thal-

TABLE 4

*Results of combined stimulation for the treatment of dysesthesia dolorosa in six patients**

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	36, M	VPM/PVG	VPM/PVG	3	75–100
2	64, M	VPM/PVG	VPM/PVG	0.5	0
3	68, F	VPM/PVG	VPM/PVG	4.5	25–50
4	45, F	VPM/PVG	VPM/PVG	5	75–100
5	26, F	VPM/PVG	VPM/PVG	2	50–75
6†	71, M	VPM/PVG	NA	NA	0

* The mean follow-up duration was 3 years. For definition of pain relief, see Table 2.

† Bilateral distal pain in upper lips and gums.

TABLE 5

*Results of combined stimulation for the treatment of phantom-limb pain in four patients**

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	71, F	VPL/PVG	VPL/PVG	0.5	0
2	67, M	VPL/PVG	VPL/PVG	6.5	75–100
3	41, M	VPL/PVG	PVG	1.5	25–50
4†	39, M	VPL/PVG	NA	NA	0

* The mean follow-up duration was 2.8 years. For definition of pain relief, see Table 2.

† Despite pain reduction of more than 50% and reduced use of pain medication, the patient wanted explantation of the leads.

amus was implanted in the side contralateral to the worst pain. In patients with bilateral, evenly distributed pain, the nondominant side was chosen (Table 6).

Poststroke Pain. Very disappointing results were found in patients with the thalamic pain syndrome or poststroke pain. Although some beneficial effects on allodynia after PVG stimulation were observed, this did not increase the patients' quality of life because of the persistent chronic burning pain component and intermittent lancinating pain attacks. Suprathreshold as well as subthreshold stimulation in the VPL usually actually increased the pain. In most patients the leads were not even internalized but were explanted after an unsuccessful test trial (Table 7).

Postherpetic Neuralgia

Because of the limited number of patients with postherpetic neuralgia, no conclusions can be drawn. We have the impression, however, that patients with long-lasting postherpetic neuralgia and complete deafferentation are poor responders due to central changes within the spinal cord or even more central sites (Table 8).

TABLE 6

*Results of combined stimulation for the treatment of central pain due to spinal cord injury in 12 patients**

Case No.	Age (yrs), Sex	DBS Location	Pain Origin	Implantation	FU (yrs)	% Pain Relief
1	60, M	Brown-Sequard	VPL/PVG	NA	NA	0
2	55, F	myelopathy	VPL/PVG	VPL/PVG	3	25–50
3	35, M	tetraplegia	VPL/PVG	VPL/PVG	5	0–25
4†	51, M	post-DREZ lesion	VPL/PVG	VPL/PVG	0.5	75–100
5	64, M	paraplegia	VPL/PVG	NA	NA	0
6	67, M	paraplegia	VPL/PVG	NA	NA	0
7	58, M	paraplegia	VPL/PVG	NA	NA	0
8	62, F	conus syndrome	VPL/PVG	NA	NA	0
9	66, M	syringomyelia	VPL/PVG	NA	NA	0
10	42, M	plexus avulsion	VPL/PVG	PVG	4	0–25
11‡	55, M	paraplegia	VPL/PVG	VPL/PVG	2.5	0–25
12	67, F	myelopathy	VPL/PVG	NA	NA	0

* The mean follow-up duration was 3.5 years. For definition of pain relief, see Table 2. Abbreviation: DREZ = dorsal root entry zone.

† Patient committed suicide.

‡ Patient was treated later with intraventricular morphine, and eventually committed suicide.

TABLE 7

*Results of combined stimulation for the treatment of central pain (poststroke pain) in 11 patients**

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	55, F	VPL/PVG	PVG	1	50–75
2	53, M	VPL/PVG	PVG	2.5	25–50
3	64, M	VPL/PVG	NA	NA	0
4	44, M	VPL/PVG	NA	NA	0
5	70, M	VPL/PVG	NA	NA	0
6	55, F	VPL/PVG	NA	NA	0
7	64, M	VPL/PVG	NA	NA	0
8	50, M	VPL/PVG	NA	NA	0
9	68, M	VPL/PVG	NA	NA	0
10	61, M	VPL/PVG	NA	NA	0
11	61, F	VPL/PVG	NA	NA	0

* For definition of pain relief, see Table 2.

Nociceptive Pain

Because of the small number of patients in this study who had this disorder, no conclusions can be drawn from findings in those with pure nociceptive pain, which is a rare condition that might benefit more from other treatments (Table 9).

Discussion

Besides the “classic” method of placing lesions in pain-conducting pathways, as described by Spiegel and Wycis,⁵¹ the idea of positive enforcement by electrical stimulation of certain brain areas was transferred from the rodent to the human brain in the mid 1950s. Heath¹⁵ and Pool et al.⁴¹ reported pain relief that was accomplished in patients with significant psychopathological disorders by stimulating the septal nuclei, including the diagonal band of Broca anterolateral to the fornix columns. These areas are considered to be mainly involved in behavioral activities. Heath and Mickle¹⁶ later reported pain relief in six patients with intractable pain due to malignancy and rheumatoid arthritis.

Stimulation of the somatosensory pathways was introduced by Mazars et al.,³⁴ who produced stimulation-induced paresthesias with simultaneous long-lasting relief in patients with deafferentation pain. Stimulation of the posterior limb of the internal capsule also evoked paresthesias and was used for permanent implantation of electrodes by some surgeons.^{2,11} Since then several series have been published that involve a large number of patients and show varying results.^{4,7–10,22–24,33,40,43,49,53,54,56,60} Nevertheless, there was a consensus that pain due to deafferentation

TABLE 8

*Results of combined stimulation for the treatment of postherpetic neuralgia in two patients**

Case No.	Age (yrs), Sex	DBS Location	Implantation	FU (yrs)	% Pain Relief
1	71, M	VPL/PVG	VPL/PVG	5.5	50–75
2	80, M	VPM	NA	NA	0

* For definition of pain relief, see Table 2.

TABLE 9

*Results of combined stimulation for the treatment of nociceptive pain in 12 patients**

Case No.	Age (yrs), Sex	DBS Location	Pain Origin	Implantation	FU (yrs)	% Pain Relief
1	60, M	coccygodynia	VPL/PVG	NA	NA	0
2	62, F	polyarthrititis	VPL/PVG	PVG	1	50–75

* For definition of pain relief, see Table 2.

responds better than nociceptive pain or pain due to “excessive afferentation”³² to lateral somatosensory thalamus or internal capsule stimulation.

The PAG has been considered a target for long-term stimulation since the observations made by Reynolds⁴² in 1969. The electrodes were originally placed close to the aqueduct at the mesencephalic level in rats, making operations without further analgesics possible. In humans, stimulation of the ventral PAG revealed an opioid-mediated mechanism, because its pain-suppressing effect is reversed by naloxone. This phenomenon was called “stimulation-produced analgesia.” In contrast, stimulation of the dorsal PAG is not opioid-mediated. The stimulation of the dorsal PAG suppresses the pain only while the current is being delivered; there is no lasting effect after cessation of stimulation. This stimulation is not well tolerated by the patients; it causes fear, anxiety, and sometimes excitation.

High-intensity stimulation in ventral and dorsal PAG elicits vertical and lateral gaze paralysis and oscillopsia, and because of these side effects the target was shifted to the PVG in humans for long-term stimulation. Stimulation-produced analgesia was proven to be effective in acute and chronic pain states in humans.^{1,21,36,44,45} The neural substrates of this endogenous analgesia pathway include the PVG, parts of the PAG, the nucleus raphe magnus, and the magnocellular part of the nucleus reticularis gigantocellularis.^{3,19} Today it is well established that brainstem descending pathways constitute a major mechanism in the control of pain transmission.³⁸ Together with the somatosensory thalamus, the PAG/PVG resembles the classic targets for DBS.

In 1991, a review article by Duncan et al.¹⁰ was published, in which the authors raised critical questions with regard to the previously published series. Their main concerns were as follows: 1) level of evidence in the published series; 2) great variation in patient selection and parameter settings; 3) uncritical test stimulation with no blinding; and 4) missing “pharmacological” dose-response relationship. After this publication, the Food and Drug Administration returned DBS for the treatment of pain to an investigational setting. Only a few series have been published since then, and the results of DBS in the treatment of different pain syndromes were reported recently.^{7,8,24,40,56}

Reviewing the literature, the criticisms described by Duncan et al.¹⁰ have to be confirmed. According to the criteria of evidence-based medicine, the reports published have usually been level V, historic case-control studies. Only a few groups used an independent third examiner for evaluation of the results. Generally there are no standard-

ized patient selection and evaluation criteria in these studies. Especially important, no blinded stimulation was performed, and finally, a pharmacological dose–response relationship was never examined.

Due to a strong and rigorous selection process, fewer than 1% of the patients with pain who were admitted to our unit were considered possible candidates for DBS. With a small but serious risk of intracranial hemorrhage (1–5%),⁴³ DBS is considered a last-chance therapy in patients in whom less invasive procedures have failed.

Double-blinded evaluations (patient and physician and/or nurse) performed during the test trial further decreased the number of candidates in whom devices were ultimately internalized. In contrast to SCS, in which paresthesias in the affected dermatome are considered a prerequisite for successful therapy,^{39,55} in DBS a subthreshold stimulation is sufficient for pain suppression. Some patients, however, like to have some slight paresthesias to know that their system is running. Nevertheless, subthreshold stimulation for the patient is possible and placebo effects can be ruled out to a large extent. In our protocol the nursing staff who record the VAS score reported by the patient are also uninformed about the status of stimulation.

In general, combined stimulation of PVG and VPL was superior to single-lead stimulation. However, a clear dose–response relationship could be found in a few patients only (Fig. 3). In most patients a certain threshold under the perceptible one was necessary to produce a pain-relieving effect. The most effective stimulation frequencies were 40 to 70 Hz in the PVG and 60 to 90 Hz in the VPM/VPL region.

Interestingly, patients with partial deafferentation pain (FBSS or CRPS II, or dysesthesia dolorosa) obtained better relief than patients with complete deafferentation, as in spinal cord injury or poststroke pain. It is well known that SCS is insufficient to produce any relief in these pain states. In the denervated parts of the thalamus in humans after spinal cord injury, there is abnormal bursting spike activity implicating increased calcium conductance^{17,29,30} in the somatosensory thalamus as well as an enlargement of reception fields, a mismatch between projection fields and reception fields, and, finally, a projection of pain into the painful region with microstimulation.^{26,27}

Pathological spontaneous neuronal activity was also recorded from medial and intralaminar thalamic nuclei.⁴⁶ The medial lemniscus sends a dense projection to the

somatosensory thalamus signaling innocuous stimuli and terminating in rods. The spinothalamic tract also terminates in the somatosensory thalamus in islands or clusters intermingled with the lemniscal rods. Central pain that occurs after lesions in the spinothalamic tract or pain-transmitting fibers leads to degeneration of these terminals. The finding of abnormal spontaneous bursting activity is the expression of deafferentation of thalamic relay neurons deprived of their normal input (Figs. 1 and 2), although other mechanisms such as altered cortical input or altered inhibitory input from the reticular thalamic nucleus may also play a role.

It is hypothesized that, according to findings in the dorsal horn, lemniscal terminals make connections to pain-transmitting neurons, which explains the findings of allodynia in patients with poststroke pain. In support of this hypothesis, studies of the spinothalamic terminals of the rat thalamus have shown convergence of the terminals of the dorsal column; lemniscal and spinothalamic fibers converge onto single postsynaptic thalamic neurons.³¹ Stimulation of these neurons in humans induces pain by antidromic activation of lemniscal fibers extending into the area where the spontaneous pain is localized. This would explain why DBS in the somatosensory thalamus increases rather than decreases pain. Stimulation of the medial thalamus, which receives mainly spinothalamic input, on the other hand, can diminish allodynia through intact descending inhibitory pathways.

Nociceptive pain occurs due to chronic activation or overactivation of peripheral nociceptors. The pain-conducting pathways, peripheral as well as central, are intact. Examples are pain due to degenerative bone and joint disease or malignant invasion of soft tissue, joints, and bones. Nociceptive pain usually responds well to opiates. Therefore, PVG stimulation is generally accepted to treat the different forms of nociceptive pain. The basis for an endogenous descending pain-modulating circuit linking the PVG, PAG, the rostral ventromedial medulla, and the spinal cord, also for neuropathic pain, has now been well established.¹² Inhibitory descending pathways originate from the rostral ventromedial medulla (serotonergic) as well as from the locus caeruleus (noradrenergic), with different target structures at the spinal level. Especially in neuropathic pain models, a facilitating circuitry is also postulated.³⁷ Injury to neural tissues will destroy the balance between facilitation and inhibition. Therefore, therapeutic long-term stimulation of these structures linked together is able not only to relieve nociceptive but also neuropathic pain in humans.⁶²

Conclusions

Deep brain stimulation is a treatment option in patients who do not respond to less invasive or more conventional therapeutic measures. A neural substrate for the origin of the pain should be obvious; patients with diffuse pain states without a detectable reason for the underlying cause of pain should be excluded. Also, pain states in the rectal, genital, or perineal region do not respond to DBS according to our experience. One reason might be the small representation of those midline areas in the thalamic somatotopy.

Medical treatment options should be exhausted before

FIG. 3. Bar graph showing the data obtained in seven patients with combined VPL and PVG stimulation. Placebo, half subthreshold, and subthreshold stimulation were assessed during a double-blinded testing trial, and the related pain intensity is shown (increments on the y axis denote VAS scores: 0 = no pain, 10 = worst pain). In five of seven patients a dose–response relationship was found.

patients are considered for brain stimulation, and should only be abandoned if the therapy is ineffective or there are intolerable side effects. A careful patient history should be taken to rule out inefficient dosages or side effects due to missing comedication. Especially patients with neuropathic pain should be treated for a sufficient amount of time with tricyclic antidepressants (amitriptyline), anticonvulsants (carbamazepine, gabapentin, pregabalin), and other medications (mexiletine, baclofen) before DBS is performed. Pain of peripheral origin should be treated first with SCS or peripheral nerve stimulation, if appropriate. A morphine test^{18,20} is not considered to be helpful before implantation.^{59,61} On the contrary, we try to withdraw all opioids before implantation.

In addition, patients should be treated in a multidisciplinary pain clinic before being referred to a neurosurgeon for DBS, and finally, psychiatric and psychological testing should be conducted before considering a patient for DBS implantation. According to the results in this study, DBS can be helpful and add to the quality of life in carefully selected patients with chronic pain syndromes.

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