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Your reference

9205058.2

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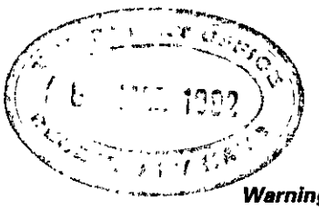

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: Techniques (N1)

❷ Applicant's details

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2b If you are applying as an individual or one of a partnership please give in full:

Surname: Filler

Forenames: Aaron Gershon

2c **In all cases**, please give the following details:

Address: 31 Copse Hill

Wimbledon

UK postcode *(if applicable)*: SW20 ONE

Country: U.K.

ADP number *(if known)*: 5708722001

RR

2d, 2e and 2f: *If there are further applicants please provide details on a separate sheet of paper.*

❑ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname Howe

Forenames Franklyn Arron

2f **In all cases**, please give the following details:

Address Division of Biochemistry
St. George's Hospital Medical School
Cranmer Terrace, Tooting

UK postcode *(if applicable)* SW17 ORE

Country U.K.

ADP number *(if known)* 608197 0001

❸ *An address for service in the United Kingdom must be supplied*

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❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☐ No ☐ ➡ ***go to 3b***

↓ ***please give details below***

Agent's name

Agent's address

Postcode

Agent's ADP number

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name Aaron Filler, MD, PhD

Address 31 Copse Hill
Wimbledon, SW20 ONE

Postcode

Daytime telephone number *(if available)* (081)946-7711

ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)*

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☐ ➡ ***go to 6***

↓ ***please give details below***

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'No' if:*
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant,* ***or***
- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventor

Please mark correct box

Yes ☑ No ☐ ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	4
Abstract		Drawing(s)	1

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡ Signed Evelyn Howe Alan G. Hill Date 9 (day) March (month) 92 (year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either:

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A.G. Filler
F.A. Howe

Technique

Neurography:

Pulse Sequence and Equipment for Production of Neurographic Images

This invention discloses a method and process for making a new type of image of the living human body to be called a neurogram. This entirely novel neurographic image shows the branching pattern of the individual person's peripheral, autonomic or cranial nerve tree so that it stands out in isolation from other structures.

Although many techniques have been developed for showing distinctive images of the brain, of the spinal cord, and of the spinal roots within the spinal canal, there has never been a successful method for creating images of the peripheral and cranial nerves as they pass among bones, muscles, lymphatics, tendons, ligaments, intermuscular septa, collections of fatty tissues, air or fluid filled spaces, veins, arteries, joints, skin, mucous membranes and other tissues. The peripheral, autonomic, and cranial nerves are relatively small compared to many other bodily tissues, and they often travel in bundles near other structures of comparable size and shape.

The lack of any method for distinctly creating an image of the nerves in a living mammal or human has been a great hindrance to physicians, surgeons, athletic trainers, pain treatment specialists, as well as for designers of ergonomic furniture, specialized body suits, boots, and various kinds of electronic or electric medical equipment which can be best used when the positions of nerves can be precisely located in advance. Although many nerves travel along straight and simple courses, there are very complex nerve arrangements such as the brachial plexus, lumbar plexus, or sacral plexus where bundles of nerves collect together, separate, rejoin, intermix, and resegregate in such a way as to create a very intricate three dimensional pattern. A compression or irritation of a small area of nerve within such a plexus (e.g. in the shoulder) can cause pain, numbness, weakness or paralysis at some distant site (e.g. in one finger). Even when a surgeon attempts to expose and examine the brachial plexus for direct inspection, the anatomic complexity can prove overwhelming, rendering surgery in this area to be extremely difficult and dangerous.

This patent application discloses a method, which quite remarkably is capable of generating a three dimensional image of an individual patient's nerves and nerve plexuses. These images are acquired in such a way as to make all other structures in the body seem to tend to disappear so that only the nerve tree remains to be seen. Although such an image will greatly ease the tasks of many professionals who work with nerves and although such an image technique has been imagined for many years, it has never previously seemed possible to actually accomplish this task.

The only prior art in this area involves methods which attempt to make nerves stand out in images by the means of administering special pharmaceuticals which give the nerves special imaging properties. These pharmaceuticals are based on two part agents which gain entry into and are transported within nerves where the second part of the agent has an imageable property (see PCT - EP 91/01780, 13 September 1991- Particulate Agents for Axonal Imaging, A.G. Filler). If the second part has elements with high nuclear density, then it may tend to increase the contrast of the nerve upon X-

ray or Computed Tomography (CT) examination, if the second part has a radioactive (e.g. positron emitting) element, then the nerve may be visible upon Positron Emission Tomography (PET) scanning, or if the second part has a magnetically active component, then the signal of the nerve may be changed upon Magnetic Resonance Imaging (MRI). These agents are injected into muscle and thereby used to selectively alter the imaging characteristics of the nerve supplying that muscle.

The main limitation with these pharmaceutical agents is that they can generally be used only to image a single nerve or nerve group. The MRI agents for nerve imaging actually gain their effect by blacking out the nerve in the image. Since nerves are difficult to see in current types of MRI images, the action of these MRI nerve imaging agents can be difficult to interpret.

Neurographic imaging is accomplished by using a set of special pulse sequence and program instructions to control the electronic equipment of an MRI scanner. For the imaging of fine nerve branches, the pulse sequences are aided by the use of special signal and imaging coils placed near or around the portion of the body of greatest interest. This does not require the administration of any pharmaceutical agent. Indeed, since neurographic imaging makes nerves appear bright and isolated in an image, it then becomes far more informative to selectively black out one of the nerves by means of administering an intraneural pharmaceutical contrast agent. Thus this invention of neurography, can be viewed as a way of effecting a process which rapidly produces an image of an entirely new kind, wherein that image can be examined for its anatomical information content, and wherein that image can be manipulated by the administration of pharmaceutical agents.

Although nerve imaging pharmaceutical agents had been designed to help in the diagnosis of nerve compressions and nerve injuries, it was not anticipated that the nerves could be seen in relative isolation without administering any pharmaceutical. Indeed, users of such agents have acutely appreciated the need for an imaging technique such as the neurography disclosed herein which would synergistically render the effects of the intraneural agents into much more useful form.

The fine spatial resolution required for creating detailed images of peripheral nerves, including their small distal ramifications and divisions, is well within the physical range of current clinical magnetic resonance imaging instruments, particularly when specially designed local signal and imaging coils are used. The inventors have discovered that there are various sets of pulse sequences and combinations of pulse sequences which can be used to unambiguously distinguish small nerves from neighbouring structures of similar shape and location. This includes the combination of some existing sequences into new groupings for use in new situations as well as the design of new sequences which incorporate optimized features for the purpose of neurographic imaging.

The ideal 'neurographic image' is analogous to a subtraction angiogram (an image showing only blood vessels), but sharply highlights a nerve rather than a vessel. Such an image is most useful for confirming the identification of nerves in a given imaging plane as well as for locating nerve injuries and nerve compressions.

The inventors carried out experiments in which they tested imaging techniques which enabled them to selectively delete the signal from non-neural structures and also evaluated techniques which permitted relative enhancement of the image signal from nerve. One very helpful scientific discovery was that neurographic imaging could be greatly aided by taking special advantage of the "anisotropic water diffusion" which is known to take place in muscle, in the central nervous system and in peripheral nerves. The inventors demonstrated that, under ideal image collection pulse sequence circumstances, the diffusion coefficient of anisotropy in peripheral nerve is greater than

that in muscle, and that it was possible to collect appropriate diffusion weighted images in such a way as to generate neurograms.

The method used in one example is to first carry out a fat suppression technique which maintains excellent image resolution, and then, within the same pulse sequence, to include an oriented pulsed gradient for selective incorporation of information from diffusion anisotropy. The various parts of the pulse sequence are selected so as to optimally destroy as many other signals as possible other than that of nerve as shown in figure 3. Then, a second sequence is carried out which selectively destroys the nerve signal as by for instance, rotating the diffusion gradient orientation to be parallel rather than perpendicular to the nerve (see figure 4). The effect of these maneuvers is to produce two images, the first of which shows up the nerve relatively brightly, and the second of which selectively destroys the nerve signal. When these two penultimate images are then mathematically or photographically, or optically subtracted from one another, and optionally divided by the signal information from a fat suppressed T2 weighted (CHESS - chemical shift suppression) spin echo sequence, the result is the neurogram.

An alternate approach explored by the inventors is to use pulsed gradients oriented in each of three axes or into specially created axes suitable to the imaging task. In this fashion, it is possible to determine a diffusion coefficient for each voxel in the image. These diffusion coefficients can be rendered themselves as a neurographic image.

To optimize the subtraction technique where subtraction is used or to optimize the voxel by voxel gradient coefficient measurement, the image sequence can be modified to interleave the different sequences and so to minimise any motion artefact which could degrade the accuracy of the final image when the different sequences are collected at times separated by several minutes. It is also possible to carry out the signal acquisition as a three dimensional acquisition for rapid assembly of the final data set.

Example

For one example, images were obtained with a 4.7Tesla, 33 cm bore SISCO system fitted with a 10 Gauss/cm high performance auxiliary gradient insert (12 cm inner bore). A three-turn solenoid coil (2.5 cm in length and 3 cm in diameter) was placed around the upper portion of the forelimb of 2 - 2.5 kg rabbits. The animals were maintained under balanced continuous intravenous infusion of an anaesthetic mixture containing 1 mg of medazolam, 1.5 mg of fluanisone and 50 μg of fentanyl per ml at rates of 4 to 10 ml/hr to achieve a deep anaesthesia minimising motion artefacts from respiration.

A specially modified multislice spin echo imaging sequence (TE=40 ms, TR=1 sec) was adjusted to provide fat suppression (CHESS) and to accommodate diffusion weighting of images. This set of modifications allows operator control of the strength of the gradients and allows various strengths and orientations to be inserted into 'slots' or reserved times within the common base sequence. After an initial image with fat suppression only, there is next collected one image with diffusion gradients perpendicular to the image plane and then one image with diffusion gradients parallel to the image plane.

The CHESS sequence consisted of a 3 millisecond (ms) gaussian pulse for selective excitation of fat followed by a 5 Gauss/cm dephasing gradient of 3 ms duration performed 3 times with orthogonal gradients prior to each spin echo sequence. For diffusion weighting, pulsed gradients of strength G_i=10 G/cm, duration δ=7 ms, and separation Δ=20 ms, were symmetrically placed about the 180° pulse. Transverse images (nerves primarily orthogonal to image plane) with slice

thickness of 2 mm were obtained for a 4 cm field of view with 256 phase encoding steps. Image data was zero filled to 512 points to give 78μm in plane resolution.

Simple spin echo images of limb anatomy prove inadequate for definitive identification of peripheral nerves because the nerves are typically surrounded by the high intensity signal from fat deposits in the intermuscular spaces. Further, there are a variety of structures similar to nerve in size and shape which follow similar routes. However, the inventors found that the fat surrounding nerves is actually beneficial for nerve identification, because in a fat suppressed image, a relatively high intensity nerve signal stands out sharply within the very low intensity space left behind by the suppressed fat signal (see figure 2).

Under these conditions the phenomenon of diffusion anisotropy was applied to the problem of nerve image enhancement and shown to be exceedingly effective (see figure 3 & 4). Apparent diffusion coefficients ($D_{\perp}$,$D_{||}$) were calculated from average pixel intensity measurements over the region of interest (ROI) from each of the three different images in a given set. Calculation employed the formula (Intensity = $A_O \cdot \exp[-TE/T_2] \cdot \exp[-bD]$, attenuation factor $b=\gamma^2 G_i^2 \delta^2 [\Delta - \delta/3] = 61.9\ 10^3\ sec/cm^2$).

Apparent Diffusion Coefficients (10^{-5} cm^2/sec)

	Muscle	Median Nerve
$D_{\perp}$	1.2	0.98
$D_{||}$	1.8	2.3
$D_{||}/D_{\perp}$	1.5	2.35

This example demonstrates that fat suppression by CHESS enhances the visualization of peripheral nerves so that when different diffusion gradient orientations are incorporated in secondary segments of the imaging pulse sequence, the ultimate yield is a far larger relative change in intensity in the nerve signal than in muscle. This intensity change then provides the basis for an image subtraction technique to achieve relative nerve image enhancement. The various subtracted or divided nerve images are then assembled mathematically by routine reconstruction techniques into a three dimensional image. Thus the objective of assembling three dimensional neurograms is conveniently achieved.

Figure 1: Diagram of transverse section of the upper fore-arm of a rabbit based on the fat suppressed image shown in figure 2. 1) triceps muscle, 2) ulnar nerve, 3) brachial veins, 4) median nerve, 5) radial nerve, 6) humerus, 7) cephalic vein, 8) biceps muscle.

Figure 2: Fat suppressed image (black=highest intensity).

Figure 3: Application of a perpendicular pulsed gradient renders the nerves as the highest intensity features in the image.

Figure 4: Reorienting the gradient parallel to the long axis of the nerve has a relatively greater effect in reducing the nerve signal than that of the muscle.

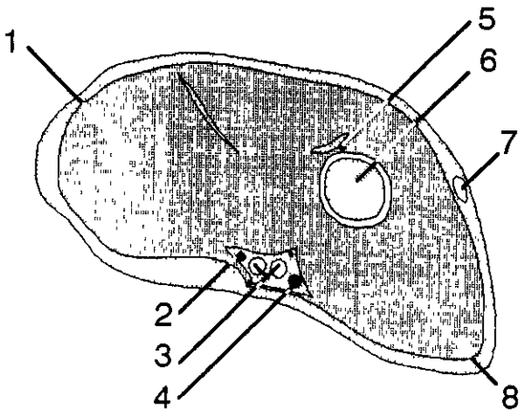

Figure 1

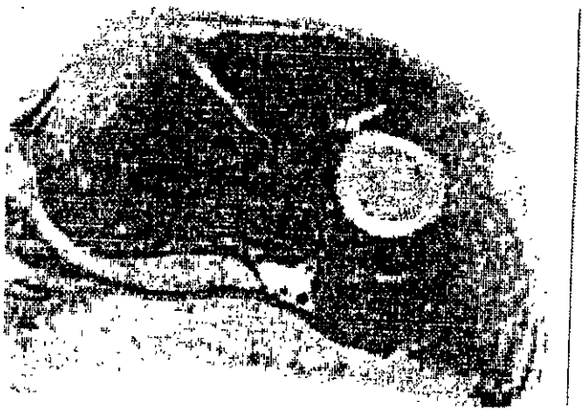

Figure 2

Figure 3

Figure 4