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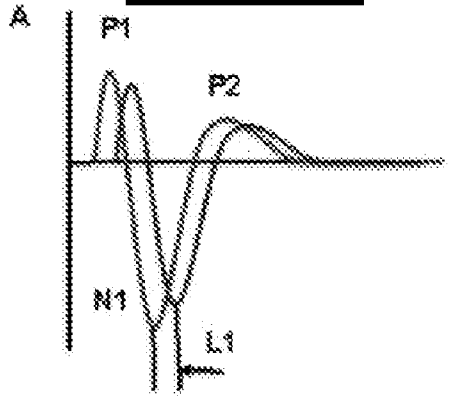
Figure 2a



(57) Abstract: A method for estimating conduction velocity of a neural response. Measurements of the neural response are obtained from at least two electrodes which are at distinct locations along a neural pathway. A delay between the time of arrival of the neural response at each respective electrode is determined from the measurements. From the delay, and from knowledge of electrode spacing, a conduction velocity of the neural response is estimated.

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METHOD AND APPARATUS FOR MEASUREMENT OF NEURAL RESPONSE - C

Cross-Reference To Related Applications

This application claims the benefit of Australian Provisional Patent Application No. 2011901822 filed 13 May 2011, Australian Provisional Patent Application No. 2011901817 filed 13 May 2011 and Australian Provisional Patent Application No. 2011901824 filed 13 May 2011, each of which are incorporated herein by reference.

Technical Field

The present invention relates to measurement of a neural response to a stimulus, and in particular relates to measurement of a compound action potential by using one or more electrodes implanted proximal to the neural pathway.

Background of the Invention

There are a range of situations in which it is desirable to measure a compound action potential (CAP). For example, neuromodulation is used to treat a variety of disorders including chronic pain, Parkinson's disease, and migraine. A neuromodulation system applies an electrical pulse to tissue in order to generate a therapeutic effect. When used to relieve chronic pain, the electrical pulse is applied to the dorsal column (DC) of the spinal cord. Such a system typically comprises an implanted electrical pulse generator, and a power source such as a battery that may be rechargeable by transcutaneous inductive transfer. An electrode array is connected to the pulse generator, and is positioned in the dorsal epidural space above the dorsal column. An electrical pulse applied to the dorsal column by an electrode causes the depolarisation of neurons, and generation of propagating action potentials. The fibres being stimulated in this way inhibit the transmission of pain from that segment in the spinal cord to the brain. To sustain the pain relief effects, stimuli are applied substantially continuously, for example at 100 Hz.

While the clinical effect of spinal cord stimulation (SCS) is well established, the precise mechanisms involved are poorly understood. The DC is the target of the electrical stimulation, as it contains the afferent Aβ fibres of interest. Aβ fibres mediate sensations of touch, vibration and pressure from the skin. The prevailing view is that SCS stimulates only a small number of Aβ fibres in the DC. The pain relief mechanisms of SCS are thought to include evoked antidromic activity of Aβ fibres having an inhibitory effect, and evoked orthodromic activity of Aβ fibres playing a role in pain suppression. It is also thought that SCS recruits Aβ nerve fibres

primarily in the DC, with antidromic propagation of the evoked response from the DC into the dorsal horn thought to synapse to wide dynamic range neurons in an inhibitory manner.

Neuromodulation may also be used to stimulate efferent fibres, for example to induce motor functions. In general, the electrical stimulus generated in a neuromodulation system triggers a neural action potential which then has either an inhibitory or excitatory effect. Inhibitory effects can be used to modulate an undesired process such as the transmission of pain, or to cause a desired effect such as the contraction of a muscle.

The action potentials generated among a large number of fibres sum to form a compound action potential (CAP). The CAP is the sum of responses from a large number of single fibre action potentials. The CAP recorded is the result of a large number of different fibres depolarising. The propagation velocity is determined largely by the fibre diameter and for large myelinated fibres as found in the dorsal root entry zone (DREZ) and nearby dorsal column the velocity can be over 60 ms^{-1}. The CAP generated from the firing of a group of similar fibres is measured as a positive peak potential P1, then a negative peak N1, followed by a second positive peak P2. This is caused by the region of activation passing the recording electrode as the action potentials propagate along the individual fibres.

To better understand the effects of neuromodulation and/or other neural stimuli, it is desirable to record a CAP resulting from the stimulus. However, this can be a difficult task as an observed CAP signal will typically have a maximum amplitude in the range of microvolts, whereas a stimulus applied to evoke the CAP is typically several volts. To resolve a 10 μV spinal cord potential (SCP) with 1 μV resolution in the presence of an input 5V stimulus, for example, requires an amplifier with a dynamic range of 134dB, which is impractical in implant systems.

CAP recordings are sometimes made during surgical procedures on the spinal cord, to provide an indication of any potential neurological damage being caused by the procedure. Typically, a site below (caudally of) the area being operated on is stimulated and recordings are made above (rostrally of) the site. A diminishing response, or a change in response, indicates a change in the neurological condition of the spinal cord and may indicate lasting damage. For example such monitoring is often performed during scoliosis surgery (straightening a curvature of the spine) to ensure that the decompression doesn't damage the spinal cord. Somatosensory potentials are also used for spinal cord monitoring during surgery. These are recorded on the scalp of the patient

and are evoked from stimulation of a peripheral nerve, usually one of the tibial nerve, median nerve or ulnar nerve. Somatosensory potentials can also be measured in response to stimulation of the spinal cord. The monitoring techniques employed in surgery are “long range” techniques, in that the stimulation site and the recording site are a large distance apart, and are thus less sensitive at least due to attenuation.

Neural damage, degeneration or change can affect neural behaviour in a number of ways, such as by changing the number of fibres recruited by a given stimulus, the type of fibres recruited, and/or propagation characteristics of the action potential along a fibre once activated. Techniques which merely monitor the presence/absence, or the strength, of a detected neural signal may thus overlook important changes in other characteristics of the neural response.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Summary of the Invention

According to a first aspect the present invention provides a method for estimating conduction velocity of a neural response, the method comprising:

obtaining measurements of the neural response from at least two electrodes which are at distinct locations along a neural pathway;

determining a delay between the time of arrival of the neural response at each respective electrode; and

estimating from the delay, and from knowledge of electrode spacing, a conduction velocity of the neural response.

According to a second aspect the present invention provides a device for estimating conduction velocity of a neural response, the device comprising:

at least two electrodes which are configured to be positioned at distinct locations along a neural pathway; and

a control unit configured to obtain measurements of the neural response from each electrode, the control unit further configured to determine a delay between the time of arrival of the neural response at each respective electrode, and the control unit further configured to estimate from the delay, and from knowledge of electrode spacing, a conduction velocity of the neural response.

The device may be configured for permanent implantation and ongoing operation while implanted. Alternatively the device may be configured for intra-operative use only.

Some embodiments of the invention may further provide for estimating from the conduction velocity of the neural response, or from changes in the conduction velocity of the neural response as detected from one measurement to a next measurement, an approximate proportion of fibre classes recruited to produce the neural response. For example, in such embodiments, a high conduction velocity may be taken as being indicative of recruitment of large fibres such as Aβ fibres. Similarly, an increased conduction velocity from one measurement to a next measurement may be taken as being indicative of increased recruitment of large fibres such as Aβ fibres. Such embodiments may be particularly useful in feedback control of an applied stimulus in order to preferentially recruit Aβ fibres to achieve beneficial therapeutic effects while minimizing recruitment of smaller fiber classes to avoid adverse side effects.

In some embodiments of the invention, a measure of conduction velocity may be obtained both caudally of the stimulus site and rostrally of the stimulus site. In such embodiments, the measurements may be used as input to a feedback controller designed to effect differential control of fibre classes recruited in an evoked ascending volley as compared to fibre classes recruited in an evoked descending volley.

In some embodiments of the invention, a measure of conduction velocity may reveal changes in stimulus efficacy, as for example may arise as a result of implant migration away from the ideal location, postural changes of the patient or changes in tissue properties over time. In such

embodiments, the measurement(s) of conduction velocity may be used for feedback control of an applied stimulus in order to adjust device operation for such changes.

According to a third aspect, the present invention provides a method for diagnosing a disease which affects neural conduction velocity, the method comprising:

repeatedly measuring a neural conduction velocity over time, using the method of the first aspect; and

determining from said measurements whether any changes in neural conduction velocity have occurred which are indicative of the disease.

In some embodiments of the third aspect of the invention, the disease may be diabetes mellitus. Diabetes mellitus reversibly slows the neural conduction velocity in patients having insufficient metabolic control, so that detection of reductions in neural conduction velocity may assist in diagnosing the onset, state or progression of diabetes mellitus, and may for example trigger revision of a treatment schedule.

In some embodiments of the third aspect of the invention, the disease may be central sensitization. Central sensitization tends to reduce the neural conduction velocity, so that detection of reductions in neural conduction velocity may assist in diagnosing the onset, state or progression of central sensitization. In such embodiments, a conduction velocity map of the spinal cord may be obtained by progressively applying stimuli using each of a plurality of electrodes of an implanted electrode array, and using spaced apart measurement electrodes to obtain a measure of the conduction velocity resulting from each stimulus site. Mapping conduction velocity against location then will give an indication of the location(s) at which central sensitization has occurred. Such a map may then be used to optimize the location of therapeutic stimuli, either through a manual fitting of the device or through an automated feedback procedure carried out by an implanted control unit.

According to a fourth aspect the present invention provides a method for characterizing incremental recruitment effected by a larger intensity neural stimulus compared to a smaller intensity neural stimulus, the method comprising:

obtaining a first measurement of a first neural response evoked by a first neural stimulus;

obtaining a second measurement of a second neural response evoked by a second neural stimulus, the second neural stimulus having different stimulus parameters and a different neural recruitment effect as compared to the first stimulus;

subtracting the first measurement and second measurement to yield a difference measurement; and

assessing the difference measurement to determine the nature of the differential recruitment effected by the first stimulus as compared to the second stimulus.

In accordance with the fourth aspect, subtracting the CAP responses from two different stimuli will yield the response from the additional fibres recruited by the additional current increment. This method thus provides a way to look at subsets of the fibres recruited, and look at their properties, which can then be used for a feedback or control signal, or for a diagnostic purpose as described elsewhere herein.

In some embodiments of the fourth aspect the recruitment effected by the first and second stimuli may differ by a margin which is a fraction of a range of interest, and the method may further comprise repeatedly obtaining the difference measurement for varying values of stimulus parameters throughout the range of interest, to thus gain a finer resolution determination of the incremental recruitment obtained at multiple points throughout the range of interest. The range of interest may be a therapeutic range, for example between a recruitment threshold and a maximum comfort threshold.

Some preferred embodiments of the invention may perform the method of the fourth aspect on each of two sense electrodes which are spaced apart along the neural pathway, in order to estimate the conduction velocity of the first and/or second neural response in accordance with the method of the first aspect of the invention. Such embodiments, combing the first and fourth aspects of the invention, may be particularly beneficial in allowing determination of both the conduction velocity and the contribution of the incrementally recruited fibres.

According to another aspect the present invention provides a computer program product comprising computer program code means to make a computer execute a procedure for estimating conduction velocity of a neural response, the computer program product comprising computer program code means for carrying out the method of the first aspect or fourth aspect.

The neural response may be a spinal cord response, or other human nerve response, or a neural response of a non-human subject.

The conduction velocity may be determined from the delay between measurements obtained from two electrodes, or from more than two electrodes.

Brief Description of the Drawings

An example of the invention will now be described with reference to the accompanying drawings, in which:

Figure 1 illustrates compound action potentials measured from a sheep spinal cord using spaced apart measurement electrodes, both in the ascending/rostral direction (Fig 1a) and descending/caudal direction (Fig 1b);

Figure 2 is a schematic diagram illustrating the relationships between the measured evoked response and the fibre properties, in which Figure 2a illustrates the compound action potential measured on two spaced apart electrodes, Figure 2b illustrates variation of peak amplitude (P2-N1) with applied stimulus current, Figure 2c illustrates the relation between fibre diameter and conduction velocity, Figure 2d illustrates the inverse relationship between the threshold current and fibre diameter, and Figure 2e is a plot of inter-electrode delay L1 vs. stimulus current level;

Figure 3 further illustrates the relation between fibre diameter and conduction velocity; and

Figure 4 illustrates an implantable device suitable for implementing the present invention.

Description of the Preferred Embodiments

Figure 1 illustrates measured compound action potentials in the sheep spinal cord, both in the ascending/rostral direction (Fig 1a) and descending/caudal direction (Fig 1b). According to current theory the fibres responsible for inhibition of pain in therapeutic SCS are the Aβ fibres in the dorsal horn. Stimulation of these fibres produces an orthodromic (ascending) volley of discharges, and also an antidromic descending volley. In Figure 1a, a single ascending compound action potential (CAP) is measured as it passes 4 measurement electrodes (E13 through E16) which are spaced apart along the neural pathway, increasingly distant from the stimulus. In Figure 1b, a single descending CAP is measured as it passes 4 measurement electrodes (E5 through E8) which are spaced apart along the neural pathway, increasingly distant from the stimulus.

As can be seen in Figure 1, in both the orthodromic and antidromic directions, the further away the measurement electrode is from the stimulus site, the greater is the delay of the CAP waveform measured by that electrode and the smaller is the peak amplitude of the measured CAP.

The present invention recognises that a great deal can be understood about the nature and properties of the fibres being recruited by electrical stimulation, by obtaining at least two measurements of a single CAP, from two spaced apart measurement electrodes along the neural pathway. Figure 2a illustrates the compound action potential measured on two electrodes which are spaced apart alongside a neural pathway and separated from each other by some known distance, this distance typically being defined by the physical layout of the electrode array and therefore accurately known. The difference in peak position, L1, is due to the propagation delay of the discharge (CAP). L1 is thus a measure of the time it takes for the action potential to travel the known distance between the electrodes. L1 may be measured from any suitable feature or group of features in the CAP measurements, such as the time between the respective P1 peaks, the time between the N1 peaks, the time between the P2 peaks, the time between the P1-to-N1 zero crossing, or the like.

The peak amplitude (P2-N1) varies with the applied current in the stimulus pulse, as illustrated in Fig 2b for each of the two electrodes used to obtain the measurements for Figure 2a. The amplitude of the response is zero until a critical threshold value (T1) is reached. The threshold is related to the fibre diameter, with smaller fibres being more difficult to recruit and requiring more current to recruit, as illustrated in Fig 2d (in which a negative stimulus current is in use). In Fig 2b the amplitude-stimulus curves for the two electrodes have the same threshold T1, but differing amplitudes above T1 due to attenuation of the neural response between the two electrodes. The fibre diameter is also related to the conduction velocity as shown in Fig 2c, and Fig 3. The present invention recognises that low stimulus currents can only recruit large fibres, which have high conduction velocities, so that plotting L1 against the stimulus current level as shown in Fig. 2e, gives an indication of the spread of fibre diameters which are being recruited. In particular, in Figure 2e, it can be seen that with a low stimulus current which is only just above the threshold T1, L1 is small and thus indicates that high conduction velocity fibres are primarily being recruited. As the stimulus current increases, L1 increases, indicating that smaller fibres having slower conduction velocity are increasingly recruited.

Fig 3 illustrates conduction velocity of a nerve fibre as a function of nerve diameter. The conduction velocity of a fibre is related to the diameter of the fibre. Larger myelinated fibres conduct faster, thought to be because the nodes of Ranvier are further apart.

The data collected by measuring the evoked response in the sheep spine (Figure 1) allows the determination of the conduction velocity from the N1 peak position in the travelling wave. A conduction velocity at 60 ms^{-1} corresponds to a fibre diameter of 10 μm.

The present invention recognises that in the superficial dorsal horn, only a small proportion of fibres (perhaps 0.5%) are greater than 10.7 μm in diameter, and that the beneficial therapeutic effect of spinal cord stimulation (SCS) is thought to be generated primarily by fibres of this diameter. Moreover, adverse side effects of SCS can arise if recruitment of non-Aβ fibre types occurs, so that selectivity of recruitment of fibre type is advantageous in maximising beneficial effects while minimising adverse side effects. That is, the efficacy of spinal cord stimulation for the relief of chronic pain is related to the Aβ fibre recruitment, which the present invention recognises can be measured by considering the conduction velocity of the evoked response.

The compound action potential measurements can thus be used to adjust the stimulation parameters and improve efficiency in a number of ways, including: 1) Maximising recruitment of specific fibre classes by adjustment of stimulus parameters, 2) Differential control of the ascending/descending volleys and associated blocking of these volleys, 3) Automatic variation of stimulation parameters to adjust for changes in use or environment, and 4) Detection of pathology within the underlying stimulated tissue.

Measurement of parameters such as those shown in Fig 2, and knowledge of their relationships, can be used for a number of further beneficial purposes as described below. The measurements themselves or parameters extracted from measurements represent properties of the neuronal populations. For instance the peak to peak amplitude measured between the largest negative peak N1 and largest positive peak P2 is proportional to the level of recruitment of the nerve fibres.

In some embodiments of the invention the evoked CAP measurements may be made at very short distances from the stimulation site(s). Such embodiments may be effected by use of the neural response measurement techniques set out in the Australian provisional patent application

No. 2011901817 in the name of National ICT Australia Ltd entitled "Method and apparatus for measurement of neural response" from which the present application claims priority. The present invention recognises that using a suitable measurement technique to obtain a CAP measurement from very close to the stimulation site offers additional benefits to past "long range" approaches, and may have utility as described below during surgery to monitor local areas of the spine.

Additionally or alternatively, the neural response measurement may be conducted in accordance with any suitable CAP measurement technique, for example the techniques set out in Daly (US 2007/0225767), the content of which is incorporated herein by reference. Additionally or alternatively, the neural response measurement may be conducted in accordance with the techniques set out in Nygard (US Patent No. 5,785,651), the content of which is incorporated herein by reference. Additionally or alternatively, the neural response measurement may be conducted in accordance with the techniques set out in King (US Patent No. 5,913,882), the content of which is incorporated herein by reference.

Local compound action potentials recorded with an electrode array placed in the epidural space in the spinal cord display a fast response occurring within 1.5 ms, from large diameter fibres (~10 μm). This response can be recorded on electrodes adjacent to the stimulating site. A number of basic fibre properties can be determined from the measurement of the compound action potentials. There are a number of neurological conditions and non-neurological conditions which can affect the parameters determined by the conduction velocity measurements and so the measurement techniques of the present invention can serve as a useful diagnostic indicator. The evoked response provides a measure of the properties of the nerve being depolarised. The conduction velocity, fibre diameter and distribution of fibre diameters of the nerve can be determined by measurement of the evoked response.

The method of the present invention may further be used to monitor the effect of a delivered compound, where the compound affects the neural conduction velocity. The administration of compounds (drugs or other chemical therapeutics) to effect a change in the nervous system is common for treatment of a wide number of diseases and disorders. Anaesthetics of various types are administered to the spinal cord for the relief of pain. Perhaps the most common form is administration of anaesthetics in the epidural space for pain relief during child birth. Treatment efficacy may be determined intra-operatively, for example by using a catheter comprising a tube

for administration of a drug into the epidural space, and an electrode array. Electrical stimulation can be delivered directly to the spinal cord and the effect of the administered drug can be directly measured in real time.

Alternative embodiments may be suitable for full implantation within the body of a subject and in such embodiments the evoked potential monitoring of the present invention could be used for ongoing administration of an active compound to produce a therapeutic benefit over time. In such embodiments the implanted system could be integrated with an implantable pump to control the administration of the compound.

Any factor which may affect the properties of the compound action potential could be subject to monitoring by the evoked response system described. For instance the conduction velocity of nerves is slowed reversibly in patients with diabetic mellitus where there is insufficient metabolic control.

The properties of the stimulated neural population may indicate an underlying pathology or the development of an underlying pathology. The detection of the pathology may be used as a control signal for the regulation of the release of a drug. One such pathology is the development of neuropathic pain via central sensitisation, and accordingly some embodiments of the invention may provide for identification of the onset, progression, or state of central sensitization, using an in-situ device in accordance with the present invention.

Central sensitisation is a well-accepted theory for development of chronic neuropathic pain. It relies on the nociceptive neurons in the dorsal horn becoming hyper-sensitised due to tissue damage or inflammation. Central sensitisation provides an explanation for allodynia (which is pain produced from what in normal circumstances would be non-noxious stimuli) due to expansion of the receptive fields. The properties of the dorsal horn neurons have been studied in animal models of central sensitisation. There is however no direct evidence of central sensitisation from measurements of dorsal horn properties in humans. In animal models the properties of all the fibres change (as recorded by patch clamp experiments). Reductions in the conduction velocity have been observed in fibres of the segments of the dorsal horn which display characteristic properties of the central sensitised state. One study recorded the electrical activity (in the form of individual neuronal spikes) in the dorsal horns of rats elicited from mechanical stimulation. Activity recorded in a control group was compared to the activity

recorded in rats with induced central sensitisation. This sensitised state was induced using the spared nerve injury model of neuropathic pain. The spontaneous activity resulting from a stimulus was different in the central sensitised state. There was an increase in higher frequency components and an increase in the after discharge rate. Central sensitisation is the result of the increase in synaptic efficiency and the reduction of inhibition of the pathways within the spinal cord for the transmission of painful stimuli. This leads to an amplification of pain and results in the experience of pain from other inputs such as the low threshold mechanical sensory inputs which would not normally produce pain inputs.

The method of the present invention provides a method for determining the properties of the neurons which are being stimulated and during normal spinal cord stimulation the target neurons are the Aβ fibres. The properties of these fibres have been reported in both normal and central sensitised model and distinct differences have been noted. Distinct changes in conduction velocity of Aβ fibres in the centrally sensitised state have been reported. The shift in conduction velocity was of the order of 25% which is clearly detectable via CAP measurements in humans. The procedure involves determining the conduction velocity in a portion of the spinal cord where it is apparently normal, and comparing that measure with conduction velocities measured over areas which correspond (according to dermatomes maps) where the central sensitisation should appear. The conduction velocity distribution could be obtained over the entire electrode array by measuring the conduction velocity (both orthodromically and antidromically) from stimulation on each bipolar pair in turn. In addition to conduction velocity other properties of the responding fibres could be used as markers of pathological change.

A spinal cord map obtained in such a way might also be used to provide an accurate indication of stimulation sites for trial in the stimulation procedure. A significant number of patients undergoing back surgery will later develop chronic pain conditions. The potential exists, particularly with back surgery, to place a spinal cord stimulator at the time of the original surgery. The device has the capability to monitor the response of the spinal cord to electrical stimulation and detect the onset of central sensitisation. In effect the device equipped with ERT recording can be used to detect the onset of the neuropathic pain condition. Through appropriate algorithms the device would start to stimulate and provide the inhibitory input which would prevent the further progression of the neuropathic condition.

A further improvement would be to include the functionality of the SCS within a spinal orthopaedic implant so that no additional implant structures are required. Figure 4 illustrates an implantable device 400 which may exploit the present invention. Device 400 comprises an implanted control unit 410, which controls application of neural stimuli, and controls a measurement process for obtaining a measurement of a neural response evoked by the stimuli. Device 400 further comprises an electrode array 420 consisting of a three by eight array of electrodes 422 which may be selectively used as either the stimulus electrode or sense electrode, or both.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:

1. A method for estimating conduction velocity of a neural response, the method comprising:

obtaining measurements of the neural response from at least two electrodes which are at distinct locations along a neural pathway;

determining a delay between the time of arrival of the neural response at each respective electrode; and

estimating from the delay, and from knowledge of electrode spacing, a conduction velocity of the neural response.

2. The method of claim 1 further comprising estimating, from the conduction velocity of the neural response, a proportion of fibre classes recruited to produce the neural response.

3. The method of claim 1 or claim 2 further comprising estimating, from changes in the conduction velocity of the neural response as detected from one measurement to a next measurement, a proportion of fibre classes recruited to produce the neural response

4. The method of claim 2 or claim 3 further comprising using the estimated proportion of fibre classes recruited as an input to feedback control of an applied stimulus, in order to control the stimulus so as to preferentially recruit one or more desired fibre classes.

5. The method of any one of claims 1 to 4, wherein the measurements of the neural response are obtained from locations both caudally of the stimulus site and rostrally of the stimulus site.

6. The method of claim 5 wherein a caudal conduction velocity and a rostral conduction velocity are each estimated from the measurements, and wherein the estimates are used as input to feedback control of the applied stimulus in order to effect differential control of fibre classes recruited in an evoked ascending volley as compared to fibre classes recruited in an evoked descending volley.

7. The method of any one of claims 1 to 6 wherein the estimate of conduction velocity is used for feedback control of an applied stimulus in order to maintain stimulus efficacy during postural changes.

8. The method of any one of claims 1 to 7 wherein the measurements of the neural response are obtained from at least three electrodes for each estimate of conduction velocity.

9. A device for estimating conduction velocity of a neural response, the device comprising:

at least two electrodes which are configured to be positioned at distinct locations along a neural pathway; and

a control unit configured to obtain measurements of the neural response from each electrode, the control unit further configured to determine a delay between the time of arrival of

the neural response at each respective electrode, and the control unit further configured to estimate from the delay, and from knowledge of electrode spacing, a conduction velocity of the neural response.

10. The device of claim 9, wherein the device is configured for permanent implantation.

11. A method for diagnosing a disease which affects neural conduction velocity, the method comprising:

repeatedly measuring a neural conduction velocity over time, using the method of any one of claims 1 to 8; and

determining from said measurements whether changes in neural conduction velocity have occurred which are indicative of the disease.

12. The method of claim 11 wherein the disease is diabetes mellitus, and wherein detection of a reduction in neural conduction velocity is used to trigger revision of a treatment schedule.

13. The method of claim 11 wherein the disease is central sensitization, the method further comprising obtaining a conduction velocity map of the spinal cord by progressively applying stimuli using each of a plurality of electrodes of an implanted electrode array, using spaced apart measurement electrodes to obtain a measure of the conduction velocity resulting from each stimulus site, and then mapping conduction velocity against location to indicate the location(s) at which central sensitization has occurred.

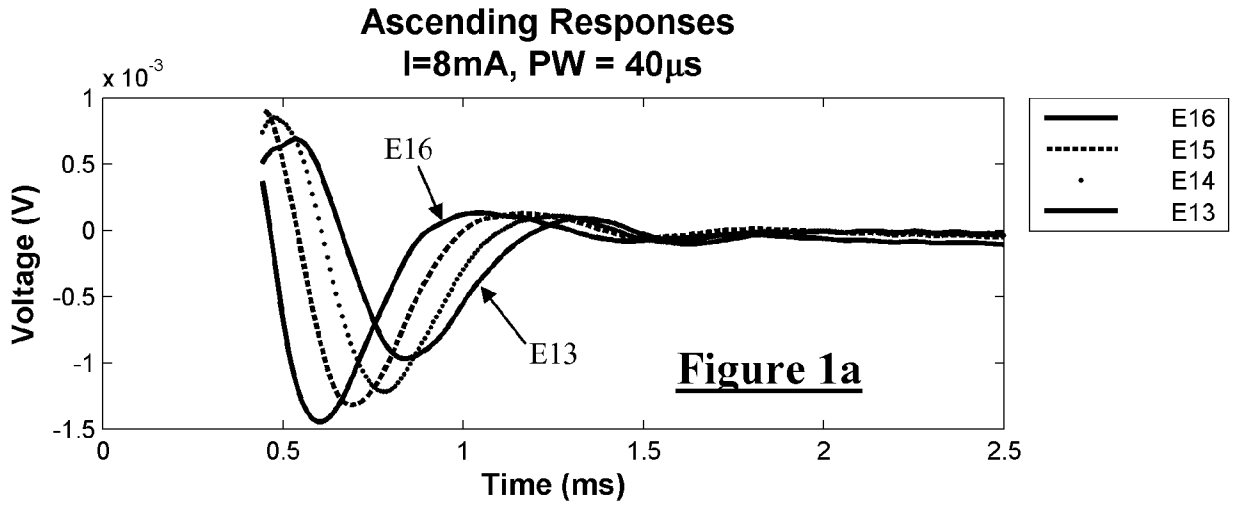


Figure 1a

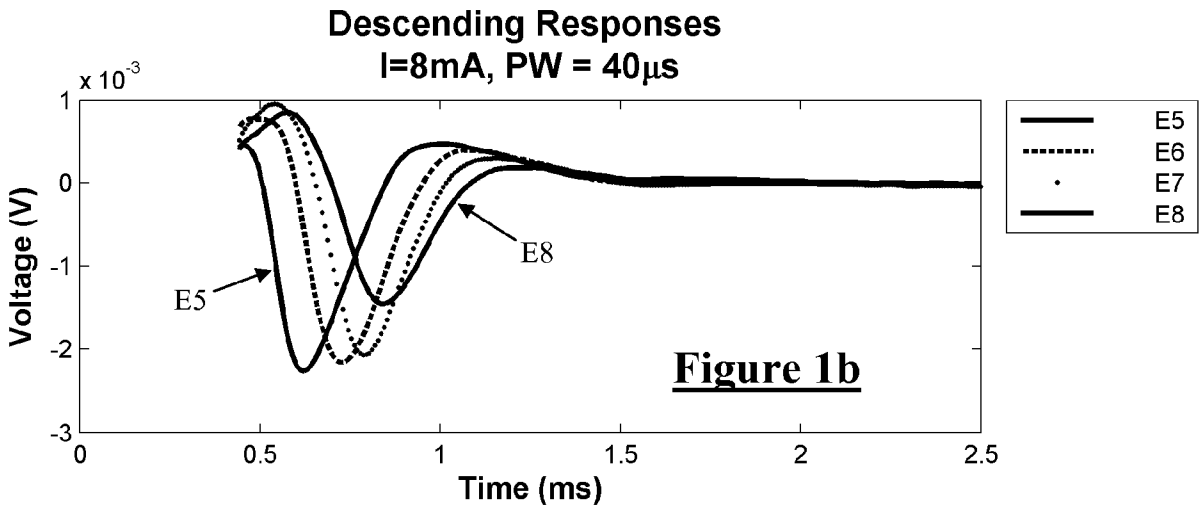


Figure 1b

Figure 2a

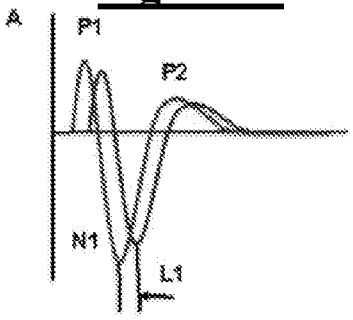
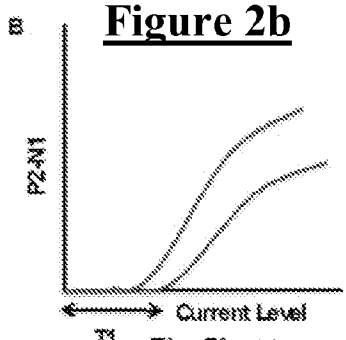


Figure 2b



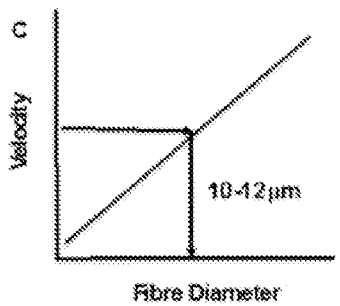


Figure 2c

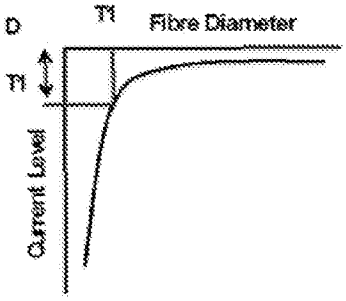


Figure 2d

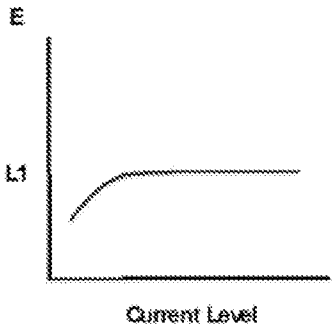


Figure 2e

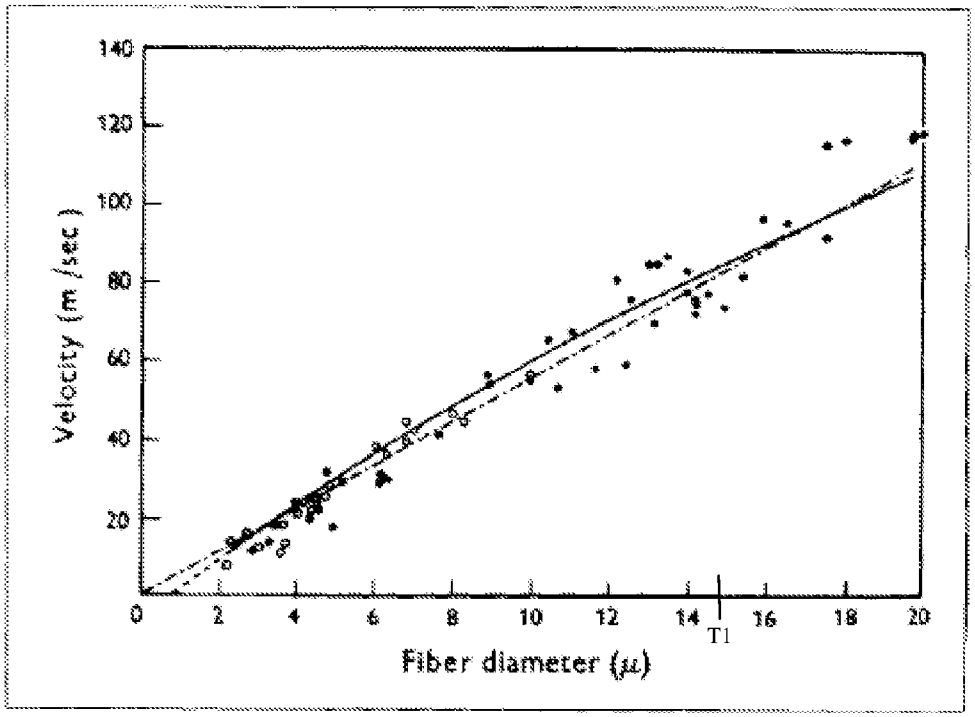


Figure 3

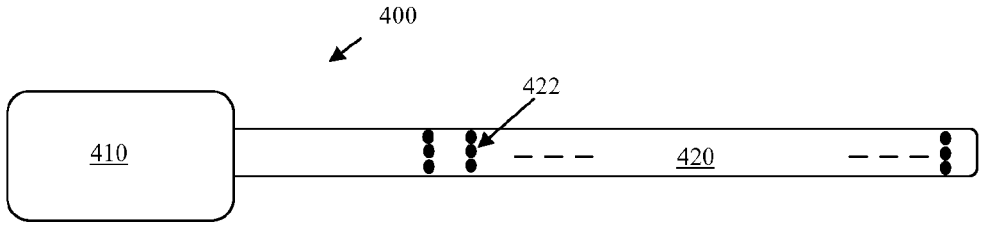


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2012/000512

A. CLASSIFICATION OF SUBJECT MATTER

A61N 1/36 (OCT 2005) A61N 1/05 (OCT 2005) A61N 1/18 (OCT 2005) A61N 1/34 (OCT 2005)
A61B 5/04 (OCT 2005) A61B 5/0408 (OCT 2005) A61B 5/042 (OCT 2005) A61B 5/053 (OCT 2005)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Espacenet & MEDLINE & Google Scholar and TXTUS0, TXTUS1, TXTUS2, TXTUS3, TXTUS4, TXTEP1, TXTGB1, TXTWO1:Keywords: (neur+ or nerv+) and (stimul+) and (potential? or response? or cap?) and (electrode?) and (measur+ or sens+ or detect+ or estimat+ or record+) and (velocity or speed) and (transmission or conduction) and (two or second+ or plural+ or multipl+ or array?) 3w (electrode?) and (delay, timing, time, interval) and (spac+, distance, dorsal, spin+, fibre? or fibre?) and like terms. **WPI & EPODOC:** IPC & EC A61B 5/-; A61N 1/- & Keywords (neur+, nerv+, stimul+, potential?, response?, cap?, electrode?, measur+, sens+, detect+, estimat+, record+, velocity or speed, transmission or conduction, (two or second+ or plural+ or multipl+ or array?) 3w (electrode?), delay, timing, time, interval) and like terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2012	11 July 2012

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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/AU2012/000512
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5215100 A (SPITZ et al.) 01 June 1993 Abstract; Column 5, line 19 to Column 17, line 19; Claim 43; Figures 1-11	1-13
X	EP 0219084 A2 (ZEALEAR) 22 April 1987 Abstract; Page 2, lines 4-30; Page 19, line 10 to Page 21, line 3; Page 27, line 6 to Page 30, line 3; Figures 1-10	1-13
X	US 4807643 A (ROSIER) 28 February 1989 Abstract; Column 1, line 61 to Column 2, line 23; Column 2, line 41 to Column 4, line 48; Figures 1-6	1-13
X	US 2004/0088017 A1 (SHARMA et al.) 06 May 2004 Abstract; Paragraphs [0006]-[0014], [0027]-[0081]; Figures 1-11	1-13
X	US 2010/0331604 A1 (OKAMOTO et al.) 30 December 2010 Abstract; Paragraphs [0088]-[0090]	1-13
A	WO 2003/103484 A (NERVETRACK LTD et al) 18 December 2003 Abstract; Claims; Figures	1-13
A	US 2003/0195580 A1 (BRADLEY et al.) 16 October 2003 Abstract; Claims; Figures	1-13
A	Goodall, E. V., et al., (1995),Modeling study of activation and propagation delays during stimulation of peripheral nerve fibres with a tripolar cuff electrode. IEEE Trans.Rehab. Eng. v 3, Pages 272-282 Pages 272-282	1-13
A	Roy, S. H.,et al.,Effects of electrode location on myoelectric conduction velocity and median frequency estimates. J. Appl. Physiol. 61(4): Pages 1510-1517, 1986 Pages 1510-1517	1-13
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2012/000512**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
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		JP 62155832 A	10 Jul 1987
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		EP 1572296 B1	05 May 2010
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		US 7415307 B2	19 Aug 2008
		WO 2004041358 A1	21 May 2004
US 2010/0331604 A1	30 Dec 2010	US 2010331604 A1	30 Dec 2010
		WO 2009119236 A1	01 Oct 2009
WO 2003/103484 A	18 Dec 2003	None	
US 2003/0195580 A1	16 Oct 2003	US 2003195580 A1	16 Oct 2003
		US 6931281 B2	16 Aug 2005

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.