Title: The midbrain central gray best suppresses chronic pain with electrical stimulation at very low pulse rates in two human cases.

Running Head: Slow midbrain stimulation for central pain

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Key words: periaqueductal gray, periventricular gray, deep brain stimulation, neuropathic pain, spinal cord injury.

Abstract

Deep brain stimulation in the midbrain's central gray (CG) can relieve neuropathic pain in man, but for unclear reasons sometimes fails intraoperatively or in early weeks. Here we describe continuous bilateral stimulation in the CG of two subjects with longstanding, severe neuropathic pain from spinal cord injury. Stimulation parameters were recursively adjusted over many weeks to optimize analgesia while minimizing adverse effects. In early weeks, adjustments were made in periodic office visits; subjects later selected ad libitum at home among several blinded choices while rating pain twice daily. Both subjects received significantly better pain relief when stimulus pulse rates were low. The best relief occurred with 2 Hz cycled on for 1 s and off for 2 s. After inferior parameters were set, pain typically climbed slowly over 1-2 days; superior parameters led to both slow and fast improvements. Over many weeks of stimulation at low pulse rates, both subjects experienced significantly less interference from pain with sleep. One subject, with major pain relief, also showed less interference with social/recreational ability and mood; the other subject, despite minor pain relief, experienced a significantly positive global impression of change. Oscillopsia, the only observed complication of stimulation, disappeared at low mean pulse rates ($\leq 3/s$). These subjects' responses are not likely to be unique even if they are uncommon. Thus daily or more frequent pain assessment, combined with slower periodic adjustment of stimulation parameters that incorporate mean pulse rates about one per second, will likely improve success with this treatment.

1. Introduction.

Deep brain stimulation (DBS) of the midbrain's central gray (CG), comprising the periaqueductal gray (PAG) and the adjacent periventricular gray matter (PVG), has been used for several decades in humans to suppress chronic pain (Boccard et al., 2013; Hamani et al., 2006; Levy et al., 2010). The mechanism, which involves a descending inhibitory system to spinal and trigeminal nociceptive neurons relayed via the medial medulla, has received intensive preclinical study (Heinricher et al., 2009). Good clinical safety is reported with CG stimulation for many types of pain, but efficacy varies considerably with etiology. Neuropathic pain due to spinal cord injury (SCI) appears to be among the least responsive (Boccard et al., 2013; Previnaire et al., 2009). However, relatively few SCI cases have been published and injuries are highly diverse, for example, in pathology and spinal location. We are currently investigating the effects of CG stimulation in subjects with debilitating pain due to cervical or thoracic SCI. This study stemmed from preclinical findings of permanently improved anatomical and functional outcomes following interim stimulation in the PAG of rats with incomplete thoracic contusion injury (Hentall and Gonzalez, 2012).

The present report focuses on the time-course of analgesic responses after a change of stimulation parameters and on the influence of the pulse rate parameter. The time-course is crucial in practice because it determines how quickly the stimulation parameters can be

optimized. Pulse rate is a critical parameter in DBS, partly because neurons use spike timing to communicate. A range of frequencies, 5-50 Hz, has been used historically in CG stimulation for pain (Bittar et al., 2005). However, the hindbrain serotonergic raphe neurons that are implicated preclinically in relaying the PAG's beneficial effects to the spinal cord fire very slowly (Hentall et al., 2000; Wessendorf and Anderson, 1983). We therefore reasoned that even 5 Hz might be faster than optimal for prolonged, continuous activation of this descending pain-suppressing pathway. Consequently, we proposed two hypotheses: first, that low frequencies are superior for producing long-term analgesia with CG stimulation; second, that changes in pain level occur slowly, over hours or days, when new stimulation parameters are set.

Here we report findings from two bilaterally implanted subjects, who were instructed in certain weeks to switch among several blinded frequency settings to obtain best analgesia with least side effects. Subjects consistently preferred the lowest offered frequency. The minimum frequency allowed by the DBS equipment was 2 Hz, but lower mean pulse rates were obtained by cycling on and off a brief 2-Hz train. Here we use the term “pulse rate”, defined as an average over 1-10 seconds, whenever cycled trains are referred to, while “frequency”, in units of Hz, is used only for regularly spaced pulses. Twice daily pain recording enabled the preference for very low pulse rates to emerge and allowed slow time-courses to be ascertained. After optimal pulse rates had been determined, we explored other parameters, such as the best monopolar or bipolar combination of active contacts among the four on each lead. The use of very low pulse rates, along with rapidly repeated pain testing and slow adjustment of parameters, has the potential to benefit both

future patients and those who currently receive suboptimal pain relief from implanted CG leads.

2. Results.

Pre-operative, Initial Post-operative and General Observations.

Subject 1 (male, 36 year-old at surgery) acquired a functionally complete SCI at segmental level C4-C5 in a motor vehicle accident 16 years earlier. His injury was rated by the international standards for neurological classification of spinal cord injury of the American Spinal Injury Association (ASIA) as ASIA-A. The subject developed neuropathic pain bilaterally that was particularly severe in the right shoulder, arm and hand; it was often excruciating in the thumb. The subject had previously tried unsuccessfully to alleviate pain with many medications, including gabapentin, various antidepressants and opioids. He continued to use an intrathecal baclofen pump for pain and spasm control during the study. Subject 1 stated that DBS gave good relief of allodynia produced by light brushing both intraoperatively (during the first surgery) and four hours after the second surgery. However, relief of pain has since been minor.

Subject 2 (female, 54 year-old) acquired an incomplete injury at segmental level T11 in an accidental electrocution from a high voltage power line 30 years earlier; the injury was rated as ASIA-B. She subsequently experienced central neuropathic pain in both lower extremities, which she described as severe, constant and shooting in character. Her pain

was managed in recent years primarily with pregabalin (Lyrica). Subject 2 showed significant intraoperative and long-term reduction of central neuropathic pain. Postoperatively, Subject 2 developed upward gaze paralysis (Parinaud's syndrome) that was independent of the stimulation; this resolved completely over the next 3 weeks.

Both subjects returned to their customary lives after the two surgeries, which included occasional long-distance travel and other physically or emotionally strenuous activities and circumstances that may have influenced their pain level. However, frequent long-term observation allowed the effects on pain caused by varying the stimulation parameters to be discerned above such fluctuations.

Pain in Early Weeks and Patient Global Impression of Change

Subject 1 received stimulation for the first 8 weeks after surgery (study weeks 8-16) at a frequency of 25 Hz. This frequency was selected as the mid-point of the range normally used for this procedure (Bittar et al., 2005; Boccard et al., 2013). In the subsequent 8 weeks, a frequency of 10 Hz was applied. Then for another 8 weeks the subject switched between 3 Hz (40% of the total time) and 10 Hz (60% of the time). During this 24 week stretch, the Patient Global Impression of Change (PGIC) significantly improved with frequency (Kruskal-Wallis $p=0.037$), but weekly pain did not change significantly ($p>0.05$) (Figure 2A).

Subject 2 showed profound stimulation-produced pain relief intraoperatively, when frequencies 3-10 Hz were explored. Her preference was 3 Hz, which was the setting chosen for the first 4 weeks, guided by the already known preference of Subject 1 for low frequencies. In the subsequent eight weeks, 2 Hz was applied. During this 12 week stretch with 3 Hz or 2 Hz, the PGIC of Subject 2 was usually perfect (zero) except during evoked eye movement complications when it was 1-2 (Figure 2B). Her weekly pain level decreased with stimulation frequency (Kruskal-Wallis $p=0.012$).

Pain Diaries: Blinded Selection of Pulse Rate

During later periods of parameter choice, subjects recorded pain levels in the morning and evening. The lowest pulse rate (2 pulses per 3 s, 2 Hz cycled) in Subject 1 was compared with higher non-cycled rates (3 and 20 s^{-1}) at home in study weeks 32-37 (Figure 3A). The highest rate (20 s^{-1}) was only briefly applied, being rejected within minutes due to visual side effects. This rate was excluded from the statistical analysis. Subject 2 compared 2 pulses per 3 s (2 Hz, cycled) with other uncycled rates (2 and 5 s^{-1}) in study weeks 20-23 (Figure 3B). She spent relatively few days (2.5) with 5 s^{-1} but they are included in the analysis.

A two-way categorical Type 1 analysis of variance (ANOVA) was performed on pain scores from diaries for these periods, using pulse rate followed by time of day (morning or evening) as categories. The data is summarized in Table 1. Levene's test detected no inequality of error variances in either subject; that is, null testing of equality gave $p>0.05$.

In Subject 1, 2 pulses per 3 s (2 Hz cycled) gave significantly ($p=0.027$) lower pain scores versus 3 pulses s^{-1} (uncycled); time of day was also significant ($p=0.003$), but its interaction with pulse rate was not significant. In Subject 2, the effect of pulse rate was significant ($p=0.001$), but neither time of day nor their interaction was significant. Bonferroni post hoc testing showed that 2 pulses per 3 s (2 Hz cycled) differed significantly from uncycled 2 s^{-1} and 5 Hz s^{-1} , (both $p=0.001$).

Over the longer term, pain was significantly higher in the evening in both subjects. In Subject 1 during study weeks 26-52, the morning pain score was 8.65 ($n=168$, ± 0.060 s.e.m.) and the evening score was 9.44 ($n=140$, ± 0.057 s.e.m.). In Subject 2 during study weeks 20-39, the morning pain score was 1.24 ($n=130$, ± 0.063 s.e.m.) and the evening score was 1.69 ($n=122$, ± 0.061 s.e.m.), giving $p<0.0001$ by t-test for both subjects.

Other Parametric Comparisons

Subsequent to optimization of pulse rate in Subject 1, over weeks 37-52, various contact combinations were examined bilaterally. One of the four contacts on each lead was made the cathode and the anode was provided either by another contact (giving bipolar stimulation) or by the implanted generator case (giving monopolar stimulation). None of the combinations tested proved significantly superior in this Subject.

After optimization of pulse rate in Subject 2, the possibility that a very low pulse rate was equivalent to an absence of stimulation was explored over study weeks 24-32. She was given the blinded option of switching from 4.5 V (both sides) to a minimal 0.1 V at home. This option was chosen on study week 26 (119 days after start of stimulation), and led to a marked increase in pain, almost reaching the pre-treatment high before the subject returned to the effective 4.5 V program (Figure 4A). Subject 2 received 75 mg pregabalin daily until week 20, when a slow tapering of dose was undertaken, based on the excellent stimulation-produced analgesia noted up to that point. Complete withdrawal resulted eventually in higher pain scores in the evenings (typically a score of 2, as in Figure 4A).

In weeks 32-48, different pairs of contacts for bilateral stimulation were compared in Subject 2. Best pain relief occurred with the cathodes situated most distally, in the PAG (Figure 4B). This arrangement restored the pain level to that achieved before withdrawal of pregabalin: 0.5-1. In study weeks 48-52, further comparisons were made in Subject 2 among very low stimulus pulse rates: 2 Hz was cycled on for 1 s and off for 2, 4 or 9 s. With a 4 s off phase, the Subject noted in her diary, “Pain is definitely fluctuating” and “Fluctuations leaving me tired”; with a 9 s off phase she noted, “Pain fluctuating between ½ & 1 ½ in slower rate”. Thus the 2 s off period, established in prior weeks, was the best of the 3 settings, whereas longer off periods with lower mean pulse rates yielded inconsistent pain scores.

Pain typically climbed slowly, for 24 hours or more, after less effective parameters were applied in Subject 2. For example, a climb lasting at least 24 hours was seen with a reduction in voltage (Figure 4A). Similar slow climbs were seen following a change in pulse rate from 2 pulses per 3 s (2 Hz cycled) to 5 s^{-1} at the start of study week 20 and to 2 s^{-1} in study week 21 (Figure 3B). A faster rise was nevertheless seen after changing to 2 s^{-1} in study week 22 (Figure 3B). When superior parameters were applied, including during intraoperative and in-office testing, pain levels generally decreased rapidly. However, twice-daily pain evaluation also revealed a slower developing component: for example, this was seen in changing from 2 s^{-1} to 2 pulses per 3 s (2 Hz cycled) just before study week 21 and at the end the same week (Figure 3B).

Pain Interference

Pain interference scores collected until the 40th week are shown as averages in Table 2. The mean use-weighted pulse rate during this period was 1.84 s^{-1} (Subject 1) and 0.24 s^{-1} (Subject 2). In comparisons of pre-surgery (n=2) and post-surgery (n=17) values, Subject 1 experienced improvements in the sleep category only (Kruskal-Wallis $p=0.012$); Subject 2 experienced improvements in the categories of social/recreational ability (Kruskal-Wallis $p=0.047$), mood (Kruskal-Wallis $p=0.023$) and sleep (Kruskal-Wallis $p=0.012$). However, the mean pre-surgery scores of Subject 1 for all categories was between five and 6, and all were therefore amenable to strong improvement. In contrast, Subject 2 had baseline scores of 1.5 or less for non-significant categories, with little room for improvement.

Stimulation-Produced Adverse Effects

The only adverse effects produced by stimulation were interference with vertical gaze and oscillopsia, which diminished and disappeared with lower pulse rates. There was otherwise no perception or observation of pulsation of other types of movement caused by the stimulation. These visual effects were seen on several occasions when the pulse rate was raised. For example, during a programming session for Subject 1, visual disturbance was noticed when 10 Hz but not 3 Hz (2.4V, 250 μ s) was applied to the right lead (contacts 8+ and 10-, left lead temporarily inactive). Subject 1 experienced more obvious visual problems upon switching to 20 Hz on two occasions, but he selected a lower frequency within minutes to remedy the problem. Subject 2, noted slight involuntary eye movements at home immediately after switching to 5 s^{-1} bilateral stimulation from 2 pulses per 3 s (2 Hz cycled).

3. Discussion

In summary, stimulation pulses at a very low mean rate (under 0.67 s^{-1}) provided superior relief of chronic neuropathic pain from SCI in the two subjects studied. In both subjects, diverse general factors also improved, such as interference of pain with sleep (both subjects), social/recreational ability and mood (Subject 2) and global impression of change (Subject 1). We emphasize that this is a report of two cases, neither of which may

be typical in their responses to DBS, and that population statistics were not testable, although each subject yielded sufficient measurements for within-subject analysis of best parameters.

According to our search of the literature, pulse rates less than 3 s^{-1} , whether cycled or non-cycled, have not been used previously in DBS for any disorder. The most common clinical use of DBS is for extrapyramidal movement disorders, in which continuous frequencies of 100-180 Hz are delivered to the thalamus or basal ganglia (Birdno et al., 2014; Breit et al., 2004). Pain suppression by stimulation of sensory thalamus or cortex also employs high frequencies (Fontaine et al., 2009; Pereira et al., 2013). Many types of neurons in the central nervous system show long-term synaptic changes (potentiation or depression) or fatigue after more than a few seconds of moderately fast activation, e.g., at 10 Hz (Cooke and Bliss, 2006; Ren and Dubner, 2007). Thus, therapies that work best at intermediate or high frequencies are in all likelihood exploiting rapid, activity-evoked changes occurring at one or more stages in activated polysynaptic pathways. Since a peak in therapeutic CG stimulation appears to occur at very low frequencies, the analgesic effect may depend on unchanging synaptic responses that decay relatively slowly ($>1 \text{ s}$). Power spectra of local field potentials recorded intraoperatively in the CG during analgesic DBS in the sensory thalamus support this idea; their strongest correlation with analgesia occurs in the lowest frequency, 0-4 Hz (delta) band (Wu et al., 2014). However, it is also conceivable that both high and low frequencies of CG stimulation produce analgesia, but via different processes. The PAG demonstrates pro-nociceptive as well as

anti-nociceptive effects (Lovick, 2008), and the former may perhaps be blocked by high frequencies.

A noteworthy technical advantage of using low frequencies is that battery lifetime can be considerably extended, to the point where standby power use and chemical stability may predominate in determining lifetimes. Furthermore, the main stimulation-produced adverse effects, involving interference with gaze, disappeared at the lowest applied frequencies. The transient insertional effect of Parinaud's syndrome, seen in Subject 2, has previously been reported to be rare (Hosobuchi, 1986; Levy et al., 2010), and could involve interference with the paramedian pontine reticular formation, located near the anterior-lateral PAG, which is a possible source of abduction paresis (Thomke et al., 1992).

The pain relief scored in the subjects' diaries usually changed slowly over many hours, for up to several days, when a new set of stimulation parameters of differing effectiveness was applied. The underlying mechanisms of the analgesia produced by this therapy may therefore include slow processes that may be humoral, although there is also a fast component that is probably neural, which was most evident in the rapid onset of analgesia when the device was first turned on. A likely candidate for the humoral process is endorphin release (Hosobuchi et al., 1979). The practical implication is that, for best pain relief with therapeutic CG stimulation, parameters should be periodically titrated at intervals of no less than several days with respect to daily or more frequent pain scores.

Based on findings in only two subjects, it cannot be concluded that low pulse rates are optimal for relieving central neuropathic pain by CG stimulation, even cases restricted to SCI pain. Conversely, however, these two subjects are unlikely to be highly anomalous. It is thus reasonable to suggest that pulse rates around 1 s^{-1} be screened routinely with this therapy, without omitting higher, traditionally used rates of up to 50 Hz s^{-1} (Bittar et al., 2005). Both subjects experienced improved analgesia with lower pulse rates but differed markedly in the degree and stability of analgesia. Possibly the segmental level of the neuropathic pain relative to the injury site is critical. Subject 2, the better responding subject, had a low thoracic injury and pain in lumbar dermatomes, whereas Subject 1 had mainly mid-cervical pain that responded minimally to DBS and matched the segmental level of the injury. Regardless of the differences, many patients with presently implanted CG leads that provide suboptimal pain relief, as well as new patients, may possibly benefit from this revised approach.

4. Experimental Procedures

Surgery

Work was carried out under an Investigative Device Exemption of the United States Food and Drug Administration (FDA IDE G120202), with ClinicalTrials.gov identifier NCT02006433, and was approved by the Institutional Review Boards of the University of Miami and the Miami Veterans Administration Hospital. Baseline measurements of preoperative pain and other injury-related clinical variables were performed in the first 6 weeks. On the seventh study week, surgery for bilateral implantation of electrode leads (Medtronic3387S-40) was performed in the University of Miami Hospital. With subjects awake, the tips of the leads were positioned in the anterior-lateral PAG, following published methods (Boccard et al., 2013). Tip locations were confirmed by post-operative computed tomography (CT) scans mapped onto pre-operative magnetic resonance imaging (MRI) scans (Figure 1). The leads have four 1.5 mm long contacts with 1.5 mm separation extending 12 mm from the tip (Figure 4C), so that the superficial contacts were located in the PVG. Seven days after insertion, leads were connected to extension cables under anesthesia and tunneled to a generator (Activa PC Neurostimulator 37601, Medtronic).

Stimulation

Trial stimulation was given during the first awake surgery, and long-term continuous stimulation was started within 24 hours of the second surgery. Subjects returned for

office visits every 4 weeks until 16 weeks post-surgery, beyond which they returned every 8 weeks, unless they requested a special visit. The office visits included various outcome tests and further parameter adjustment. In the parameter adjustment, the active electrode contacts and the delivered charge (product of voltage and pulse width) were set to achieve best immediate pain relief for a given stimulation pulse rate without causing visual or other side effects. The device did not offer frequencies less than 2 Hz, so these were approximated when needed by rapid cycling. Cycled trains are described in this paper in terms of “pulse rate”, expressed as an average 3-10 seconds in units of s^{-1} . The term “frequency”, in units of Hz, is reserved here for regularly spaced pulses. In the present work, 2 Hz was cycled on for 1 s and off for 2, 4 or 9 s, giving a rate of 0.67, 0.3 or $0.2 s^{-1}$.

A choice of pulse rates, with other parameters constant, was offered in study weeks 24 through 37 to Subject 1 (range $0.67-10 s^{-1}$) and in study weeks 20 through 24 to Subject 2 (range $0.67-3 s^{-1}$). Both the subjects and the investigators were blinded to the choice. After the approximate best pulse rate had been adequately determined, other parameters were explored similarly through blinded choice. Subjects selected from 2-4 program groups with a standard patient programmer (Model 37642, Medtronic) and saw no details of the programs, only the labels A-D. In some periods, two labels referred to identical programs, to control for action bias. Subjects were instructed to wait at least 24 hours before making a program change, unless the choice seemed clearly worse, and to remain as long as desired with any program group that seemed clearly better. Both subjects

sometimes maintained a worse setting for several days, either because they were uncertain about effects or because they anticipated longer-term benefit.

Outcomes Measures

Pain and associated factors were assessed during home telephone interviews or office visits. An integer rating scale for overall pain, ranging from 0 to 10, was the only measure used to set stimulation parameters. Simultaneous pain scores from several sites or scores taken within a few hours by averaged to give non-integer values. The pain score was obtained twice before surgeries in the 2nd and 6th week and weekly following the two surgeries until a choice of programmed parameters was presented. When a parameter choice was available, subjects recorded a numerical pain score twice daily, unless prevented by extraneous circumstances.

Two less frequent periodic measures are reported in the Results section. First, the patient global impression of change score (PGIC), scaled from 0 (much better) through 5 (no change) to 10 (much worse), was measured every 7 days, beginning after the surgeries. Second, pain interference was scored every 14 days via the International SCI Pain Basic Data Set (ISCIPBDS), first version (Widerstrom-Noga et al., 2008). ISCI-PBDS categories are: self-limiting activities employed to prevent worsening, change in social/recreational ability, change in satisfaction (e.g., family-related activities), interference with day-to-day activities, interference with mood, interference with sleep. They are all scaled from 0 (no interference) to 6 (extreme interference). Other periodic

measures of pain, including quantitative sensory testing, and related aspects of SCI such as autonomic function or stimulation-produced changes in injury status given by the ASIA score were obtained less frequently, during office visits, and are not reported here.

Statistical Analysis

Statistical testing employed SPSS (version 21, IBM) and only examined effects within subjects. The independent samples Kruskal-Wallis test analyzed pain interference by comparing pre-surgery with post-surgery scores; it analyzed long-term changes in weekly pain and PGIC scores by comparing different stimulation pulse rates. The effect of stimulation parameters within periods when a fixed set was offered to the subject was evaluated by two-way univariate analysis of variance (ANOVA); twice daily pain scores were grouped by stimulation parameter and time of day (morning or evening), with Bonferroni post-hoc testing used when a parameter had more than two values.

Acknowledgements

This research was supported by the United States Department of Defense, Spinal Cord Injury Research Program, under award number W81XWH-12-1-0559. We are grateful for technical assistance with pain evaluation from James Adcock and Maydelis Escalona, for initial device programming by Dr. Bruno Gallo and for the excellent critical reading of the manuscript by Dr. Melissa Carballosa, all of the University of Miami.

Consultations on targeting were kindly provided Drs. Alex Green and Erlick Pereira, University of Oxford (UK).

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Tables

Table 1. Pain scores recorded in diaries on a 0-10 scale during 4 weeks when subjects were given a blinded choice of pulse rates that included 0.67 s^{-1} . These data are also represented in Figures 3A and 3B. Abbreviations: S.D., standard deviation. * signifies that pulse rate was rapidly cycled on and off. The statistical analysis is presented in the Results section.

Subject	Pulse rate* (s^{-1})	24-hr Pain Mean $\pm$ S.D. (n=)	Morning pain Mean $\pm$ S.D. (n=)	Evening pain Mean $\pm$ S.D. (n=)
Subject 1	0.67	8.97 $\pm$ 0.95 (35)	8.55 $\pm$ 0.90 (20)	9.53 $\pm$ 0.72 (15)
	3.00	9.29 $\pm$ 0.59 (17)	9.18 $\pm$ 0.64 (11)	9.50 $\pm$ 0.45 (6)
Subject 2	0.67	0.93 $\pm$ 0.63 (27)	0.88 $\pm$ 0.68 (13)	0.96 $\pm$ 0.60 (14)
	2.0	1.74 $\pm$ 0.75 (21)	1.68 $\pm$ 0.93 (11)	1.80 $\pm$ 1.54 (10)
	5.0	1.70 $\pm$ 0.97 (5)	1.50 $\pm$ 0.87 (3)	2.00 $\pm$ 1.41(2)

Table 2. Interference from pain, measured with the ISCIBPDS, in the two subjects.

Scores (range 0-6) are averaged from baseline pre-surgery weeks (2 assessments) and post-surgery weeks (17 assessments). Post-surgery results ($\pm$ standard deviation) are from study weeks 10 to 42 for both subjects. Results from Kruskal-Wallis non-parametric tests are also listed.

	Subject 1			Subject 2		
	Baseline	Post-surgery	p	Baseline	Post-surgery	p
Self-limiting to prevent pain	6.0 $\pm$ 0.00	5.53 $\pm$ 0.52	0.351	1.5 $\pm$ 2.1	0.95 $\pm$ 1.25	0.842
Social-recreational ability	6.0 $\pm$ 0.00	6.0 $\pm$ 0.0	1.00	3.0 $\pm$ 0.0	0.59 $\pm$ 1.00	0.047
Social satisfaction	5.5 $\pm$ 0.71	5.59 $\pm$ 0.62	0.842	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	1.00
Daily activities	5.5 $\pm$ 0.71	4.9 $\pm$ 0.33	0.234	1.5 $\pm$ 2.1	0.71 $\pm$ 0.99	0.655
Mood	5.0 $\pm$ 0.00	4.9 $\pm$ 0.49	0.842	1.5 $\pm$ 0.71	0.12 $\pm$ 0.33	0.023
Sleep	5.0 $\pm$ 0.00	3.8 $\pm$ 0.92	0.047	4.5 $\pm$ 0.71	0.59 $\pm$ 1.18	0.012

Figure captions

Figure 1. Merged images in three planes of the post-operative CT scan and the pre-operative MRI scan from Subjects 1 (top row) and 2 (bottom row). The small black squares marked 'L' in each photograph mark the distal location of the leads (left lead in Subject 1, right lead in Subject 2). The surrounding irregular white areas, and the equivalent contralateral areas, are local electromagnetic effects of the leads on the image. The small white square in the coronal plane of Subject 2 marked 'PC' indicates the location of the posterior commissure. The arrow in the axial plane of Subject 2 marks the cerebral aqueduct (CA). Abbreviation for directions: sup., superior direction; inf., inferior direction; ant., anterior direction; post., posterior direction. Abbreviations for structures: BP, basilar pons; Hip, hippocampus; IC, inferior colliculus; MG, medial geniculate; PC posterior commissure; RN, red nucleus; SC, superior colliculus; V3, 3rd ventricle.

Figure 2. Time courses of pain in the two subjects. Weekly scores for overall pain and PGIC are shown for Subject 1 (A) and Subject 2 (B). The study began on week 1, with surgery on weeks 7 and 8 (marked by the short vertical lines). Frequency, shown by the right axis, is shown as a use-weighted mean for Subject 1 in weeks 24-32; otherwise it was constant for the periods shown.

Figure 3. Pain measured in the Subject 1 (panel A) and Subject 2 (panel B) during weeks of blinded selection of different programmed pulse rates. The weeks displayed are those

when the different choices of pulse rate included 2 pulses per 3 s (2 Hz cycled). Other parameters were kept constant, as follows. Subject 1, left contacts cathode 3 and anode 1, pulse width 250 μ s, 3.7 V; right contacts cathode 8 and anode 11, pulse width 250 μ s, 1.5 V. Subject 2, left contacts cathode 3 and anode 0, pulse width 180 μ s, 4.5 V; right contacts cathode 11 and anode 8, pulse width 180 μ s, 4.5 V. Pain scores were usually recorded twice daily; omissions, which were unavoidable in daily living, are indicated by gaps in connecting lines. Evening and morning scores are represented by filled and empty symbols, respectively. A change of program (pulse rate) took place just after pain assessment, so that the first data point reflects the pain score after approximately 12 hours with a newly selected parameter.

Figure 4. Effects on pain scores in Subject 2 of changes in voltage (panel A) or bipolar contacts (panel B), with other parameters kept constant. 4A: Time-course of pain score upon switching the amplitude bilaterally from 4.5 V to a minimal 0.1 V. Other parameters: pulse rate 2 per 3 s (2 Hz cycled), cathodal contacts 3 and 11, anodal contacts 0 and 8, pulse width 180 μ s on both leads. 4B: Varying pain relief produced by different bilateral anodal (+) and cathodal (-) contact pairs active on left and right leads. Other parameters: pulse rate 2 per 3 s (2 Hz cycled), pulse width 180 μ s on both leads, amplitude 4.5 V on both leads. 4C: Diagram showing the physical order of numbered electrical contacts on the left (L) and right (R) leads; each contact and the space between them is 1.5 mm in length.

Figure 1

Figure 2

Figure 3

Figure 4