

Minimally-invasive recording of action potentials in the human spinal cord: applications

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Electrical stimulation of the spinal cord provides effective pain relief to hundreds of thousands of chronic neuropathic pain sufferers. The therapy involves the implantation of an electrode array into the epidural space of the subject and then stimulation of the dorsal column (DC) with electrical pulses. The stimulation depolarises neurons and generates propagating action potentials which interfere with the perception of pain. Despite the success of the therapy in about 65% of eligible patients¹, the mechanism of action is not understood and no direct evidence of the properties of neurons being stimulated has been presented. Here we report novel measurements of evoked compound action potentials from the spinal cords of patients undergoing stimulation for pain relief. The results reveal that A β sensory nerve fibres are recruited at therapeutic stimulation levels and the amplitude of the A β potential correlates with the degree of coverage of the painful area. Other nerve fibres recruited coincident with stimulation generate uncomfortable side-effects. Our results contribute toward efforts in the field to define the mechanism of spinal cord stimulation (SCS). The minimally-invasive recording technique we have developed provides data

that previously was obtained only through micro electrode techniques in spinal cords of animals **ref JC Eccles first to measure postsynaptic inhibitory potentials from the SC**. Neuropathic pain models in animals have revealed extensive neuroplasticity changes^{2,3,4}, however no direct evidence has been reported in humans. The new techniques reported here will enable such investigations. Our observations also allow the development of systems that utilise neuronal recording in a “feedback loop” to control neurostimulation on a continuous basis and deliver more effective pain relief. There are a large number of additional neuromodulation treatments which can benefit from this technique.

Background

Introduction to SCS as a therapy

Spinal cord stimulation (SCS) induces paraesthesia, a pleasant tingling sensation, as a result of the stimulation of nerve fibres in the dorsal column (DC). The qualitative description of the induced sensation has been used to hypothesise that $A\beta$ fibres, which carry touch and pressure information, are recruited during SCS⁵. Inducing this artificial sensation replaces the feeling of pain in the body areas innervated by the stimulated fibres. The goal of SCS is to completely cover – in a perceptual sense – the area of pain with paraesthesia, as it has been established that a high level of coverage is essential for effective pain relief⁶.

History of SCS and its mechanisms

SCS was first attempted⁷ in the 1960s following research into the “gate control theory” of pain, where it was observed that non-noxious (e.g. touch and vibration) activation of surface fibres in the DC of the spinal cord inhibits pain transmission by a “gate” at the spinal segmental level⁸. This idea is generally accepted but the details are absent and the literature on the mechanisms of SCS is sparse and contradictory.

Meyerson et. al. have postulated that SCS ameliorates pain through gamma-aminobutyric acid (GABA)ergic and adenosine related inhibitory mechanisms^{5,9}. They propose that electrical stimulation of spinal cord afferents produces orthodromic and antidromic action potentials⁹, and that the antidromic activity regulates transmission of pain via an interneuron pool and second order wide dynamic range (WDR) neurons. Further, Meyerson et. al. propose that SCS recruits the A β fibres in the DC. However, even this has never been directly demonstrated in humans.

El-Khoury et. al. have tried to determine if the therapeutic effect of SCS occurs through segmental or supraspinal mechanisms. In a rat model of neuropathic pain they employed SCS rostral to a spinal cord lesion and produced strong inhibitory effects on the model-generated allodynia, suggesting that inhibition is activated by the ascending A β fibres¹⁰. The role of ascending activation versus local activation at the segmental level is currently not understood.

In order to provide more direct evidence of these mechanisms, we have studied the electrical responses of the spinal cord in humans with chronic pain receiving SCS treatment.

Previous research on number of fibres recruited during SCS

Evidence for the recruitment of particular fibre types during SCS has previously been restricted to simulated models. A β fibres are the largest diameter sensory fibres and their recruitment is predicted by such modelling. Holshiemer et. al.¹¹ concluded that SCS recruits fibres with a diameter greater than 10.7 μm in a 0.250 mm layer of pia and a small number of fibres between 9.4 and 10.7 μm in diameter in dorsal columns (at the T11 segment). Relatively small numbers of these fibres are present in the DC (i.e. less than 60), and because the DC is innervated by 12 dermatomes at this level, Holshiemer concluded that there are only 4-5 fibres per dermatome recruited during SCS¹⁰. The resistivity of the cerebrospinal fluid (CSF) is low compared to the resistivity of the grey matter and for this reason only the very surface neurons see sufficient potential difference to be depolarised. The fibre diameter required for stimulation

has been estimated from the calculated current density produced by epidural stimulating electrodes¹¹. Feirabend et. al. have studied the diameter and distribution of fibres in the superficial dorsal columns and conclude that only a small number of fibres are the correct size and available for stimulation¹².

Background summary

Current theory on the mechanism of pain relief via SCS can be summarised as follows:

1. The antidromic activity of A β fibres is inhibitory
2. Orthodromic activity of A β fibres may play a role in pain suppression
3. Only a small number of fibres are stimulated in the DC
4. Stimulation occurs primarily in the DC and propagates antidromically into the dorsal horn (where A β fibres synapse with WDR neurons in inhibitory fashion)

In order to provide direct evidence and thus a better understanding for a mechanism, we report the first electrically evoked spinal cord compound action potentials (ECAP) recorded in SCS patients at therapeutic stimulation amplitudes which are associated with pain relief.

Methods

As part of a human research ethics committee approved protocol, patients undergoing routine trial SCS as assessment for implantation of an SCS system were selected based on willingness to participate in the study protocol. Two standard octopolar (8 electrode) leads were implanted according to standard clinical procedures under fluoroscopic examination. The details of the patients, their type and origin of pain, electrical stimulation parameters and neural responses at perceptual threshold and at therapeutic levels are detailed in Table 1.

ECAP's were successfully recorded in four out of the five patients tested. Fig. 1b shows typical neural responses from subject 1 at a fixed stimulus current level, measured on seven successive electrodes (*a-f* in Fig. 1) ascending the spinal cord and four successive electrodes (*l-o* in Fig. 1) descending the spinal cord. The response shifts in time and decreases in amplitude as the ECAP ascends the spinal cord. An evoked response waveform comprises a first positive (P1), first negative (N1) and second negative (P2) series of peaks (Fig. 1). The P1 peak is only observable after the signal has propagated a sufficient distance away from the stimulation electrode.

The average conduction velocity of the responding fibres can be determined from the difference in timing between the negative peaks and the distance travelled determined from X-ray (Fig. 1a). Fig. 2 plots the N1 peak time positions against the distances from the stimulation electrodes for a number of stimulation current amplitudes. The nerve conduction velocity determined in this way for all the patients is detailed in Table 1.

At high stimulation amplitudes a slower propagating response is measured and this was always accompanied by reports of discomfort from the patients. Fig. 3 displays an example of this slow response, which in this case is only present in the data taken from electrodes caudal to the stimulating electrode. Slow responses were observed in 3 of 5 patients and were present on electrodes caudal and rostral to the stimulating site.

The amplitude of the ECAP – determined by the difference between the N1 and P2 peaks – varied with the stimulus current applied, and was linear over the range of measurement. Fig. 4 shows an example of the amplitude growth of the evoked response with increasing stimulus current. The stimulation intensity changes the area of paraesthesia which was recorded by the subject by shading in the paraesthesia area in

a body map of the patient's pain area. The threshold of perception, the point at which the subject first feels the sensation accompanying the stimulation, corresponded to the first detectable evoked response in 3 of 4 patients, while in patient number 3 there was no discernable response at this point (Table 1).

Discussion

The ECAP measurements presented are novel in terms of their proximity to the stimulus, and offer unique opportunities to advance: the study of spinal cord neurophysiology and SCS mechanisms; treatment regimes for SCS; and diagnostic tools for surgery, neurological testing and pain management.

Why are our measurements novel? Proximity to stimulus

Somatosensory evoked potentials (SSEPs) to peripheral stimulation are routinely measured at the scalp for diagnostic purposes^{13,14} and high cervical epidural monitoring of spinal cord potentials (SCPs) in response to peripheral nerve stimulation during spinal scoliosis surgery^{15,16,17} and other procedures for estimating spinal cord integrity is well established. These techniques have in common a large separation between the recording and stimulation sites. For example, Maruyama et. al. report the use of epidural SCP recordings made at the cervical (C5-7) spinal level in response to stimulation at the cauda equina¹⁸. Their recordings show ECAP amplitudes of 5 μ V at a stimulus intensity two times threshold, and 13 μ V at 32 times threshold. Our measurements differ from these techniques in that we have measured the evoked response in the human spinal cord within 14mm of the stimulation, allowing local neural activity to be studied. Further, we have made ECAP recordings in the order of hundreds of microvolts at stimulus intensities less than twice threshold. This level of proximity and sensitivity in neuronal recording has not been presented previously with epidural electrodes, but rather has necessitated micro-electrode recording directly from the spinal cord.

Utility of measuring fibre responses proximal to the stimulus

Electrodes placed in the epidural space are separated from the spinal cord by a thickness of intervening CSF and spinal meninges of as much as 6mm. CSF is the preferred conductive path and so there are several possible mechanisms for activation of the DC fibres: direct electrical stimulation of the superficial layer of the DC or the stimulation of adjacent spinal nerve root fibres which are bathed in the CSF. Regardless of the precise site of stimulation the measurements taken are of the propagating ECAP in the DC. This ECAP represents the summation of the responses from a large number of single fibres [sum of the single fibre action potentials (SFAP)] and its characteristics reveal a great deal about the properties of the responding fibre. The conduction velocity, stimulation threshold and response amplitude can be determined directly and the fibre diameter can be inferred.

How do we conclude they are indeed Aβ fibres and thus confirm long-held theories? Conduction velocity

The conduction velocity measurements demonstrate that SCS recruits Aβ fibres in the dorsal columns, thus confirming long-held theory⁸. Aβ fibres are large, thickly myelinated fibres with conduction velocities typically in the range of 30 to 70 ms⁻¹ and carry touch and pressure information¹⁹. In comparison, Aδ neurons are thinly myelinated fibres responsible for sharp pain and have much slower conduction velocities (typically 10 to 30 ms⁻¹)¹⁹. C fibres have even slower conduction velocities (1 to 2 ms⁻¹) and are responsible for dull aching pain¹⁹. Results from the four patients tested revealed a range of conduction velocities from 49 to 65 ms⁻¹, indicating that the Aβ fibres of the DC are generating the recorded ECAPs.

Correlation of paraesthesia coverage and Aβ amplitude – SCS treatment

The relationship between the induced paraesthesia and the $A\beta$ amplitude of subject number 1 is shown in Fig. 4. The ECAP amplitude increases with increasing current level, as does the area of paraesthesia coverage. The area of coverage and hence the effectiveness of the pain relief is not constant with current because of postural variations but is positively correlated with ECAP amplitude for a given posture. It is proposed that this result may provide a quantitative neurophysiological measure for the level of pain relief experienced by SCS implant recipients. Further, this measure may be employed to optimise the treatment afforded by SCS on a continuous basis, and hence improve the therapeutic outcome for the patient. Previous ECAP measurement studies^{16,18} have not employed a recording technique on a single electrode array that may be utilised practically in a neurostimulation system.

Importance of $A\beta$ response amplitude: Neural recruitment levels

The amplitude of the $A\beta$ responses provides a direct indication of the number of fibres responding to the stimulus, which is directly related to the area of coverage of the induced paraesthesias. Coverage of the complete area of the leg requires at least 5 dermatomes, which according to Holshiemer's model¹¹ would involve approximately 25 fibres in the dorsal horn surface. The magnitude of the $A\beta$ response we measured for SCS coverage varied with each patient (Table 1). The contribution to the ECAP from a signal fibre is likely to be small (less than $1\mu V$)²⁰. Thus, for a number of patients the magnitude of their ECAPs were considerably larger than predicted, indicating many more fibres are recruited than predicted by modelling.

Importance of conduction velocity: Neural recruitment levels

The conduction velocity is linearly related to the fibre diameter²¹ (approximately 6ms^{-1} per μm). From our measurements for the first subject the fibre diameter estimated for 48.6ms^{-1} velocity is $8.1\mu\text{m}$ (Table

1), which is smaller than predicted by the simulation models¹¹. The measurement of the velocity is made over a relatively long distance (42mm) and is linear over the range of measurements (Fig. 2). The A β fibres branch on entry into the dorsal columns and as they branch the fibres become smaller and slower conducting. It is possible that recruitment occurs prior to branching and that the measurements are indicative of the fibre having reached its final diameter as they propagate up and down the cord. Approximately 8.7% of the fibres in DC have a diameter greater than 8.1 μ m which would yield more than 1000 fibres of suitable diameter in the superficial dorsal column¹². Further studies are required to resolve these uncertainties.

Importance of conduction velocity: Distributions of neurons recruited

A relatively narrow distribution of fibre sizes responded to the stimuli during our studies. Low currents would produce responses from low threshold fibres which are larger in diameter and hence have a faster conduction velocity. The conduction velocity measured at 10% above threshold is no faster than the conduction velocity measured at the therapeutic levels, which indicates that a relatively narrow distribution of fibre sizes are being recruited by SCS. Fig. 2 shows the negative peak positions against distance for 5, 7 and 10mA. The conduction velocity is almost the same, despite doubling the delivered current.

Relevance of the slow response

Patients treated with SCS systems often report shocks and uncomfortable paraesthesia induced by movement. These side effects were observed during the clinical recording sessions (Fig. 3). The fast A β responses have increased in magnitude but a slower response starting 5 to 10ms after stimulus is also present. The slow response in this example is present in the antidromic direction and only weakly displayed in the orthodromic direction. The origin of this slow neuronal response occurs at the spinal

segmental level and is likely to originate from either activation of the nociceptive reflex arc, or activation of the muscle afferents of the dorsal roots, both of which trigger a muscle response and subsequent sensory responses²².

Conclusion

In summary, we have presented novel measurements of ECAPs in the human spinal cord in patients undergoing SCS for treatment of chronic pain. Much larger populations of fibres are responding to the stimulus than suggested by modelling. A key step in the mechanism of SCS is via A β fibre recruitment which confirms postulated theory. Recruitment of slower fibres at higher potentials is accompanied by uncomfortable paraesthesias. The in situ measurement and characterisation of the ECAP yields new insights into the mechanisms of SCS and provides a unique tool to characterise the fibres responding to the stimulation.

Numerous additional neuromodulation treatments and diagnostic procedures exist which can benefit from the recording technique presented. With respect to SCS, the A β potential is a measure of the level of neural recruitment and provides a potential feedback parameter to optimise the operation of neuro-modulation function on a continuous basis as well as providing new insights into SCS optimisation and the design of new stimulation paradigms.

Methods

For each study, the patient's electrodes were connected via custom fabricated connector box to a TDT (Tucker-Davis Technologies, Fl. USA) RZ5 amplifier and bio-processor system and a WPI (World Precision Instruments, Fl. USA) A385 current source. The current source was connected to electrodes

chosen for stimulation and all other electrodes were connected to the bio-amplifier. Output from the current source was a charge-balanced biphasic waveform with the pulse width for a single phase and frequency indicated in Table 1. Data were acquired at a sampling rate of 24.4kHz on 8 to 16 channels. Custom software was used to control the measurement and initiate stimulus. ECG (three lead) was measured by the system and data blocks where ECG was present were removed from the analysis. The signal to noise ratio was improved by ensemble averaging sets of approximately 80 samples. Data were analysed with the MATLAB software toolkit (Math Works Inc., MA, USA).

ECAP's were recorded continuously during experimental sessions. During each session the amplitude of the stimulus was varied from zero until the patient reported complete coverage of pain area with paraesthesia or a maximum level of tolerance. At each stimulus level patients recorded and matched areas of SCS induced paraesthesias to pre-existing areas of pain by colouring body maps. Also, a visual analogue scale (VAS) pain score was recorded before SCS and at each interval where the stimulus condition was changed.

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Supplementary Information line

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Supplementary Information (to be put in a separate file)

Organisation of the spinal cord

A β fibres are organised into layers in the dorsal column (DC). A new layer is added at each vertebral segment, pushing the existing layers toward the midline. Afferent fibres enter the dorsal root entry zone

(DREZ) and bifurcate into the DC or dorsal horn (Fig. S1). DC fibres ascend (orthodromic) or descend (antidromic) into the dorsal horn, thus leaving the DC within a few segments. The fibres which remain in the DC exhibit a reduction in size as they ascend the spinal cord, because each fibre branches into a number of collateral branches from their entry point, and each branching point results in a diminution of the diameter of the axon. The smaller fibres are pushed toward the midline at each successive spinal segmental level and it is postulated that they remain unstimulated by SCS¹. The distance that the fibre travels in the ascending direction depends on the peripheral receptor type and can be as short as one or two segments or can travel all the way to the medulla.

Proposed mechanism of spinal cord stimulation

Activation of an A β fibre in the dorsal column results in antidromic propagating action potentials which are conducted down the A β collateral branches (Fig. S1) and inhibit C and A δ fibre conduction via an interneuron (wide dynamic range neuron). It is proposed that this inhibitory action is a mechanism for pain relief via SCS.

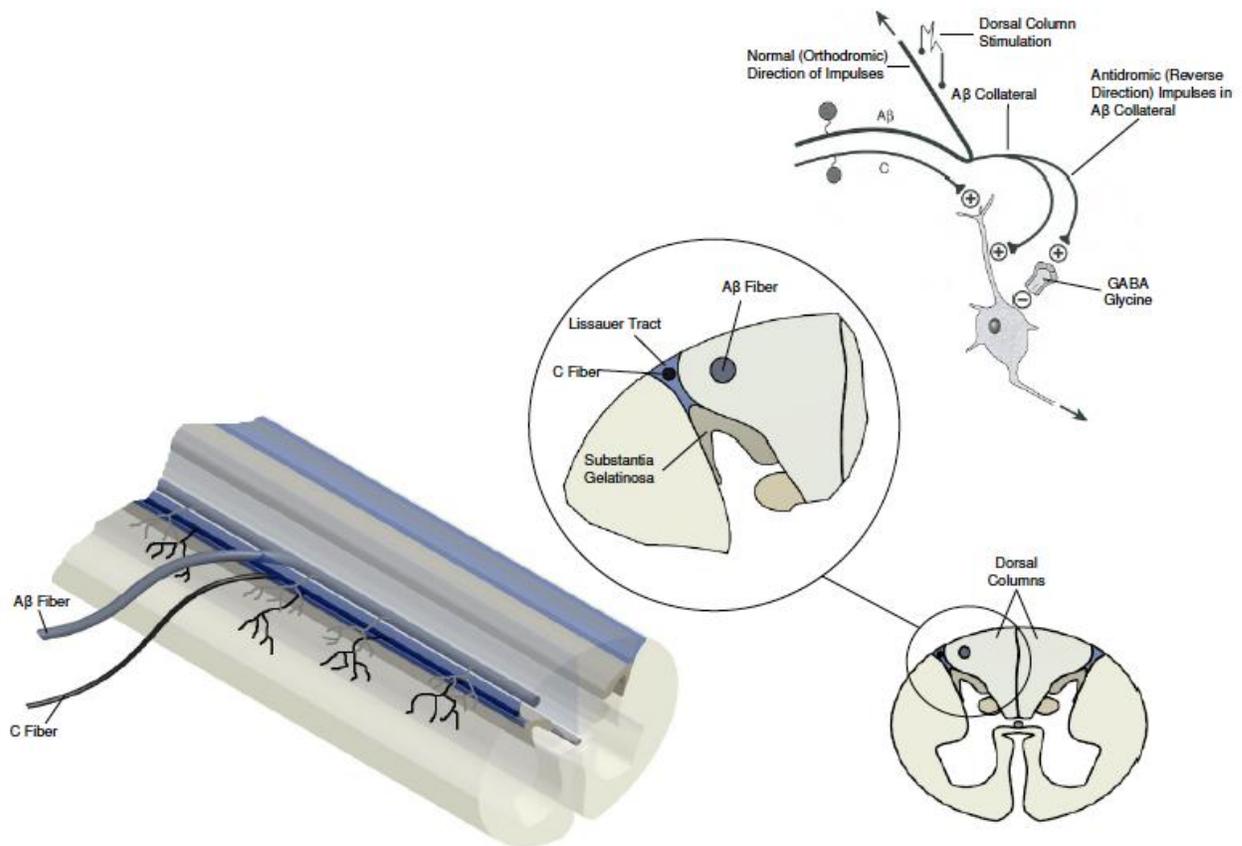


Figure S1: Schematic representation of the organisation of spinal cord neurons related to the transmission and inhibition of pain signals.

Dermatomal Body Chart

Dermatomes are the area of skin which are supplied with afferent nerve fibres by a single posterior spinal root (Fig. S2). Stimulation at a site above the entry of the posterior spinal root can produce paraesthesias in all the dermatomes which enter at lower segments.

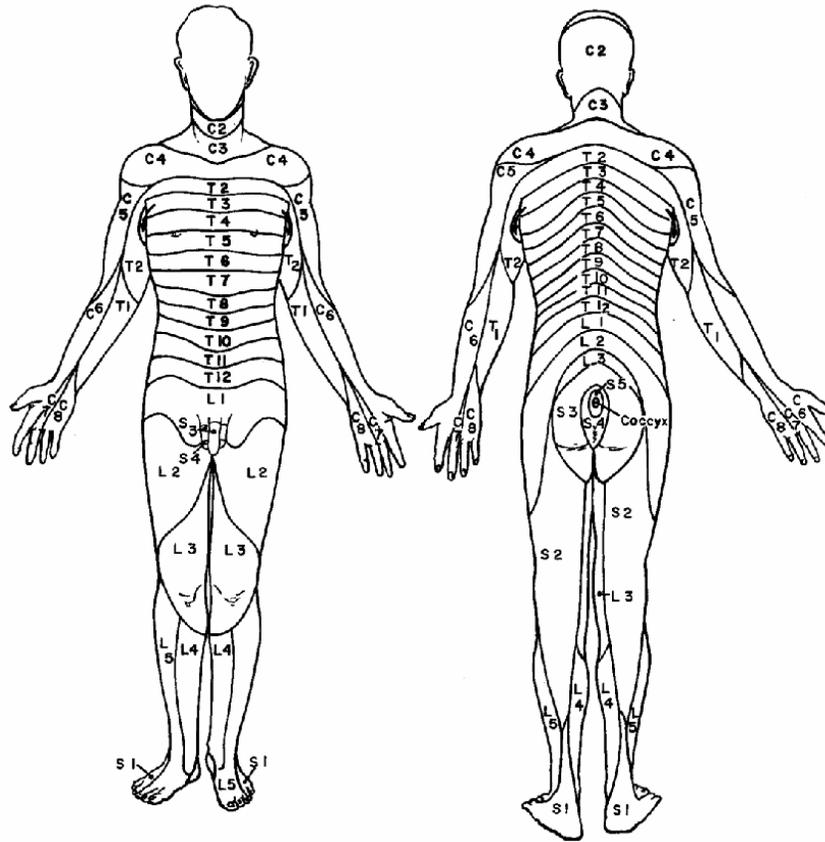


Figure S2: Dermatome map of the human body.

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Author contributions

J.L.P. conceived of the utility in measuring spinal cord potentials in the context of pain management, researched its neurophysiological foundation and drafted the manuscript. M.J.C. enrolled the patients, performed the

surgeries, provided clinical oversight of the trials and guidance on the neurophysiology involved. D.M.K. and P.S.S developed and assembled the experimental hardware and software, performed the experiments, and contributed towards the interpretation of the data. M.O. assisted in performing the experiments and performed the data analysis. All authors discussed the results and commented on the manuscript.

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The authors declare no competing interest.

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Tables

Table 1: Patient information, stimulation inputs and the measured parameters from evoked response recording.

Subject No.	Sex and age	Site of pain	Cause of pain	At percept threshold		At comfort level			Conduction velocity (ms ⁻¹)	Estimated Fibre Diameter (µm)
				Aβ amplitude (µV)	Stimulus parameters (current, pulse width, rate)	No. of Dermatomes with	Aβ amplitude (µV)	Stimulus current (mA)		
1	F,65	Sacral, buttock, lower limb	Unknown Neuropathic	17.4	5 mA, 80 µs, 40 Hz	10	150	10.0	49	8.1
2	F,38	Left leg below knee	Ankle/knee fall injury Neuropathic	18.9	4.3 mA, 120 µs, 40 Hz	5	36	4.6	65	10.8
3	F,32	Lower back, bilateral leg	Unknown Neuropathic Musculoskeletal	0.0*	0.93 mA, 120 µs, 60 Hz	8	310	2.6	52	8.6
4	F,64	Lower back, right leg	Lifting injury Neuropathic	14.7	9 mA, 200 µs, 60 Hz	8	54	11.5	59	9.8

The percept threshold represents the point at which the patient first perceives the paraesthesia as the stimulation current is increased. The current level and the Aβ amplitude at this point are recorded along with the pulse width and stimulation frequency. The comfort level is defined as the maximum stimulus level obtained prior to a report of an uncomfortable stimulation. This is the stimulation strength where the individual received the maximum pain relief benefit, and the stimulation current and Aβ evoked amplitudes are recorded. Conduction velocities were determined from the negative peak position as illustrated in Fig. 2.

* No discernable Aβ response was measured at percept threshold.

Figure Legends

Figure 1: **a**, Fluoroscope image of the electrode placement in the epidural space. The electrodes are labelled *a* through *o* and responses recorded from those electrodes are similarly labelled in **b**. The tip electrode of the rostral array (i.e. adjacent to *a*) was used as the common electrode for measurement. **b**, Spinal Cord Evoked Compound Action Potentials (ECAP) for patient number 1. The propagating action potentials in the orthodromic and antidromic direction are plotted on the positive and negative side of the abscissa, respectively. The stimulus cathode is labelled *i* and its two most adjacent electrodes formed the anode. The stimulus was a biphasic current pulse of width 120 μ s and amplitude 10mA. Note the shaded region is used to mask the period of stimulation and subsequent electrical artefact.

Figure 2: The negative peak time position of the compound action potentials plotted against the propagation distance in the spinal cord. The distance was estimated from the fluoroscope image in Fig. 1 and the known intra-electrode spacing. The different series represent the stimulation currents: 10, 7 and 5 mA. The “ortho” and “anti” legends indicate the points measured in the orthodromic and antidromic directions, respectively.

Figure 3: Measurement of the evoked response at a stimulus magnitude which was uncomfortable for the patient. The antidromic activity is plotted on the negative scale. Present is a large slow response (from 6 to 17 ms) which is barely present in the orthodromic direction. Inset shows waveform detail over 0 to 4ms. Electrodes *a-f* and *m-o* are shown in the positive and negative time scale, respectively.

Figure 4: **a**, ECAP recorded at different current levels and correlated with the area of overlap of paraesthesia and pain. Responses were recorded for patient number 1 with a pulse width of 80 μ s for a current level from 16mA to

30mA in 2mA increments. At threshold (line 1 = 16mA) the paraesthesia was confined to the ankles, on the next increment it spread to the toes and up the knees (line 2), up both sides (3), into buttocks (4), across back (5) and complete coverage was obtained at 28mA (7). **b**, The amplitude of the ECAP measured from N1 to P2 for the entire range of currents. **c**, The percentage area of paraesthesia overlap of the painful area as a function of the ECAP amplitude.