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2012 Physiol. Meas. 33 2003

(http://iopscience.iop.org/0967-3334/33/12/2003)

IOP PUBLISHING PHYSIOLOGICAL MEASUREMENT

Physiol. Meas. **33** (2012) 2003–2015 doi:10.1088/0967-3334/33/12/2003

A new device concept for directly modulating spinal cord pathways: initial *in vivo* experimental results

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Received 26 June 2012, accepted for publication 28 September 2012
Published 15 November 2012
Online at stacks.iop.org/PM/33/2003

Abstract

We describe a novel spinal cord (SC) stimulator that is designed to overcome a major shortcoming of existing stimulator devices: their restricted capacity to selectively activate targeted axons within the dorsal columns. This device overcomes that limitation by delivering electrical stimuli directly to the pial surface of the SC. Our goal in testing this device was to measure its ability to physiologically activate the SC and examine its capacity to modulate somatosensory evoked potentials (SSEPs) triggered by peripheral stimulation. In this acute study on adult sheep ($n = 7$), local field potentials were recorded from a grid placed in the subdural space of the right hemisphere during electrical stimulation of the left tibial nerve and the spinal cord. Large amplitude SSEPs (>200 μV) in response to SC stimulation were consistently obtained at stimulation strengths well below the thresholds inducing neural injury. Moreover, stimulation of the dorsal columns with signals employed routinely by devices in standard clinical use, e.g., 50 Hz, 0.2 ms pulse width, produced long-lasting changes (>4.5 h) in the SSEP patterns produced by subsequent tibial nerve stimulation. The results of these acute experiments demonstrate that this device can be safely secured to the SC surface and effectively activate somatosensory pathways.

Keywords: neuromodulation, spinal cord stimulation, intradural device

(Some figures may appear in colour only in the online journal)

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Introduction

Spinal cord stimulation (SCS) was first employed clinically in 1967 (Shealy *et al* 1967, 1970). This novel surgical treatment was developed as a therapeutic extrapolation of the Melzack and Wall 'gate theory' of pain modulation (Melzack and Wall 1965), and SCS devices were placed initially in cancer patients suffering from medically refractory pain. Over the ensuing decades the clinical indications for SCS and the devices themselves have evolved significantly (Atkinson *et al* 2011). At present, over 35 000 SCS devices are surgically implanted each year in North America alone (Kumar and Bishop 2009), largely for treatment of medically refractory chronic pain, and there is now clear evidence that this approach indeed reduces certain chronic pain symptoms (Kumar *et al* 2007, North *et al* 2007).

The physiological mechanisms that mediate therapeutic effects of SCS are poorly understood and are the subject of extensive ongoing research (Linderoth and Meyerson 2010, Oakley and Prager 2002). One particularly useful research method has involved the development of computational biophysical models to study the distribution of electrical current densities within realistic representations of the human spinal canal and cord (Holsheimer 2002, Struijk *et al* 1991). Models correlating electrical field distributions with the locations of spinal cord pathways provide a conceptual framework that is used to inform the design of new devices and improve stimulation paradigms (Holsheimer and Wesselink 1997, North 2008). Given that close to half of all implanted patients do not experience significant sustained benefit from SCS, there is a pressing need for such improvements (Eldabe *et al* 2010, Taylor *et al* 2005).

In this report, we describe a new device concept that is designed to overcome the most significant deficiency of the present epidurally placed SCS devices: their limited capacity to selectively activate targeted axons within the spinal cord. The concept for the new intradural stimulator that we present here is intended to overcome this deficiency, allowing the neurosurgeon to selectively activate virtually any pathway within the spinal cord. A description of this concept from the general medical physics perspective is available elsewhere (Howard *et al* 2011a) as are the technical details of various preclinical testing protocols for it (Howard *et al* 2011b, Oya *et al* 2012, Wilson *et al* 2012). We have also developed fixation techniques used to position and stabilize this device (Gibson-Corely *et al*), which is termed the Iowa-Patch^{TM} or I-Patch, on the surface of the spinal canal. In what follows, we present the results from the first *in vivo* test of the neurosurgical implantation of an early I-Patch prototype onto the pial surface of the spinal cord in a large animal model.

Materials and methods

The I-Patch concept

The I-Patch concept was designed to circumvent existing barriers to delivering electrical stimuli to select spinal cord pathways. One such barrier is the relatively high-conductivity cerebrospinal fluid (CSF) that surrounds the spinal cord. The electrical shunting effect of the CSF can be ameliorated significantly by placing a very thin, malleable electrode array directly on the pial surface of the spinal cord, thus enabling selective activation of spinal cord pathways that are in close proximity to the spinal cord surface. In these first *in vivo* studies, we chose to secure the implant to the surface of the spinal cord using a dentate ligament attachment technique (Gibson-Corely *et al*). In that arrangement, the surface-array electrodes would protrude approximately 1/3 mm from the underside of the I-Patch body and only their tips would be in direct contact with the pial surface, in order to accommodate the surface blood vessels and to allow for free movement during the spinal cord's pulsations.

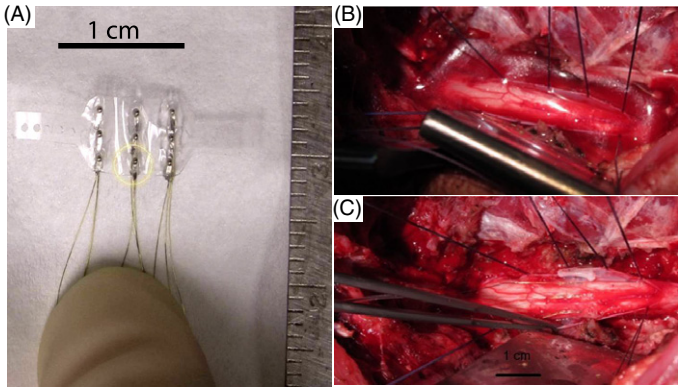

Figure 1. (A) Photograph of the prototype I-Patch device used in the ovine *in vivo* experiments (ventral view). There are nine electrodes mounted on the underside of the nearly transparent, 0.13 mm thick silicone film, the arms of which were attached to the dural-construct, dentate ligament surrogates. The yellow circle highlights the contact used during *in vivo* stimulation. (B) The dura is reflected to reveal the pial surface of the ovine spinal cord. (C) The I-Patch in place on the spinal cord, with the attachment arms secured to the dural-construct dentate ligament surrogates by Weck clips.

Our original design called for the clinical I-Patch to incorporate a receiver coil and microelectronics into the body of the device so that power and control signals could be conveyed to it wirelessly by an epidural transmitter (Howard *et al* 2011a, Song *et al* 2012). Wireless control of epidural neuromodulators and various neuroprostheses has been reported by a number of workers (Hsu *et al* 2011, Mandal and Sarpeshkar 2008, Sharma *et al* 2010) and the corresponding design requirements for an intradural device like the I-Patch are within the capabilities of existing microfabrication technology. However, because of the large development costs for such a system, we chose to perform our initial feasibility studies with a simpler wired version of the device. Our first *in vivo* test results, described below, were obtained using a prototype designed specifically for acute experiments in anesthetized sheep, and the primary goal of our work was to measure I-Patch physiological activation threshold characteristics using electrical stimulation-induced somatosensory evoked potentials.

Wired I-Patch

The I-Patch devices were built to custom specifications by Evergreen Medical Technologies, LLC (St. Paul, MN, USA). The body of the wired I-Patch is constructed from 0.13 mm thick transparent silicone. As shown in figure 1(A), attachment arms for securing the device to the dentate ligaments extend laterally approximately 6 mm from either side of the body. There are nine hemispherical 90/10 platinum–iridium electrodes, nominally 0.5 mm in diameter, embedded into the I-Patch in a 3×3 rectangular grid that occupies 28 mm^2, and which is designed to achieve the optimal coverage of the dorsal columns of the sheep spinal cord. The electrode leads are of 44 AWG (0.05 mm) MP35N wire with polyimide insulation, approximately 50 cm long. The leads are connected to a Tucker-Davis Technologies IZ2 stimulator (Alachua, FL, USA) which is able to apply signals to the electrodes over the range from 0.2 to 20 V. With reference to figure 1, the cathode for monopolar stimulation was placed over the midline dorsal surface of the spinal cord, an area heavily representing ascending sensory fibers of the lower extremity (Smith and Deacon 1984). The anode electrode was

placed in subcutaneous tissue. The *in situ* impedance measurements for the electrodes ranged from 28 to 41 kΩ.

Experimental preparation

Sheep ($n = 7$) were selected as the preferred I-Patch experimental animal model for several reasons. The size and configuration of the sheep spinal cord and spinal canal are well suited for studies of I-Patch mechanics and investigations of electrical interface properties between electrode contacts and the spinal cord. Additionally, the anatomy and physiological properties of the sheep peripheral and central somatosensory systems are well described (Dolan and Nolan 2002, Flo *et al* 2009, Ghazi and Gholami 1993a, 1993b, Herrero and Headley 1995a, 1995b, 1995c, Johnson *et al* 1974, Rose 1942, Vialle *et al* 2006, Wilson and Beerwinkle 1986). The institutionally approved, acute, non-survival experiments described in this report were all carried out under general anesthesia: inhaled isofluorane was used for induction and during the surgical dissections, followed by continuous infusion of propofol (0.4 mg kg^{-1} h^{-1}) during experimentation and data acquisition. Body temperature and blood pressure were maintained within normal limits throughout the experiments.

Following induction of anesthesia a right-sided hemicraniectomy was performed and the dura opened to expose the lateral surface of the hemisphere. Local field potentials were recorded using a 3.3 × 2.1 cm, 60 contact grid array with an inter-contact spacing of 2.3 mm (Ad-Tech Medical Instruments, Racine, WI, USA) positioned over the somatosensory cortex. (The position of the array relative to the cortical surface and the numbering pattern for the contacts are shown in figure 3(A)). In two sheep, a multi-level thoracic laminectomy was performed centered at the T8–9 levels. The dura was incised and reflected to achieve broad exposure of the spinal cord. In one of these two sheep, the wired I-Patch was gently draped over the dorsal surface of the spinal cord and the dentate ligament attachment arms were secured to the lateral dura using polymeric Hem-o-lock™ clips (length = 5 mm, cross-section = 1 mm) (Teleflex Inc., Research Triangle Park, NC). A dural attachment technique was used because the sheep dentate ligament is too small to accurately replicate the anatomical properties of the human dentate ligament (Gibson-Corley *et al*).

Following surgical exposure, a series of electrophysiological experiments was performed. In order to delineate the anatomical boundaries of the sheep somatosensory cortex and define baseline SSEP response characteristics, electrical stimuli were delivered through needle electrodes to the surgically exposed left tibial nerve in all seven sheep, while SSEPs were recorded from the right-sided cortical grid (*constant current* mode, 0.2 ms square wave, inter-stimulus interval = 1.4 s). The intensity of the tibial nerve electrical stimuli was systematically varied to determine SSEP threshold and study the effects of stimulus intensity on cortical responses. In one sheep, SSEPs were recorded in response to electrical stimuli delivered directly to the spinal cord through I-Patch electrode contacts (*constant voltage* mode, 0.2 ms square wave, inter-stimulus interval = 1.4 s). The intensity of I-Patch electrical stimuli was also systematically varied to determine SSEP thresholds. After these peripheral nerve and direct SCS thresholds were determined, an additional experiment was carried out to see how I-Patch electrical stimulation modulated the SSEP recorded in response to tibial nerve electrical stimulation. During this experiment, electrical stimuli were continuously delivered through the I-Patch (0.2 ms pulse width, 50 Hz pulse train, 15 min total duration). At the same time, SSEPs were recorded in response to tibial nerve electrical stimulation (0.2 ms pulse width, 0.5 Hz pulse train, 15 min total duration).

In a separate supplementary experiment, a simple two-pole neurostimulator with a pair of hemispherical electrodes at its tip (see the Results section, figure 4(A)) was used to deliver

monopolar constant voltage stimuli (1 and 9 V; 0.1 ms pulse width, ISI = 1.4, number of presentations = 80) to the medial aspect of the dorsal columns. The purpose of this experiment was to elucidate the low voltage requirements of the intradural approach and explore its capability to activate dorsal column fibers when compared to the standard epidural approach.

At the completion of the electrophysiological experiments the animal was sacrificed and the exposed spinal cord was resected and processed for histological analysis. The specimens were fixed in 4% paraformaldyhyde for 48 h, followed by secondary fixation with 10% neutral buffered formalin for another 72 h. The spinal cord segments were serially cross-sectioned and routinely processed, embedded, further sectioned (4 μm), and stained with hematoxylin and eosin (H&E) for histological examination.

Results

The surgical preparation was effective in achieving the required exposure of the right hemisphere of the brain, the T8–10 region of the spinal cord, and the left tibial nerve. Representative intraoperative photographs of spinal cord exposure and subsequent fixation of the I-Patch are shown in figures 1(B) and (C), respectively.

Large amplitude, tibial-nerve stimulation SSEPs were consistently recorded in all seven sheep, per the example shown in figure 2(A), over cortex abutting and immediately adjacent to the anterior suprasylvian sulcus, consistent with a prior report describing the location of sheep somatosensory cortex (Johnson *et al* 1974). Direct electrical stimulation of the spinal cord through the I-Patch resulted in SSEPs with cortical topographic distributions that conformed closely to those observed following tibial nerve stimulation (TNS), as shown in figure 2(B). The midline position of the IPATCH contact (figure 1(A)) allowed us to stimulate the medial region of the dorsal column which is predominantly carrying sensory input from the ipsilateral lower extremity (Smith and Deacon 1984). This in turn allowed subsequent comparison to, as well as modulating response from, TNS. At stimulation strengths well above the I-Patch threshold, the area of I-Patch stimulation-induced brain activation expanded into other cortical regions as well. Although the spatial distribution of cortex activation differed slightly for averaged evoked potential waveforms and spectro-temporal power displays, the stimulus intensity thresholds required to induce a response were the same for the two different analytical approaches. These threshold values required to achieve cortical activation with I-Patch electrical stimulation ranged from 3.0 to 3.5 V. Increasing I-Patch stimulus strength beyond threshold was associated with a ceiling effect whereby the magnitude of SSEP responses remained stable as stimulus intensities were incrementally increased. Full details of the ceiling threshold measurements and their biophysical interpretation will be published elsewhere (Flouty *et al*).

Continuous activation of the I-Patch using stimulus parameters relevant to clinical SCS (50 Hz, 0.2 ms pulse width) markedly altered cortical evoked responses and high-gamma-band envelope in response to TNS (figures 3(B) and (C) respectively). This strong modulatory effect of I-Patch stimulation on somatosensory processing was even observed at stimulus strengths below threshold for generating an I-Patch stimulation-evoked cortical response. In general, the patterns of these modulatory effects were complex. For instance, a wide range of cortical response changes were noted, including decreases and increases in ECoG power, and alterations in averaged evoked potential waveform amplitudes and morphologies that differed across brain sites (figures 3(B), (C) and 5). Of note, high frequency stimulation (HFS) was able to attenuate and sometimes abolish high-gamma-band envelope peaks occurring approximately 100 ms after TNS, figure 3(C). These findings reflect the robust and complex effects of SCS on supraspinal processing of sensory stimuli.

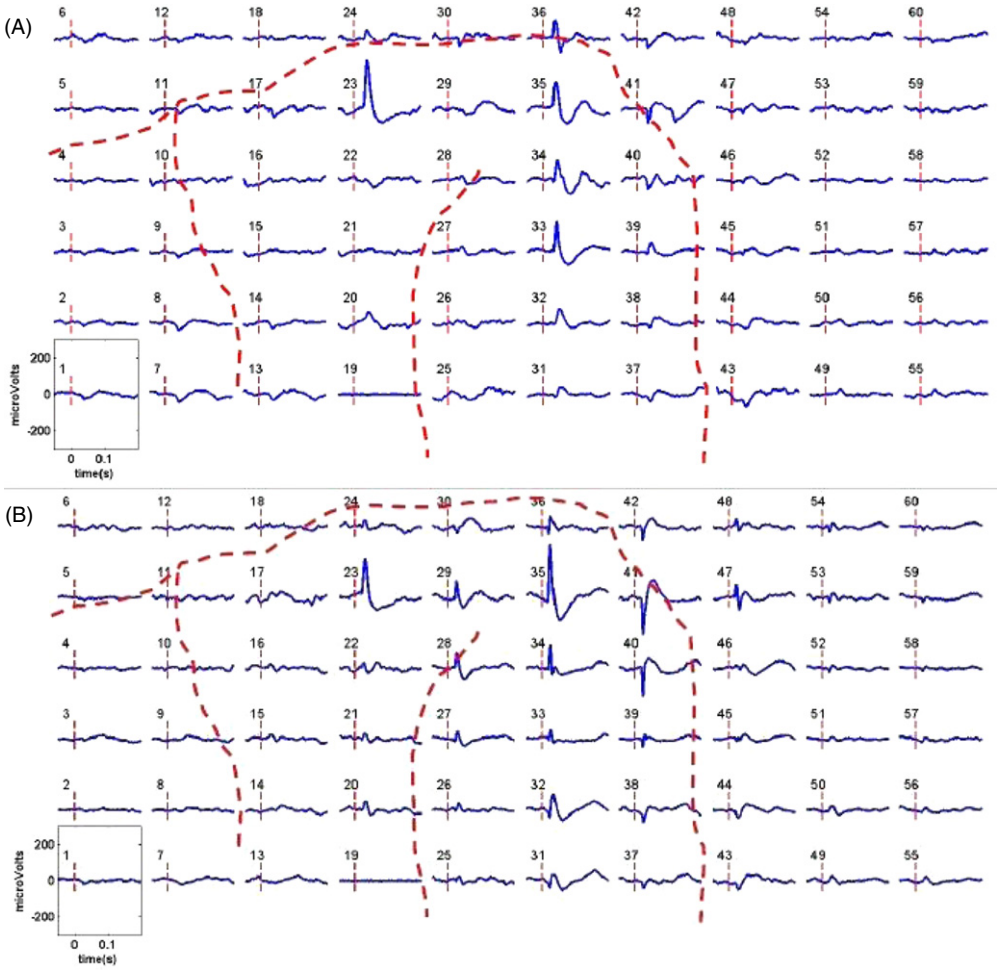

Figure 2. (A) Average evoked waveforms in response to tibial nerve stimulation (TNS) (12 V, 0.2 ms pulse width, ISI = 1.4 s). (B) Average waveforms in response to I-Patch stimulation (12 V, 0.2 ms pulse width, ISI = 1.4 s). The dashed lines delineate the anterior suprasylvian and the sylvian sulci relative to the contact locations on the grid from which the respective waveforms were recorded.

When comparing epidural with intradural stimulation, cortical activation was achieved at lower voltages with intradural stimulation (figure 4). At 1 V average evoked potentials and high-gamma-band envelope were clearly observed with intradural but not with epidural placement of the neurostimulator. When the signal strength was increased to 5 V, both locations elicited a cortical response as seen by the average waveforms and high-gamma-band envelope curves. However, the magnitude of the response was higher when the neurostimulator was placed intradurally (figure 4(B)). Flouty *et al* present other data on and a more detailed comparison of these modes of stimulation.

Histological analysis of the sheep spinal cord tissue directly under the I-Patch implants showed no evidence of neuronal cell loss, tissue disruption or demyelination. Blood vessels within the pia-arachnoid membranes in direct contact with the I-Patch device showed no evidence of thrombosis, as per the pathology finding shown in figure 6.

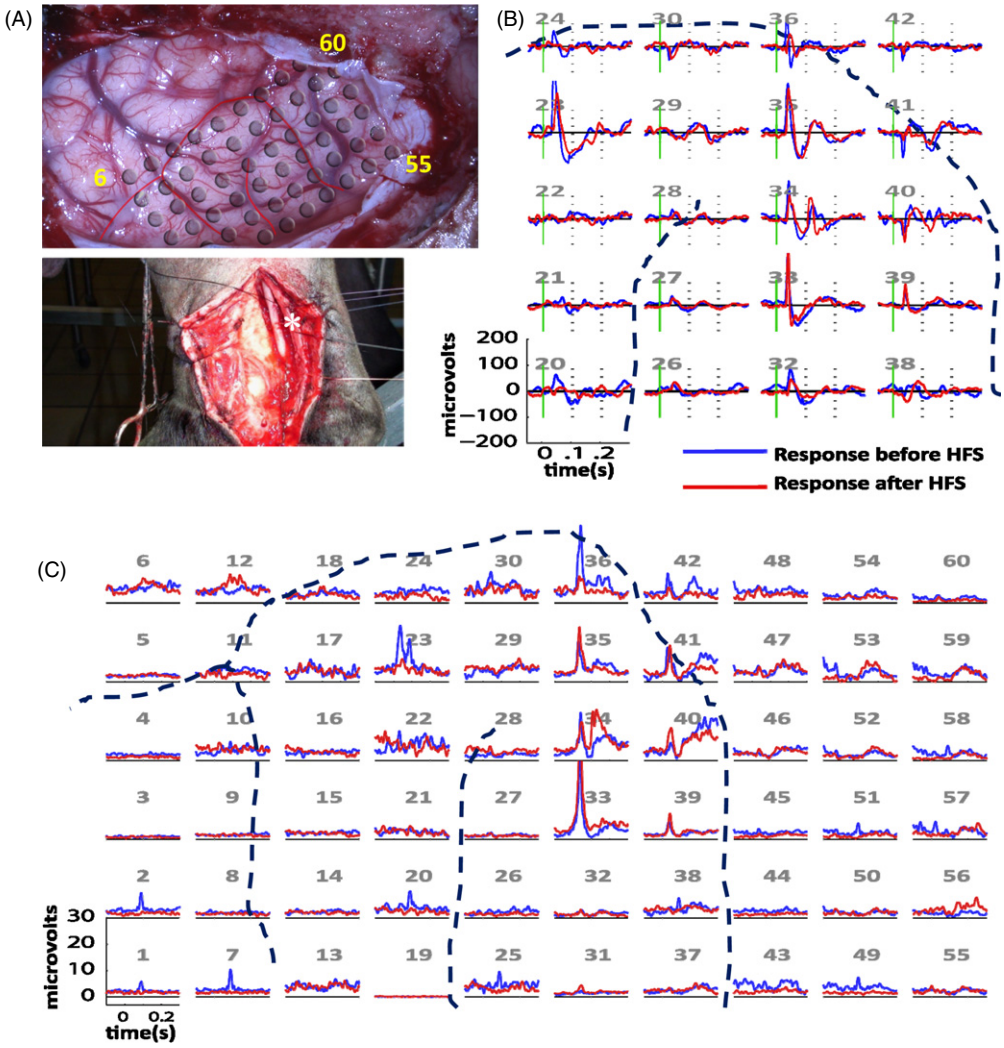

Figure 3. (A) Upper figure: Hemicraniectomy revealing the anterior suprasylvian sulcus (demarcated by a red inverted U) and the position of the recording array numbered contacts shown in yellow. Lower figure: tibial nerve exposure (asterisk marks the nerve). (B) Zoomed version of the average evoked potential results showing SSEPs in response to TNS before (blue trace) and after (red trace) high frequency stimulation (HFS). Vertical bars are placed to aid in appreciating the time course of the response (green bar represents stimulus onset). (C) Time-varying high-gamma-band envelope in response to TNS over the whole subdural grid (presented in A). Blue and red traces represent response before and after HFS, respectively. Many peaks are abolished or attenuated after HFS. The dashed blue lines indicate position of major sulci shown in part A (red trace).

Discussion

In order to selectively activate targeted structures within the spinal cord it is necessary to deliver supra-threshold levels of electrical stimuli to the targeted sub-region of the spinal cord while at the same time exposing nearby non-targeted structures to only sub-threshold levels. For example, when targeting axons within the laterally positioned low back somatotopic region of the dorsal columns to achieve pain relief, activation of the immediately adjacent

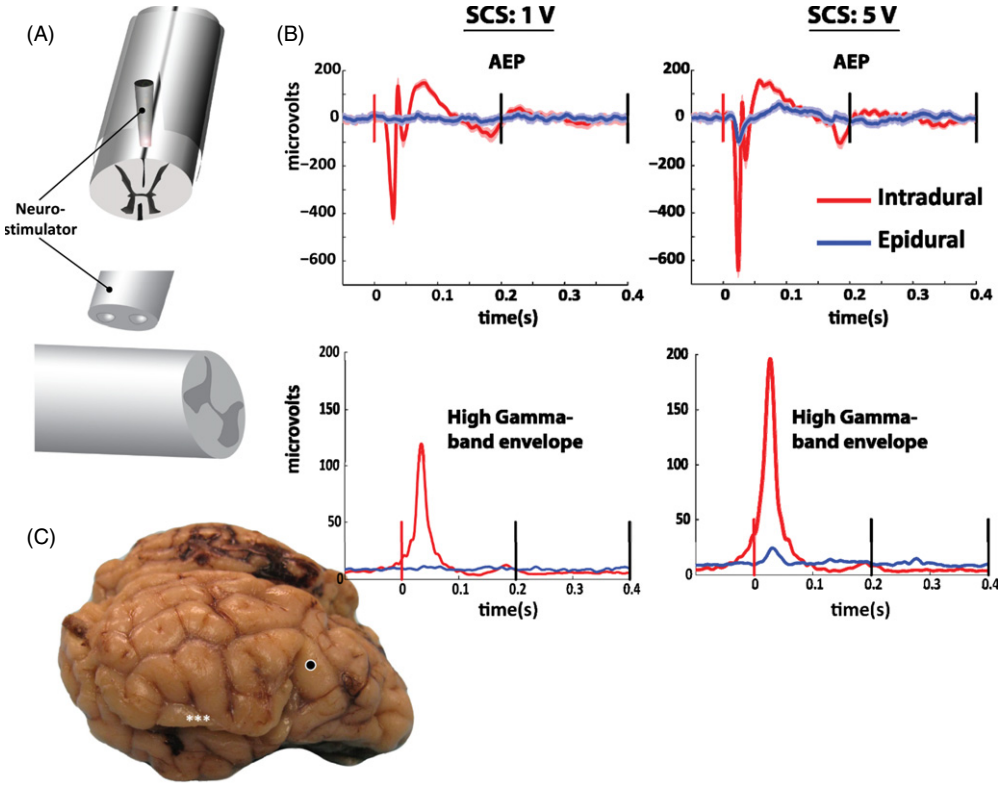

Figure 4. (A) Experimental setup showing the bipolar neurostimulator placed over the dorsal surface of the sheep's spinal cord (upper figure). Monophasic constant voltage stimulation was performed with the dura intact and post-durotomy. The lower figure shows the shape and configuration of the bipolar leads that delivered the electrical pulses. Contact diameter is 1 mm and inter-contact distance is 2 mm (cathode was rostral). (B) Average evoked potentials (upper two graphs) at 1 volt (left) and 5 volts (right) following spinal cord stimulation (SCS) using the setup described in A). Red and blue traces represent intra- and epidural stimulation respectively. The thickness of the line represents the 95% confidence interval (1.97 × SEM). The lower two graphs represent the time-varying high-gamma-band envelope. (C) post-mortem brain of the sheep showing the contact location situated just posterior to the anterio-most bank of the supra-sylvian sulcus. Asterisks show an area of brain disruption which is an artifact that occurred during extraction of the brain.

dorsal rootlets must be avoided, as rootlet activation is associated with aversive sensations and uncomfortable reflex activity. The inability to achieve these conditions is thought to be an important contributing factor to poor outcomes in many patients, and this theory is supported by the results of finite element computational models that objectively quantify the spatial distribution of extradurally driven current densities inside and around the spinal canal (Holsheimer 2002, Struijk *et al* 1991). As shown in such studies, there is a steep gradient of stimulation effects on or within neural tissue as a function of distance from a stimulating electrode on or within neural tissue, and it is becoming clear that >95% of all the potentially targetable fibers cannot be activated within the therapeutic window available to standard epidural stimulators.

One of the reasons for this situation is that in humans the dorsal spinal cord surface and overlying dura are separated by a layer of CSF that has a conductivity ∼20 × larger than that found transversely in the SC white matter. In the thoracic spine the CSF layer can be up to

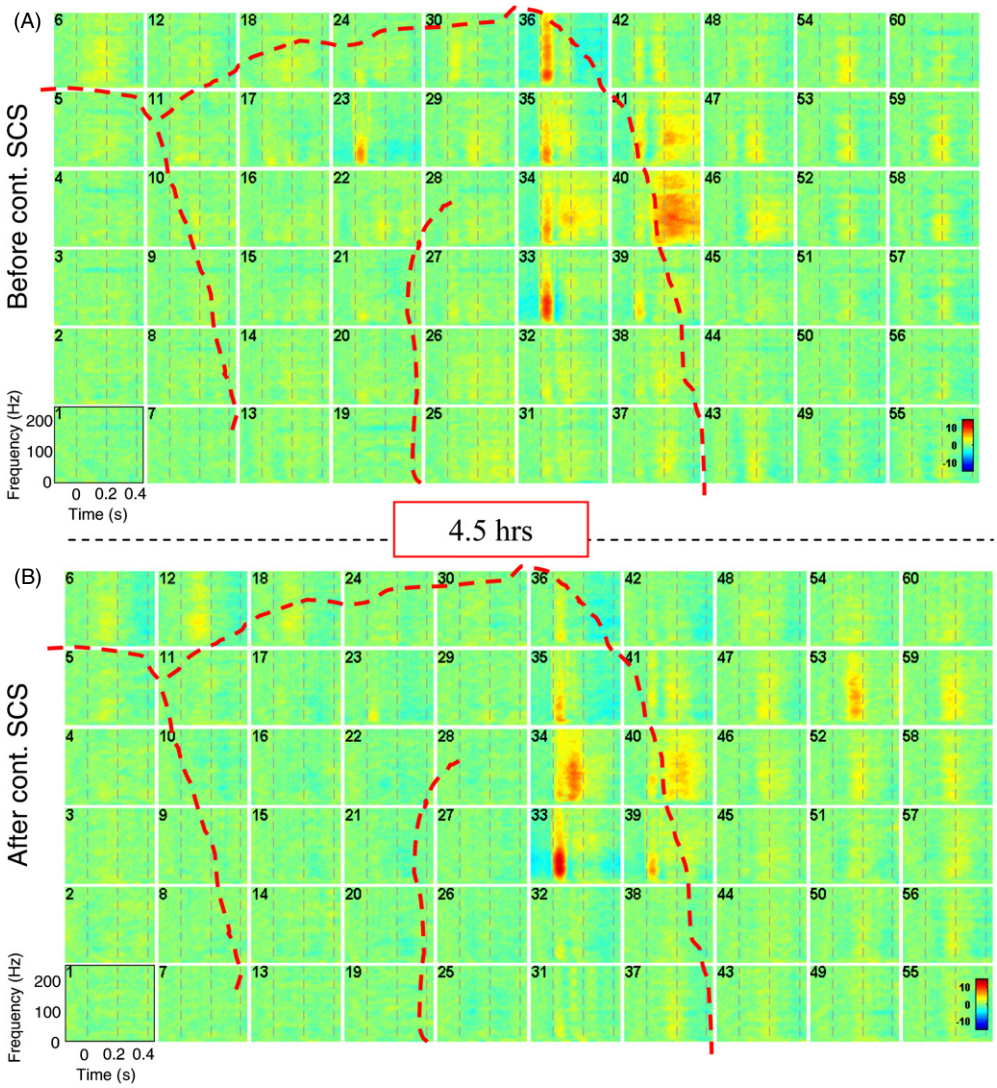

Figure 5. Comparison between two periods before and after 15 min of continuous SCS separated by 4.5 h. Multi-taper short-time Fourier transform was used to derive the time-frequency plots of each channel for the period corresponding to 200 ms before and 400 ms after TNS. Each plot represents a single channel. The x-axis represents time from -200 to 400 ms in relation to stimulation time 0 s. The y-axis represents frequencies from 0 to 250 Hz, and color represents the power in decibels (range -10 to 10 dB). The period before continuous SCS is shown in (A), while the period after continuous SCS is shown in (B). It is visually evident that cortical activation in response to TNS was depressed in some contacts following 15 min of a continuous train of SCS. The dashed lines show the locations of the suprasylvian and sylvian sulci relative to the contact locations on the grid from which the respective waveforms were recorded.

10 mm thick (Lee *et al* 2010). As a result, the source currents of up to 5–8 mA in amplitude (Schade *et al* 2010) delivered through extradural electrodes, which can have surface areas as large as $\sim$10 mm^2, are attenuated within the low-resistivity CSF ($\rho = 60\ \Omega$ cm) and are spatially diffused. It can thus be difficult for epidural stimulators to selectively activate targeted neural pathways within particular dermatome layers (which might be $\sim$400 μm $\times$ 2 mm in

Figure 6. Representative photomicrograph of the sheep spinal cord that was in direct contact with the I-Patch. H&E, scale bar = 1 mm. The box contains the magnified image shown in the inset, highlighting the pial blood vessels on the dorsal surface of the spinal cord (scale bar = 100 μm).

cross-sectional size) without stimulating nearby non-targeted structures. Shunting of the current by the CSF also leads to power inefficiencies since the dissipation levels can vary from 1 to 45 mW for presently used stimulators, which typically operate at frequencies of 20–100 Hz, pulse widths on the order of 100 μs, and corresponding low-end duty cycles of 0.2%. As noted above, in patients with pain localizing to the low back, these are particularly significant limitations because the axons processing sensory information from the low back are thought to be somatotopically positioned immediately adjacent to the dorsal root entry zone (Davidoff 1989, Feirabend *et al* 2002, Smith and Deacon 1984).

The I-Patch system seeks to overcome these difficulties by positioning small electrodes directly on the targeted sub-regions of the spinal cord. Direct SCS strategies exploit the steep gradient effects, exposing targeted tissue to the supra-threshold levels of stimulation, while nearby non-targeted tissues fall within regions of the gradient that are below the activation threshold. In contrast, considerable distances and intervening layers of tissues and fluids separate stimuli delivered to the epidural space from both targeted and non-targeted spinal cord structures. In that setting, the targeted and non-targeted spinal cord regions are in closer proximity to each other than either region is to the stimulating electrode, thus making it impossible to create sharp stimulation effect gradients between the two regions. The results of our *in vivo* experiments are consistent with models predicting steep declines in stimulation effect thresholds as a function of distance from the stimulating electrode, as well as the effects of intervening tissue (e.g., dura mater) positioned between the stimulating electrode and spinal cord. While our findings provide initial support for the improved stimulation scenario described above, they are nevertheless limited in scope and much additional work will be needed in order to establish the potential advantages of the direct intradural approach. We have taken some steps in that direction via our ongoing investigations of epidural versus intradural protocols (Flouty *et al*). However, evaluations of SSEP responses arising from other peripheral nerve

locations, as well as controlled testing of the effects caused by varying the stimulus signal parameters in the appropriate acute and chronic *in vivo* models, will also be needed.

The acute, *in vivo* ovine experiments described here also demonstrated the technical workability of securing a highly malleable I-Patch implant directly to the spinal cord and electrically activating the somatosensory system without causing tissue injury. In the acute intra-operative setting, it was feasible to gently drape the I-Patch device over the dorsal surface of the cord and achieve direct mechanical coupling between the electrode contacts and the pial surface. The results demonstrate the utility and mechanical safety of the lateral fixation technique that was employed. Large amplitude somatosensory evoked potentials in response to I-Patch electrical stimulation were consistently obtained at stimulation strengths that are well below the threshold for creating stimulation-induced neural injury (McCreery *et al* 2004). I-Patch electrical stimulation of the dorsal columns also produced long-lasting changes in the patterns of somatosensory evoked responses to subsequent TNS. Because of safety considerations and various technical barriers to human experimentation, there are no comparable data published examining the effects of SCS on brain electrophysiological responses to somatosensory system activation in patients, thus adding to the uniqueness of the large animal model results presented here. Histological analysis of explanted spinal cord tissue showed no evidence of surface blood vessel thrombosis or tissue injury resulting from securing the malleable I-Patch onto the spinal cord surface. Although these preliminary electrophysiological studies were designed to facilitate medical device development, the robust and complex nature of the brain responses observed using an intracranial recording method highlight opportunities for future basic neuroscience investigations examining the influence of ascending spinal cord pathway signals on cortical signal processing.

Current technical limitations of this wired version of the I-Patch include CSF leak and tethering of the spinal cord. In order to reduce these risks, the clinical I-Patch system will include device design features that make use of FDA approved dural substitute materials to enable the surgeon to achieve a water-tight seal of the dura at the completion of the implantation procedure. A completely alternative approach to avoiding such complications would be to incorporate a wireless receiver into the implant, as discussed above.

Conclusions

The results of these acute experiments demonstrate that the very soft, flexible I-Patch electrode array can be safely attached to the spinal cord surface using a lateral fixation technique and effectively activate somatosensory spinal cord pathways. Our experimental protocol also demonstrated the ability of this approach to modulate the SSEPs produced by TNS, up to 4.5 h post-excitation. We have also shown that intradural stimulation requires a lower voltage to activate specific targets in the spinal cord when compared to epidural stimulation. This finding can prove to be very important given its implication on the therapeutic window and battery life. Therefore, a separate study should be made to further quantify the differences between epidural and intradural stimulation. Future experiments will examine the safety and efficacy of chronically implanted I-Patch devices in behaving animals, using quadruped gait-analysis techniques and other appropriate measures of performance.

Acknowledgments

We thank our University of Iowa colleagues D Fredericks, B D Dalm, N S Dahdaleh and Haiming Chen for assistance with the experimental arrangements and for several useful

discussions. The prototype I-Patch devices were made by Evergreen Medical Technologies, LLC, and we thank R Shurig, S E Scott and R S Nelson for their careful device assembly efforts and pre-deployment performance checks. The work was funded in part by the University of Iowa GIVF Seed Funds Program, the University of Virginia Biomedical Innovation Fund, and the Kopf Family Foundation, Inc.

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