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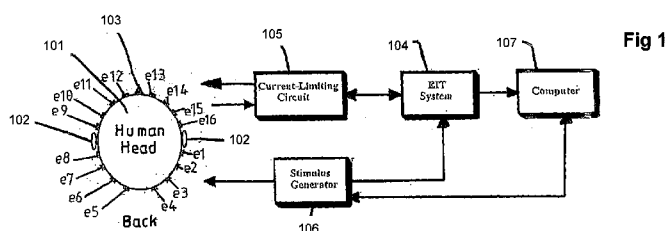
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(54) Title: NERVOUS SYSTEM MONITORING METHOD



(57) Abstract: A method for monitoring the response of a nervous system of a body to a stimulus. The method comprises collecting a set of voltage measurements between selected areas on a surface of the body whilst current is being passed between selected regions of the surface of the body. The set of voltage measurements is collected over a predetermined measurement period, the predetermined measurement period is based upon a time after application of the stimulus, and the collected voltage measurements are compared with reference measurements to determine normal or abnormal response of the nervous system.

NERVOUS SYSTEM MONITORING METHOD

The present invention relates to methods and apparatus for acquiring tomographic data. More particularly, but not exclusively, the invention relates to methods and apparatus for acquiring tomographic data from a human or animal subject, for example for monitoring the response of a nervous system of a body to a defined stimulus, such as a flash of light before a subject's eyes or an audible sound adjacent to a subject's ears, or another event or sequence of events.

There is a well-known requirement for a method capable of imaging the activity of a nervous system such as a human brain which is sufficiently fast to capture neural activity with sub-second resolution. For example, Susan Greenfield, a professor of pharmacology at Oxford University, England, giving the Andrew Olle Memorial Trust lecture in Sydney, Australia in May 2000 stated that "I think that there is the plausible prospect in this century of being able to devise very good imaging techniques that enable us to catch that which we can't catch at the moment because the imaging techniques are too slow". The present invention is concerned with delivering a method which is capable of imaging the activity of human brain to sub-second resolution.

As described by Pomfrett C.J.D. and Healy T.E.J. (1995), "Awareness and the Depth of Anaesthesia", Healy T.E.J and Cohen P.J. (eds) "A Practice of Anaesthesia", Edward Arnold, pages 864-878, it is well known that activity within the human brain can be monitored using standard EEG approaches. For example auditory, visual and somatosensory evoked responses can be generated which show that there is a latency after the occurrence of a stimulating event such as an audible sound or a light flash before sensory pathways in the brain respond. Typically there is a delay of at least several tens of milliseconds after a stimulating event before the evoked response can be detected by EEG equipment. Furthermore, although EEG equipment is capable of picking up signals showing that some response has been generated, the location of the source of such signals within the brain cannot be accurately determined from the detected signals.

It is known to use MRI and PET techniques to produce images of cerebral activity, but such techniques respond to haemodynamic and/or metabolic recovery processes which occur over time periods of typically many seconds or minutes and cannot therefore be used to image short term neural activity.

Electrical impedance tomography (EIT) has also been proposed as a method of imaging neurological functions within a body. US patent number 5919142 describes various EIT systems which have been proposed for measuring changes in impedance taking place within the brain and using those measurements to image the progress of information along circuits within the brain. It is stated that the brain may be stimulated by for example a visual signal and EIT images subsequently reconstructed for each millisecond or so of the recording "window", thus enabling the resultant action potential processes to be tracked along their pathways in the subject's brain. Although such a theoretical reconstruction to a resolution of milliseconds is discussed, it is conceded in US 5919142 that there is no established technique to permit accurate imaging of neuronal depolarisation with millisecond or sub-millisecond time

resolution. It is stated that impedance changes associated with action potentials are generally very small and very rapid and the impedance of the tissue as a whole which is interposed between locations at which impedance measuring electrodes must be positioned may not change in proportion to changes in local action potentials.

Individual impedance measurements (or voltage measurements during current injection) take a finite length of time, typically measured in milliseconds, and in order to build up a sufficient number of impedance measurements to enable the generation of a single image of local impedance distributions within the brain a number of individual impedance measurements must be taken. Typically therefore it takes a few hundred milliseconds to collect sufficient impedance measurements to produce a single image of the brain, although it is feasible to measure voltages in parallel during current injection, thus reducing the measurement period to a few tens of milli-seconds.

A further problem encountered with EIT systems when used for brain imaging is that changes of impedance resulting from neural activity within the brain are thought to be relatively small, for example between 0.1 and 1% of baseline impedance. If true, this makes it very difficult to distinguish impedance fluctuations resulting from changes in neural activity from background noise. The approach suggested in US patent 5919142 seeks to improve sensitivity to changes in impedance resulting from neural activity by taking a first set of impedance measurements whilst a first electrical input signal is being applied to the brain for a period of for example 100 milliseconds or more, taking a second set of impedance measurements when a second electrical input signal that is the reverse of the first is applied to the brain, calculating the difference between the two sets of measurements, and generating an image on the basis of the calculated difference. The application of the first and second input signals can be synchronised with the application of separate stimulus signals to the body. The problem with this approach is that there is a 100 millisecond delay between the generation of the two sets of signals which are compared so as to generate the data from which an image is subsequently generated. It is quite clear therefore that such a system cannot be sensitive to changes in impedance resulting from cerebral activity occurring over periods of only a few milliseconds and improved tomographic data acquisition apparatus appropriate for use in a clinical setting is therefore desirable.

US patent 5919142 dates from a priority date of 22nd June 1995. Since that date the same research group has continued with research into the use of electric impedance tomography for studying human brain activity. This is indicated by the paper "3-Dimensional Electrical Impedance Tomography of Human Brain Activity", Tidswell T., Gibson A., Bayford R.H. and Holder D.S., *Neuro Image* 13, 283-294 (2001). That paper describes the use of EIT to detect local changes in cerebral blood flow and blood volume. The data measurement for each impedance image was recorded over a period of 25 seconds. Before recording measurements, the neural stimulation process was initiated and remained active for several minutes. It is stated that reproducible impedance changes of about 0.5% lasted from 6 seconds after the onset of a stimulus to 41 seconds after stimulus cessation. The described system was however looking at the side-effects of brain activity, that is changes in blood flow and blood volume,

rather than the neurological activity of which such changes are merely side effects. Furthermore, although some interesting results were generated, the paper itself concedes that problems of low resolution and reconstruction error remain which must be overcome if EIT is to be used as a fast neuro imaging tool with clear clinical applications. It is stated that a faster EIT system is being tested which will allow more measurements to be made per image but however many measurements are made, it still cannot be expected that the above technique will be sensitive to neuronal or synaptic phenomena occurring over a period of for example only one or a few milliseconds.

The inventors' European patent 1615550 describes an EIT system in which a stimulus is applied and after a user-variable time delay current is injected between pairs of electrodes during a predetermined measurement period. Whilst current is injected between some pairs of electrodes voltage is measured between other pairs of electrodes. The measurement period therefore begins at a time determined by the user-variable delay and the time at which the stimulus is applied. Data obtained during the measurement period represents neurological behaviour of the nervous system caused by the stimulus and occurring after the user-variable delay. It is an object of some aspects of the present invention to provide an improved implementation of this system.

According to a first aspect of the invention, there is provided a method for monitoring the response of a nervous system of a body to a stimulus, comprising providing a plurality of electrodes on a surface of a body and passing current between at least one pair of electrodes of said plurality of electrodes, said current being provided by a current source external to the body, collecting voltage measurements between selected ones of said electrodes while said current is passed between said at least one pair of electrodes, said voltage measurements being collected independently of stimulus application, and processing a subset of the collected voltage measurements to determine a response of the nervous system to the stimulus, wherein the subset of the collected voltage measurements is collected over a predetermined measurement period, the predetermined measurement period beginning a particular time after application of the stimulus.

In this way, voltage measurements are collected continuously and independently of stimulus application. The voltage measurements that are processed are extracted from a set of voltage measurements based upon the time at which the stimulus is applied and the particular time.

The collection of voltage measurements independently of stimulus application may provide a number of benefits. In particular, where voltage measurements are continuously collected and a stimulus is applied during a time in which voltage measurements are collected, any change in voltage measurements following stimulus application can be reliably attributed to the stimulus, thereby avoiding any risk that the commencement of measurement causes artefacts which somehow affect the collected voltage measurements which could lead to incorrect determinations relating to the response of the nervous system.

The collected voltage measurements may be compared with reference measurements to determine normal or abnormal response of the nervous system.

If a single set of measurements is taken, that set may be compared with predetermined data to assess neurological behaviour. If a series of sets of measurements are taken, neurological behaviour may be assessed by comparing different sets, and images representative of that behaviour may be generated.

The stimulus may be applied by the system, or alternatively may occur spontaneously. Occurrence of the stimulus may be detected, and this detection may start computation of the particular time. The stimulus may be a feature of an environment in which the body is located or may be a physiologically occurring event (for example a heart beat or breath of a subject).

The said regions and/or areas may be selected on the basis of a neurological model of the nervous system and the applied stimulus such that sensitivity of the derived impedance measurements to changes in the predetermined part of the nervous system is maximised.

For example, if activity of the Lateral Geniculate Nucleus (LGN) is of interest, current may be passed between regions at the front and rear of the head to maximise the effect of activity in the LGN on the voltage measurements.

An input time delay may be received, and the measurement period may begin after a delay based upon the input time delay.

That is, processing may be based on collected voltage measurements of interest, the measurements of interest being selected based upon the time at which the stimulus is applied, and the input time delay. In this way, the response of the nervous system at a time, based upon the input time delay, after application of the stimulus can be effectively determined.

The processing can be based upon a subset of the voltage measurements collected during the predetermined measurement period. That is, only some of the voltage measurements collected during the predetermined measurement period may be used as a basis for processing to determine a response of the nervous system to the stimulus.

Current may be sequentially passed between a plurality of pairs of electrodes and voltage measurements may be collected between selected ones of said electrodes while current is passed between each pair of said plurality of pairs of electrodes.

In some embodiments, current may be repeatedly sequentially passed between the plurality of pairs of electrodes.

The method may further comprise applying the stimulus..

The stimulus can take any suitable form. For example, the stimulus may be a sensory stimulus such as a visual stimulus or an auditory stimulus, or alternatively may be transcranial magnetic stimulus.

The processing may comprise producing an image representing a distribution of impedance within the body. Additionally or alternatively, the processing may comprise comparing at least some of the collected voltage measurements with reference data. Such comparison may allow a determination to be made as to whether the response of the nervous system corresponds to normal or abnormal behaviour.

Passing current between at least one pair of electrodes may comprise injecting electrical current for a first time period through at least a first pair of electrodes of a plurality of electrodes affixed to a

subject, during said first time period, measuring electrical voltage between selected ones of said plurality of electrodes, subsequent to said first time period, injecting electrical current for another time period through at least another pair of said plurality electrodes and during said another time period, measuring electrical voltages between selected ones of said electrodes of said plurality of electrodes. The steps subsequent to said first time period of injecting electrical current and measuring electrical voltages between selected ones of electrodes may be repeated for different electrodes.

The first time period and another time period may have substantially equal lengths. Current injection may be carried out independently of stimulus application.

The processing may include a comparison of voltage measurements taken at a particular time after application of the stimulus with voltage measurements obtained at a time before application of the stimulus. In this way, an effective indication of the response of the nervous system to the applied stimulus can be obtained. Indeed, the measurements before application of the stimulus may be considered to be reference measurements, with measurements made at a particular time after application of the stimulus being considered to be experimental measurements of interest which can be compared with the reference measurements.

A further aspect of the invention provides a tomographic data acquisition apparatus comprising a plurality of electrodes arranged for attachment to a measurement subject; a current source; a current supply line connected to said current source and connectable to each of said plurality of electrodes; a controller arranged to connect electrodes of a selected pair of electrodes to said current supply line, so as to provide current between the selected pair of said plurality of electrodes; and measurement circuitry arranged to obtain voltage measurements between selected ones of said plurality of electrodes while current is being provided between said selected pair of electrodes.

The current supply line (also referred to herein as a current bus) therefore provides a convenient way of providing current between a selected pair of the plurality of electrodes. More specifically, where each of the electrodes is connectable to the current supply line, current can easily be provided between the selected pair of electrodes.

The current supply line may comprise first and second current supply lines, and the controller may be arranged to connect a first electrode of the selected pair of electrodes to said first current supply line and to connect a second electrode of the selected pair of electrodes to said second current supply line. The current source may comprise first and second current sources. The first current source may be connected to said first current supply line. The second current source may be connected to said second current supply line. As such, the controller may control the first current source to provide a first current on said first current supply line and control the second current source to provide a second current source on said second current supply line. The first and second currents may be alternating currents having substantially equal magnitude, but which are 180 degrees out of phase with respect to one another (i.e. the second current may be an inversion of the first current). The provision of first and second currents of this type is advantageous given that the current flow to ground is minimised on the basis that the current

flowing from the first electrode to ground is substantially equal and opposite to the current flowing from the second electrode to ground.

In some embodiments each electrode of said plurality of electrodes may be connectable to each of said first and second current supply lines so as to provide flexibility as to the pairs of electrodes between which current can be provided. Each electrode of said plurality of electrodes may be connectable to each of said first and second current supply lines by a respective switch. In other embodiments some of the plurality of electrodes may be connectable only to the first current supply line and others of the plurality of electrodes may be connectable only to the second current supply line. The controller may be arranged to control the switches so as to control which electrode is connected to each current supply line, and thereby control the pair of electrodes between which current is provided.

The apparatus may further comprise current measurement circuitry arranged to obtain a measurement of current provided between said at least one selected pair of electrodes. As is known, current is a parameter used in the analysis and processing of voltage measurements which are collected in the manner described herein. The provision of current measurement circuitry enables current to be accurately determined, and avoids reliance being placed upon the accuracy of the current source. The current measurement circuitry may be arranged to obtain a measurement of current provided on each of said first and second current supply lines.

The apparatus may further comprise further electrodes which are arranged for attachment to a measurement subject but which are not connectable to the current supply line.

The apparatus may further comprise a processor arranged to process said obtained voltage measurements (and optionally said obtained measurement of current) to generate data indicating a distribution of conductivity in at least a part of said subject. The data may comprise at least one image indicating conductivity distribution.

A further aspect of the invention provides a tomographic data acquisition apparatus comprising: a plurality of electrodes arranged for attachment to a measurement subject; a current source arranged to provide current between a selected pair of said plurality of electrodes; voltage measurement circuitry arranged to obtain voltage measurements between selected ones of said plurality of electrodes while said current is being provided between said selected pair of electrodes; and current measurement circuitry arranged to obtain a measurement of current provided between said selected pair of electrodes. The current source is arranged to receive as input an indication of a current to be applied. The current source is arranged to provide, to an approximation, the indicated current.

In the prior art, it is known to acquire voltage measurements and use the acquired voltage measurements together with data indicating current which it is believed was applied to the subject (i.e. the current input to the current source). The present inventors have realised that it is beneficial to measure the current that is actually provided, rather than assuming that the provided current is as would be expected. The measurement of current in this way therefore removes a source of error in the processing of obtained voltage measurements.

The current source may comprise a first current source and a second current source, a first electrode of the selected pair of electrodes may be connected to said first current source and a second electrode of the selected pair of electrodes may be connected to said second current source. The current measurement circuitry may be arranged to obtain a measurement of current provided to each of said first electrode and second electrode.

A processor may be arranged to process said obtained voltage measurements and said obtained measurement of current to generate data indicating a distribution of conductivity in at least a part of said subject, and the generated data may comprise at least one image.

A further aspect of the invention provides a tomographic data acquisition apparatus comprising: a plurality of electrodes arranged for attachment to a measurement subject; a current source arranged to provide current between a first pair of said plurality of electrodes during a current injection time period; and voltage measurement circuitry arranged to obtain voltage measurements between at least one second pair of said plurality of electrodes during a part of said current injection time period designated as a measurement time period; wherein said current injection time period comprises a first time period of predetermined duration designated as a settling time period during which voltage measurements are not obtained, and the measurement time period is a part of said current injection time period following said settling time period; and said voltage measurement circuitry comprises at least one measurement component (e.g. an amplifier), the or each measurement component being connected to one of said second pairs of electrodes and the or each measurement component having a saturation recovery time which satisfies a criterion defined with reference to the duration of the settling time period. The criterion may be that said saturation recovery time is less than the duration of said settling time period.

The inventors have surprisingly realised that in the construction of a tomographic data acquisition system, it is important that a measurement component forming part of the measurement circuitry has a saturation recovery time which satisfies a criterion of the type set out above. Such an approach improves the reliability of voltage measurement.

The current source may provide an alternating current which may have a frequency of about 10kHz. The current injection time period may have a duration of 500 μ s, and said settling time period may have a duration of 100 μ s. The or each amplifier may have a saturation recovery time of less than 100 μ s, for example a saturation recovery time of less than 50 μ s, such as a saturation recovery time of about 10 μ s.

The controller may be arranged to provide current between a plurality of selected pairs of said plurality of electrodes in turn, current being provided between each selected pair of electrodes in a respective current injection time period. The measurement circuitry may be arranged to obtain a plurality of voltage measurements between selected ones of the plurality of electrodes during a part of each current injection time period designated as a measurement time period. Each current injection time period may comprise a first time period of predetermined duration designated as a settling time period during which

voltage measurements are not obtained, and each measurement time period may be a part of a respective current injection time period following said settling time period.

A further aspect of the invention provides a tomographic data acquisition apparatus comprising first and second units, wherein: the first unit comprises connections to a plurality of electrodes arranged for attachment to a measurement subject; a current source arranged to provide current between at least one first pair of said plurality of electrodes, voltage measurement circuitry arranged to obtain voltage measurements between at least one second pair of said plurality of electrodes while said current is being provided between one of said at least one first pairs of electrodes and data processing circuitry arranged to process said obtained voltage measurements to generate processed data and provide the processed data to said second unit, the voltage measurements being represented by a first quantity of data, and the processed data comprising a second quantity of data, the second quantity of data being smaller than said first quantity of data; and the second unit comprises data receiving circuitry arranged to receive the processed data from said first unit.

As such, the first unit is arranged to both obtain voltage measurements and reduce the quantity of data used to represent these voltage measurements, the reduced quantity of data being provided from the first unit to the second unit. As such, the bandwidth requirements between the first and second units are reduced.

The current may be an alternating current. The voltage measurements between one of said at least one second pair of electrodes, may comprise a plurality of voltage values each obtained at a respective time. The processed data representing voltage measurements between one of the at least one second pair of electrodes may comprise an in-phase value. The in-phase value may be indicative of correlation between the obtained voltage measurements and a reference waveform. The data processing circuitry may be arranged to generate the in-phase value from the obtained voltage measurements and the reference waveform.

The processed data representing voltage measurements between the or each of the at least one second pair of electrodes may further comprise a quadrature value. The quadrature value may be indicative of a correlation between the obtained voltage measurements and a phase-shifted reference waveform.

The processed data representing voltage measurements between the or each of the at least one second pair of electrodes may comprise 32-bits of data comprising a 16-bit in-phase value and a 16-bit quadrature value.

A further aspect of the invention provides a printed circuit board comprising a first conductor extending in a first direction in a first plane, the printed circuit board providing a screen for said first conductor, the screen comprising first and second screening conductors extending substantially in said first direction in said first plane, and third and fourth screening conductors extending substantially in said first direction in respective third and fourth planes, wherein the first, third and fourth planes are

substantially parallel to one another, and offset from one another, and the first plane is located between said third and fourth planes.

Such an arrangement provides good screening of the first conductor both from conductors in a layer (or plane) of the printed circuit board in which it is disposed and from conductors in adjacent layers (or planes) of the printed circuit board.

A connection may be provided between said first conductor and said first, second, third and fourth screening conductors, the connection being arranged to maintain the first, second, third and fourth screening conductors at the potential of the first conductor. The connection may comprise an amplifier.

A non-conducting material (e.g. a fibreglass material) may be interposed between said first and third planes and between said first and fourth planes. A non-conducting material may be interposed between said first conductor and said first screening conductor in said first plane and between said first conductor and said second screening conductor in said first plane.

This aspect of the invention may also provide a tomographic data acquisition apparatus comprising: a plurality of electrodes arranged for attachment to a measurement subject; a current source arranged to provide current between a selected pair of said plurality of electrodes; measurement circuitry arranged to obtain voltage measurements between selected ones of said plurality of electrodes while said current is being provided between said selected pair of electrodes; and a printed circuit board of the type described above, wherein the first conductor is arranged to provide current from said current source to electrodes of said plurality of electrodes.

The printed circuit board may further comprise a second conductor extending substantially in said first direction in said first plane, and the printed circuit board may provide a screen for the second conductor. More particularly, the printed circuit board may provide a screen for said second conductor comprising fifth and sixth screening conductors extending substantially in said first direction in said first plane, and seventh and eighth screening conductors extending substantially in said first direction in said third and fourth planes. The second conductor may be arranged to provide current from said current source to electrodes of said plurality of electrodes. Each of the electrodes may be connectable to each of said first and second conductors.

The current source may comprise first and second current sources, the first current source being connected to said first conductor and the second current source being connected to said second conductor. A controller may be arranged to control said first current source to provide a first current on said first conductor and to control said second current source to provide a second current on said second conductor, wherein said first and second currents have substantially equal magnitude, but phases which differ by approximately 180 degrees (i.e. the first and second currents may be alternating currents which are such that the second current is an inverted form of the first current).

A further aspect of the invention provides a tomographic data acquisition apparatus comprising: a plurality of electrodes arranged for attachment to a measurement subject; analog circuitry arranged to provide current to pairs of said electrodes and measure voltage between selected ones of said electrodes;

digital control circuitry; and a housing defining an interior volume in which the analog and digital circuitry is disposed; wherein the volume has an inner portion and an outer portion, the analog circuitry being disposed in the outer portion, the digital circuitry being disposed in the inner portion, and the electrodes being connected to the analog circuitry through the housing.

This aspect of the invention therefore provides a tomography system having a housing in which analog and digital components are conveniently housed. More particularly, analog and digital components are conveniently separated from one another. Furthermore, the location of digital circuitry in an inner part of the housing and the location of analog circuitry in an outer part of the housing can provide a long mixed signal boundary for connections between the analog and digital circuitry.

Indeed, the apparatus may further comprise digital-to-analog and/or analog-to-digital conversion circuitry. The volume may further have an intermediate portion located between the inner portion and the outer portion, and the conversion circuitry may be disposed in the intermediate portion.

The outer portion may be defined by an outer boundary of the housing and a first line extending generally parallel to the outer boundary of the housing. The intermediate portion may be defined by the first line extending generally parallel to the outer boundary of the housing and a second line extending generally parallel to the outer boundary of the housing, the second line defining said inner portion in a central portion of the housing. The housing may have an outer boundary defined by two straight parts and a curved part joining said two straight parts. The two straight parts may be substantially parallel to one another.

A further aspect of the invention provides a tomographic data acquisition apparatus for obtaining tomographic data from a human or animal subject, the apparatus comprising: a plurality of electrodes arranged for attachment to a human or animal subject; circuitry arranged to provide current to pairs of said electrodes and measure voltage between selected ones of said electrodes; and a housing in which the circuitry is disposed, the electrodes being connected to the circuitry through the housing, the housing defining a collar arranged, in use, to support the neck of the human or animal subject.

The provision of a tomographic data acquisition apparatus in this form is advantageous as a convenient means is provided to support the neck of the subject. This is particularly valuable in particular clinical environments such as operating rooms. The housing may be generally U-shaped and may define an opening to receive the neck of the human or animal subject.

A further aspect of the invention provides a tomographic data acquisition apparatus comprising first and second units, wherein: the first unit comprises a plurality of electrodes arranged for attachment to a measurement subject; a current source arranged to provide current between at least one first pair of said plurality of electrodes, voltage measurement circuitry arranged to obtain voltage measurements between at least one second pair of said plurality of electrodes while said current is being provided between said at least one selected pair of electrodes and control circuitry arranged to control said current source and said voltage measurement circuitry and to provide voltage measurement data to said second unit; and the second unit comprises data receiving circuitry arranged to receive voltage measurement data

from the first unit, and a power supply, the second unit being arranged to condition power generated by said power supply and to provide conditioned power to the first unit, the power supply being isolated from said first unit.

The control circuitry may be arranged to control the provision of current and measurement of voltage independently of the second unit. That is, the first unit may operate essentially autonomously to obtain voltage measurements and provide data based upon the obtained voltage measurements to the second unit.

The second unit may comprise a housing defining an interior volume having first and second portions, the first portion housing said data receiving circuitry and the second portion housing said power supply. An isolation barrier may be provided between said first and second portions. The second unit may further comprise a data processing interface arranged to provide received voltage measurement data to a computer. Voltage measurement data may be provided to said data processing interface from said data processing circuitry via at least one isolator. The second unit may be arranged to provide power to said first unit from said power supply via said isolation barrier. The second unit may further comprise an interface to a stimulus generator arranged to cause the stimulus generator to apply a stimulus to the measurement subject.

A further aspect of the invention provides a tomographic data acquisition apparatus for obtaining tomographic data from a human or animal subject, the apparatus comprising first and second units, wherein: the first unit comprises data receiving circuitry arranged to receive stimulus data, indicating a time at which a stimulus occurs, a plurality of electrodes arranged for attachment to a measurement subject, a current source arranged to provide current between at least one first pair of said plurality of electrodes, voltage measurement circuitry arranged to obtain voltage measurements between at least one second pair of said plurality of electrodes while said current is being provided between said at least one selected pair of electrodes and data processing circuitry arranged to provide obtained voltage measurements and received stimulus application data to the second unit; and the second unit comprises data receiving circuitry arranged to receive voltage measurements and said stimulus application data from the first unit.

The second unit may further comprise a stimulus application controller arranged to cause application of a stimulus to the measurement subject and to provide stimulus application data indicating times of stimulus application to the first unit.

The apparatus may be arranged to receive user input indicating a time delay and to process voltage measurements obtained at a time following stimulus application determined by said delay time so as to generate data indicating activity of the subject's nervous system at the time following stimulus application.

Alternatively, the apparatus may further comprise a monitor monitoring a physiological process of said human or animal subject, wherein said stimulus data is generated by said monitor.

Apparatus provided by various aspects of the invention described above may be such that the electrodes are arranged for attachment to the human or animal body so as to obtain data from a human or animal subject. For example, the electrodes may be arranged for attachment to a head of the human or animal subject. The electrodes of the or each at least one selected pair of the plurality of electrodes may be arranged to be attached to the head at substantially diametrically opposed positions.

Apparatus provided by various aspects of the invention described above may further comprise a stimulus application signal generator, arranged to generate a signal to cause a stimulus generator to apply a stimulus to the subject. The apparatus may be in communication with the stimulus generator. The stimulus generator may be arranged to generate a sensory (e.g. visual or auditory) stimulus or a transcranial magnetic stimulus.

Apparatus provided by various aspects of the invention described above may be arranged to receive user input indicating a delay time and to process voltage measurements obtained at a time following stimulus application determined by said delay time, so as to generate data indicating activity of the subject's nervous system at the time following stimulus application. That is, the apparatus can be effectively used in monitoring the behaviour of the nervous system in response to a stimulus. Indeed, obtained voltage measurements can be compared with reference data to determine whether the nervous system exhibited normal or abnormal response to the applied stimulus. In this way, aspects of the invention may provide a functional EIT system, that is a system in which tomographic data indicative of neurological function is obtained and processed.

Apparatus provided by various aspects of the invention described above may be such that the electrodes are arranged for attachment to a head of a human or animal measurement subject, and the electrodes of the or each at least one selected pair of said plurality of electrodes may be arranged to be attached to the head at substantially diametrically or nearly-diametrically opposed positions. The measurement circuitry may be arranged to obtain voltage measurements between electrodes arranged for attachment adjacent to one another.

In some embodiments a controller is arranged to provide current between a plurality of selected pairs of said plurality of electrodes in turn, and the measurement circuitry may be arranged to obtain a plurality of voltage measurements between selected ones of the plurality of electrodes while current is provided between each of said plurality of selected pairs of electrodes. This process may be repeated continuously.

According to a further aspect of the invention, there is provided a method for monitoring the response of a body to a stimulus, comprising providing a plurality of electrodes on a surface of a body and passing current between at least one pair of electrodes of said plurality of electrodes, said current being provided by a current source external to the body, collecting voltage measurements between selected ones of said electrodes while said current is passed between said at least one pair of electrodes, and processing at least some of the collected voltage measurements to determine a response of the body to the stimulus. The stimulus may be a physiologically occurring stimulus.

The various aspects of the invention described above can be used to monitor cerebral blood flow. Voltage measurements obtained between a pair of electrodes may define a saw-tooth waveform and characteristics of the saw-tooth waveform may be used to monitor cerebral blood flow. First voltage measurements obtained between a first pair of electrodes may be compared with second voltage measurements obtained between a second pair of electrodes to generate data indicating characteristics of cerebral blood flow. The first voltage measurements may define a first saw-tooth waveform and the second voltage measurements may define a second saw-tooth waveform. Characteristics of the first and second saw tooth waveforms may be compared to generate data indicating blood flow between a first part of a brain associated with the first pair of electrodes, and a second part of the brain associated with the second pair of electrodes.

It will be appreciated that features described in the context of one aspect of the invention can be applied to other aspects of the invention. It will further be appreciated that the various aspects of the invention can be combined with one another.

It will be appreciated that aspects of the invention described above also provide corresponding methods and apparatus for obtaining tomographic data. Each method can be carried out by suitably programmed computers. As such aspects of the invention further provide a computer program, a computer readable medium or data carrier (e.g. a disc) carrying such a computer program and an appropriately programmed computer.

Embodiments of the present invention will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 is a schematic representation of an apparatus used in accordance with the method of the present invention;

Figure 2 is a graph showing application of current in measurement frames in an embodiment of the invention;

Figure 3 shows six impedance images generated at various times after the application of a visual stimulus;

Figure 4 is a schematic illustration of a functional electrical impedance tomography (EIT) system in accordance with an embodiment of the present invention;

Figure 5 is a schematic illustration showing a head box of the system of Figure 4 in further detail;

Figure 6 is a state transition diagram showing operating modes of the head box of Figure 5 and transitions between those operating modes;

Figure 7 is a circuit diagram showing a part of circuitry included in the head box of Figure 5;

Figure 8 is a schematic illustration showing an arrangement of electrodes on a subject's head in a planar array;

Figure 8A to 8E are schematic illustrations showing an arrangement of electrodes on a subject's head in a three-dimensional array;

Figure 9 is a schematic illustration, in cross-section, of part of a printed circuit board used to implement the circuitry of Figure 7 in the head box of Figure 5;

Figure 10 is a schematic illustration of a base unit of the system of Figure 4;

Figure 11A is a flow chart showing processing carried out to obtain and process voltage measurements;

Figure 11B is a circuit diagram of a circuit arranged to implement the processing of Figure 11A;

Figure 12 is a graph showing an applied current waveform;

Figure 13 is a schematic illustration of a measured voltage waveform;

Figure 14 is a schematic illustration of a data packet format used to provide data from the head box to the base unit in the system of Figure 4;

Figure 15 is a timing diagram showing the passage of data between the head box and base unit in the system of Figure 4; and

Figure 16 is a schematic illustration of an alternative embodiment of the head box of Figure 5.

Figure 1 illustrates an apparatus for putting the invention into effect. A subject's head 101 has adhered to it sixteen electrodes e1 to e16 distributed in a plane around the head. In some circumstances it may be preferred to have a non-planar distribution of electrodes as described in Polydorides N., Lionheart W.R.B., and McCann, H.: "Krylov Subspace Iterative Techniques: On the detection of brain activity with electrical impedance tomography" IEEE Transactions on Medical Imaging, Volume 21, No 6, June 2002 pages 596-603. The subject's ears 102 and nose 103 are schematically illustrated to indicate the orientation of the subject's head. Calibrated headphones (not shown) are provided to deliver an auditory evoked response (AER) stimulus to the subject's ears and goggles (not shown) are provided which include light emitting diodes for generating a visually evoked response (VER) stimulus. Each of the sixteen electrodes is a silver-silver chloride EEG electrode of a type which presents a relatively small contact impedance on contact with the scalp.

An EIT system 104 is provided to deliver current to selected pairs of electrodes via a current limiting circuit 105 and to perform voltage measurements between other selected pairs of electrodes. A stimulus generator 106 also provides an input for the EIT system 104 such that EIT measurement can be effected at appropriate times relative to application of a stimulus. A computer 107 is provided to control the overall operation of the system and to log experimental results.

The equipment illustrated in Figure 1 may be a conventional EIT system or may be an EIT system as described in further detail below with reference to Figures 5 to 18. Characteristics of conventional EIT equipment are well known and details may be derived for example from the documents referred to above.

In use, a stimulus such as a VER stimulus or an AER stimulus is applied to the subject. Current is injected between each pair of electrodes in turn. For each current injection a series of voltage measurements are taken between pairs of electrodes.

Measurements are made without regard to the time at which the stimulus is applied. Rather, voltage measurements are collected continuously and processed with regard to the time at which the stimulus was applied and the required time delay.

Figure 2 shows a graph of current injections against time. Current injections are arranged in a plurality of measurement frames 109, 110, 111, 112 (only part of the measurement frame 112 being shown in Figure 2). In each measurement frame current is sequentially injected between eight pairs of electrodes, while voltage measurements are taken between others of the electrodes. Specifically, a first current injection is made between electrodes e1 and e9, a second between electrodes e2 and e10, a third between electrodes e3 and e11, a fourth between electrodes e4 and e12, a fifth between electrodes e5 and e13, a sixth between electrodes e6 and e14, a seventh between electrodes e7 and e15 and an eighth between electrodes e8 and e16. Each current injection lasts for a time of 500 μ s. During each current injection, twelve voltage measurements are taken. Voltage measurements for a particular current injection are taken simultaneously. That is, while current is injected between a diametrically opposed pair of electrodes, voltage measurements are simultaneously taken between all adjacent pairs of electrodes other than those used for current injection. For example, in one embodiment during a current injection, voltage measurements are simultaneously taken between all electrode pairs of interest during a period of 400 μ s beginning 100 μ s after the start of a current injection lasting 500 μ s.

In other embodiments, voltage measurements may be taken sequentially. Where voltage measurements are taken sequentially, for example during application of current between electrodes e1 and e9, twelve voltage values are measured between adjacent electrodes in sequence, that is electrodes e2-e3, e3-e4, e4-e5, e5-e6, e6-e7, e7-e8, e10-e11, e11-e12, e12-e13, e13-e14, e14-e15, and e15-e16. No measurements are made between electrode pairs including either of the electrodes (e1 and e9) between which current is passed. During a first current injection period, the first voltage measurement is taken between electrodes e2 and e3, (electrode e1 being used for current injection) whereas the first voltage measurement during the second current injection period is taken between electrodes e3 and e4 (electrode e2 being used for current injection). The same rolling pattern of electrode selections continues through the full series of eight current injection periods.

Measurement frames occur continuously, that is the measurement frame 110 follows directly after the measurement frame 109, and the measurement frame 112 follows directly after the measurement frame 111. The continuous application of current injections, resulting in a regular series of voltage measurements, allows data to be continuously obtained.

By applying a stimulus and obtaining a complete set of voltage measurements as described above, an image of the impedance distribution in the brain can be created using known image reconstruction algorithms (see for example "Krylov Subspace Iterative Techniques: on the detection of brain activity with electrical impedance tomography" as referred to above). Such an image can then be viewed by a medical practitioner to determine whether or not the brain has responded to the application of the stimulus in a normal manner. That is, it is known from neurological models which part of the brain

should be active at a predetermined t_d value (Figure 2) after application of a particular type of stimulus, and thus the image can be analysed to determine whether or not activity is present as expected in the brain. Specifically, if a stimulus 113 is applied at a time t_s , and measurements taken after a time delay t_d following application of the stimulus are required, voltage measurements taken during the measurement frame 111 can be processed, the measurement frame 111 beginning after the time delay t_d .

It will be appreciated that in the example shown in Figure 2 the measurement frame 111 begins at the time at which measurements are required (as indicated by the time delay t_d) and as such the measurement frame 111 can be used as a basis for the reconstruction of images of the type shown in Figure 3 below. It will also be appreciated that in other examples a measurement frame may not begin at the required time. In such a case measurements from two measurement frames can be used as a basis for image reconstruction. For example, if it is desired to base image reconstruction on measurements taken after a time delay t_D following stimulus application at time t_s , measurements made during eight current injections 114 can be used as a basis for image reconstruction. That is, measurements made during six current injections of the measurement frame 111 and measurements made during two current injections of the measurement frame 112 can be used.

As indicated above, each current injection is carried out over a time of 500 μ s. Time delays after stimulus application at which information is required are typically of the order of tens of milliseconds, and as such a particular current injection will begin within an acceptable tolerance of any specified delay time of likely magnitude. That is, for any specified delay time measurements based upon activity within 0.25ms (250 μ s) of that delay time can be used as a basis for image reconstruction.

Since measurements are continuously obtained, it will be appreciated that reconstruction of images representing neural activity at a particular time after stimulus application can be carried out as an offline process, by simply selecting the appropriate measurements from the continuously obtained measurements, the obtained measurements being selected based upon the required time delay. In this way, it will be appreciated that a sliding window of time can be moved through the collected measurements so as to monitor changes in neural activity following stimulus application.

In Figure 2, the stimulus 113 is shown to occur at a particular point in time. It will be appreciated that the stimulus 113 in fact has an associated duration. For example, a visual stimulus may be applied to a subject for a time of 30 to 50ms. The time delay after which measurements are taken may be defined relative to the start of stimulus application.

Referring to Figure 3, there are illustrated six impedance measurements generated based upon measurements taken after different delays after the application of a visual stimulus. The top left hand image of Figure 3 was generated based upon EIT measurements at approximately 80 milliseconds after the application of a visual stimulus. The lateral geniculate nucleus (LGN) 115 is shown as being active at the time at which this image was generated. At this time, the LGN was receiving information on brightness and location of the visual stimulus, originating from the rods of the retina. The LGN receives

an input from the optic nerve. The LGN is active through most visual processing as can be seen from the six images of Figure 3.

The upper centre image of Figure 3 was generated based upon EIT measurements obtained approximately 105 milliseconds after the application of a visual stimulus. The LGN 115 is still active but at this time neurological modelling shows that information on the colour of the visual stimulus is being processed, originating from the cones of the retina. Brightness and contour information is processed in an area 116 (known as area V1), at the back of the brain. The area 116 is brighter in this image, indicating the expected activity.

The upper right image was generated based upon EIT measurements obtained 137 milliseconds after the application of a visual stimulus. It can be seen that activity in the area 116 has increased considerably with this part of the brain working to integrate colour stereo and texture information, ready for relay to higher brain regions. In addition, feedback information is being relayed back to the LGN 115 in order to fine tune its processing of future information. Intense activity in LGN area 8 and increased activity in V1 area 116 is indicated in this image.

The lower left image of Figure 3 was generated based upon EIT measurements obtained 186 milliseconds after the application of a visual stimulus. It can be seen that information is now being passed to other visual centres 117, 118 at either side of the brain. These areas 117, 118 are responsible for colour processing and the identification of objects.

The lower centre image of Figure 3 was generated based upon EIT measurements obtained 201 milliseconds after the application of a visual stimulus. Large dark areas 119, 120, 121 correspond to activity in the left anterior cingulate gyrus and connected regions of the limbic system. These regions are responsible for many things, but most relevant here is the emotion accompanying the recognition of an object. These same regions 119, 120, 121 are responsible for deciding whether a noxious stimulus is actually painful. In the present circumstance, we can assume that these areas of the brain are determining information of the form "that was another flash". It is not surprising that imaging using this technique is able to directly visualise human emotions arising as a result of the sensory stimulus.

The lower right image of Figure 3 was generated based upon EIT measurement obtained 248 milliseconds after the application of a visual stimulus. Most visual processing is complete by this stage and higher brain regions are determining the action to be taken in response to the received information. Large parts of the brain are preparing for any subsequent flash, and thus there is a need for random sequences of flashes to eliminate habituation as described above.

The time delay t_d between application of the stimulus and the time at which the set of EIT measurements used as the basis for generating an image is obtained may be variable by a user, using functionality provided by the computer 107 (Figure 1). Thus, a plurality of images may be generated based upon EIT measurements collected at a different t_d values after application of a stimulus. Using this method a plurality of images can be created which can be arranged in order of increasing t_d to represent changing brain activity at different times following application of a stimulus.

If the computer 107 is programmed to apply a plurality of stimuli, delays between successive stimuli are varied in a random manner so as to avoid the subject's brain being "trained" to expect stimuli at particular times.

It will be appreciated that in some embodiments each set of measurements may be accumulated after a respective stimulating event while in others, all the sets of measurements could be accumulated after a single stimulating event.

In the described embodiments, each stimulating event is of short duration. A stimulating event could however be relatively prolonged, extending into a subsequent period during which impedance measurements are made.

It may be desired to use other stimuli occurring in the patient's environment, the application of which cannot be controlled, in place of the deliberate application of stimuli as described above. This is possible, providing accurate timing between occurrence of the stimulus and the time at which measurements are obtained is available.

In the embodiments of the invention described above it has been explained that sixteen electrodes are adhered to a subject's head. In some embodiments of the invention a larger number of electrodes may be used, for example thirty-two electrodes may be adhered to the subject's head. The use of a larger number of electrodes can result in image reconstruction having improved accuracy. The electrodes have been assumed to be arranged on the head in a planar array, to provide measurements that allow the reconstructions of images showing impedance changes in that plane. In some embodiments of the invention, the electrodes may be arranged on the head in a 3-dimensional arrangement, to provide measurements that allow reconstruction of images showing 3-dimensional distribution of impedance changes within the subject's head.

The embodiments described above may be carried out on any suitable apparatus, for example, a conventional EIT system may be used. The following description sets out various improvements to EIT systems in general, and in particular, improvements to EIT systems suitable for carrying out the above methods.

Referring first to Figure 4, a tomography system arranged to obtain tomographic data from which a conductivity distribution within the head 1 of a subject can be estimated is shown. A plurality of electrodes 2 are affixed to the scalp of the subject. Each of the electrodes is a silver-silver chloride EEG electrode of a type which presents a relatively small contact impedance on contact with the scalp.

The electrodes are electrically connected to a head box 3, each electrode being connected to the head box 3 by a respective cable 2a. The head box 3 is connected to a base unit 4, and more particularly, to a tomography sub-system 5 of the base unit 4. The connection between the head box 3 and base unit 4 allows data to pass bi-directionally between the head box 3 and the base unit 4, and also allows power to be provided to the head box 3 from the base unit 4.

The base unit 4 is connected to a computer 6, such that tomographic data received at the tomography sub-system 5 of the base unit 4 can be transferred to the computer 6 for further processing and storage.

The system shown in Figure 4 is arranged to provide a stimulus to a subject, and to obtain and record tomographic data indicative of the effect of the stimulus on the subject's nervous system. To this end, the base unit 4 comprises a stimulation control subsystem 7 which is connected to a stimulation device 8 which applies a stimulus to the subject, such that the stimulation control subsystem 7 controls operation of the stimulation device 8. In one embodiment, the stimulation device 8 provides visual or auditory stimuli, and comprises calibrated headphones to provide an auditory evoked response stimulus to the subject's ears and goggles including light emitting diodes for providing a visually evoked response stimulus to the subject's eyes.

Although only four electrodes are shown affixed to the patient's head in Figure 4, in some embodiments a larger number of electrodes is employed. In particular, in the embodiment described in further detail below, 33 electrodes are affixed to the patient's head. 32 of these electrodes are used for the purposes of acquiring tomographic data, while one electrode is used as a reference electrode (referred to herein as EREF). The reference electrode provides a low-impedance connection between a location on the subject (e.g. the subject's neck) and a reference voltage within the head box 3. In some embodiments the reference voltage is a local ground potential of the head box 3 but in other embodiments a time-varying voltage may be used. Indeed, the use of such a time varying voltage may be useful in the cancellation of common mode effects. Current is injected between a plurality of pairs of the 32 electrodes in turn, and during each current injection a plurality of voltage measurements between other pairs of the 32 electrodes are obtained as has been described above. Specific methods used to obtain tomographic data are described in further detail below.

The system of Figure 4 is suitable for use in a medical environment. Components shown in Figure 4 within dotted lines 9 are therefore manufactured so as to comply with relevant legislation relating to the safety of medical devices. For example, it may be that the head box 3 and stimulation device 8 are arranged for easy disinfection to prevent the spread of infection from one patient to another, and as such the head box 3 may have a sealed housing complying with International Protection Rating (IP) 65. The provision of the tomography system of Figure 4 by way of the head box 3 and the base unit 4 allows high voltage components to be isolated from the patient, by being located in the base unit 4, not the head box 3, this isolation being provided by the components used within the head box 3 and base unit 4. Such an approach reduces the number and size of heat generating components which are located close to the subject. The provision of such isolation is described in further detail below.

The provision of the tomography system by way of the head box 3 and the base unit 4 allows the head box 3 which is located proximal the subject to be of small size. This can be important in clinical situations in which space is restricted (e.g. operating rooms). Furthermore, the location of the head box 3 close to the subject means that cable lengths between the head box 3 and the electrodes 2 are minimised,

thereby reducing the susceptibility of the cables 2a to noise and meaning that the cables 2a may not need to be screened. Bulky and potentially dangerous parts of the tomography system are provided in the base unit 4, which can be located some way away from the subject, given that a single cable or pair of cables (providing data and power) connect the head box 3 to the base unit 4. Given that the base unit 4 is not located close to the patient, it need not meet standards such as IP65 described above.

Figure 5 shows the internal structure of the head box 3. It can be seen that the head box 3 has a “tombstone” shape, providing a relatively long external boundary around which connections 2b to the electrodes 2 are provided. The interior of the head box is generally divided into three portions. A first outer portion 10 is defined by the periphery of the headbox 11 and a first dotted line 12 extending generally parallel to the periphery of the head box 3. A second inner portion 13 is defined by a second dotted line 14. A third boundary (or intermediate) portion 15 is provided between the first outer portion 12 and the second inner portion 13, and is defined by the portion of the head box between the two dotted lines 12, 14.

The first outer portion 10 is arranged to house analog circuitry, the second inner portion 13 is arranged to house digital circuitry and the third boundary portion 15 is arranged to house partly analog and partly digital circuitry – for example analog to digital converters which convert signals from the analog to digital domains. Each portion of the head box is described in further detail below. However, it can be noted that the provision of the third boundary portion 15 between the dotted lines 12, 14 provides a relatively long mixed-signal boundary between the first outer portion 10 housing analog circuitry and the second inner portion 13 housing digital circuitry. In particular, the mixed-signal boundary is of sufficient length to easily accommodate as many analog to digital converters and switches as there are electrodes 2, as described below.

As described above, current is injected between pairs of the electrodes 2 (Figure 4), and while current is being so injected, voltage measurements are made between other pairs of the electrodes 2. As such, the head box 3 is arranged to provide current to the electrodes 2, and measure voltage between pairs of the electrodes 2. Current is provided to the electrodes 2 connected to the connections 2b by a current source 16 located in the first outer portion 10. Current is provided along a current bus 17 which extends around the head box in the boundary portion 15. Each of the connections 2b is connected to the current bus 17 by a respective switch, and by appropriate control of the switches (discussed below), current can be provided to the desired connections 2b.

The first outer portion 10 of the head box 3 comprises protection circuitry 18, which is arranged to protect circuitry in the head box and circuitry connected to the head box from electromagnetic noise which may be present in the vicinity of the head box 3 or the vicinity of the electrodes 2 and their cables 2a. Such electromagnetic noise may arise from a variety of sources, for example, from equipment used in the practice of electro surgery. The first outer portion 10 of the head box 3 also comprises measurement circuitry 19 which is operable to obtain voltage measurements between pairs of the electrodes 2 connected to the connections 2b, and the measurement circuitry 19 is described in further detail below.

The second inner portion 13 of the head box 3 comprises a field programmable gate array (FPGA) 20 which is configured to control operation of the head box 3, and to process received data. For example, the FPGA 20 provides a digital representation of a desired current waveform to the current source 16, and the current source 16 then provides a current in accordance with the desired current waveform on the current bus 17.

As indicated above, power is provided to the head box 3 from the base unit 4. Power is received at a power inlet 21. It can be seen that the power inlet 21 is located in a portion of the head box 3 which is separate from each of the first outer portion 10, the second inner portion 13 and the third boundary portion 15, allowing the power inlet 21 to be isolated from other components of the head box. The power inlet 21 is arranged to filter the received power so as to remove the effects of noise in the received power supply. The power inlet 21 is connected to an analog power conditioning unit 22 which is located in the first outer portion 10 of the head box 3. The analog power conditioning unit 22 is arranged to provide electrical power to analog circuitry in the first outer portion 10, and also to generate a reference voltage. The generated reference voltage is provided to analog-to-digital converters located in the boundary portion 15 and to amplifiers which form part of the measurement circuitry 19 located in the outer portion 10. The provided reference voltage is used by the analog-to-digital converters and amplifiers in a conventional way. The power inlet 21 is also connected to a digital power conditioning unit 23. The digital power conditioning unit 23 provides electrical power to digital components in the second inner portion 13 of the head box 3.

The second inner portion 13 of the head box 3 further comprises an interface component 24. The interface component 24 is arranged to receive data from and provide data to the base unit 4. Additionally, two input devices 25, 26 are connected to the interface component 24.

A user input device 25 comprises a single button which is used to change the operating mode of the head box 3. More particularly, the head box 3 has a plurality of operating modes which define an sequence, and by pressing the single button provided by the user input device 25, a user controlling the acquisition of data can select one of the operating modes by moving through the sequence of operating modes until the desired operating mode is reached in the sequence. The head box 3 has four operating modes which are shown in Figure 6. A first Idle state is the initial state of the head box 3. The head box 3 remains in the Idle state until the user input device 25 is activated. When the user input device 25 is activated, the head box assumes a Measure Only state. In this state voltage measurements are obtained. A further activation of the user input device 25 causes the head box to assume an EIT state in which current is injected between pairs of electrodes and voltage measurements are obtained between others of the electrodes. The head box 3 remains in the EIT state for a predetermined time (1 minute in some embodiments), and at the end of this predetermined time, the head box again assumes the Measure Only state. A Fault state is assumed if a subject input device 26 (described in further detail below) is activated. The head box 3 remains in the Fault state until the user input device is activated for at least a minimum period of time (e.g. five seconds) in which case the head box returns to the Idle state. The head box 3 is

provided with a status indicator indicating its current state. Such a status indicator can conveniently take the form of a plurality of LEDs of various colours.

The subject input device 26 is provided for use by the subject from which data is to be acquired. This second input device again includes a single button which effectively operates as a “Stop” button, so as to end the collection of data. The subject input interface 26 can be useful in providing comfort to a subject from which data is being collected, providing the subject with control to stop data acquisition in the event that the subject experiences any discomfort. In some embodiments activation of the subject input device 26 does not terminate the application of stimuli by the stimulation device 8, but merely affects the collection of tomographic data.

Referring back to Figure 5, the third boundary portion 15 of the head box 3 comprises analogue to digital converters which are arranged to receive voltage measurements from the measurement circuitry 19 and provide a digital representation of the received voltage measurements to the second inner portion 13 of the head box 3. Additionally, the third boundary portion comprises digital-to-analog conversion circuitry which is arranged to receive data from the FPGA 20 indicating a desired current, and provide an analog representation of that current to the current source 16. The third boundary portion 15 also comprises switches arranged to connect selected ones of the connections 2b to the current bus 17.

Operation of the head box 3 is now described in further detail with reference to the circuit diagram of Figure 7. Figure 7 shows that the current bus 17 (Figure 5) comprises a first current bus 17a and a second current bus 17b. Similarly, the current source 16 (Figure 5) comprises a first current source 16a which provides current on the first current bus 17a and a second current source 16b which provides current on the second current bus 17b.

In the case of the first current bus 17a, current is provided from the current source 16a through a low resistance resistor 27a of known resistance. Voltage across the low resistance resistor 27a is determined by a difference amplifier 28a, the output of which is provided to an analog to digital convertor 29a. The analog to digital convertor 29a is therefore arranged to provide a digital representation of the voltage across the low resistance resistor 27a. Given knowledge of the resistance of the low resistance resistor 27a, it will be appreciated that the current passing through the low resistance resistor 27a can be easily deduced using Ohm's law.

An equivalent arrangement is provided in connection with the second current bus 17b. More particularly, current is provided to the second current bus 17b from the second current source 16b through a low resistance resistor 27b, the voltage across which is measured by a difference amplifier 28b. The output of the difference amplifier 28b is input to an analog to digital convertor 29b, which provides as output a digital representation of the relevant voltage.

With reference to Figure 5, it can be noted that the analog to digital convertors 29a, 29b are located in the third boundary portion 15 of the head box 3, and provide their digital outputs to the second inner portion 13, in which digital circuitry is housed.

Five electrodes 2 are shown in Figure 7 by way of example. Others of the electrodes described with reference to Figure 5 are similarly arranged. The five illustrated electrodes comprise four measurement electrodes, E1 to E4, and the reference electrode EREF. It can be seen that each of the four illustrated measurement electrodes E1 to E4 are connected to each of the two current busses 17a, 17b through respective switches 30a, 30b. As such, each of the electrodes can be connected to either of the first and second current busses 17a, 17b.

It can be noted that in alternative embodiments of the invention some of the electrodes may be connectable only to the first current bus 17a, while others of the electrodes may be connectable only to the second current bus 17b. Such an arrangement allows current to be injected between any pair of electrodes comprising a first electrode connectable to the first current bus 17a, and a second electrode connectable to the second current bus 17b.

Each adjacent pair of measurement electrodes E1 to E4 is connected to an instrumentation amplifier 31 (which form the measurement circuitry 19 of Figure 5). The output of each instrumentation amplifier 31 is input to a respective analog to digital convertor 32. This allows the voltage between any adjacent pair of measurement electrodes to be measured, and a digital representation of the voltage to be provided to the FPGA 20 (Figure 5). The reference electrode EREF is connected to a reference voltage VREF which, as indicated above, can be a local ground potential, or a time varying voltage. Operation of the circuit of Figure 7 will be described in further detail below with reference to both Figures 7 and 8.

Referring first to Figure 8, an embodiment of the invention in which 33 electrodes are attached to a subject's scalp in a substantially planar array is shown in an arrangement similar to that of Figure 1. In use, an alternating current of predetermined frequency magnitude and phase is injected between a pair of electrodes which are arranged on the subject's scalp in substantially diametrically opposed positions, such as the electrodes E1 and E17 shown in Figure 8. The injection of current is achieved by connecting the electrode E1 to the first current bus 17a, and the electrode E17 to the second current bus 17b, the connections being achieved by appropriate control of the switches 30a, 30b. In use, the first current source 16a is controlled to provide a current of predetermined frequency magnitude and phase (denoted I_1) on the first current bus 17a, while the second current source 16b is controlled to provide a current of the same predetermined frequency and magnitude but having a phase which differs by 180° (denoted $-I_1$) on the second current bus 17b. This has the effect of achieving injection of the desired current between the electrodes E1 and E17, while minimising the current passing to ground via the reference electrode EREF. More particularly, a current of I_1 passes from the electrode E1 to a grounded reference electrode EREF, while a current of $-I_1$ passes from the electrode E17 to the grounded reference electrode EREF. The net current flowing to the reference electrode EREF is therefore $I_1 - I_1 = 0$.

Current is provided in the manner set out above to each pair of electrodes located in substantially diametrically opposed positions in turn. During each injection of current, voltage measurements are made between all adjacent pairs of electrodes. Measurements between electrodes E22 and E23 and between electrodes E23 and E24 are schematically shown in Figure 8 for the purposes of example. It will be

appreciated that although measurements between all adjacent pairs of electrodes are obtained, any measurement taken between an electrode currently used for current injection (E1 and E17 in the example) and any other electrode is not meaningful and can be discarded.

It is to be noted that injection between diametrically opposed electrodes and measurement between adjacent electrodes is advantageous. This is because each electrode of an adjacent pair will be affected to a similar extent by the current injection, meaning that the resulting voltage measurement provides a good indication of impedance. Additionally, injecting current between diametrically opposed pairs of electrodes provides good depth sensitivity for measurements.

In use, current is injected between each pair of electrodes which are substantially diametrically opposed for 500 μ s. The injected current is an alternating current having a frequency of 10kHz. During each injection voltage measurements are simultaneously taken between adjacent pairs of electrodes, and these voltage measurements are used as a basis for the estimation of the distribution of conductivity in the head. During each current injection of 500 μ s, a first period of 100 μ s is designated as a settling time during which no voltage measurements are taken between each adjacent pair of electrodes. During the remaining 400 μ s 200 voltage measurements are taken, 50 during each of the four current cycles occurring during that 400 μ s.

Given that the same electrodes are used for both voltage measurement and current injection, and given that amplifiers 31 are always connected to their respective electrodes, the amplifiers 31 used for voltage measurement are carefully selected. More particularly, it is desirable to ensure that the amplifiers 31 are able to accurately measure voltage between a pair of electrodes, even if one electrode in that pair of electrodes has been used to inject current only a short time earlier (as little as 100 μ s in the described arrangement). As such, it is desirable that the amplifiers 31 have a saturation recovery time and settling time which is no greater than the period of a current injection which is designated as a settling time (i.e. 100 μ s in the described arrangement) and during which voltage measurements are not taken. More preferably, an amplifier having a shorter saturation recovery time and settling time is used. For example, it has been found that when current injection and voltage measurement proceeds as described above, an amplifier having a saturation recovery time of 10 μ s gives good results. From the preceding discussion, however, it will be appreciated that the saturation recovery time required from the amplifier will depend upon the duration of the settling time in the voltage measurement process, which is in turn dependent upon the duration of each current injection and the frequency of the applied current.

When selecting the amplifiers 31 another factor to which consideration should be given is the common mode rejection ratio of the amplifiers. Specifically, given that the signal common to the two electrodes used for measurement is based upon the injected current, the amplifiers 31 should be selected to as to properly handle that common signal. It has been indicated that the injected current, in the described embodiment, has a frequency of 10 kHz. As such amplifiers able to reject a common signal of that frequency are selected in the described embodiment. Those skilled in the art will appreciate that many amplifiers are optimised to reject common signals of much lower frequencies (e.g. 50Hz). In the

described embodiment of the present invention, the amplifiers 31 are selected to have good common mode rejection at the frequency of the injected current, even if the maximum common mode rejection ratio across all frequencies is reduced as a result.

It has been found that the arrangement described with reference to Figures 6 and 7 can be effectively implemented where the amplifiers 31 are Analog Devices Precision Instrumentation Amplifiers AD-8221 which have a setting time of 4 μ s (to settle to 0.01% with a gain of 10). Experiments have shown that even after saturation settling time does not exceed 50 μ s.

In an alternative embodiment of the invention, the electrodes are arranged on the subject's scalp in a non-planar array, as is now described with reference to Figures 8A to 8E. In general terms, the arrangement of electrodes described with reference to Figures 8A to 8E is based upon the International 10-20 system which is used for the placement of electrodes on a subject's head in EEG data acquisition.

Figure 8A shows, in plan view, a subject's head to which 32 electrodes are affixed. Four groups of electrodes (differentiated by cross-hatching) are shown. A first group of electrodes G1 comprises eighteen electrodes arranged in a ring around the subject's head. A second group of electrodes G2 comprises eight electrodes arranged within the ring of electrodes defined by the first group of electrodes G1. A third group of electrodes comprises five electrodes arranged at the back of the subject's head, just below the inion, and the fourth group G4 comprises a single electrode which is located on the apex of the head.

Figure 8B shows the subject's head in side view. The location of the electrodes shown in Figure 8A on the subject's head can be seen. In particular, it can be seen that the first group G1 of eighteen electrodes extends around a relatively low part of the subject's head, with the second group G2 of eight electrodes extending about a relatively high part of the subject's head. The percentages indicated in Figure 8B are percentages of the total distance between the inion and naison of the subject, or between the preauricular points on each side of the subject's head, as appropriate.

In the following description, and in Figures 8A to 8E, the 32 electrodes are referenced e1 to e32. Table 1 shows the relationship between the references used in this description, and the location identifiers used in the International 10-20 electrode placement system.

Group	Electrode No.	International 10-20 locator
G1	e1	Fpz
G1	e2	Fp1
G1	e3	AF7
G1	e4	F7
G1	e5	FT7
G1	e6	T7
G1	e7	P7
G1	e8	PO7
G1	e9	O1
G1	e10	Oz
G1	e11	O2

G1	e12	PO8
G1	e13	P8
G1	e14	T8
G1	e15	FT8
G1	e16	F8
G1	e17	AF8
G1	e18	Fp2
G2	e19	Fz
G2	e20	F3
G2	e21	C3
G2	e22	P3
G2	e23	Pz
G2	e24	P4
G2	e25	C4
G2	e26	F4
G3	e27	-
G3	e28	-
G3	e29	Iz
G3	e30	-
G3	e31	-
G4	e32	Cz

TABLE 1

As indicated above, it is desirable to inject current between electrodes which are substantially diametrically opposed. This is achieved by injecting current between 20 distinct pairs of electrodes. Figure 8C shows eleven current injections carried out between the eighteen electrodes which make up the first group of electrodes G1. It can be seen that each injection is carried out between a pair of electrodes which are located in substantially diametrically opposed locations. Figure 8D shows four current injections between the eight electrodes which make up the second group of electrodes G2. Figure 8E shows five current injections carried out between the electrode E1 located centrally on the front of the subject's head (in alignment with the subject's nose) and the five electrodes of the third group of electrodes G3. It can therefore be seen from Figures 8C to 8E that current is injected between twenty distinct pairs of electrodes.

The order in which current is injected between pairs of electrodes can be important. In particular, injecting current between pairs of electrodes in a particular order may cause unwanted physiological symptoms. One order for the injection of current between the twenty pairs of electrodes detailed above which has been found to be effective is as follows:

Injection number	Electrodes
1	e1, e30
2	e1, e27
3	e22, e26
4	e9, e18
5	e7, e16
6	e3, e12

7	e1, e28
8	e8, e12
9	e5, e15
10	e1, e29
11	e4, e13
12	e8, e17
13	e7, e13
14	e20, e24
15	e6, e14
16	e1, e31
17	e1, e10
18	e2, e11
19	e21, e25
20	e19, e23

TABLE 2

When determining the order in which current should be injected between pairs of electrodes, one symptom which should be particularly taken into account is trigeminal neuralgia. This is an excruciating pain originating from stimulation of the trigeminal nerve. As such, it is important that the injection of current does not provide such stimulation of the trigeminal nerve. The trigeminal nerve innervates the forehead, and other regions of the face. In the arrangement described with reference to Figures 8A to 8E a number of electrodes are located on the subject's forehead, and as such care is required to ensure that the injection of current involving those electrodes located on the subject's forehead does not stimulate the trigeminal nerve. That is, care is required to ensure that current is not injected in a manner which results in unacceptable reinforcement of signals already propagating in the trigeminal nerve as a result of preceding current injections. That is, the timing of current injections must consider neural signals which are still propagating as a result of previous injections.

Studies using laser stimulation of the forehead have shown that the conduction velocity of nociceptive, unmyelinated fibres within the trigeminal nerve is around 1.2 ms⁻¹. These unmyelinated fibres are called C fibres, and because of their lack of myelination (which acts as a natural insulator) they are particularly prone to stimulation by current injection at the skin. This is described in, for example, Cruccu G, et al. "Unmyelinated trigeminal pathways as assessed by laser stimuli in humans", Brain 2003 Oct; 126(Pt 10):2246-2256.

The circumference of the adult human head typically varies from 53 cm to 64 cm. Studies have shown that the mean circumference for males is 58 cm, and the mean circumference for females is 55 cm. If eight electrodes are placed across the front of the head, and a conduction velocity of 1.2 ms⁻¹ (as mentioned above) is assumed, this suggests that it takes between 2.75 ms to 3.38 ms for a current injecting, stimulating pulse to travel from one electrode in order to induce an action potential volley within the trigeminal nerve. This means that it is desirable to avoid current injection frequencies of 296 Hz to 363 Hz between adjacently located pairs located on the subject's forehead. The current injection pattern described above achieves this aim.

In the arrangement described with reference to Figures 8B to 8E voltage measurements are taken between sequentially numbered electrodes. Additionally, two further voltage measurements are obtained by taking a measurement between the electrode e1 and the reference electrode EREF and the electrode e32 and the reference electrode EREF. By processing these two further voltage measurements, an indication of voltage between e32 and e1 can be obtained. The described arrangement of electrodes and current injections and voltage measurements has been found to generate data which allows relatively good estimates of conductivity within the subject's head to be generated.

Referring back to Figure 7, it can be seen that each of the current busses 17a, 17b is provided with a screen. Specifically, the voltage of the first current bus 17a is passed to an amplifier 33a, the output of which is provided to screening conductors 34a. A similar arrangement is provided in relation to the second current bus 17b by the amplifier 33b and the screening conductors 34b.

The circuit of Figure 7 is implemented using three layers of a printed circuit board which are shown in schematic cross section in Figure 9 so as to illustrate the physical configuration of the screening arrangement. Figure 9 shows that the printed circuit board comprises three conducting layers A, B, C which are mounted in a fibreglass structure 35.

The first current bus 17a is surrounded by screening conductors 36a, 37a, 38a, 39a which correspond to the schematically illustrated screening conductors 34a of Figure 7. It can be seen that two screening conductors 38a, 39a extend parallel to and in the same plane as the first current bus 17a. Two screening conductors 36a, 37a also extend parallel to the first current bus 17a but in planes that are offset both from one another, and from the plane in which the current bus 17a extends, that is, while the current bus 17a and the screening conductors 38a, 39a are provided in a first plane defined by the layer B of the printed circuit board, the screening conductor 36a is provided in a plane defined by the layer C of the printed circuit board while the screening conductor 37a is provided in a plane defined by the layer A of the printed circuit board. Each of the screening conductors is held at the voltage of the current bus 17a by the arrangement described with reference to Figure 7.

Each layer of the printed circuit board is separated from its adjacent layers by a distance of 0.18mm, indicated by arrows a. Each layer has a thickness of 0.018mm indicated by arrows b. The current bus has a width, indicated by an arrow c of 0.254mm, and is separated, within the plane defined by the layer B, from the screening conductors 38a, 39a, by a distance of 0.2 mm as indicated by the arrows d. Each of the screening conductors 38a, 39a has a width, indicated by the arrows e of 1.235mm. The screening conductors 36a, 37a extending in respective planes offset from the plane in which the first current bus 17a extends each have a width of 3.125mm, as indicated by the arrow f. It can be seen, therefore, that the first current bus 17a and its screening arrangement provided by the screening conductors 36a, 37a, 38a, 39a has a width of 3.125mm in each of the three layers A, B, C of the printed circuit board.

Figure 9 also shows the second current bus 17b, together with its screening conductors 36b, 37b, 38b, 39b. The second current bus 17b and its screening conductors have the same dimensions as the first

current bus and its screening conductors, as indicated by arrows marked c to f which represent, in relation to the second current bus 17b, the dimensions described above with reference to the first current bus 17a.

The first and second current busses 17a, 17b and their associated screening arrangements are separated from one another in the planes of the printed circuit board by a distance of 0.18mm, indicated by an arrow g.

It can be seen from Figure 9 that any leakage from one of the current busses 17a, 17b to a ground layer of the printed circuit board (not shown) is blocked, as is leakage between the two current busses 17a, 17b. For leakage to occur from one of the current busses 17a, 17b, current must pass through a relatively extensive region at or close to the potential of the relevant current bus. The screening conductors are arranged to surround each current bus in four directions. As such, leakage is minimised.

Having described the head box 3 in some detail, a description of the base unit 4 is now presented with reference to Figure 10. In Figure 10 the base unit 4 is shown to comprise the tomography subsystem 5 and the stimulus control subsystem 7. It can also be seen that the base unit 4 comprises a filtered power inlet 40 which is arranged to receive a supply of electrical power. The received electrical power is passed to a local power distribution module 41, which is arranged to provide electrical power to the various components of the base unit 4. In more detail, the local power distribution module 41 comprises three AC/DC converters. A first AC/DC converter receives AC electrical power from the supply inlet 40 and passes DC power to the stimulus control subsystem 7. A second AC/DC converter receives AC power from the supply inlet 40 and provides DC power to a power inlet 42 associated with the tomography subsystem 5. In one embodiment the second AC/DC converter is a 120W medical grade power supply unit. A third AC/DC converter provided by the local power distribution module 41 receives electrical power from the filtered power inlet 40 and provides DC electrical power to a data acquisition module 43. The data acquisition module 43 is arranged to receive data from the tomography subsystem 5 and pass processed data to the computer 6 (Figure 5).

The tomography subsystem 5 is now described. A galvanic isolation barrier 43 separates components of the tomography subsystem which communicate directly with the head box 3 from those that do not. This provides high-grade isolation between many of the components base unit 4 and components of head box 3 which is intended to be placed in close proximity to a human subject, possibly in a medical setting. There are only two paths that cross the galvanic isolation barrier 43. A first provides a path for the supply of power to the head box 3. A second provides a path for the bi-directional passage of data between the head box 3 and the base unit 4. Each of these paths is described below. In each case the paths which cross the galvanic isolation barrier are arranged to meet all medical and other electrical safety criteria.

The isolation in the supply of power to the head box 3 is achieved by providing high-isolation DC/DC converters 44 along the galvanic isolation barrier 43, the DC/DC converters receiving electrical power from the power inlet 42 and providing electrical power to a head box power supply 45 which is arranged to condition the received electrical power, before providing power to the head box 3.

The tomography subsystem 5 further comprises a data interface 46 which is arranged to receive data from and provide data to the head box 3. It can be seen that the data interface 46 is within the galvanic isolation barrier 43. As such, to ensure that isolation is maintained, data received through and passed to the data interface 46 passes through high-isolation optical isolators 47 which are located on the galvanic isolation barrier 43. The optical isolators 47 therefore provide the second path for the bi-directional passage of data, as has been mentioned above. Data is passed to and from the optical isolators 47 from a digital data processing module 48. The digital data processing module 48 is arranged to receive data and pass received data to an interface 49 of the tomography subsystem, the interface 49 being arranged to provide data to the data acquisition module 43. In some embodiments, the data acquisition module 43 provides a USB interface through which data can be provided to the computer 6. For example, in one embodiment the data acquisition module is a National Instruments USB-6221 data acquisition module.

It has been described above that the systems described herein can be used to determine a response of a nervous system to an applied stimulus at a particular time after stimulus application. In order to achieve this, the stimulus control subsystem 7 provides control commands to the stimulation device 8 (Figure 5) which is connected to the stimulus control subsystem 7. In one embodiment the stimulus control subsystem is a CED Micro 1401 MKII unit, providing a USB interface to the computer 6, such that stimulus application can be controlled by the computer 6. When such commands are provided to the stimulation device 8, the stimulus control subsystem 7 provides timing flags to a stimulus control interface 50 provided by the tomography subsystem 5. These timing flags are passed from the stimulus control interface 50 to the digital data processing module 48. In turn, the digital data processing module 48 passes received timing flags to the data interface 46, via the optical isolators 47. The head box 3 is therefore provided with the timing flags, and is arranged to incorporate the timing flags into a data stream comprising obtained voltage measurements. As such, the digital data processing module 48 receives data from the head box 3 via the optical isolators 47 comprising both voltage measurements and an 'echo' of the provided stimulus timing flag.

Additionally the tomography subsystem 5 comprises an optically isolated digital input 51 to which other stimulation devices may be connected. Signals indicating the application of a stimulus by a device connected to the isolated digital input 51 can be handled by the data processing module 48 in the same way as signals provided by the stimulus control subsystem 7. It can be noted that in this way the base unit 4 can record data indicating a time at which a stimulus is applied by a stimulation device, rather than relying upon the time at which a command to provide a stimulus is provided to the stimulation device. This is particularly beneficial when the stimulation device is not able to provide stimuli exactly on demand, and is also beneficial where it is desired to allow the stimulation device to provide stimuli in a random manner, and simply record their application.

Operation of the head box 3 to obtain voltage measurements and provide obtained voltage measurements to the base unit 4 is now described with reference to Figures 11A to 15.

Figure 11A is a flow chart showing general processing carried out by the head box 3 during the acquisition of tomographic data. At step S1 a current injection between a pair of electrodes begins. Figure 12 shows a graph of the injected current. It can be seen that the injected current is an alternating current having a frequency of 10kHz, and that the current injection is carried out over a time of 500 μ s. As described above, the current injection time comprises a settling time of 100 μ s (step S2 of Figure 11), with voltage measurements being obtained during a 400 μ s measurement period after the settling time has elapsed (step S3 of Figure 11). It can be seen that 4 complete cycles of the current waveform occur during the 400 μ s measurement period.

Figure 13 shows how voltage between a pair of electrodes typically varies while current is being provided during the measurement period discussed above. As would be expected, the waveform is cyclic and comprises four cycles during the 400 μ s measurement period. 200 voltage measurements are obtained during the 400 μ s measurement period, that is, 50 voltage measurements are obtained during each voltage (and current) cycle within the voltage measurement period.

A voltage measurement is obtained at step S3 and multiplied by two reference waveforms described below at step S4 to provide two multiplication results. The multiplication results are summed with the results of other multiplications using the same reference waveform at step S5. At step S6 a check is carried out to determine whether 200 voltage measurements have been processed. If this is the case, the two summation results are output at step S7. Otherwise, processing continues at step S3 where another voltage measurement is obtained.

Figure 11B shows a circuit arranged to implement the processing of steps S4 and S5 of Figure 11A. An obtained voltage measurement is input to first and second multipliers 55, 56. A reference sinusoid 60 is also input to the first multiplier 55 and a reference co-sinusoid 61 (i.e. a version of the reference sinusoid 60 after a phase shift of $\pi/2$ or 90 degrees) is input to the second multiplier 56. The reference sinusoid is generated based upon the input digital current waveform generated by the FPGA 20 (Figure 5) and provided to the current source 16.

The multiplier 55 multiplies the obtained voltage measurement by a corresponding point on the reference sinusoid 60. A point on the reference sinusoid corresponding to each voltage measurement is determined with reference to the time at which the voltage measurement was obtained. More specifically, given that 200 voltage measurements are obtained over the course of 400 μ s, one voltage measurement is obtained every 2 μ s. As such, a voltage measurement obtained 2 μ s after the start of the measurement period (or the start of any voltage cycle) is multiplied by a point on the reference sinusoid defined with reference to a time of 2 μ s, and so on. Put another way, given that 50 measurements are taken during each cycle, each measurement value is multiplied by a point on the reference sinusoid 60 which is $360/50 = 7.2$ degrees advanced in phase as compared to the previous value.

Thus, in the described embodiment, the fifty measurements obtained in each cycle are analogously processed. That is, measurements of the reference sinusoid 60 with fifty distinct phase values are each processed four times, once in each cycle. In an alternative embodiment 200

measurements with unique phase values may be processed. This can be achieved by varying the times at which voltage measurements are obtained, and the values of the reference sinusoid 60 in the multiplications described above.

The second multiplier 56 operates similarly, multiplying a received voltage measurement by a corresponding point on the reference co-sinusoid 61.

The output of the first multiplier 55 forms the input to a first summation block 57 which simply adds the input value to a running total. The output of the first summation block 57 provides an in-phase value I which provides an indication of correlation between the voltage waveform which has been measured and the reference sinusoid 60.

A second summation block 58 takes as input the output of the second multiplier 56 and adds the input value to a running total. The output of the second summation block 58 provides a quadrature value Q which provides an indication of correlation between the voltage waveform that has been measured and the reference co-sinusoid 61.

It will be appreciated that each of the summation blocks 57, 58 sums 200 values, each corresponding to one of the voltage measurements, to generate the in-phase and quadrature values.

As such, it can be seen that the 200 voltage measurements associated with a particular pair of electrodes during a particular current injection can be reduced to two numbers which can be processed so as to obtain the necessary voltage data.

It will be appreciated that the processing of step S3 to S7 is carried out simultaneously for all pairs of electrodes between which voltage measurements are made during a particular current injection.

Given that in the arrangements of Figures 8A to 8E voltage measurements are taken between 33 pairs of electrodes during a particular current injection as described above (i.e. measurements are taken between each adjacent pair of electrodes, including those involving electrodes used for current injection, although the measurements obtained from electrodes used for current injections are discarded during further processing) and given that current is injected between twenty pairs of electrodes in turn, in a complete measurement frame, it will be appreciated that a large number of voltage measurements are collected, in each measurement frame. Indeed, all acquired voltage and current measurements provide data at a rate of 16.7 MB/s. Given that data which is generated is provided from the head box 3 to the base unit 4, it is desirable to reduce the quantity of data which needs to be transferred across the relatively low bandwidth link between the head box 3 and base unit 4. This is achieved by the processing described with reference to Figures 11A and 11B which means that voltage measurements between a single pair of electrodes during a single current injection are represented by two values: a quadrature value and an in-phase value.

It will be appreciated that alternative methods of reducing the quantity of measurement data may similarly be employed.

Referring back to Figure 11A, at step S8 a current measurement is received based upon the output of one of the analog to digital convertors 29a, 29b (Figure 7). Although the current sources 16a,

16b aim to provide a specified current, there is inevitably a limit to their accuracy, and it is therefore desirable to measure current that is actually provided on each of the current busses 17a, 17b, and use the measured currents when processing the obtained voltage measurements rather than assume that the provided current is that which was specified to the current sources 16a, 16b. 200 measurements of each current are obtained during a 400 μ s measurement period.

At step S9 the input current measurement is multiplied by the reference sinusoid 60 and reference co-sinusoid 61 in the manner described above with reference to step S4 and Figure 11B. At step S10 the results of the multiplications are added to respective summations. At step S11 a check is carried out to determine whether 200 current measurements have been processed. If this is not the case, processing returns to step S8. The processing of steps S8 to S11 generates in-phase I and quadrature Q values based upon the 200 processed current measurements. Given that current measurements for each of the current busses 17a, 17b are processed, it will be appreciated that the processing of steps S8 to S11 is carried out for each of the current busses 17a, 17b in parallel.

At step S12 the processed voltage and current measurements are arranged into a predetermined data packet format, and provided from the head box 3 to the base unit 4. At step S13 a next current injection is selected, before processing returns to step S1.

Figure 14 schematically illustrates a data packet format used to provide measurement data from the head box 3 to the base unit 4. The data packet is a fixed length data packet of length 152 bytes, and comprises seven fields of data. A sync code field 62 comprises a synchronisation code 62 of length 24 bits which is used as a marker of the start of a data packet.

A flags field 63 comprises 44 bits of data and provides various information indicating the validity of various data. More specifically, 33 bits of data are used to indicate whether any of the voltage measurements should be considered invalid, on the basis that they resulted from the respective ADC operating outside its normal operating range. This is likely, for example, where an ADC is provided with a signal from an electrode which is currently being used for the purposes of current injection, and from which no valid voltage measurement can be obtained. 8-bits of data are used to indicate error conditions associated with the current sources 16a, 16b, and in particular incorrect amplitude or distortion of the produced current wave forms. Two bits of data are used to indicate whether, in the time period (500 μ s) associated with the data packet a stimulus was applied. The two bits can indicate simple true/false data relating to stimulus application or can encode data relating to the nature of the applied stimulus.

A voltage measurements field 64 comprises 32 bits of data for each of 33 voltage measurements, providing a total of 1056 bits of data that is provided from the head box 3 to the base unit 4. The data representing each voltage measurement comprises a 16-bit I (in-phase) value, and a 16-bit Q (quadrature) value which are generated as described above.

A current measurements field 65 comprises 64 bits of data, 32 bits for each of the two current measurements which are obtained one for each of the current busses 17a, 17b. Each current measurement

is again represented by two 16-bit values, a first value indicating the I (in-phase) value, and a second value indicating a Q (quadrature) value, which are again generated as described above.

A current pattern identifier field 66 comprises 8 bits of data which identify the pair of electrodes between which current was injected to generate the obtained voltage measurements.

A current pattern counter field 67 comprises 20 bits of data which uniquely identify a block during measurements, that is a particular current injection of which there are twenty in a complete frame. The provision of 20 bits allows for unique identification of all blocks within measurements obtained during a measurement period of about 8 minutes. More specifically, given that 100 frames of data are obtained each second, and each frame comprises 20 blocks, 1 second of measurement data comprises 2000 blocks. One minute of measurement data comprises 120,000 blocks, while 8 minutes of measurement data comprises 960,000 blocks. Although in some embodiments measurement data is only obtained during a one minute time period, the use of 20 bits, allowing the collection of measurements over an 8 minute time period can be useful in allowing unique identification of a block over a longer time period. This can be useful if measurement is interrupted.

Data is provided from the head box 3 to the base unit 4 over a serial communications link. As shown in figure 15, each data packet takes a time of 304 μ s for transmission. Given that each data packet comprises data obtained over 500 μ s it will be appreciated that the no data is transmitted for 196 μ s following the transmission of a data packet.

Although Figure 14 shows one format for a data packet used to provide data from the head box 3 to the base unit 4 it will be appreciated that other data packet formats can be used.

The collection of data using the methods and systems described above may be used in a system in which electrodes are placed on a subject's head as described above with reference to Figures 8A to 8E. Current may be injected and measurements collected in any convenient way. For example current may be injected and measurements may be collected as described above with reference to Figure 2. As has been described, clinically valuable information can be obtained from voltage measurements taken at a particular time delay following application of a stimulus. In general terms obtained voltage and current measurements are processed to generate data indicating a distribution of impedance in the subject's head. The data indicating a distribution of impedance in the subject's head may be processed to generate images such as the images of Figure 3.

Figure 16 shows an alternative implementation of the head box 3 of Figure 4. Here, the head box is implemented in the form of a collar 90. This is particularly advantageous in applications where it is desired to support a patient's neck, for example during surgery. Four electrodes 2 are shown affixed to the patient's head, and these electrodes are connected to respective connections 2b provided by the collar 90 by respective cables 2a. It can be seen that the provision of the head box in the form of a collar not only provides a means of support for the patient's head, but also enables convenient connection of the electrodes to the collar with short cable lengths, thereby improving the usability of the device.

Figure 16 shows a connection 91 which connects the collar 90 to the base unit 4. The internal components of the collar 90 are similar to those of the head box 3 described above, and data is passed between the head box 3 and the base unit 4 in the general manner described above. Digital components which are located in the inner portion 13 of the head box 3 can be located in a lower part of the collar 90, while analog components which are located in the outer portion 10 of the head box 3 can be located in an upper part of the collar 90. An intermediate portion to house analog-to-digital and digital-to-analog conversion circuitry can be located in an intermediate part of the collar 90 between the upper part and the lower part.

The described embodiments could be used to assist in the diagnosis of a patient presenting with blindness. Possible reasons for blindness, caused for example by a blow to the head, include a detached retina or brain damage. Application of a visual stimulus to the patient and examination of an image or images of the patient's brain created using the above-described tomography technique will allow analysis of the cause of blindness. In such examination, a medical practitioner will know where in the brain activity can be expected at particular delay times after stimulus application. If any brain activity is observed, clearly the retina is not detached as signals are being sent to the brain, thus indicating that the blindness may be caused by brain damage. If however no response is observed in the brain to the stimulus, the cause could either be a detached retina, or more serious brain damage. If some brain activity is observed, images can be generated based upon voltage measurements obtained at different delay times after stimulus application, such that images generated after a particular time delay do not show expected behaviour. The medical practitioner is therefore provided with an indication of the location of the brain damage.

As a further example, if a patient presents with symptoms of a stroke, an embodiment of the present invention may be used to image brain condition. Electrodes are applied to the patient's head as illustrated in Figures 5 and 9 and as described above. Stimuli are then presented to the patient and response monitored. A nerve stimulator is placed on the patient's leg, and triggered to provide a number of unequally temporally spaced stimuli. EIT measurements obtained at a predetermined time after each stimulus are used as a basis for the creation of an image as described above. When this imaging process is complete, an audio stimulus is provided and a series of images is again created. Similarly, a visual stimulus is provided and a number of images created. The three sets of images created, each in response to a different type of stimulus, allow a thorough assessment of brain function to be made, thus allowing evaluation of the severity of the stroke.

The imaging apparatus required for this procedure is relatively small in size, and relatively cheap to provide, particularly compared to the apparatus used in imaging technologies such as Magnetic Resonance Imaging and Positron Emission Tomography, therefore the apparatus may be provided to a general practitioner, allowing him to quickly and easily assess the need for a patient to be referred to a neurologist.

In some embodiments of the present invention, for example those concerned with diagnosing the cause of blindness, only specific parts of the brain need be imaged. By referring to a known neurological model of the brain, the specific parts of the brain that need to be imaged can be identified. Using this information, the number of current injections required can be reduced to one or two carefully selected injections. For example, when imaging the visual pathway current may be passed between regions at the front and the back of the head. That is, injection is parallel to the visual pathway which generally runs from the eyes to the back of the brain. If response to an auditory stimulus is to be monitored, the pathway from the ears to auditory cortex at the side of the brain needs to be monitored, and so electrodes must be placed at least at the side of the head. In alternative embodiments, all current injections described with reference to Figure 16 may be used, but only a limited number of voltage measurements taken for each injection. Alternatively, both the injections and measurements may be selected on the basis of a neurological model and the applied stimulus.

It may be desired to use other stimuli occurring in the patient's environment, the application of which cannot be controlled, in place of the deliberate application of stimuli as described above. This is possible, by accurately recording the time of occurrence of the stimulus and using the recorded time in the selection of voltage measurements.

Various stimuli have been described above. In some embodiments of the invention the applied stimulus is a transcranial magnetic stimulus, that is a stimulus which comprises rapidly changing magnetic fields which cause brain activity which can be observed using the techniques described above. The stimulus may be a physiologically occurring stimulus (e.g. a heartbeat or breath) which is monitored by an appropriate physiological monitor arranged to provide a signal indicating occurrence of the stimulus. The signal indicating occurrence of the stimulus can then be used as a basis for the selection of measurements in the manner described above.

The apparatus described above can be used to effectively monitor cerebral blood flow. Using the techniques described above, where the stimulus is a heartbeat monitored using an electrocardiogram, measurements taken at particular times after occurrence of the heartbeat may be analysed to determine cerebral blood flow at those particular times after occurrence of the heartbeat. For example, when it is detected that a heart beat has occurred, measurements taken at particular times after occurrence of the heartbeat (e.g. 15ms, 30ms and 45ms) may be compared to determine the variation in cerebral blood flow over time after the heart beat. Where it is determined that cerebral blood flow changes slowly after a heartbeat this may be taken as indication of bleeding.

The voltage signals obtained may comprise saw-tooth waveforms, and characteristics of the saw-tooth waveforms (e.g. amplitude and/or frequency) may provide an indication of cerebral blood flow. For example, the time at which a saw-tooth waveform with amplitude exceeding some predetermined minimal amplitude is observed may provide useful information as to the vascularisation of the neck and Circle of Willis. Characteristics of a saw-tooth waveform between a single pair of electrodes over time may therefore provide clinically useful data.

Additionally, waveforms obtained from different pairs of electrodes may be compared to obtain data indicating blood flow/pressure between different parts of a subject's brain – for example between hemispheres of a subject's brain or between the brainstem and the cerebral cortex. Such data may be useful in identifying thromboses or embolism. The comparison of waveforms obtained from different pairs of electrodes may comprise a comparison of various characteristics of the two waveforms (e.g. frequency, and amplitude).

It will be appreciated from the preceding description that although the voltage measurements obtained can be used to generate images in the manner described above, useful information can be obtained by determining characteristics of the obtained voltage measurements without any generation of an image.

In the embodiments described above, it has been explained that current is provided to electrodes attached to a subject's head by the electrodes being connected to two current buses 17a, 17b (see Figure 7). It will be appreciated that some aspects of the present invention can be implemented in a system in which each electrode is provided with its own current source, thereby obviating the need for the current buses, but requiring a larger number of current sources.

In the embodiments described above it has been explained that voltages are measured between pairs of electrodes while current is injected between a selected pair of electrodes. In alternative embodiments of the invention a voltage may be applied between a selected pair of electrodes, and currents may be measured between other pairs of electrodes while the voltage is applied.

The measurement data may be processed to reduce sensitivity to effects such as noise and the temporal variation of impedance within the brain during the measurement sequence. For example, a Kalman filter may be used in a conventional manner. In some embodiments of the invention, a plurality of stimuli's may be applied, and a number of sets of voltage measurements collected at a particular time after application of each respective stimulus. Sets of voltage measurements collected in this way can then be averaged so as to provide greater accuracy.

Although various embodiments have been described above, it will be appreciated that various modifications can be made to the described embodiments without departing from the spirit and scope of the invention.

CLAIMS

1. A method for monitoring the response of a nervous system of a body to a stimulus, the method comprising:

providing a plurality of electrodes on a surface of the body and passing current between selected areas of the surface of the body by passing current between at least one pair of electrodes of said plurality of electrodes, said current being provided by a current source external to said body;

collecting voltage measurements between selected ones of said electrodes while said current is passed between said at least one pair of electrodes, said voltage measurements being collected independently of stimulus application; and

processing a subset of said collected voltage measurements to determine a response of the nervous system to the stimulus;

wherein said subset of said collected voltage measurements is collected during a measurement period beginning after a particular delay following occurrence of said stimulus.

2. A method according to claim 1, wherein current is sequentially passed between a plurality of pairs of electrodes and voltage measurements are collected between selected ones of said electrodes while current is passed between each pair of said plurality of pairs of electrodes.

3. A method according to any preceding claim, wherein current is repeatedly sequentially passed between the plurality of pairs of electrodes and voltage measurements are collected between selected ones of said electrodes while current is passed between each pair of said plurality of pairs of electrodes.

4. A method according to any preceding claim, further comprising applying said stimulus.

5. A method according to any preceding claim, wherein the stimulus is selected from the group consisting of a visual stimulus, an auditory stimulus, a sensory stimulus and a transcranial magnetic stimulus.

6. A method according to any preceding claim, wherein said processing comprises producing an image representing the distribution of impedance within the body.

7. A method according to any preceding claim, wherein said processing comprises comparing said at least some of said collected voltage measurements with reference data.

8. A method according to any preceding claim, wherein the stimulus occurs spontaneously.

9. A method according to any preceding claim, wherein the stimulus is a feature of an environment in which the body is located or the stimulus is a physiologically occurring stimulus which is monitored
10. A method according to any preceding claim, wherein passing current between selected areas of the surface of the body comprises:
- injecting electrical current for a first time period through at least a first pair of electrodes of a plurality of electrodes affixed to a subject;
 - during said first time period, measuring electrical voltage between selected ones of said plurality of electrodes;
 - subsequent to said first time period, injecting electrical current for another time period through at least another pair of said plurality electrodes;
 - during said another time period, measuring electrical voltages between selected ones of said electrodes of said plurality of electrodes.
11. A method according to claim 10, wherein said first time period and said another time period have substantially equal lengths.
12. A method according to claim 10 or 11, wherein said injecting is carried out independently of said stimulus application.
13. A method according to any preceding claim, further comprising:
- identifying a predetermined part of the nervous system for which a response is monitored;
 - wherein said particular delay is based upon a neurological model of the nervous system and the predetermined part of the nervous system for which a response is monitored.
14. A method according to any preceding claim, wherein the stimulus is selected from the group consisting of a visual stimulus, an auditory stimulus, a sensory stimulus and a transcranial magnetic stimulus.
15. A method according to any preceding claim, wherein said processing comprises producing an image representing the distribution of impedance within the body.
16. A method according to any preceding claim, wherein said processing comprises comparing said at least some of said collected voltage measurements with reference data.
17. A method according to any preceding claim, wherein said processing is arranged to determine normal or abnormal behaviour of the nervous system.

18. A method according to any preceding claim, wherein said processing is arranged to diagnose brain dysfunction.
19. A method according to claim any preceding claim, wherein said particular delay is based upon a user input.
20. A computer program comprising computer readable instructions configured to cause a computer to carry out a method according to any one of claims 1 to 19.
21. A computer readable medium carrying a computer program according to claim 20.
22. A computer apparatus for monitoring the response of a nervous system of a body to a stimulus, the apparatus comprising:
a memory storing processor readable instructions; and
a processor arranged to read and execute instructions stored in said memory;
wherein said processor readable instructions comprise instructions arranged to control the computer to carry out a method according to any one of claims 1 to 19.
23. An apparatus for monitoring the response of a nervous system of a body to a stimulus, the apparatus comprising:
a current source external to said body;
a plurality of electrodes arranged to be attached to a surface of the body, the electrodes being connected to said current source to allow current to be passed between at least one pair of electrodes of said plurality of electrodes;
circuitry arranged to collect voltage measurements between selected ones of said electrodes while said current is being passed between said at least one pair of electrodes, said voltage measurements being collected independently of stimulus application;
wherein said apparatus is arranged to process a subset of said collected voltage measurements to determine a response of the nervous system to the stimulus, said subset of said collected voltage measurements being collected during a measurement period beginning after a particular delay following occurrence of said stimulus.
24. A tomographic data acquisition apparatus for obtaining tomographic data from a human or animal subject, the apparatus comprising:
a plurality of electrodes arranged for attachment to a human or animal patient;

circuitry arranged to provide current to pairs of said electrodes and measure voltage between selected ones of said electrodes; and

a housing in which the circuitry is disposed, the electrodes being connected to the circuitry through the housing, the housing defining a collar arranged, in use, to support the neck of the human or animal subject.

25. Apparatus according to claim 24, wherein the housing is generally U-shaped and defines an opening to receive the neck of the human or animal subject.

26. Apparatus according to claim 24 or 25, wherein the circuitry is controlled to provide current between a plurality of selected pairs of said plurality of electrodes in turn, and to obtain a plurality of voltage measurements between selected ones of the plurality of electrodes while current is provided between each of said plurality of selected pairs of electrodes.

27. Apparatus according to any one of claims 24 to 26, further comprising a stimulus application signal generator, arranged to generate a signal to cause a stimulus generator to apply a stimulus to the subject.

28. Apparatus according to claim 27, wherein said stimulus generator is arranged to generate a sensory or transcranial magnetic stimulus.

29. Apparatus according to claim 27 or 28 arranged to:
receive user input indicating a delay time; and
to process voltage measurements obtained at a time following stimulus application determined by said delay time, so as to generate data indicating activity of the subject's nervous system at the time following stimulus application.

30. A tomographic data acquisition apparatus for obtaining tomographic data from a human or animal subject, the apparatus comprising first and second units, wherein:

the first unit comprises data receiving circuitry arranged to receive stimulus data indicating a time at which a stimulus occurs, a plurality of electrodes arranged for attachment to a measurement subject, a current source arranged to provide current between at least one first pair of said plurality of electrodes, voltage measurement circuitry arranged to obtain voltage measurements between at least one second pair of said plurality of electrodes while said current is being provided between said at least one selected pair of electrodes and data processing circuitry arranged to provide obtained voltage measurements and received stimulus application data to the second unit; and

the second unit comprises data receiving circuitry arranged to receive voltage measurements and said stimulus data from the first unit.

31. Apparatus according to claim 30, wherein the second unit further comprises a stimulus application controller arranged to cause application of a stimulus to the measurement subject and to provide said stimulus data to the first unit.

32. Apparatus according to claim 31, wherein said stimulus is a sensory or transcranial magnetic stimulus.

33. Apparatus according to claim 31 or 32 arranged to:
receive user input indicating a delay time; and
to process voltage measurements obtained at a time following stimulus application determined by said delay time, so as to generate data indicating activity of the subject's nervous system at the time following stimulus application.

34. Apparatus according to any one of claim 30, further comprising a monitor monitoring a physiological process of said human or animal subject, wherein said stimulus data is generated by said monitor.

35. Apparatus according to any one of claims 24 to 34, wherein said electrodes are arranged for attachment to the human or animal body so as to obtain data from a human or animal subject.

36. Apparatus according to any one of claims 24 to 35, wherein the electrodes are arranged for attachment to a head of a human or animal measurement subject, and the electrodes of the or each at least one selected pair of said plurality of electrodes are arranged to be attached to the head at substantially diametrically opposed positions.

37. Apparatus according to any one of claims 24 to 36, wherein the measurement circuitry is arranged to obtain voltage measurements between electrodes arranged for attachment adjacent to one another.

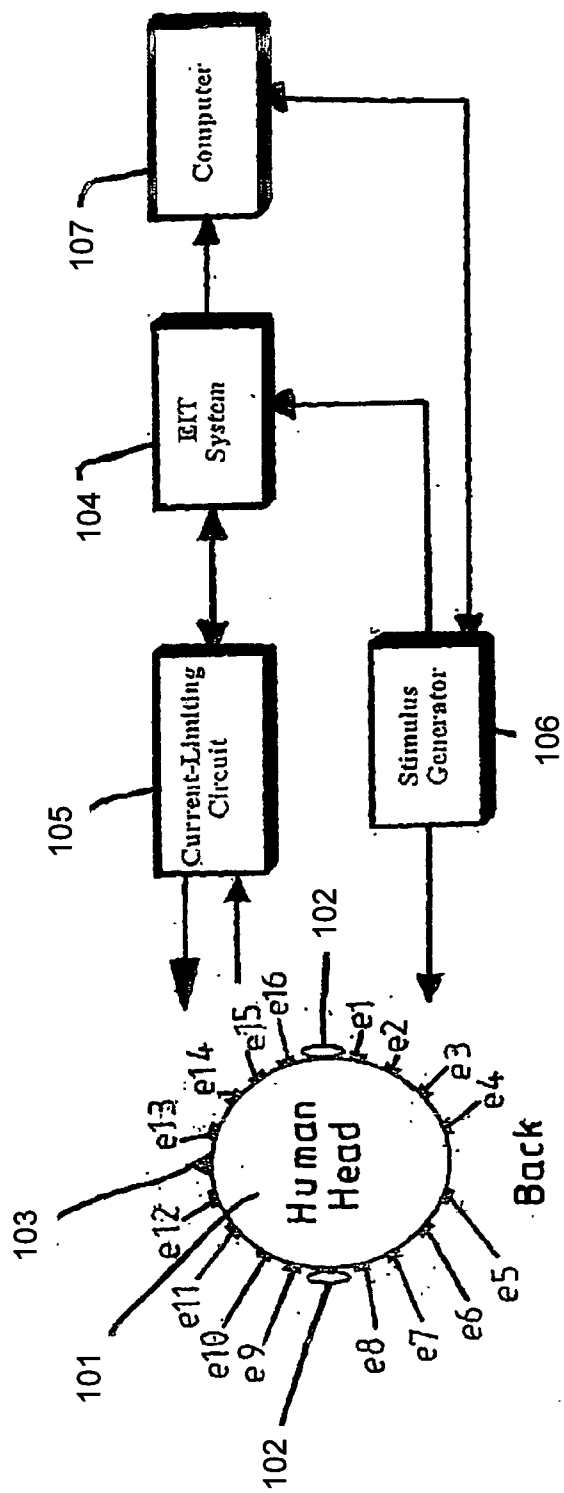


Fig 1

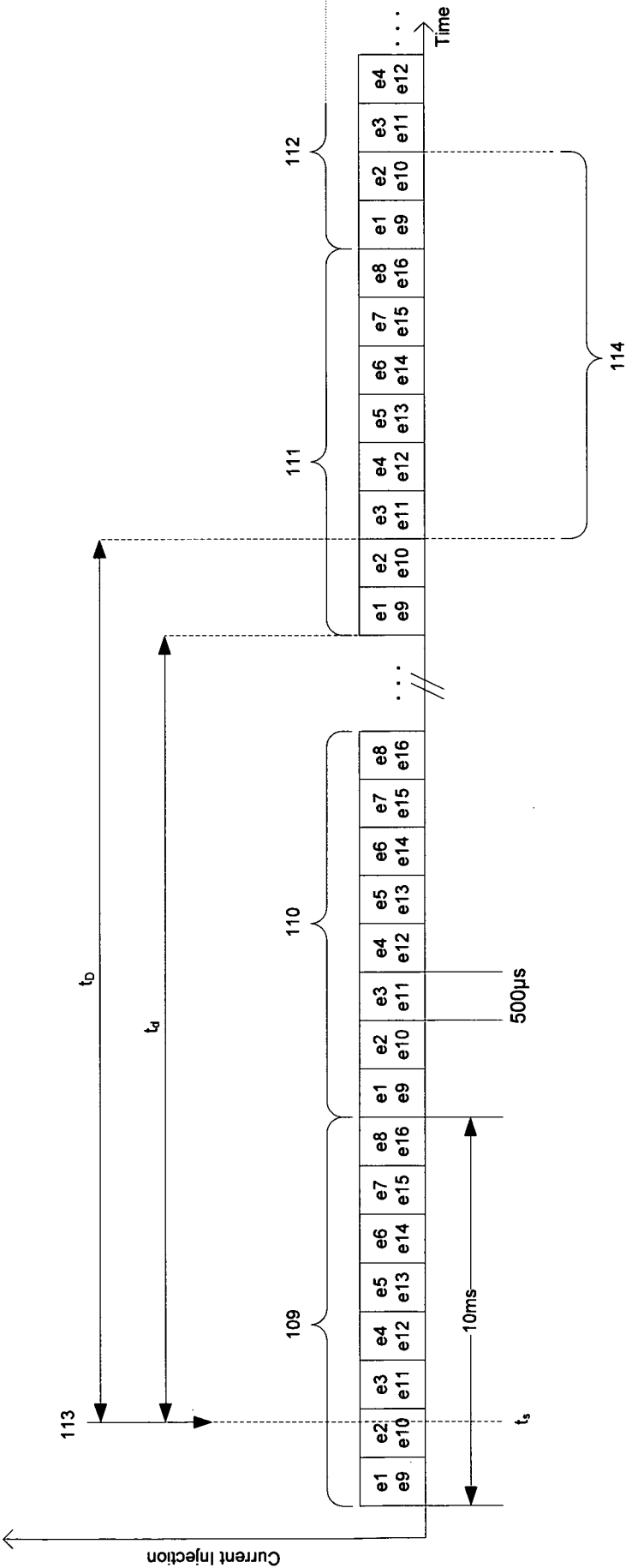


Fig 2

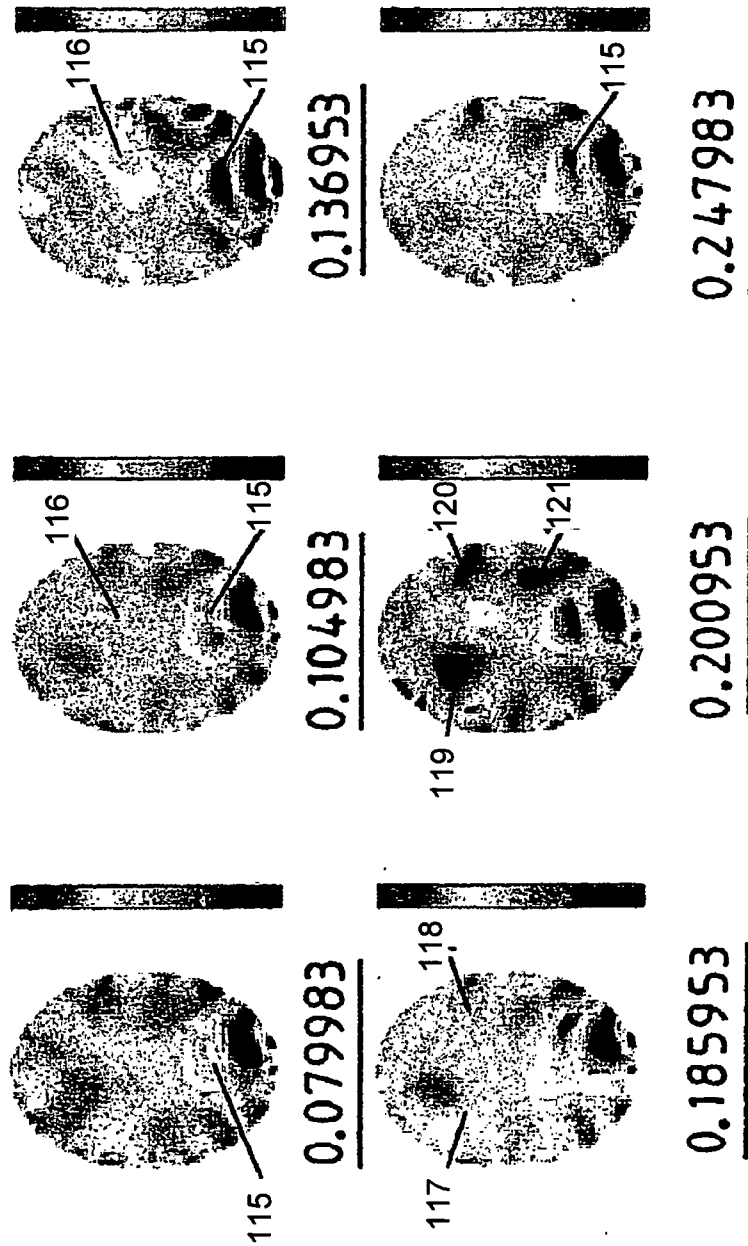


Fig 3

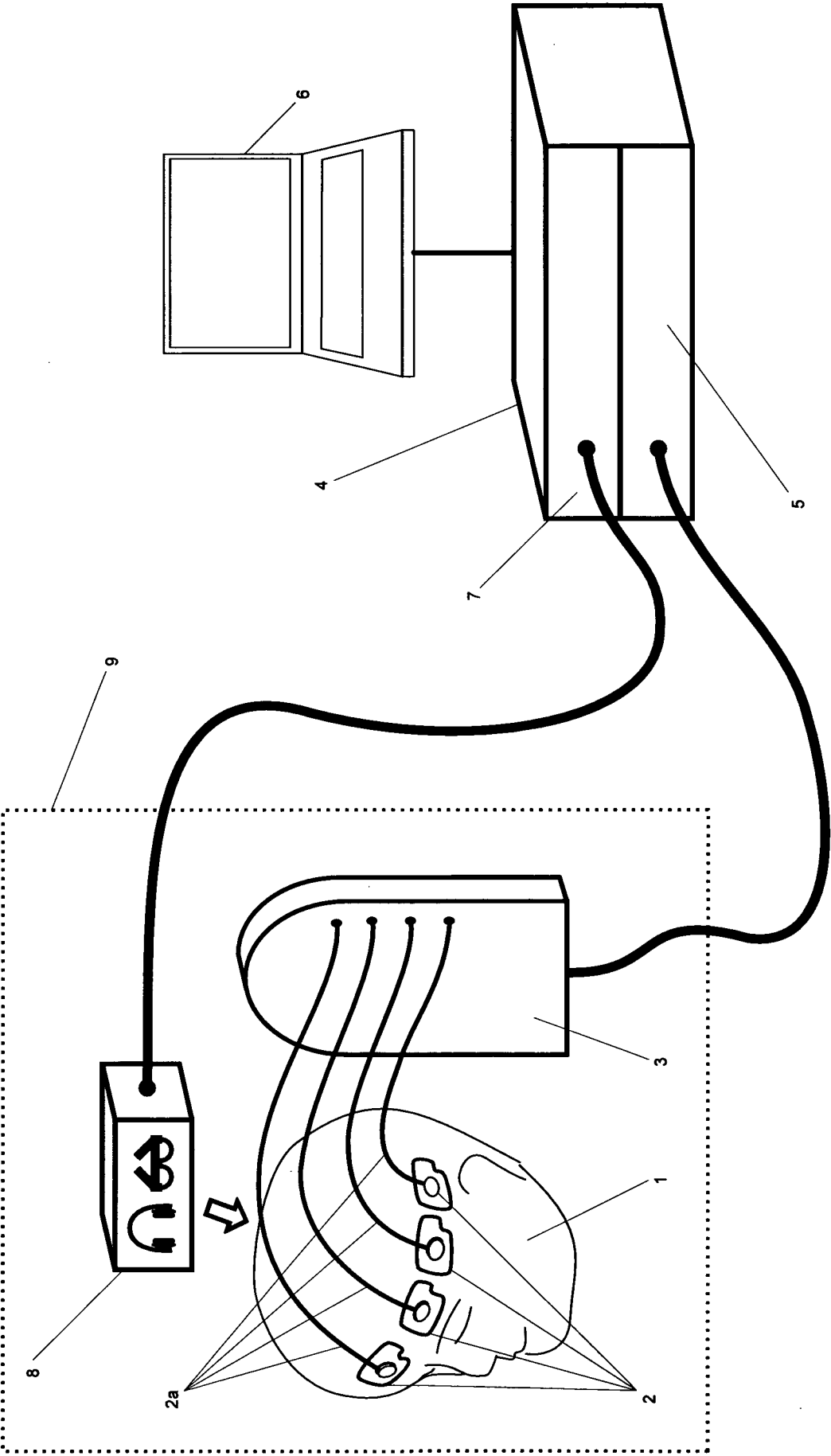


Fig 4

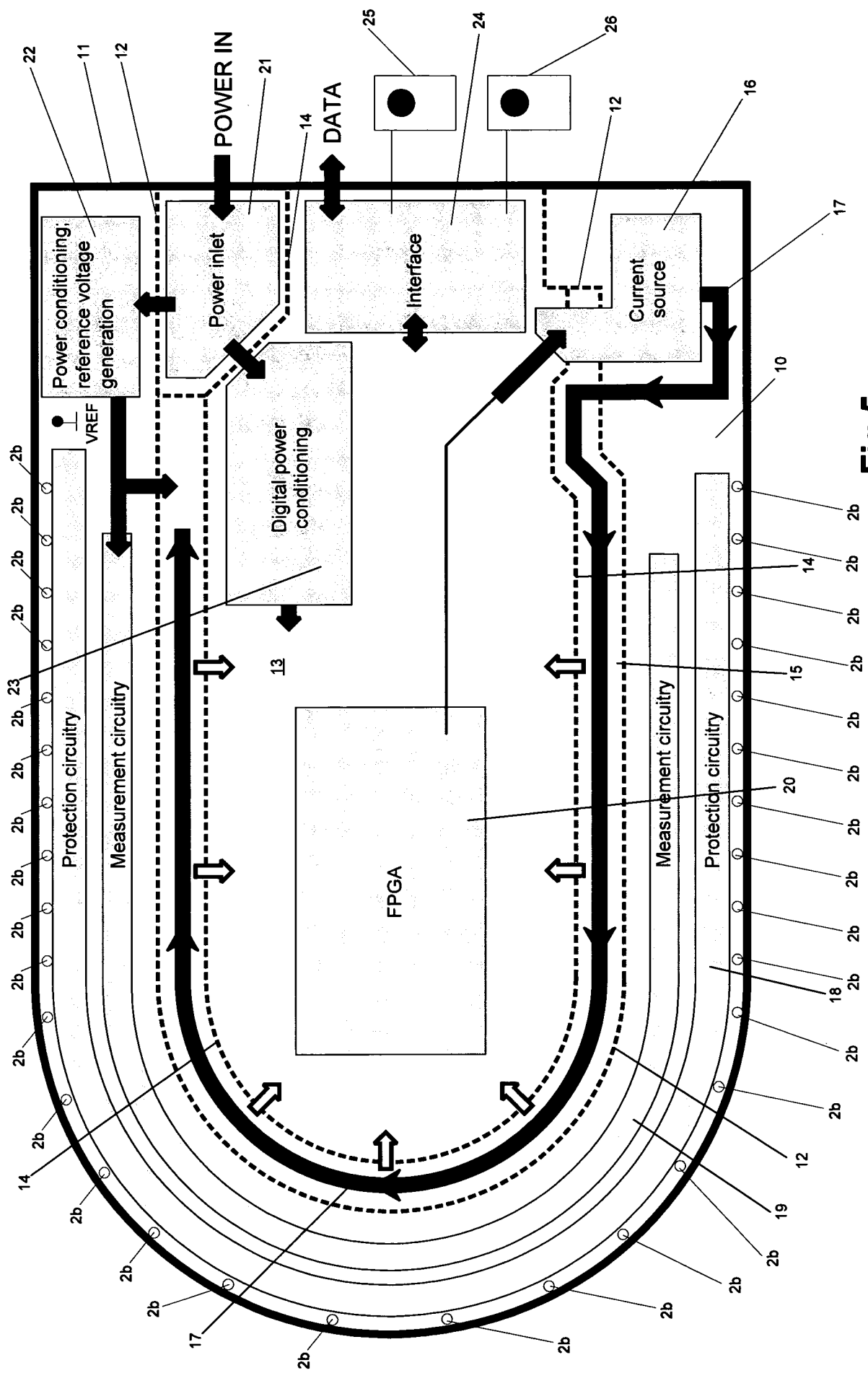
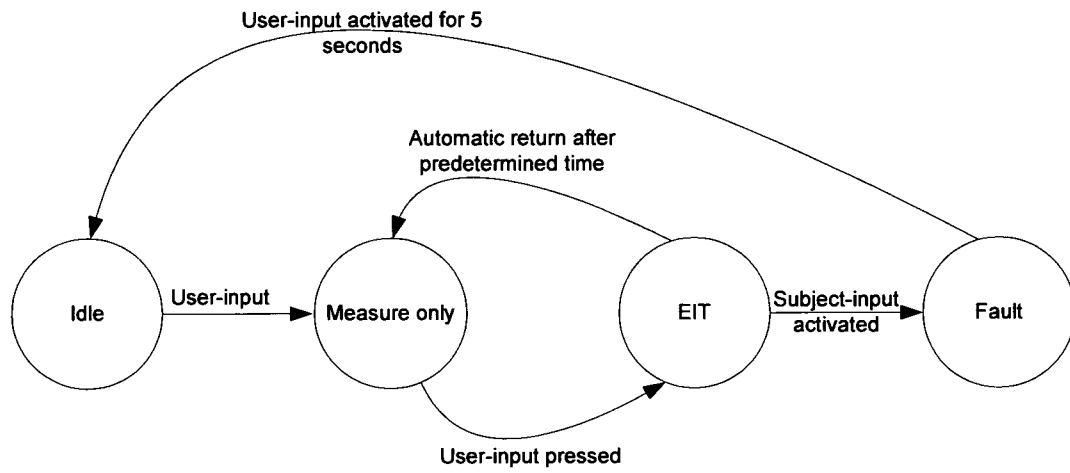
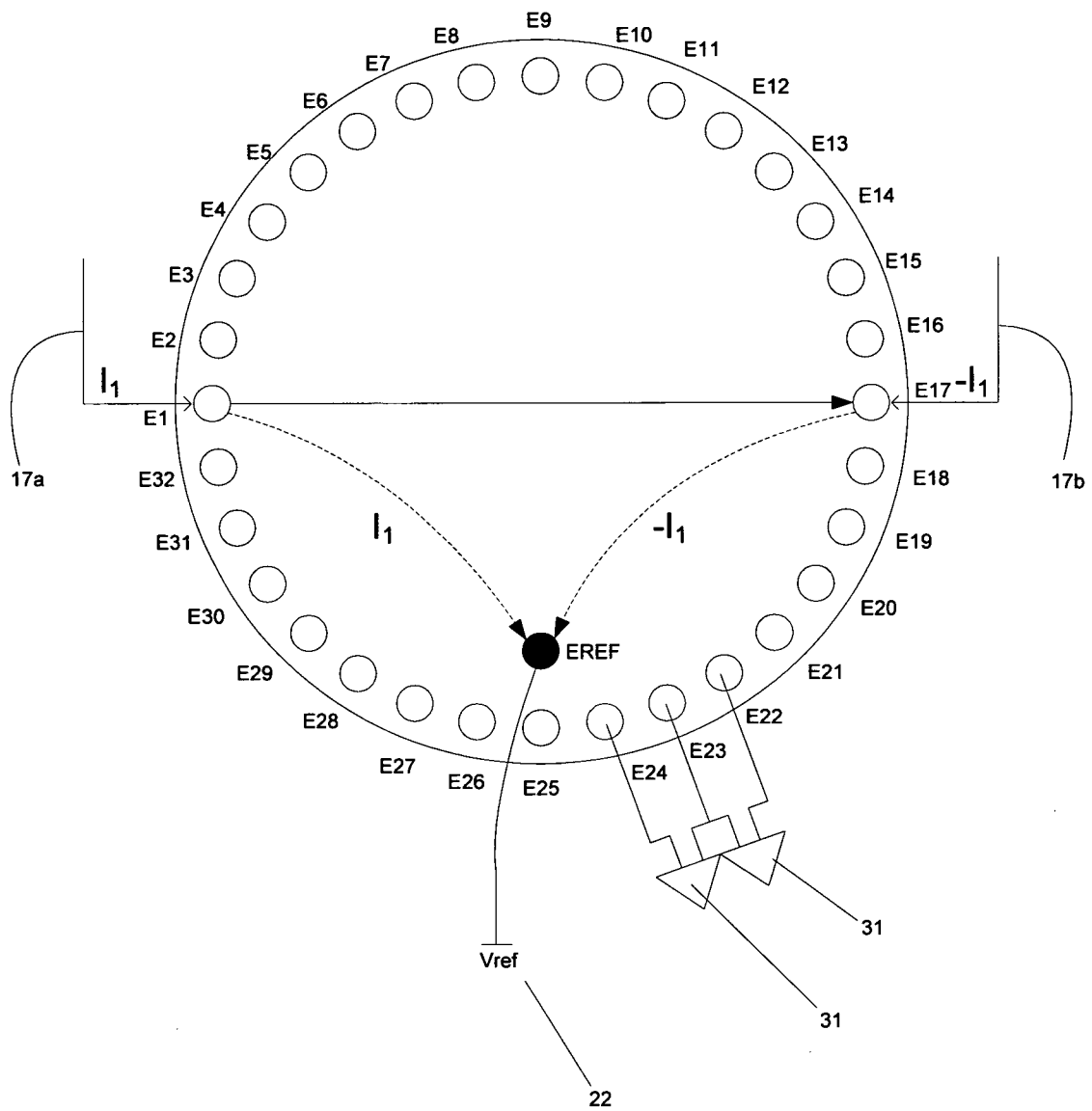


Fig 5

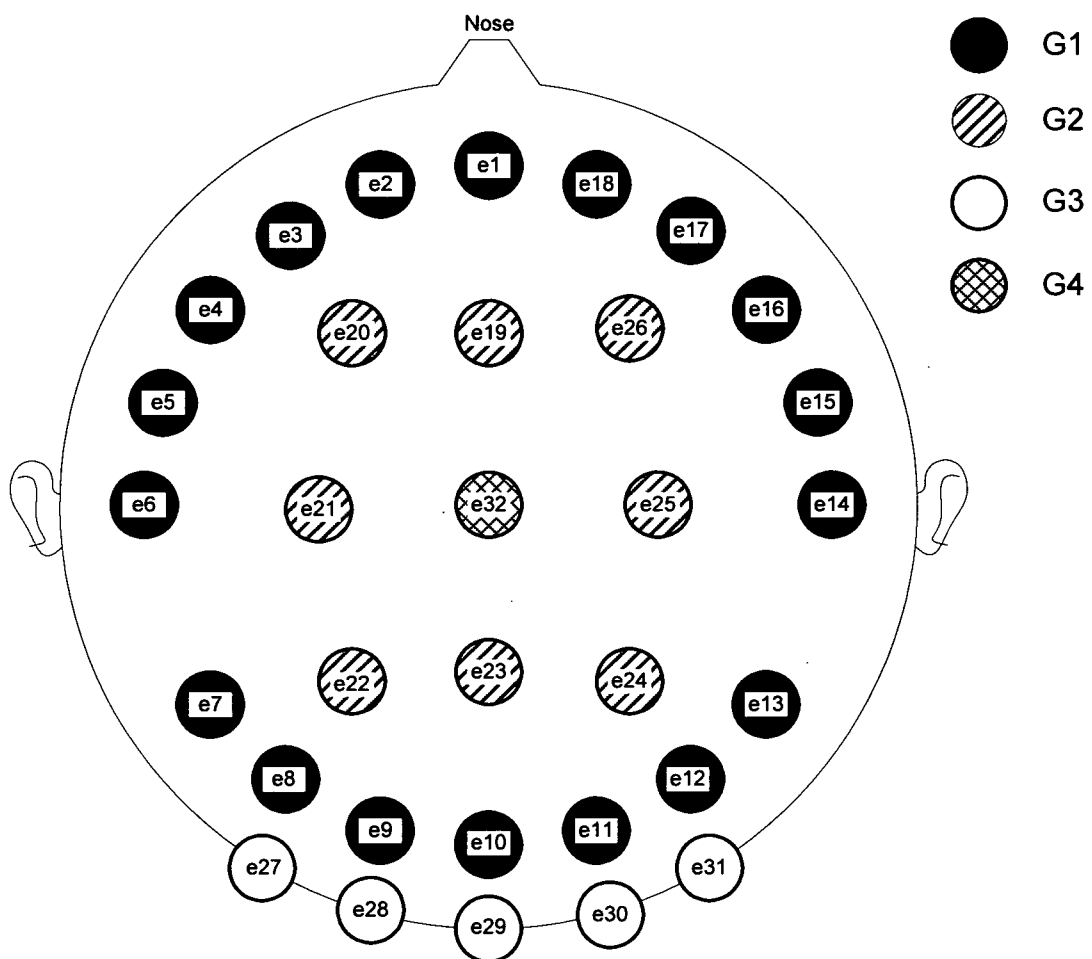
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**Fig 6**

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**Fig 8**

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**Fig 8A**

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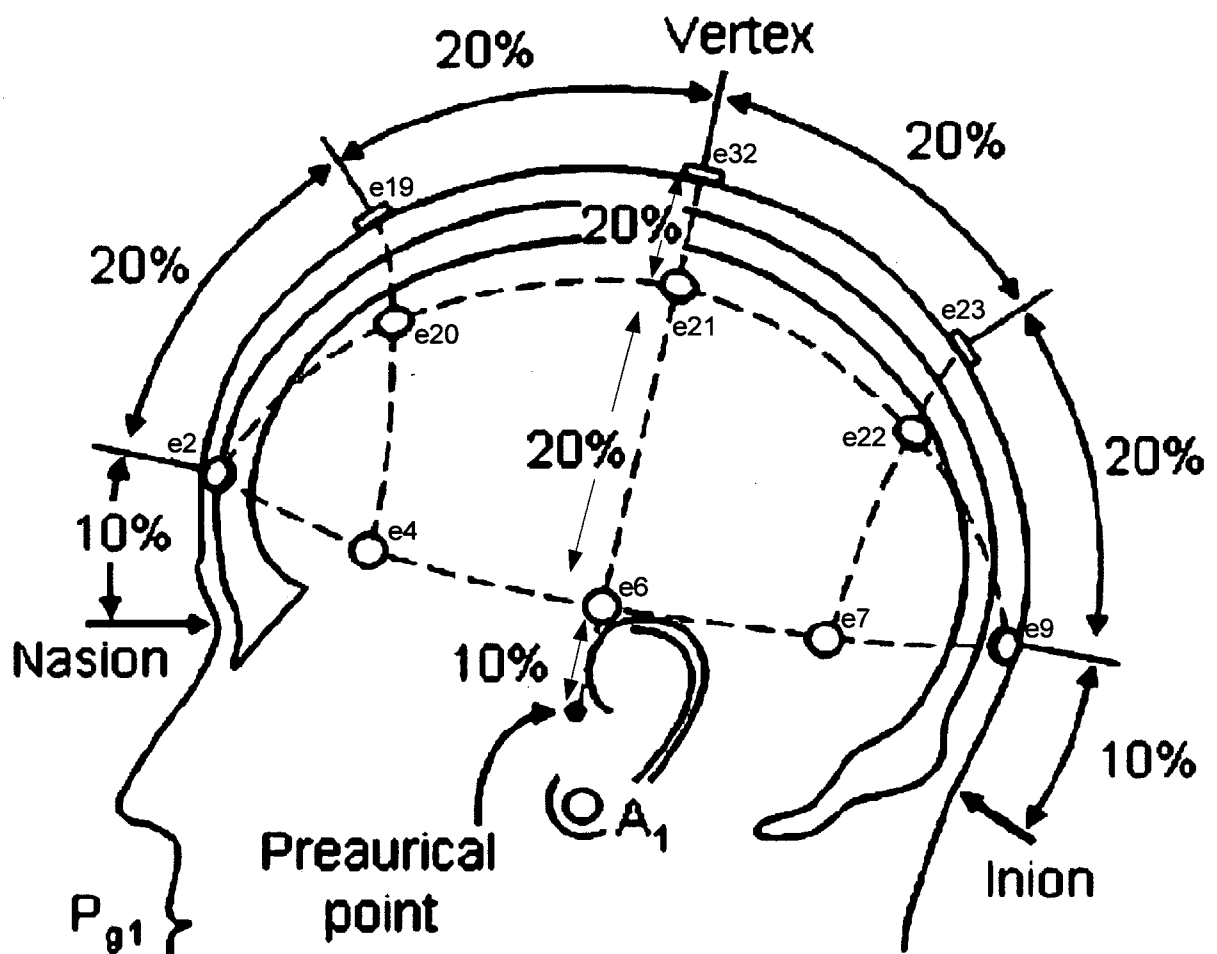


Fig 8B

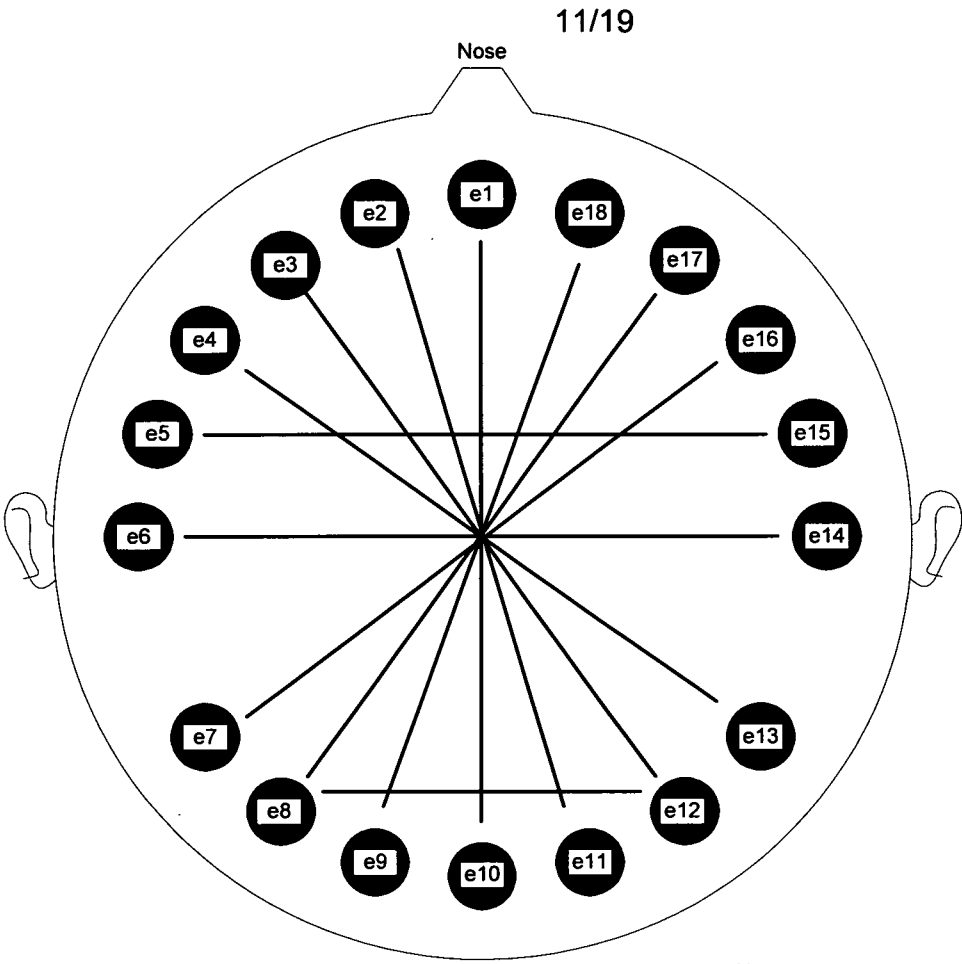


Fig 8C

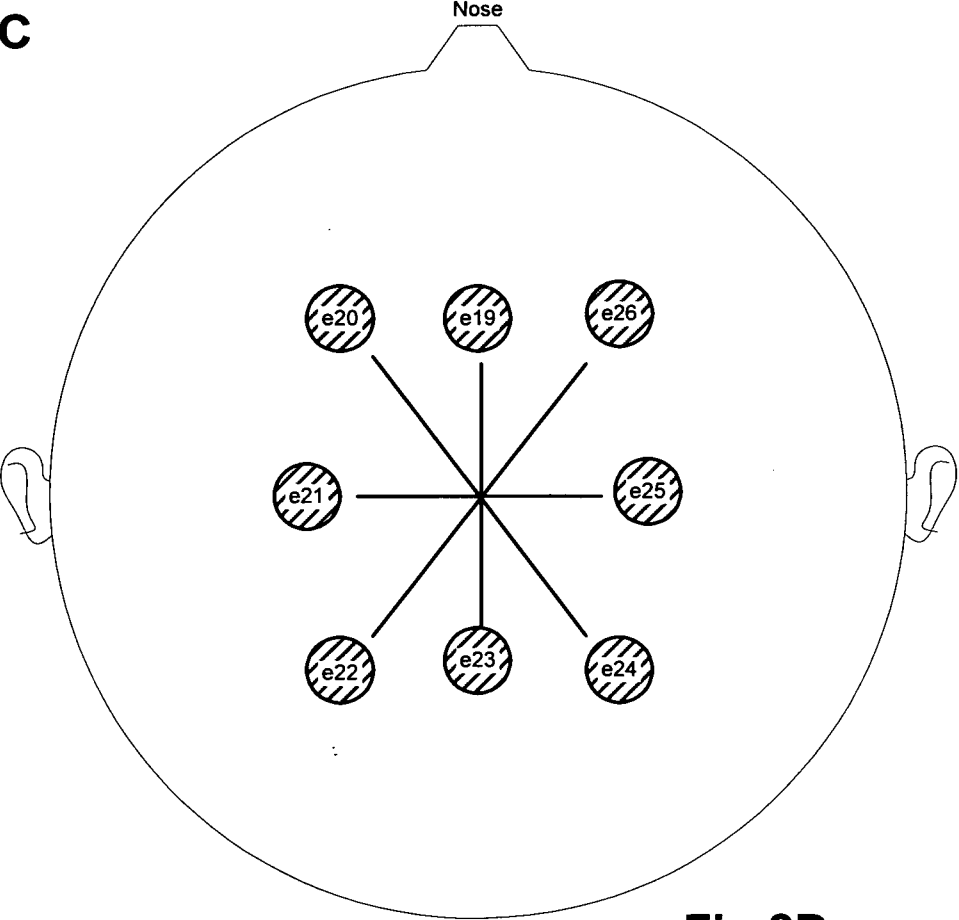


Fig 8D

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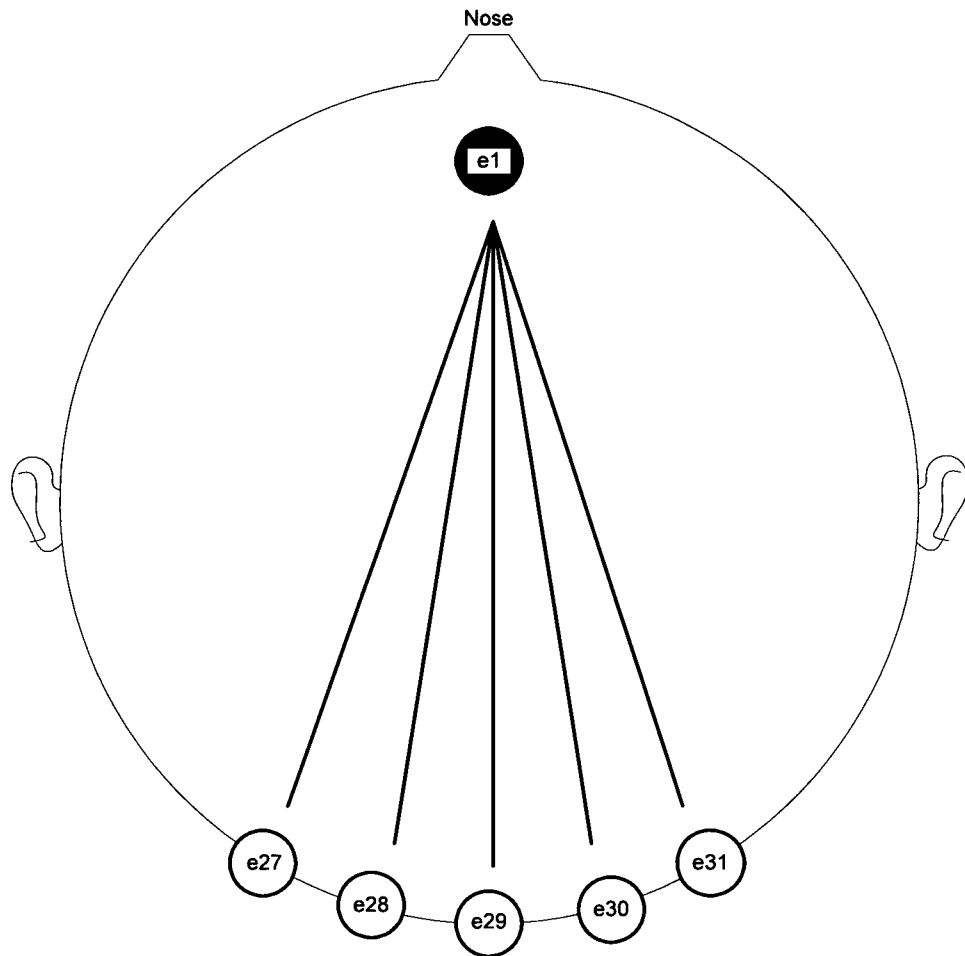


Fig 8E

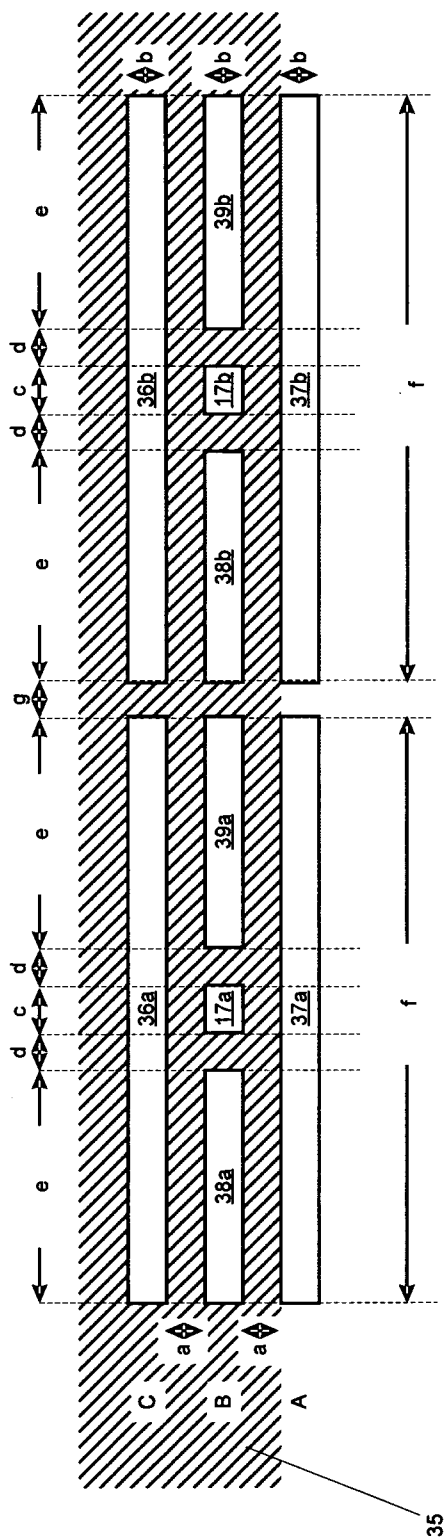


Fig 9

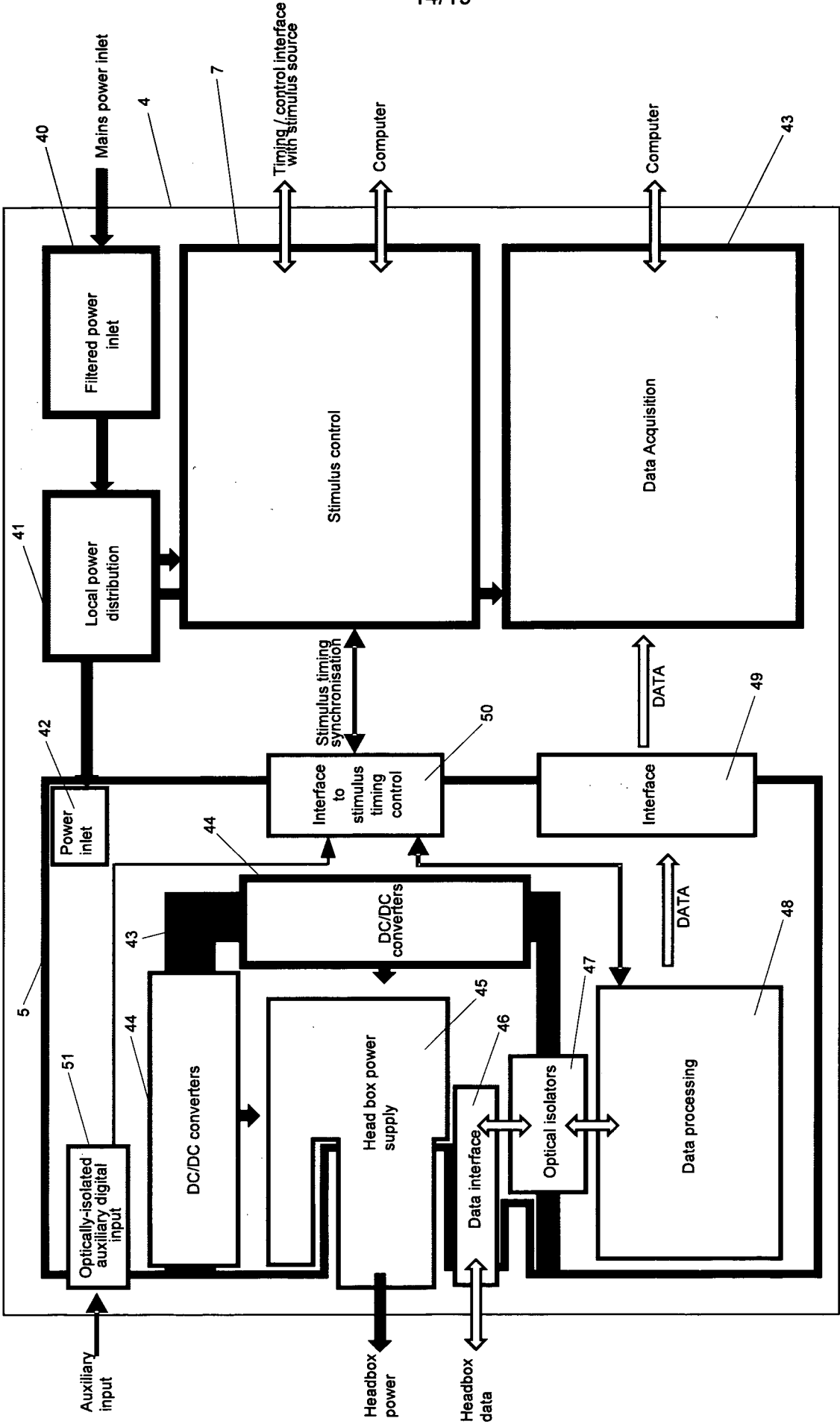
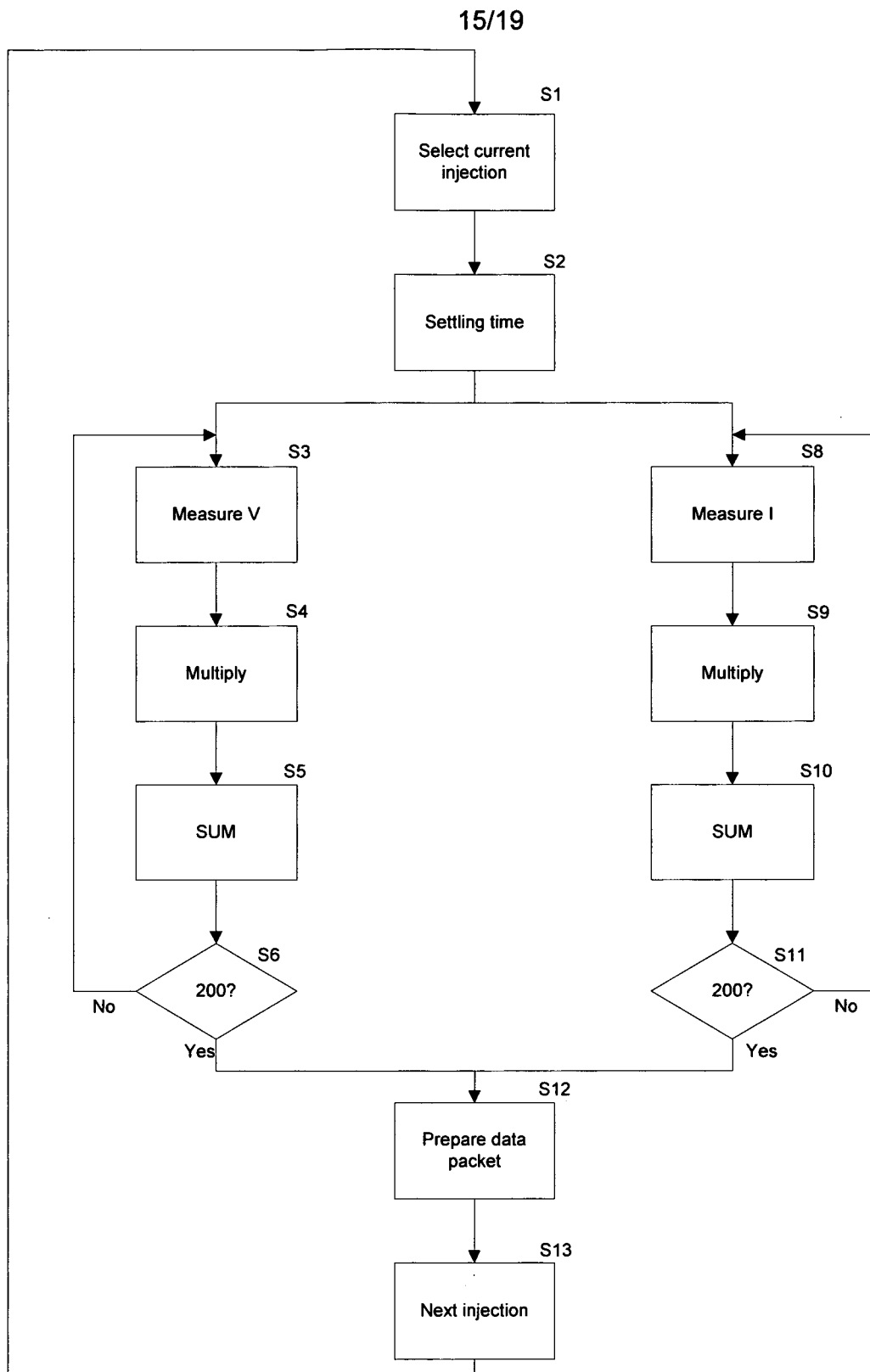


Fig 10

**Fig 11A**

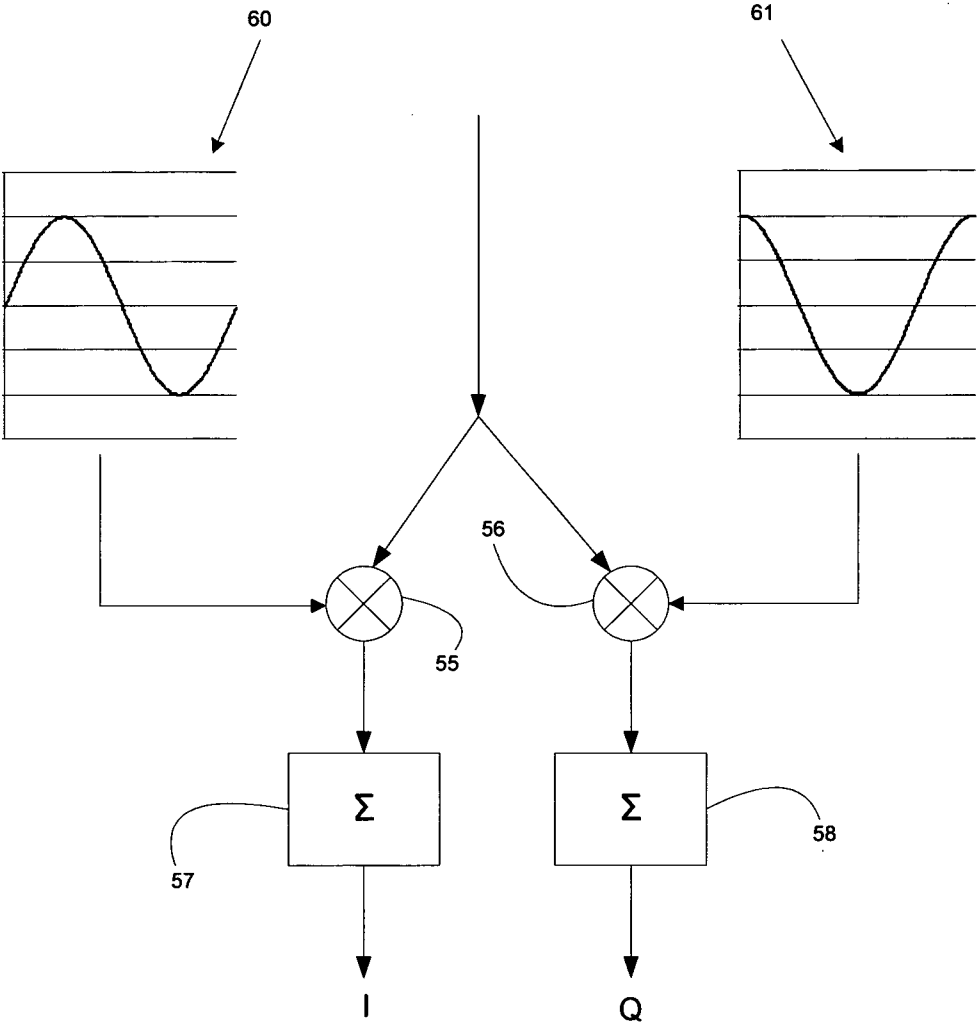


Fig 11B

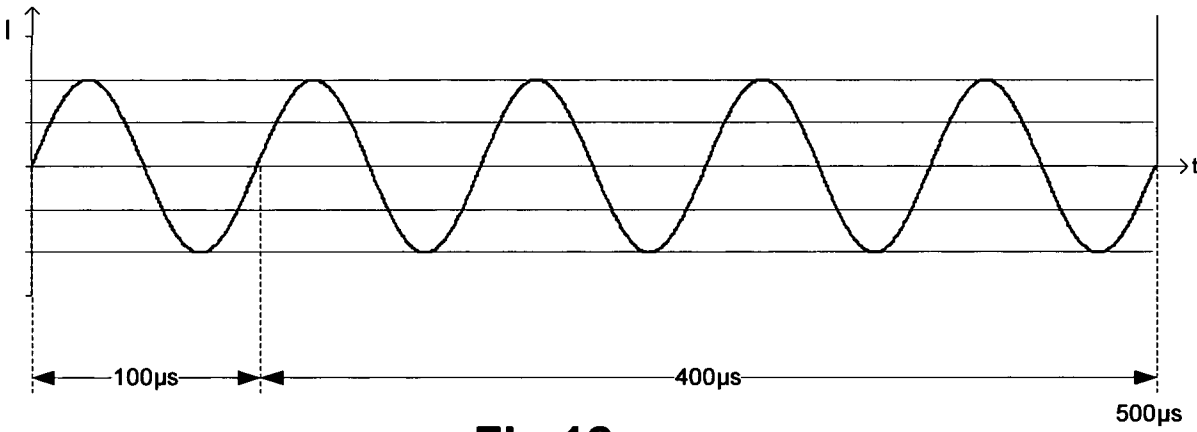


Fig 12

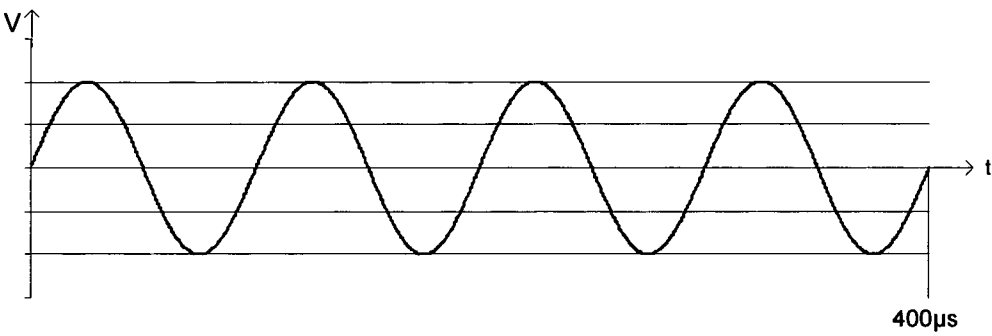


Fig 13

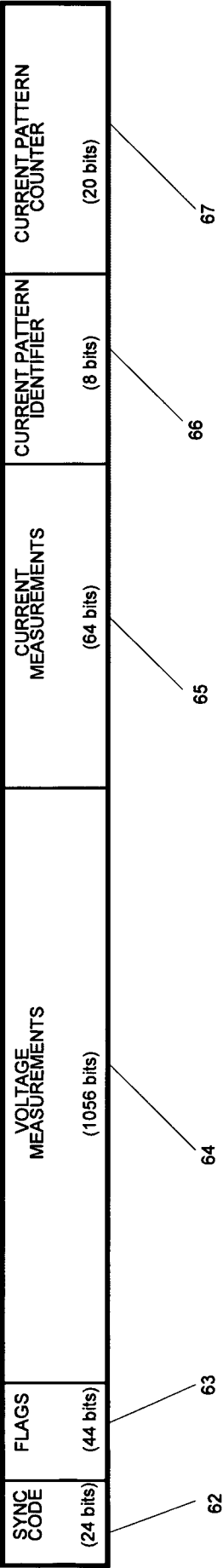


Fig 14

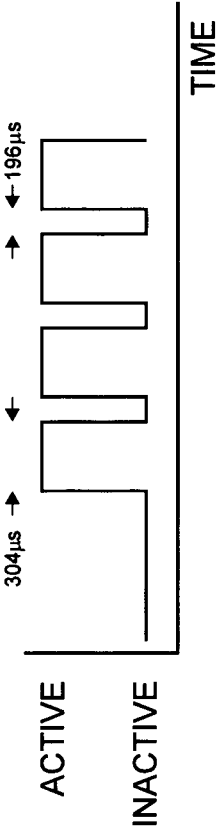


Fig 15

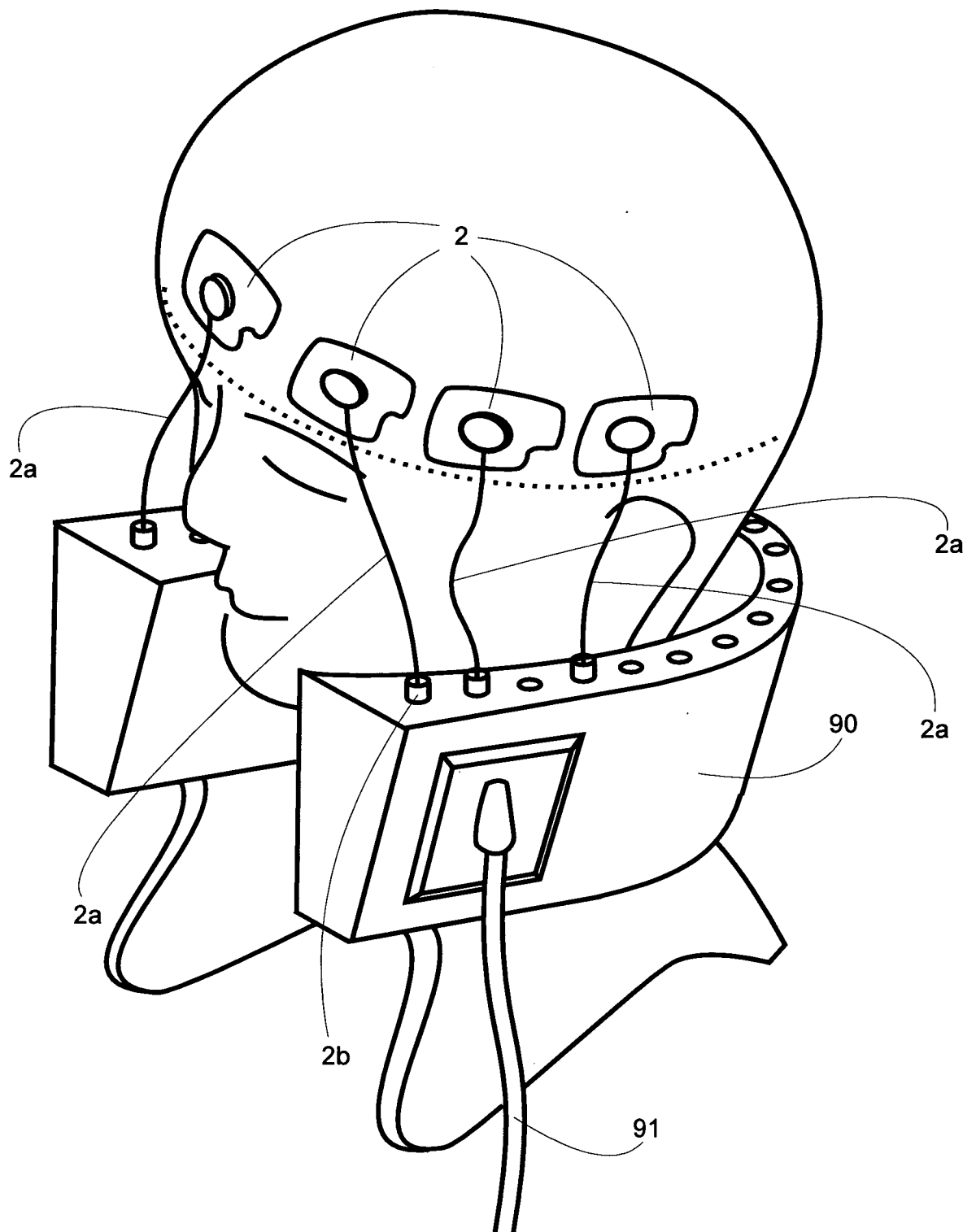


Fig 16