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14. ABSTRACT

This project is a study of electrical deep brain stimulation as a method for treating pain and autonomic dysreflexia in patients with chronic spinal cord injury. It is collaboration between the University of Miami and the Miami Veterans Administration Hospital. The first year was mainly taken up with obtaining regulatory approval. In the second year and third year (report year), four subjects were enrolled, with one later withdrawing. Best pain relief in both completed subjects was given by a very low pulse rate, which is a new finding for this therapy. Pain changed for up to several days when new stimulation parameters were set, suggesting that that frequent pain assessment is need to correctly titrate stimulation parameters. Visual side-effects were the only observed complication of stimulation, but they disappeared when a very low, maximally analgesic pulse rate was set. Thus this therapy is not only more effective at lower pulse rates, it is also safer. No serious adverse effects have been observed. Protocols (FDA and IRB) were modified to extend study of each subject for 2 additional years (funded by other sources), and to use a device (PC+S) that additionally allows recording from electrodes for added information. A no-cost extension year is in progress.

15. SUBJECT TERMS
Spinal Cord Injury; Pain; Autonomic Dysreflexia; Deep Brain Stimulation; Midbrain

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1. Introduction

Deep brain stimulation (DBS) has been used for several decades to treat drug-refractory pain of various types. A major stimulation site for this is the periaqueductal/ periventricular gray region (PAG/PVG). Chronic pain severely affects the quality of life of many spinal cord injury (SCI) patients. Autonomic dysreflexia (AD) is another major problem in SCI, presenting as hypertension and other signs of sympathetic over-activity that can be elicited by noxious cutaneous or visceral stimuli below the injury level. Our preclinical studies on rats have shown that PAG stimulation, given for one to a few weeks, can permanently reverse AD and some motor deficits of SCI.

We propose testing of PAG/PVG stimulation for acute palliation and long-term remediation of pain and AD in a human study of safety and efficacy. All subjects will have moderate to severe chronic neuropathic pain due to SCI, with or without concomitant AD. They will be recruited, if possible, from the Spinal Cord Injury Service of the Miami Veterans Administration Medical Center. Recruitment was last year extended to other VA Centers and to civilian subjects. Eight subjects will be studied. We shall test whether DBS in the PAG/PVG region of SCI patients is safe, relative to other current uses of DBS and to other (drug) treatments for pain and AD in SCI. We will furthermore determine whether acute DBS in the PAG/PVG lowers ongoing chronic pain severity caused by longstanding SCI. Finally, we will explore how prolonged PAG/PVG stimulation, over 10 months, cumulatively affects the sensory, motor and autonomic deficits of SCI, including the frequency of AD episodes.

If DBS in the PAG/PVG proves successful in ameliorating the immediate pain and autonomic deficits of SCI, or reverses symptoms in the longer term, a new treatment for individuals whose lives are severely degraded by these symptoms will become available. It will offer veterans and active service members with debilitating SCI the possibility of return to a productive and enjoyable life, including work activities that were not previously feasible.

2. Keywords

Spinal Cord Injury; Pain; Autonomic Dysreflexia; Deep Brain Stimulation; Midbrain.

3. Overall Project Summary

In this reporting period, study of the first two subjects was completed. A third subject was enrolled then subsequently decided not to participate due to an interest in receiving a different, incompatible treatment, and was de-enrolled. A fourth subject was enrolled and began the 52-week study in late September 2015.

Two major changes in the protocol were granted by the FDA and the two local IRBs (University of Miami and Miami VAH). First, we received permission to extend the study of subjects for another 104 weeks, to roughly 3 years, allowing analysis of longer term effects of DBS on SCI symptoms. Second, we received permission to use the Medtronic PC+S device, which allowed electrical brain activity to be recorded from the stimulating leads. This will be provide additional information about the treatment without its effect and with minimal additional procedures (a few minutes of data recording) for subjects. This device will be implanted first in Subject DBS004 Added costs will be funded internally by the University of Miami or Medtronic Inc. There have been no other changes substantially affecting the original approved Statement of Work (SOW), apart from some timing changes due to slower progress.

A no-cost extension has been requested to continue the work for one more year. We will continue accruing subjects according to the original proposal. This includes surgical implantation of DBS devices and longitudinal study or pain and other symptoms before and after. Regarding communication of findings, a second article focusing on detailed quantitative sensory evaluation of the first two subjects will be prepared and submitted. We will continue to attend meetings to report our progress. The PI or a co-investigator will present findings at the North American Neuromodulation Society meeting in Las Vegas in December.

The first subject (DBS001, male veteran) acquired a C5-C6 complete SCI in 1998. He was enrolled on 3/14/2014. His cranial surgery for electrode lead placement was done on July 23, 2014 and the generator was implanted on July 30 2014. This subject showed initially some good pain relief, but since then overall pain relief has been minimal. This subject left the study in early June 2015 after completing the entire protocol of one year, but enrolled in the 2 year continuation study.

The second subject (DBS002, female veteran) has a T10-T11 incomplete (ASIA B) injury since 1984. Lead implantation surgery took place on November 5 2014 and generator implantation on November 12 2014. This subject experienced dramatic bilateral pain relief, going from almost three decades with an overall score of 7-8. The pain relief has been stable a level of 1-2 for over 44 weeks. We found that unusually low frequencies are optimal for her analgesia, which is a new finding for the literature (see publication, Appendix B). The subject has experienced fewer leg spasms. Antispasmodic (pregabalin) dosage was tapered from 75 mg to 0 mg in February 2015. She also was enrolled for the 2-year continuation study.

The third subject (DBS003, male non-veteran) was enrolled on Feb 18, 2015, with a C6/C7 ASIA-B injury. After receiving a pain-relieving procedure (radiofrequency ablation) with an outside physician he decided not to participate further and was de-enrolled in June 2015.

The fourth subject (DBS004, male non-veteran) was enrolled on September 18, 2015, with a C5/C7 injury and ASIA-D disability. He is scheduled for his first surgery on December 2, 2015.

Statement of work, from grant proposal:

Task 1. Regulatory review and approval processes for studies of human subjects.
All completed.

Task 2. Setting up project
All completed.

Task 3. Recruitment of subjects
In progress.

Task 4. Enrollment of first subject
Completed.

Task 5. Pre-surgery testing, screening and consenting for first subject
Completed.

Task 6. Surgery for first subject
Completed.

Task 7. Post-surgery testing for first subject
Completed.

Task 8. Procedure on subjects after the first, following template of Tasks 4-7

8a Subject #2
Completed.

8b Subject #3
Subject withdrew.

8c Subject #4, months
In progress

8d Medical monitors routine review of first subjects
Completed 3/6/2015. Report attached (Appendix A).

8e Subject #5
Not started.

8f Subject #6
Not started.

8g Subject #7
Not started.

8h Subject #8
Not started.

8i Medical monitors routine review of last 4 subjects
Not started.

Task 9. Regulatory reporting

Annual reports were submitted to IRBs, FDA and Medtronic Inc. Quarterly reports were submitted on time to the DOD SCIRP.

Task 10. Publication and Dissemination of Findings

See Section 6 below.

4. Key Research Accomplishments

We found that best pain relief in both subjects studied occurred at a very low pulse rate (2 Hz, cycled on for 1 s and off for 2 s). This is a new finding for this therapeutic method. This discovery depended on frequent pain assessment by subject pain diaries and the ability of the subject to choose at home between several blinded programs that differed in frequency.

Pain changed over many hours to several days when new effective stimulation parameters were set. This confirms more rigorously what has been implied in previous reports for this method. Again, its demonstration depended on frequent pain assessment and a blinded choice of programs given to the subjects. We conclude that frequent pain assessment is need to correctly titrate stimulation parameters with this method.

Visual side-effects were the only observed complication of stimulation. These disappeared completely when a very low, maximally analgesic pulse rate was set. Thus this therapy is not only more effective at lower pulse rates, it is also safer, and stimulation parameters can be optimized for analgesia without evoking adverse effects.

5. Conclusion

Novel findings are that low mean frequencies are optimal for relief of SCI pain or other types of pain by DBS in the midbrain central gray (PAG/PVG). The frequencies also prevent adverse effects from gaze problems. Also, the time-course of changes in pain level after a change in stimulation in effective parameters can take several days. This knowledge, if replicated, can be used to increase significantly increase the probability of success with this treatment. Thus further replication and long-term study of subjects is the plan for the immediate future.

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6. Publications, Abstracts, and Presentations

1. One publication was submitted to Brain Research in August 2015 and subsequently the journal required a moderate revision. The recently submitted revision is attached as Abstract B.

2. One abstract was presented by Dr. Corneliu Luca to the American Neurological Association 2015 Annual Meeting, September 27-29, 2015, in Chicago.

3. One abstract was accepted for a future conference presentation by Dr. Corneliu Luca to be given in December 2015 at the Annual Meeting of the North American Neuromodulation Society in Las Vegas, NV.

7. Inventions, Patents and Licenses

Nothing to report.

8. Reportable Outcomes

Nothing additional to report.

9. Other Achievements

Nothing additional to report.

10. References

None.

11. Appendices

Appendix A. Safety Monitoring Board Report

Appendix B. Submitted manuscript.

Appendix A

Safety Monitoring Board Report

Phase 1 Study of Treatment of Pain and Autonomic Dysreflexia by Deep Brain Stimulation in Participants with Spinal Cord Injury

IDE 120202

Principal Investigators: Hentall I., Jagid J.

Reporting Period Covered in this Report: 01/01/14 to 02/28/15

The 2 members of the Safety Monitoring Board, Dr. Diana Cardenas, M.D., Chair, Department of Physical Medicine and Rehabilitation and Dr. R. Bullock, M.D., Ph.D., Director of Clinical Neurotrauma, JMH/UM, met with the two Principal Investigators and their two Clinical Coordinators. Summary and detailed data for the two currently enrolled subjects namely DBS001, 36 year old male and DBS002, 54year old female were reviewed in detail. The review included post-operative MRI scans after placement of the electrodes and pain scales, and neuro assessments pre and post insertion.

Main Finding

Although, both these patients report transient DBS related adverse events neither of these adverse events resulted in prolonged hospitalization, need for modification of therapy, or change to management as per the protocol. Both transient events disappeared spontaneously.

In the opinion of the two members of the Safety Monitoring Board the study should continue as planned.

Adverse Event Details

For the first subject DBS001, 36 year old male, C4 quadriplegia ASIA Impairment Scale grade A, the patient developed oscillopsia of the right eye following placement of the deep brain stimulation electrode. Oscillopsia was self-limiting, decreased in frequency over time and disappeared after programming frequencies had been changed with the deep brain stimulation system. It should be noted that the stimulation frequency chosen by the patient to achieve his own optimal pain relief was very low - approximately 7.2 to 1.8 Hz. This patient is now 28 weeks status post-placement of electrodes. There have been no further issues with oscillopsia. No other adverse events.

The patient has experienced some degree of improvement in the quality and character of his pain. The patient also has sustained some improvement in sensory function within the C5 and C6 dermatomes (previously insensate) after placement.

Appendix A

2-DBS002

This 54 year old female who sustained a parachuting electrocution accident as a result of contacting high voltage power lines, during a jump, is classified as T10 paraplegia. The patient also sustained burns as a result of the power line accident. This patient sustained post DBS electrode placement **Parinaud syndrome,** meaning that the patient developed difficulty with upward and medial gaze in both eyes. This persisted for approximately 2.5 weeks, resolving spontaneously and as with patient 1, the best pain relief was found at low frequency stimulation i.e. 0.67 Hz.

In the case of patient 2, follow-up has been approximately 25 weeks and the patients pain has reduced from 6-7 out of 10 on the pain assessment score to 1 to 2 on the pain assessment score, and the patient has been discontinued from all pain medications. No change in neurologic function has been seen in the patient.

It should be noted that the study is funded for 8 patients, approved for 12 by the UM IRB, and 2 have thus far been recruited.

Discussion. –the possibility of placing the electrodes 2-3 mm less caudal, i.e. less deep in the brainstem, in order to avoid the Median longitudinal fasciculus, (which is involved in eye movement control) was discussed with the PI's.

Respectfully submitted.

M Ross Bullock., MD, PhD; Diana Cardenas, MD

Appendix B

Title: Midbrain central gray best suppresses chronic pain with very low stimulation pulse rate in two human cases.

Running Head: Slow midbrain stimulation for central pain

Authors: Ian D. Hentall[a], Corneliu C. Luca[a], Eva Widerstrom-Noga[a], Alberto Vitores[a], Letitia D. Fisher[a], Alberto Martinez-Arizala[a, b], Jonathan R. Jagid[a].

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

Abstract

Appendix B

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.

Appendix B

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.

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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

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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 $p=0.001$).

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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).

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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 μs) 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 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).

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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 CT scans mapped onto pre-operative MRIs (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

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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 2^{nd} and 6^{th} 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). ISCIPBDS 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

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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.

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

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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 (± 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 ±0.00	5.53 ±0.52	0.351	1.5 ±2.1	0.95 ±1.25	0.842
Social-recreational ability	6.0 ±0.00	6.0 ±0.0	1.00	3.0 ±0.0	0.59 ±1.00	0.047
Social satisfaction	5.5 ±0.71	5.59 ±0.62	0.842	0.0 ±0.0	0.0 ±0.0	1.00
Daily activities	5.5 ±0.71	4.9 ±0.33	0.234	1.5 ±2.1	0.71 ±0.99	0.655
Mood	5.0 ±0.00	4.9 ±0.49	0.842	1.5 ±0.71	0.12 ±0.33	0.023
Sleep	5.0 ±0.00	3.8 ±0.92	0.047	4.5 ±0.71	0.59 ±1.18	0.012

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Figure captions

Figure 1. Merged images in three planes of post-operative CT scan and 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 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 µs, 3.7 V; right contacts cathode 8 and anode 11, pulse width 250 µs, 1.5 V. Subject 2, left contacts cathode 3 and anode 0, pulse width 180 µs, 4.5 V; right contacts cathode 11 and anode 8, pulse width 180 µs, 4.5 V. Pain scores were usually recorded twice daily; omissions were unavoidable in daily living and 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 with a newly selected parameter reflects the pain score after approximately 12 hours with that 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 µs 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 µs 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.

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Figure 1.

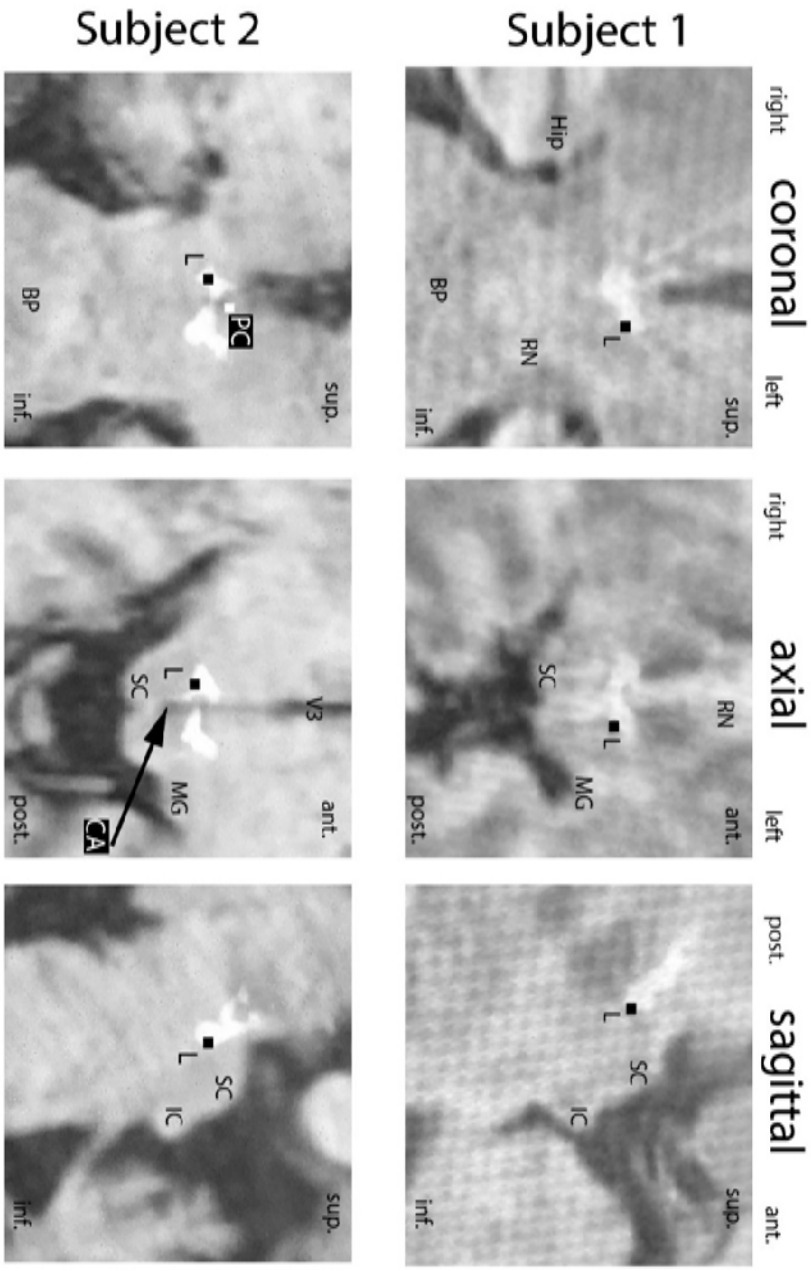

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Figure 2.

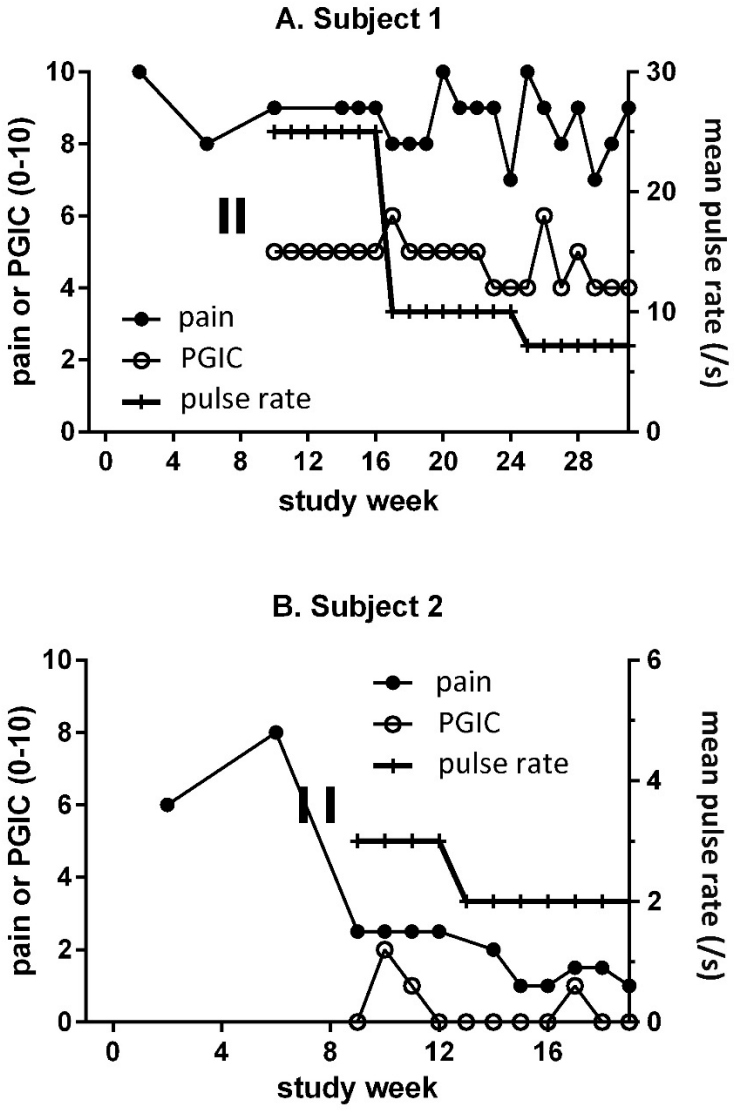

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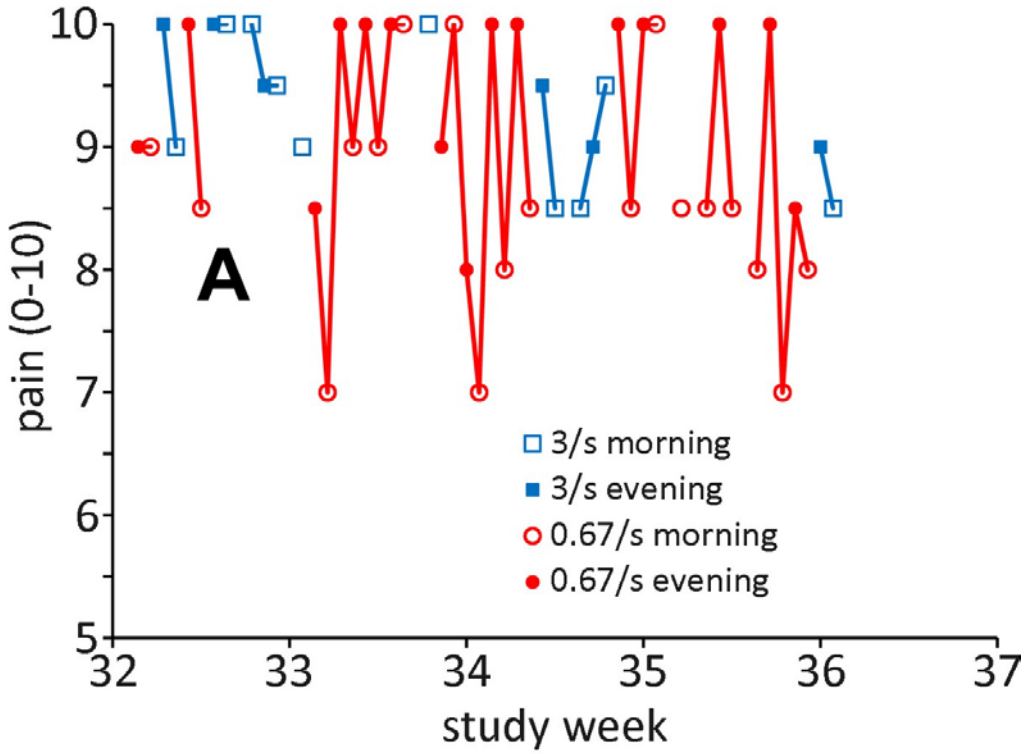
Figure 3.



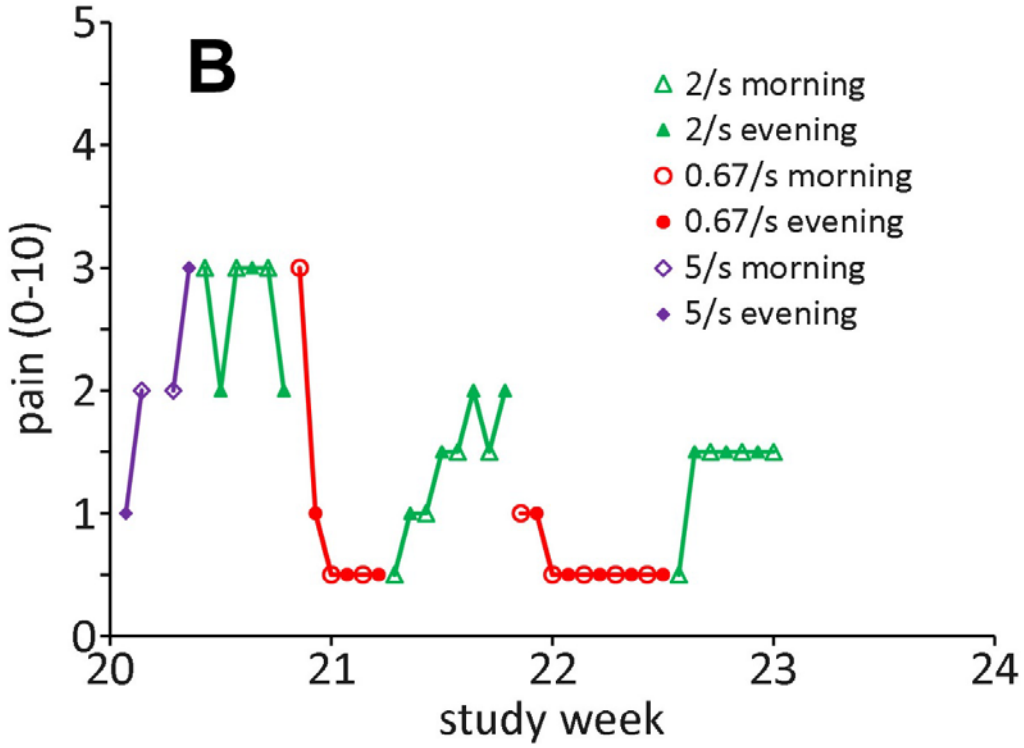


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Figure 4.