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Thalamic stimulation in neuropathic pain : 27 years later

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Abstract

An overview is given of CNS mechanisms which are behind the beneficial effects of VPL-VPM thalamic stimulation in the treatment of neuropathic pain. Further research in this field is urgently needed and the recent possibility to combine Deep Brain Stimulation with positron emission tomography (PET) will certainly help to unravel the brain circuitry implicated in stimulation-produced analgesia. Brain stimulation is an artificial way to activate nervous tissue that is reversible and, when correctly applied, has few complications.

The clinical results warrant a continued dissemination of brain stimulation as a treatment in well selected cases of neuropathic pain.

Key words : Neuropathic pain ; deep brain stimulation ; human ; mechanisms ; clinical results ; structural and functional neuroimaging.

The first publication on somatosensory thalamic stimulation for the treatment of neuropathic pain appeared in 1973 (Hosobuchi *et al.*, 1973). However, in a paper published 27 years ago, Mazars and colleagues stated that they practiced VPL-VPM (Ventralis Posterior Lateralis,-Medialis) in the early 1960s, i.e. before the proposal of the gate control theory (Mazars *et al.*, 1973). Their theoretical framework was the theory of Head and Holmes, which was proposed in the early nineteenth century and holds that pain results from an imbalance between protopathic and epicritic sensory functioning. Stimulation of the thalamic sensory relay nuclei would presumably increase the epicritic component and hence inhibit the protopathic inflow.

Real interest in deep brain stimulation (DBS) for the treatment of chronic pain in humans arose at the end of the 1960s. Important incentives for this sudden interest were Reynolds' discovery of stimulation-produced analgesia (SPA) in the rat (Reynolds, 1969) and the proposal of the gate control theory by Melzack and Wall (Melzack and Wall, 1965).

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It were behavioural studies in animals which prompted neurosurgeons to try PAG-PVG (Peri-Aqueductal Grey,-Ventricular) stimulation for pain alleviation in humans. In sharp contrast, no such experimental data were available for the somatosensory thalamus. The two studies that had been performed failed to show VPL-VPM stimulation-induced analgesia (SPA) (Schmidek *et al.*, 1971 ; Mayer and Liebeskind, 1974). Experimental evidence for its presumed role in SPA was hence exclusively based on electrophysiologic data obtained from anesthetized animals. This led to the paradoxical situation that VPL-VPM stimulation was already successfully used in humans for more than two decades before the first behavioural data in the awake animal could show VPL-induced SPA (Kupers and Gybels, 1993).

The mechanism by which VPL-VPM stimulation abolishes chronic pain is unclear. It is not likely to result from the activation of an endogenous opioid system, because the analgesic effect of VPL-VPM stimulation is not reversed by naloxone (Hosobuchi *et al.*, 1977). Although investigators found that after thalamic stimulation, ß-endorphin levels were more than twice the resting level, no differences in ß-endorphin levels could be demonstrated between patients reporting complete pain relief and those reporting only partial relief. Moreover, a much higher increase in ß-endorphin levels was found after PAG stimulation.

Experimental work in the rat has shown that VPL stimulation suppresses neuronal activity evoked by noxious stimuli in the parafascicular thalamic nucleus (Benabid *et al.*, 1983). In addition, electrical stimulation of the VPL in monkeys strongly inhibits spinothalamic tract neurons (Gerhart *et al.*, 1983 ; Dickenson, 1983). Although the responses to both innocuous and noxious stimuli are inhibited, the responses to C-fiber volleys are reduced to a greater extent than are those to A-fiber volleys. Therefore, some investigators have

suggested that the neural substrate of VPL-VPM stimulation lies in its capacity to inhibit spinothalamic tract cells. However, no significant descending projections from the VPL-VPM to the dorsal horn have been described. Anatomic studies have shown that spinothalamic tract neurons not only project to the thalamus but that they also send axon collaterals to the PAG and nucleus raphe magnus (Giesler *et al.*, 1981). Because stimulation of these structures may inhibit spinothalamic tract neurons, VPL-VPM stimulation may antidromically activate the descending inhibitory pathways in these structures (Tsubokawa *et al.*, 1982). Tsubokawa and colleagues have argued that the neural basis of this VPL-VPM-induced excitation of raphe-spinal neurons involves a dopaminergic mechanism. This hypothesis is supported by the clinical observation that administration of an antidopaminergic agent antagonized the analgesic effect of brain stimulation in patients with somatosensory thalamic, but not with PAG, electrodes. (Hosobuchi, 1990). Evidence also exists for the involvement of a serotonergic mechanism in VPL-VPM induced analgesia. For instance, microdialysis studies in anesthetized monkeys have shown that stimulation of the VPL releases serotonin in the lumbar spinal cord (Sorkin *et al.*, 1992).

The relevance of these experimental findings to the explanation of the analgesic effect of VPL-VPM stimulation in humans, however, remains questionable. First, VPL-VPM stimulation in humans has been shown to be an effective treatment for chronic (neuropathic) pain, whereas most animal experiments studied the effect on acute noxious stimuli in intact animals. Second, although the inhibition of spinothalamic tract neurons is in the order of milliseconds, the observed clinical pain relief after VPL-VPM stimulation can last for hours and occasionally longer.

A recent study by Duncan and colleagues (Duncan *et al.*, 1998) used PET (positron emission tomography) to study the mechanisms underlying VPL-VPM induced analgesia. Five patients suffering from neuropathic pain for whom electrical stimulation of the somatosensory thalamus had produced satisfactory long-term pain relief were included in the study. The patients were scanned before and during thalamic stimulation and regional changes in blood flow (rCBF) across the two conditions were examined. VPL-VPM stimulation produced significant increases in rCBF around the thalamic stimulation site itself, contralateral to the patients' clinical pain, and in the anterior insula, ipsilateral to the thalamic stimulation site. A subsignificant increase in rCBF was observed in the primary somatosensory cortex ipsilateral to the stimulation side. An earlier PET study by Katayama *et al.* (1986) also reported a significant increase in rCBF in the thalamus and postcentral gyrus after somatosensory thalamic stimulation. Taken together, these PET data seem to confirm Mazars's hypothesis (Mazars *et al.*, 1973) that activation of the thalamo-cortical pathways mediates thalamic stimulation produced analgesia.

DBS also offers a possibility to study the neural network underlying the perception of chronic pain without the confounding affects of the analgesic procedure, as is illustrated in case report 1 (Kupers *et al.*, 2000).

Case report 1

In 1989, T.G. had an adenocarcinoma resected from the right cheek. Since this operation, T.G. complained of a sharp, stinging and shooting pain in the right side of the face (V2 area). In addition, he developed hypoesthesia to pinprick and temperature in the affected area. Various surgical and pharmacological treatments (including high doses of morphine up to 540 mg/24 h) were tried but provided no significant pain relief. In 1992, a thalamic stimulation electrode (ITREL III, Medtronic, Minneapolis, MN) was implanted in the left ventroposterior medial thalamic nucleus (VPM). The electrode tip was located 7 mm lateral, 20 mm posterior and 2 mm ventral to the anterior commissure. Thalamic stimulation (10 Hz ; pulse width : 0.2 ms, stimulation intensity : 1.7 V) produces tingling and a sensation of warmth in the painful zone. The patient can completely suppress his pain by thalamic stimulation. However, he needs to stimulate permanently to remain painfree since the original pain reappears several hours after switching of the thalamic stimulator (Fig. 1).

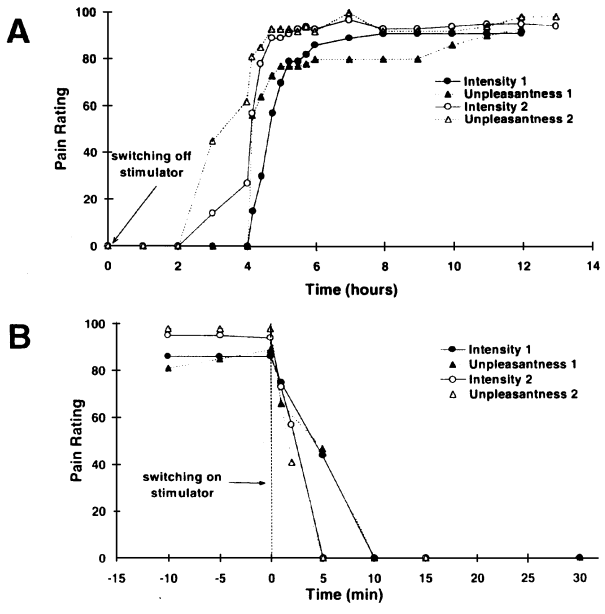

Fig. 1. — Case report 1. Patient's home ratings. (A) Time course of reappearance of pain after switching off the stimulator. (B) Time course of pain relief after switching on again the thalamic stimulator. The suffixes 1 and 2 refer to a first and second pain assessment session, respectively (with permission).

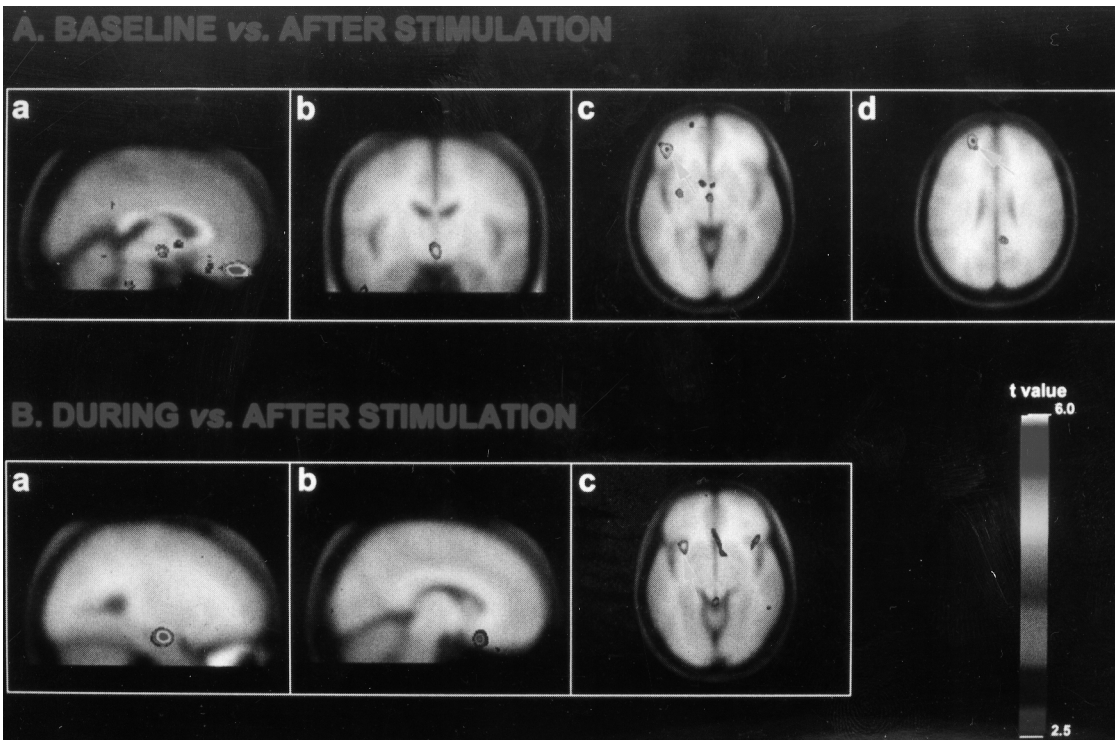

FIG. 2. — PET data from 'baseline – after' and 'during – after' subtractions coregistered with an average MRI volume of 305 normal subjects and mapped in Talairach space. (A) Baseline (pain) compared with stimulator off (no pain). Significant rCBF increases were observed in BA 11 (a), the hypothalamus (b), BA 47 (c) and BA 9 (d). (B) Stimulation on compared with after stimulation (no pain) condition. Significant rCBF increases occurred in the amygdala (a), BA 11/25 (b) and the anterior insula (c) (with permission).

The patient was scanned in the following conditions : before thalamic stimulation (pain, no stimulation), during thalamic stimulation (no pain, stimulation) and after successful thalamic stimulation (no pain, no stimulation) (Fig. 2). Comparing baseline scans during pain with scans taken after stimulation, when the patient had become pain-free, revealed significant rCBF increases in the prefrontal (Brodmann areas (BA) 9, 10, 11 and 47) and anterior insular cortices, hypothalamus and periaqueductal gray associated with the presence of chronic pain. No significant rCBF changes occurred in thalamus, primary and secondary somatosensory cortex and anterior cingulate cortex, BA 24. Significant rCBF decreases were observed in the substantia nigra/nucleus ruber and in the anterior pulvinar nucleus. During thalamic stimulation, blood flow significantly increased in the amygdala and anterior insular cortex. These data further support that there are important differences in the cerebral processing of acute and chronic pain. Indeed, the present results suggest that chronic pain can be experienced in the absence of activation of the lateral pain system.

It should be emphasized that single case studies have their importance in that the data are not averaged across subjects. As chronic pain patients often vary considerably with respect to the location and etiology of their pain, averaging across a group of pain patients is difficult or arbitrary and may reduce the likelihood of detecting relevant individual rCBF changes.

Patient selection

Just as for other neurosurgical procedures in pain control, a basic rule for considering DBS is that an organic cause should be identified for the pain syndrome, and that when several procedures are possible, preference should be given to the least invasive and least expensive one that causes the lowest morbidity and the highest comfort for the patient. Many clinical data support the hypothesis that nociceptive pain is preferentially suppressed by stimulation of the PAG-PVG, and neuropathic pain by stimulation of the VPL-VPM. Therefore, an analysis of the physiopathology of the pain syndrome is mandatory. In certain complex conditions in which neuropathic as well as nociceptive components may be involved, such as in low back pain, pharmacological tests may be of help.

A temporary trial stimulation is the final test before a neurostimulation device is implanted. This test must be sufficiently long, and the results should preferentially be evaluated by an independent third party. The aim of the test is to ensure that the pain relief is sufficient to justify permanent implantation and that the patient is able to use the neurostimulator device properly.

The localization of the lesion in the nervous system determines the part of the nervous system to be stimulated. Therefore, DBS is preferentially used in pain of central origin and pain in the face. However, even in cases in which the pain is of peripheral neuropathic origin, DBS may be indicated when a more peripheral location of the electrode does not succeed in providing paresthesia in the painful part of the body.

Surgical technique

Useful information regarding the surgical technique can be found in many publications, and as a reference source, a few are listed in "Selected Readings". Electrodes have been implanted in the brain for many years ; this procedure is accomplished by means of a stereotactic neurosurgical procedure. Stereotactic calculations of the various targets are usually based on the results of contrast ventriculography and atlases of stereotactic anatomy, and more recently, computed tomographic (CT) or nuclear magnetic resonance images.

Monopolar and quadripolar electrodes (Medtronic ®) are used for the VPL-VPM stimulation site. These electrodes come with a central stylet, which makes them less traumatizing for the brain. To obtain pain relief, the electrode has to be placed in the somatotopic part of the VPL-VPM nuclei that represents the painful body site. The target is usually determined by the patient's verbal response to intraoperative stimulation. Evoked potentials, induced by peripheral nerve stimulation, alone or in combination with the patient's verbal report, may also be used for target localization. When the electrode is correctly placed, stimulation should induce paresthesiae in the painful region. However, the production of paresthesias in the painful body region is no guarantee for success ; paresthesias may cover the painful site without any effect on the pain.

Stimulation parameters differ among the authors, but most common values are 30 to 100 Hz, 0.2- to 1-millisecond pulse duration, and 0.1- to 0.5-mA intensity. Somatosensory thalamic stimulation is mostly used at an intensity at which paresthesias are felt. Because the poststimulatory effect is generally short lasting, most patients use their stimulator most of the time.

Case report 2

V.M. was operated on in 1992 for left-sided facial pain in the left arm and leg after a cerebrovascular accident. A monopolar electrode (Medtronic) was implanted in the right VPL with the help of a magnetic resonance imaging (MRI)-compatible stereotactic frame (BRW, Radionics). With the patient under local anesthesia, the frame was mounted to the patient's head by use of MRI-compatible pins. The patient was then taken to an MRI scanner. The linearly polarized head coil was used. An axial topogram was taken to plan 3-mm-thick adjacent T1-weighted sagittal sections around the midline. The sagittal section on which the anterior and posterior commissures were best visualized was selected (Fig. 3A).

Seventeen 5-mm-thick adjacent T2- and proton density-weighted axial sections were taken parallel to the line AC-PC for visualization of the thalamus and internal capsule. The MRI images were sent to a stereotactic workstation in the operating room (Vandermeulen *et al.*, 1989). The computer calculated the three-dimensional coordinates of the anterior and posterior commissure in the midsagittal plane, as well as the length of the AC-PC line. On this line, the target was placed 2 mm anterior to CP and 14 mm right lateral. The coordinates of the entry point were measured on the skull with the help of the Brown-Roberts-Wells phantom base. The trajectory intersection was displayed on all the MRI slices, and a reslice through the trajectory was made (Fig. 3B). This image revealed that no functionally important structures or sulci were hit by the chosen trajectory. The arc system angles were calculated by the workstation and installed on the frame. With the Brown-Roberts-Wells microdrive, the electrode was gradually lowered to the target in 2-mm steps, starting 10 mm above the target. After each step, the patient was stimulated, and his verbal response was reported. On target, stimulation induced paresthesias that overlapped the painful body site.

The electrode was then fixed in position by the use of polymethyl methacrylate fixed in the burr hole, and its lead was tunnelled under the scalp and connected to a wire, which was led out of the skin at the right side of the head. In the first stage, lasting 10 days, the effect of stimulation on clinical pain and other parameters was evaluated. In the second stage, which occurred with the patient under general anesthesia, the electrode was connected to a radioreceiver implanted under the skin of the thoracic region.

It is well known that MRI and MR angiographic images have an inherent degree of geometric distortion. Errors of up to 8 mm are common, depending on the slice orientation and the field of view of the measurements. However, by appropriate selection of the imaging parameters, the errors can be minimized, resulting in a maximal spatial misregistration of the one pixel.

Results of clinical studies

Because brain stimulation is not yet a generally accepted method for the treatment of persistent pain (Gybels *et al.*, 1998), a discerning analysis of the clinical results must be conducted. However, the lack of well-controlled studies obscures an

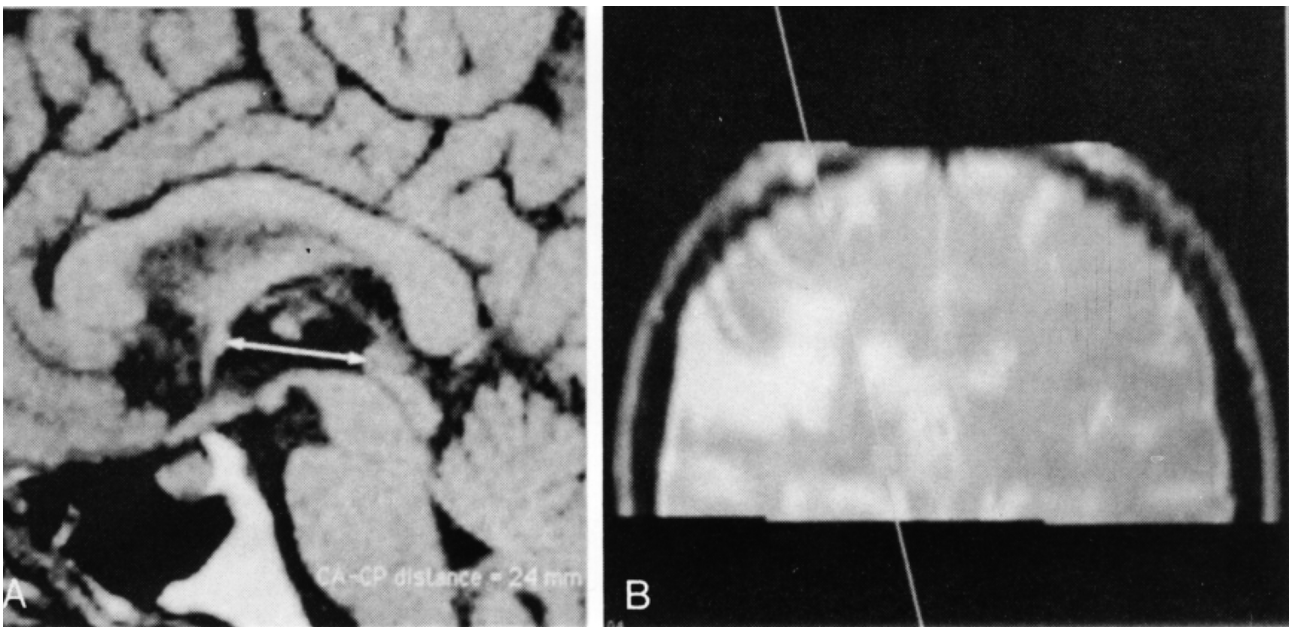

FIG. 3. — Case report 2 (A) CA-CP as determined on MRI (T_1-weighted axial topogram). (B) Electrode trajectory through target as determined with stereotactic workstation (with permission).

objective evaluation of the clinical efficacy of brain stimulation. A substantial part of the available data on DBS derive from case reports, limited patient series and retrospective and non-randomized clinical trials. The outcome measures are often too rough or uncomprehensive, making a rigorous statistical analysis extremely difficult. Few studies assessed the effect on pain as well as on other outcome measures, such as consumption of analgesics, physical activities, and lifestyle. Rarely has the therapeutic outcome been assessed by an uninterested third party and practically no double-blind, placebo-controlled studies have been conducted. However, it should be acknowledged that genuine double-blind procedures are difficult to accomplish.

GENERAL RESULTS

We reviewed the literature on DBS up to 1998 (Gybels and Kupers, 2000).This survey comprised 38 reports, with a total of 1863 patients. In studies in which the authors reviewed their clinical data more than once, only their latest results were considered. Because the way of quantifying the results differed among the authors, the following scoring system was adopted : pain relief scores of 50 percent or more and verbal ratings of excellent to good were considered successes. Patients in whom no electrode or stimulator was internalised because they did not respond favourably to trial stimulation were considered therapeutic failures. However, not all the authors reported these early treatment failures, and hence the following results overestimate the real therapeutic efficacy.

It appears that 47 percent of the 872 patients suffering neuropathic pain benefited from brain stimulation. We made a distinction between the results at trial stimulation, and the long-term results. These data reveal a significant decrease in therapeutic effectiveness over time, from an initial success rate of 66 percent to a success rate at long-term follow-up of 42 percent.

Much variability exists in the therapeutic outcome reported by the different authors. It is unlikely that this variability can be accounted for by differences in pain pathology because (1) in the larger studies, the major pain syndromes are all approximately equally well represented, and (2) even when the results obtained in a particular diagnostic category are compared, the same variability between the authors remains. The larger and older series generally reported much more favourable results than did the smaller and more recent series. Several factors such as stimulation parameters, electrode configuration, exact target localization, patient selection, have been proposed to influence therapeutic outcome, but they have not been investigated in controlled studies.

Results per specific pain condition

With respect to the question of whether certain pain syndromes respond better to brain stimulation than others, we analysed the data per diagnostic category. Because we were afraid that the mean success percentages might unduly reflect the (usually much better) results obtained in the larger series instead of giving a view of what is found among the authors, we also calculated median suc-

cess scores. Thereto, we selected the studies in which a certain diagnostic category appeared at least four times. Then, all the results were transformed into a percent success score. In this way, the results of the smaller series got the same impact as the results of the larger studies. After this, we calculated the median value of these transformed scores. Figure 4 shows the results of this survey.

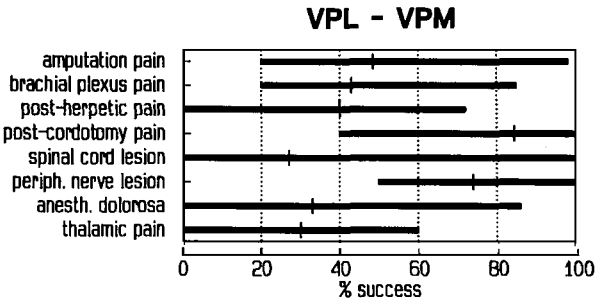

FIG. 4. — Results of brain stimulation per diagnostic category for VPL-VPM stimulation. The bars show the range of successes reported by the different authors. The left side of each bar represents the worst results, and the right side represents the best results. The vertical line on each bar gives the *median* success rate calculated over the different studies (with permission).

Complications and side effects

Provided the necessary precautions are taken, complications are rare. Occasionally, an intracranial hemorrhage or an infection may occur. In the latter case, the element of the neuroprosthesis at the site of the infection must be temporarily removed. Erosion of the hardware through the scalp, particularly in older patients, can be troublesome. In contradistinction with dorsal column stimulation, electrode migration and increase of impedance is very uncommon in DBS. In a few instances, compulsive thalamic self-stimulation has been reported.

Conclusion

The possibility of activating more or less selectively pain inhibitory pathways without destruction of nervous tissue has tremendous appeal : unwanted side effects can be avoided, the effects of electrical stimulation are reversible, test stimulation is possible, and reliable hardware is available. There are many clinical indications that DBS can be very valuable for treating persistent neuropathic pain, even in conditions in which alternative treatments have failed. Major goals to be pursued now are the search for more rigorous selection criteria and the evaluation of the results and reporting of them in a way that is accepted by the scientific community at large.

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