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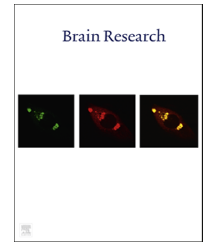

Research report

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

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ABSTRACT

Deep brain stimulation in the midbrain's central gray 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 central gray 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 (≤ 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.

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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 3 s or more, 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

2.1. *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. He 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. Subject 2 showed significant intraoperative and long-term reduction of central neuropathic pain. Postoperatively, she 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.

2.2. *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