Experimental study of electrophysiology using the fEITER system

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ACRONYMS AND ABBREVIATIONS

ADC	Analogue to Digital Convertor
AEP	Auditory Evoked Response
Ag/AgCl	Silver/Silver Chloride
AP	Applied Part
ASR	Auditory Startle Response
BOLD fMRI	Blood-Oxygenation-Level-Dependant fMRI
BS	British Standard
CBCT	Cone-Beam CT
CBF	Cerebral Blood Flow
CED	Cambridge Electronics Device
CF	Carotid Flow
CNS	Central Nervous System
CP	Current Projections
CSF	Cerebral Spinal Fluid
CT	x-ray Computed Tomography
DAQ	Data Acquisition
DH	Declaration of Helsinki
ECG/EKG	Electrocardiography

EEG	Electroencephalography
EIDORS	Electrical Impedance tomography and Diffuse Optical tomography Reconstruction Software
EIS	Electrical Impedance Spectroscopy
EIT	Electrical Impedance Tomography
EMC	Electro Magnetic Compatibility
EMG	Electromyography
ER	Evoked Response
ERP	Event Related Potentials
ERS	Evoked Resistance Shift
ESU	Electrosurgery
EUT	Equipment Under Test
fEITER	functional Electrical Impedance Tomography of Evoked Responses
fMRI	functional Magnetic Resonance Imaging
FPGA	Field Programmable Gate Array
GDT	Gas Discharge Tubes
HP	Hewlett Packard
ICP	Intra-Cranial Pressure
IPT	Industrial Process Tomography
LHS	Left Hand Side

MCA	Medicines Control Agency
MD	Measuring Device
MDD	Medical Devices Directorate
MEG	Magnetoencephalography
MHRA	Medicines and Healthcare Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Measurement Sites
NC	Normal Condition
NRES	National Research Ethics Service
PK-PK	Peak-to-Peak
PET	Positron Emission Tomography
REG	Rheoencephalography
RHS	Right Hand Side
RMS	Root-Mean-Square
SD	Standard Deviation
SE	Standard Error
SFC	Single Fault Condition
SNR	Signal-to-Noise Ratio
SQUIDS	Superconducting Quantum Interference Device
ST_MARKER	Stimulus Marker

WMA	World Medical Association

Abstract

Within neurophysiology, there is need for improvements to functional brain imaging devices. Neural processing within the brain occurs on milli-second through to second timescales. Currently there are no systems with the sufficient temporal resolution and depth sensitivity. Electrical impedance tomography (EIT) is a technique that offers milli-second imaging, depth sensitivity, portability and low cost. It is already applied routinely in other medical applications such as lung function monitoring and breast imaging. The research presented in this thesis has contributed to the design and development of a 32-electrode EIT system, known as fEITER (functional Electrical Impedance Tomography of Evoked Responses). fEITER has been designed to be a brain imaging device that has a temporal resolution of 100 fps with an overall SNR of greater than 70 dB operating at 10 kHz.

In order to carry out human tests using fEITER, the system required applications to the local and national ethics (NRES) as well as safety standards regulation (MHRA). These processes were successfully completed, receiving a 'notice of no objection' for a clinical trial using fEITER at The University of Manchester and Manchester Royal Infirmary. A series of tank tests were analysed as a method of understanding the system performance. The data obtained from human tests showed unique results. The reference data showed a repeating 'saw tooth' that is time-locked to the heart beat of the volunteer, which is a novel observation in medical EIT. Furthermore, the auditory stimuli data showed topographical differences across the scalp with respect to the startle and controlled auditory stimuli. These observations are based on single-event evoked responses, which is unique within the field of evoked potential studies. From the observations reported in this thesis it is plausible that fEITER is measuring voltages changes that are due to the neural processing.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

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LIST OF PUBLICATIONS AND PRESENTATIONS RELATED TO THIS THESIS

INTERNATIONAL CONFERENCE PAPERS

Davidson J.L., Wright P., Ahsan S.T., Robinson R.L., Pomfrett C.J.D and McCann H (2010) 'fEITER – a new EIT instrument for functional brain imaging,' J. Phys. Conf. Ser. Florida, USA, 224.

Robinson R.L., Davidson J.L., Wright P., Pomfrett C.J.D and McCann H (2009) 'Analysis and Interpretation Composite Electrode-Tissue Impedances,' Proc. 10th Int. Conf. on Biomedical Applications of Electrical Impedance Tomography (Manchester, UK) Available: http://www.maths.manchester.ac.uk/eit2009

Davidson J.L., Wright P., Ahsan S.T., Robinson R., Pomfrett C.J.D and McCann H (2009), 'fEITER – A new biomedical EIT instrument for OR and ICU applications,' Proc. 10th Int. Conf. on Biomedical Applications of Electrical Impedance Tomography (Manchester, UK) Available: http://www.maths.manchester.ac.uk/eit2009

Robinson R.L., Davidson J.L., Wright P., Pomfrett C.J.D. and McCann H (2008) 'A study of composite electrode-tissue impedances,' Proc. of 30th Inter Conf of the IEEE EMBS (Vancouver, Canada) pp:1171-1174

Robinson R.L., C.J.D. Pomfrett and McCann H (2008) 'Composite electrode-tissue impedance for EIT design,' Proc. 9th Int. Conf. on Biomedical Applications of Electrical Impedance Tomography (Dartmouth, USA) Available: http://www.engineering.dartmouth.edu/eit2008

OTHER PRESENTATIONS/POSTERS

Poster: Robinson R.L., Davidson J.L., Wright P., Ashan S.T., Pomfrett C.J.D and McCann H. 'fEITER: functional Electrical Impedance Tomography of Evoked Responses,' First Annual

Showcase of Biomedical Imaging Institute (BII), University of Manchester, held November 2009.

Poster: Robinson R.L., Davidson J.L., Wright P., Pomfrett C.J.D and McCann H. ‘A study of composite electrode-tissue impedance,’ EEE Post-Graduate Research (PGR) poster conference, University of Manchester, held November 2008.

Chapter 1 Introduction

The human brain is a complicated structure that enables an individual to perceive the external world through the senses, such as touch, sight and hearing. The mechanisms of the brain have been of great interest for many years, the earliest understanding coming from direct contact with and manipulation of the cortex. Currently, there are imaging modalities that can image the functioning brain without the need for direct cortical contact (Dendy and Heaton, 1999). Some of these techniques exploit the contrasts in density of the different tissues using x-ray computed tomography (CT), whilst others rely on the magnetic moments of hydrogen atoms using magnetic resonance imaging (MRI). Detailed comparisons of some modalities are discussed in this chapter. However, in terms of spatial resolution, temporal resolution, cost, portability and availability each modality has advantages and disadvantages. More recently an alternative imaging modality, electrical impedance tomography (EIT), has been developed to image different parts of anatomy by measuring the change in conductivity distributions in the tissues.

This thesis will discuss the use of a new EIT brain imaging device which was designed and built at the University of Manchester, known as fEITER (functional Electrical Impedance Tomography of Evoked Responses). Using fEITER the author has explored the possibility of measuring the brain's response to sensory stimuli. The main objective for the research presented in this thesis is to test the feasibility of using EIT as a functional brain imaging device. The author investigates the composite impedances involved in EIT, which should enable a better understanding of fEITER measurements. A primary aim is to develop a series of auditory stimuli that elicit an evoked potential that is measurable by fEITER.

1.1 Human Physiology

Similar to CT and MRI, one of the aims of fEITER is to provide information about the brain without the need for direct cortical contact. When considering non-invasive imaging techniques such as EIT or electroencephalography (EEG) it is important to note that they use surface electrodes.

1.1.1 Skin

To fully understand the medical images produced from EIT it is necessary to understand the underlying physiology. Skin is characterized as having three layers: the epidermis, the dermis and the subcutaneous layer which is also known as the hypodermis (figure 1.1). The most resistive layer is the epidermis (Martini, 2004). Within the epidermis there are many different layers: the stratum corneum, the stratum lucidum, the stratum granulosum, the stratum spinosum and the stratum germinativum.

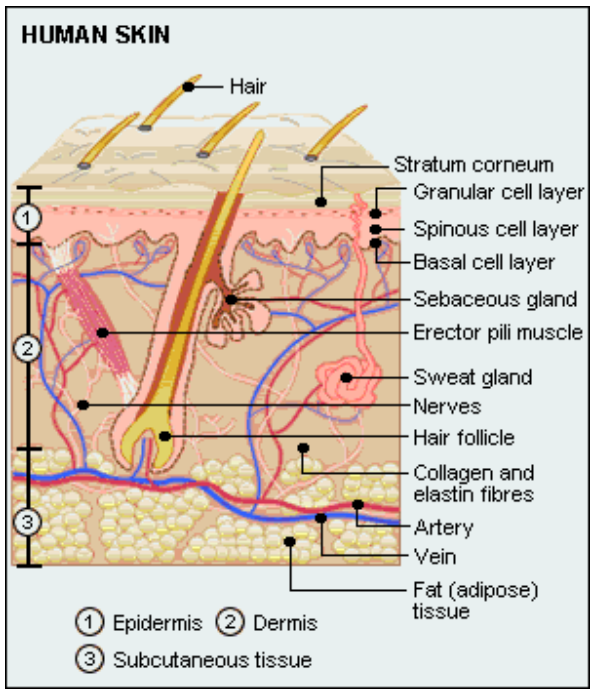


Figure 1.1 A detailed cross-section of the skin structure and the subcutaneous layers (Martini, 2004).

In the stratum germinativum the cells divide and grow outwards causing them to be dispersed upwards into the stratum granulosum. Here the cells begin to die and lose the inner nucleus material, a process known as keratinisation. It takes the cells about 15 to 20 days to move into the stratum corneum, the membrane on the outer surface of the skin. The fact that these cells are dead is important to the electrophysiology of the skin as they have different electrical characteristics to living cells.

Biological tissues consist of cells with an outer wall membrane, that are surrounded by extra-cellular fluid. Contained within the cell is intra-cellular fluid. Due to the cell membrane's high capacitance at dc and low frequency, the current will flow around the cells (Webster, 1998). Conversely at higher frequencies the capacitive membrane effectively disappears allowing current to pass through the cells (Regan, 1989).

1.1.2 Neuron

When considering using EIT for functional brain imaging it is necessary to understand the electrical signals within the brain. The central nervous system (CNS) consists of the brain and the spinal cord. Networks of sensory receptors are distributed around the body transmitting information to the brain via the spinal cord. The information collected by the brain is then organised and interpreted, usually leading to a response signal for the appropriate action to be sent via the CNS (Kandel *et al*, 2000).

The brain achieves this communication by using nerve cells and the connections between them, known as neurons (figure 1.2). The brain is a complicated structure that is made up of a network consisting of 10^{11} (100 billion) neurons. Neurons have the ability to communicate with each other through synaptic connections, where ions

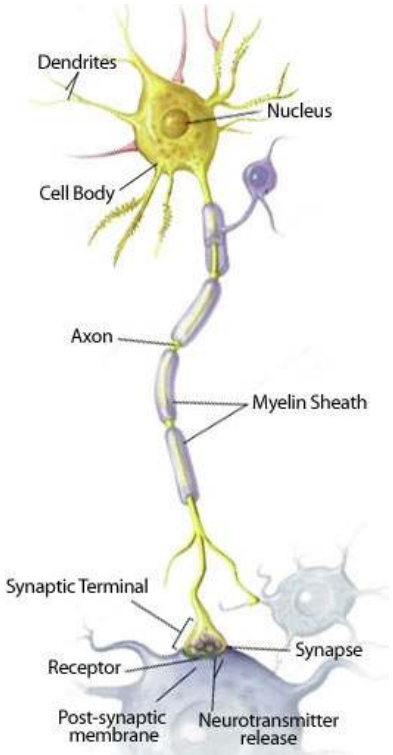


Figure 1.2 A diagrammatic view of the structure of a neuron. (Martini, 2004)

flow in and out of the communicating neurons. Each neuron has approximately 10,000 synaptic connections. Neurons are specialised cells that are used for the generation, integration and conduction of excited states (Regan, 1989). The structure of a neuron consists of four elements; the cell body, the dendrites, the axon and the synapse.

The Cell Body:

Within the cell body there is a large nucleus composed of DNA. Surrounding the nucleus is cytoplasm containing neurofilaments. Neurofilaments are specifically found in neurons. They extend outwards to the dendrites and axon providing support for the long dendrites.

The Dendrites:

Each neuron has a large number of dendrites which branch out from the cell body. These help to increase the surface area of the neurons. The dendrites represent 80-90% of the neuron's total surface area. Information can be passed from one neuron to another at the dendritic spine. This occurs through small structures that appear along the dendrite and can form a 'graded potential' to enable communication. The 'graded potential' has different values depending on the stimulus input. If the stimulus does not continue the potential in the dendrites will become degraded. It is therefore a combination of many potentials that build up to produce a potential sufficiently large to reach the threshold, that can then lead to the triggering of an action potential in the axon, seen in figure 1.3 (the action potential is defined below). Since graded potentials are localised it is possible to consider many neurons reacting to a stimulus, creating bulk graded potential activity. It is these bulk potentials that are detectable using surface electrodes on the scalp, i.e. EEG measurement.

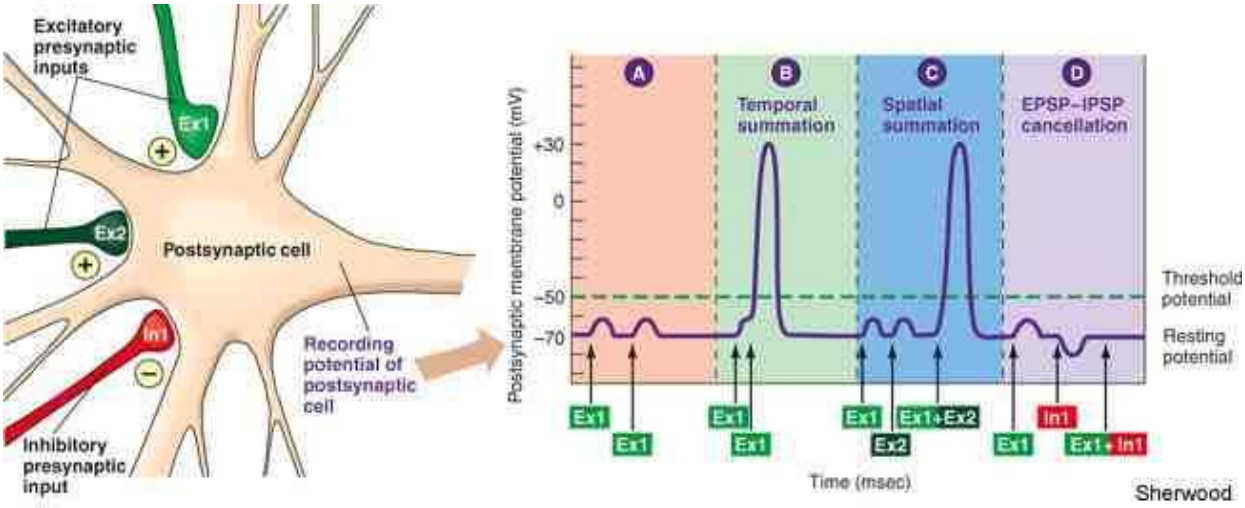


Figure 1.3 The graded potential, showing both the temporal summation of graded potentials and the spatial summation of graded potentials (both summations of graded potentials must reach the threshold at the axon hillock to trigger the action potential). (Martini, 2004).

The Axon:

A neuron can only have one axon. The axon is capable of propagating a short duration electrical impulse known as an action potential (Waxman *et al,* 1995). If the action potential (a comprehensive description is given below) is activated, no other stimuli can cause the depolarisation of the cell. Unlike the dendrites and the cell body, the axon is covered in a myelinated sheath which is electrically insulating. This is important to note when considering EIT on the scalp, as these action potentials will not be detectable by the surface electrodes.

The following description explains the process of the action potential. Figure 1.4 shows a plot of the voltage changes that occur during this cycle, illustrated with the corresponding ion movements.

At rest, when the neuron is not sending a signal, the neuron is at -70mV, known as the resting potential, compared to the extracellular fluids surrounding it (point (a) in figure 1.4).

When the graded potential reach the voltage threshold (usually -55mV) the sodium channels (Na^+) open. (Identified as (b) on figure 1.4). This allows sodium to enter the cell. This stage of the process is known as depolarisation.

This is followed by more sodium channels opening until the cell reaches +30mV (point (d) in figure 1.4).

Following this stage there is the repolarisation, during which time the cell closes the sodium channels and opens up the potassium channels (K^+), enabling the potassium that was in the intracellular fluid, to move outside the cell (point (e) in figure 1.4).

Point (f) on the plot is known as the hyperpolarisation, where there is a slight imbalance of ions, i.e. there are slightly more potassium ions outside the cell compared to sodium ions inside the cell.

Finally there is the refractory period which occurs when the cell membrane changes its properties by forcing sodium ions out of the cell and draws in potassium, restoring the initial set-up (shown at point (g) on figure 1.4).

Throughout this process the cell is resistant to another depolarisation. As shown in figure 1.4 the action potential lasts for a period of approximately 4-6 ms.

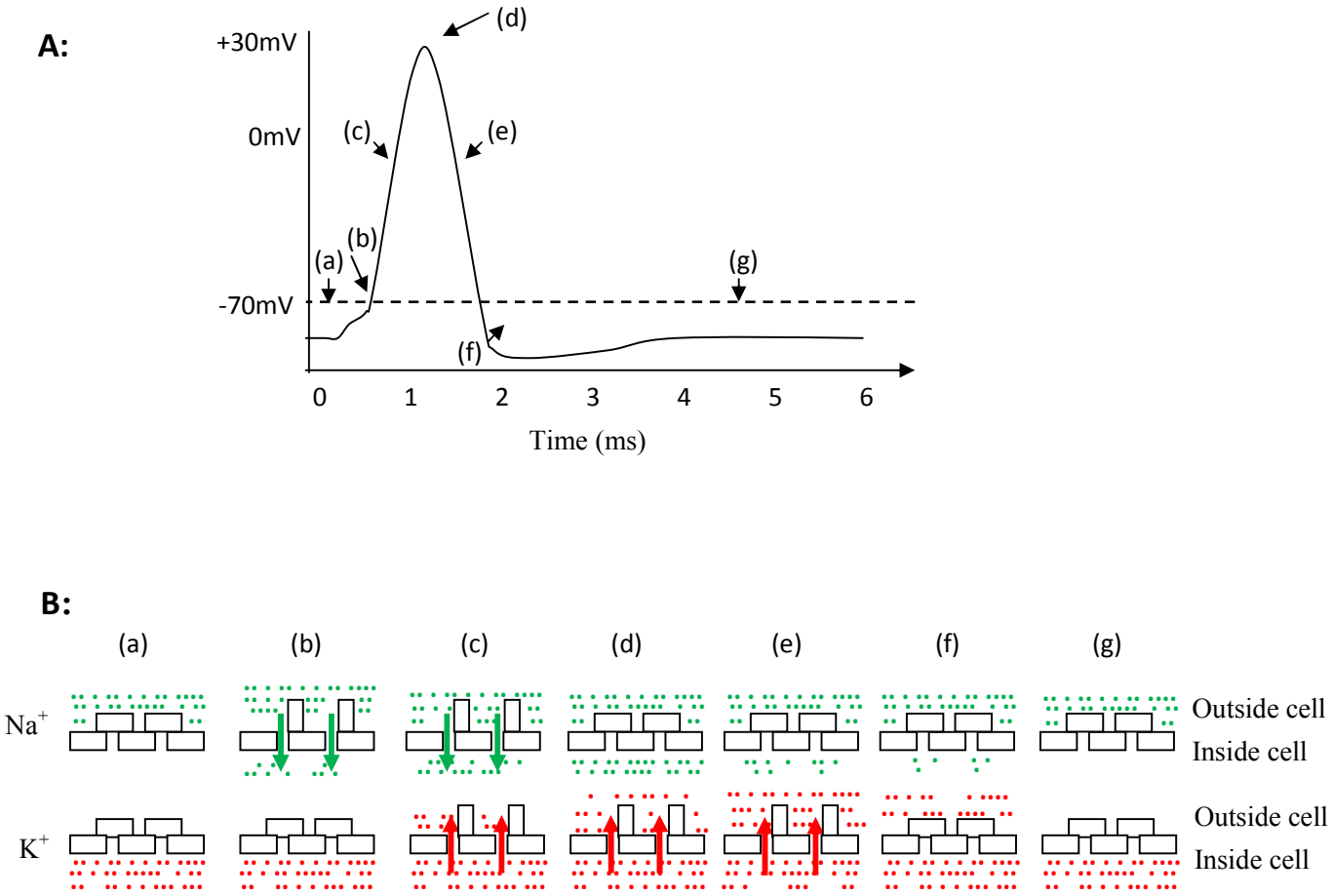


Figure 1.4 A: Graphical representation of the time course of the membrane potential labelled with distributing processes, shown in B. B: Ion movement at particular stages during the action potential.

The Synapse:

The synapse consists of a pre-synaptic cell (a neuron) which has the synaptic terminal that sends the message, and a post-synaptic cell that receives the message. The post-synaptic cell can be a neuron or another type of cell (e.g. myofibrils - muscle cells). The space between them is called the synaptic cleft, as shown in figure 1.5. There are two types of synapses: electrical and chemical.

An electrical synapse provides the fastest type of neuronal signalling. A current generated by the action potential in the pre-synaptic cell flows directly into the post-synaptic neuron via bridging channels. The information is 'passed' from the pre-synaptic cell to the post-synaptic cell quickly, allowing for almost simultaneous responses, presumably developed as a defence against danger (Martini, 2004).

The other type of synapse is chemical. The communication between the cells at the synapse involves the release of chemicals called neurotransmitters by the synaptic terminal (Bennett, 2001). These chemicals affect the activity of the postsynaptic cell. The release is triggered by electrical events, such as the arrival of an action potential.

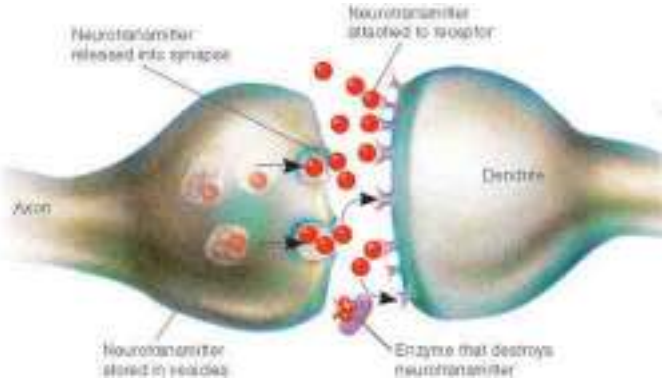


Figure 1.5 Schematic drawing of the chemical synaptic cleft (Losos and Raven, 2007).

If the concentration of a particular ion is greater in the extra-cellular fluid compared to the intra-cellular fluid, the ionic concentration gradient across the cell membrane generates an electrical potential. An equilibrium will be ultimately established (shown at point (g) on figure 1.4), and the cross-membrane potential at this point (-70mV) is known as the Nernst potential (Hille, 1992).

1.1.3 Brain Anatomy

The brain is divided into large paired cerebral hemispheres, as shown in figure 1.6(a). The surface is covered by the neural cortex which is highly folded to increase the surface area. Underneath the neural cortex is the white matter, and three deep-lying structures; the basal

ganglia, the amygdala and the hippocampal formation (Kandel *et al*, 2000). The cortex is composed of four lobes; the frontal lobe, parietal lobe, temporal lobe and the occipital lobe, identified in figure 1.6(b). Each of these can be topographically mapped to show more detailed sensory and motor information processing.

The brain can be categorised into anatomical regions which are correlated to certain functions, some of which are labelled in figure 1.7. In 1909 Korbinian Brodmann published a book called 'Localisation of Function in the Cerebral Cortex' (Brodmann, 1909). This was a revolutionary study that clearly described and illustrated the brain by correlating the anatomy and the function.

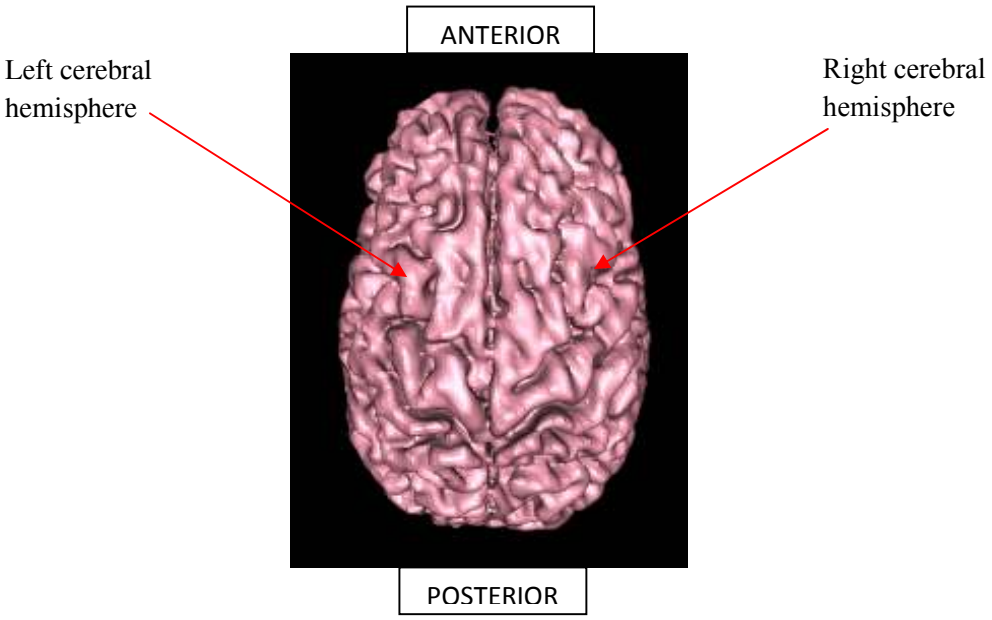


Figure 1.6 (a) Superior view of the brain. Image produced by author using SCIRun. (Parker *et al,* 1998)

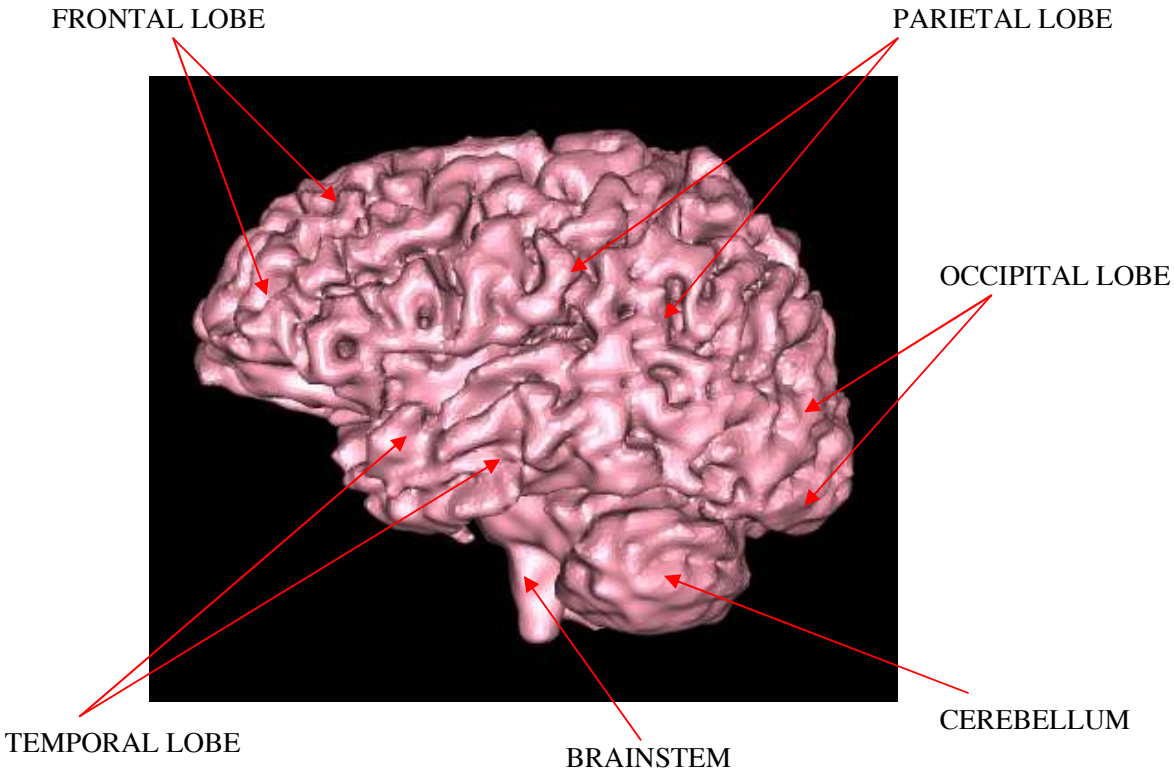


Figure 1.6 (b) A lateral view of the brain. Image produced by author using SCIRun. (Parker *et al,* 1998)

There are six primary sensory regions. This thesis will mainly consider the processing associated with the auditory cortices. The primary and secondary auditory cortices are found in the Brodmann areas 41 and 42 which are located in the temporal lobe (identified in figure 1.7). If sound is presented to the right ear the processing is contralaterally weighted (i.e. it will be predominantly in the left auditory cortex), however a small percentage of the processing occurs in the right temporal lobe (Katz, 2009).

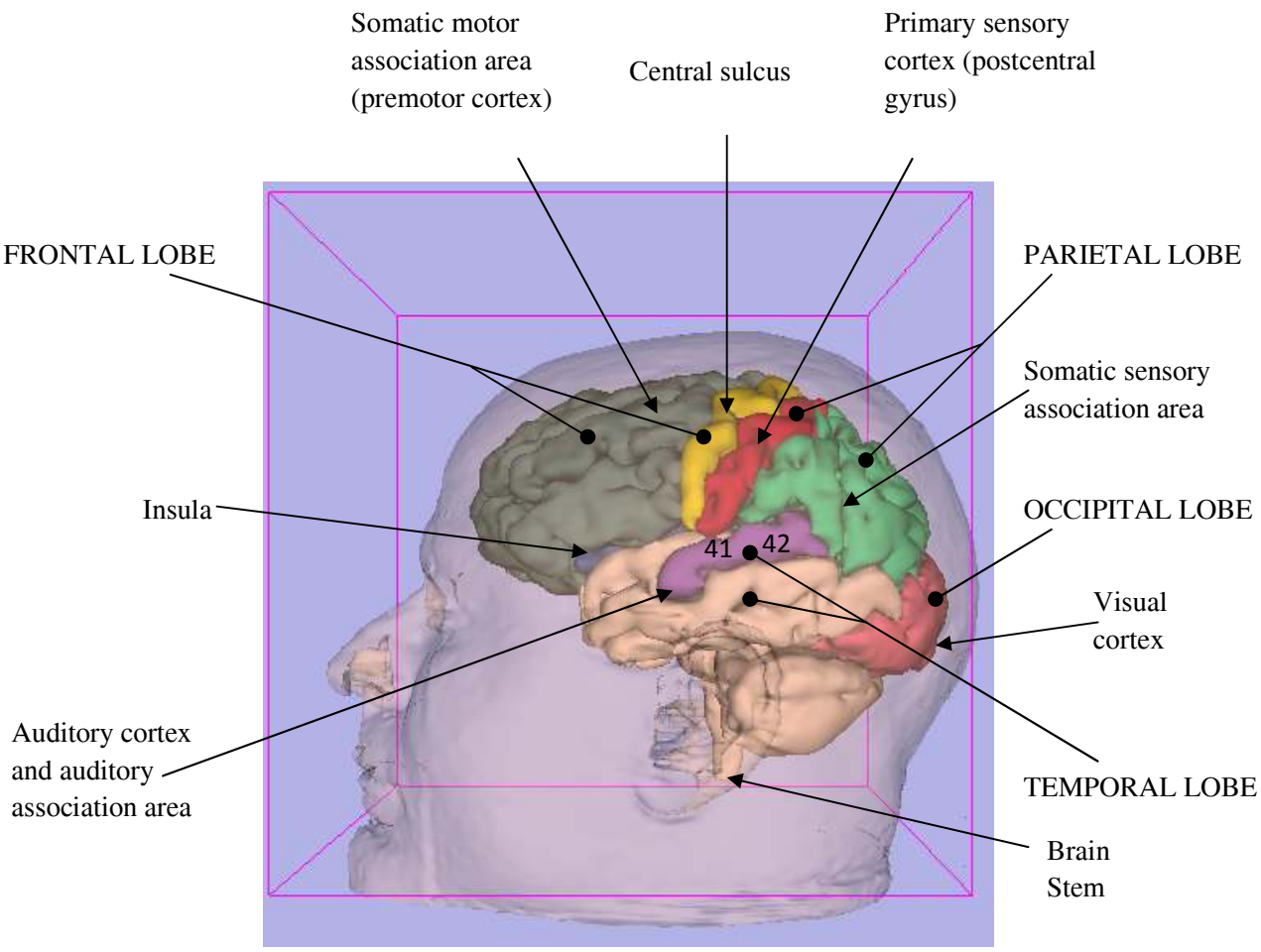


Figure 1.7 A superior view of the left cerebral hemisphere with the major areas landmarked. Image produced by author using 3DSlicer, Version 3.4. (Pieper *et al,* 2004).

When the brain is stimulated, bulk synaptic activity takes place as discussed in section 1.1.2. This requires oxygen which is delivered to the cells via the cerebral blood supply, as shown in figure 1.8. In turn this leads to an increased blood flow to the stimulated region.

Figure 1.8 shows the main blood supply territories to the brain, arising from the arch of the aorta and leading into the left and right common external and internal carotid arteries and the vertebral artery. Typically the cerebral blood flow in a healthy adult is about 750 ml per minute, which equates to 15% of the cardiac output (Khurana, 2006). Each hemisphere is

supplied by the anterior cerebral artery, the middle cerebral artery and the posterior cerebral artery, supplying blood to different areas of the brain.

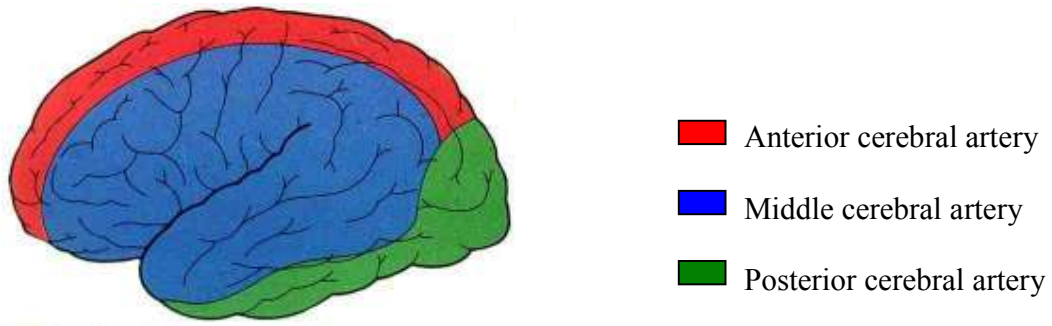


Figure 1.8 (a) A schematic view of the blood supply territories in the cerebral hemispheres.

Sensory neural activity is dependent on stimulus occurring. However, as described above, the voltage changes experienced by a single neuron are very small. This thesis concentrates on the bulk changes associated with external stimuli. In this case it focuses on the changes due to auditory stimulus. It is assumed that there is a constant conductivity of the scalp, skull and cerebral spinal fluid with respect to the measurements made at the electrode positions. Therefore it is assumed that the change in conductivity will be due to the changes occurring within the brain. One hypothesis is that the voltage change due to stimuli could be measured as a change in voltage from a build up of many graded potentials in the areas associated with the stimulus. In other words, using EIT to take voltage measurements of the brain may mean it is sensitive to conductivity changes arising from the 'bulk synaptic activity' in volumes of brain tissue that are spatially resolvable. Another hypothesis is that it is possible to measure changes that are related to the change of blood flow associated with the energy demands of the neuron (i.e. need for oxygenated blood). The increase of blood to a region would result in a local change in conductivity that may be measurable by fEITER. These changes in the brain's electrical properties are expected to occur on both short and long time scales. The times associated with the bulk synaptic activity is expected to be over a period ranging from tens to

hundreds of milliseconds after stimulus. However there will be later and longer periods of electrical change relating to the changes in cerebral blood-flow which accompany the neural activity; these occur a few seconds post-stimulus lasting for periods of 2 to 10 seconds (Holder and Tidswell, 2005), and are termed haemodynamic (or neurovascular by some authors).

Both hypotheses require an understanding of the larger regions of the brain that are associated with certain sensory and motor processing functions.

1.2 Medical Imaging Techniques

There are several established medical imaging techniques, each having advantages and disadvantages. To compare EIT to other modalities it is important to understand these limitations. To create an image of the brain there are two main types of medical images that can be produced; structural and functional (Kandel *et al*, 2000). These can be used to identify different medical conditions depending on their nature. Functional imaging of the brain can give an insight into some neurological disorders by showing the haemodynamic and neural responses to certain conditions or tasks, whereas a structural image would only provide information about the structure of the tissues in the head.

1.2.1 Structural Imaging

X-ray computed tomography (CT) was established in the 1970's (Hounsfield, 1973). It uses similar x-ray technology to that of the original x-ray, using a short burst of ionising radiation which passes through the tissues with different absorption rates. The resistance to x-ray penetration is known as radio-density. The CT scan uses numerous x-ray beams and a large number of electronic detectors, rotating around the subject. Using image reconstruction techniques a 3-D structural image can be reproduced. This can identify many soft tissues including vessel walls, in addition to larger structures such as fat and bones (Garvey and Hanlon, 2002).

The ability to have a good spatial resolution is advantageous for diagnosis and structural understanding; CT has the capability to distinguish tissues which differ in density by less than 1%. This is important when considering imaging the brain, given that the range of tissue

density in the brain is only a few percent. However, it is encased by the comparatively dense skull. Using the traditional radiology techniques, most of the x-ray dosage would be absorbed by the skull (Webster, 1998).

Modern CT scanners are able to scan large parts of the body within a few seconds resulting in a temporal resolution of less than a second (Martini, 2004). However to obtain superior image quality of the brain using CT the subject is required to inhale, or be injected with a contrast medium, usually in the form of xenon. This is absorbed into the bloodstream resulting in higher density of the tissues, which modifies the x-ray absorption characteristics. The disadvantage to this technique is that the patient must inhale a large amount of xenon (35% by weight with air), which has an anaesthetic effect and is expensive. The other disadvantages of CT are that the equipment is large, heavy and very expensive, and it uses ionising radiation meaning that it needs to be kept in a specially designed room away from certain areas within the hospital.

Magnetic resonance imaging (MRI) also resolves structural images, and was invented a decade later in the 1980's (Mansfield, 1973; Lauterbur, 1973). Unlike CT, MRI does not depend on ionising radiation to create an image. A high magnetic field is produced by a large solenoid and part or all of the body can be placed in this field. The body contains billions of hydrogen atoms, the nuclei of all of which have a magnetic moment. However in the presence of the field the magnetic moments of the protons within the hydrogen atoms align parallel to the field. An electromagnetic radio wave pulse is then directed at the protons throughout the body causing them to flip (Martini, 2004). When the wave pulse ends, the protons realign themselves to the magnetic field. Whilst realigning, the protons release an energy that can be detected (Young and Freedman, 2000). The time it takes for the protons to realign depends on the tissue type. Dense tissue takes longer to realign than soft tissue. On an MR image this is observed as dense areas in white and less dense areas in black.

As there are more hydrogen nuclei in water molecules, an MRI image effectively shows the differences in water content between various body tissues. As a result, it is suitable to detect disorders that have an increased fluid in the diseased areas of the body. An example is an area affected by a tumour.

An advantage of MRI compared to CT is its ability to image any plane. MRI can create images with a spatial resolution of approximately 1mm and temporal resolution of 100ms (Strangman *et al*, 2002). The disadvantages to MRI systems are that they are large and expensive. Due to their weight and the large electromagnetic field they have to be located in a shielded room on a reinforced floor. MRI systems are also very noisy; without any efforts to dampen the noise it could reach levels of 130dB.

1.2.2 Functional Imaging

Functional brain imaging can be utilised to produce images of the activity within the tissues, such as blood flow, oxygen use, and glucose metabolism. These can inform clinicians about the physiology, functional structure and dynamics of the interactions within the brain.

1.2.2.1 Positron Emission Tomography

Positron emission tomography (PET) is an example of nuclear medicine. It uses a radioactive material, known as a radio-labelled tracer, which is injected into the subject's bloodstream, swallowed or inhaled as a gas. Commonly used isotopes are carbon-11, nitrogen-13 and fluorine-18 (Kandel *et al*, 2000). The radiotracer gathers in the organ or area of the subject's body which has the most chemical activity. The positrons travel 2-3 mm in the tissue, then annihilate with electrons to form pairs of photons that are emitted at 180° to each other (Bailey, 2005).

Table 1.1 Characteristics of the most commonly used isotopes in PET

Isotope	Maximal Kinetic Energy	Half-life	Broadening
^{13}N	1.2 MeV	10 min	3.0 mm
^{11}C	960 keV	20.4 min	1.9 mm
^{18}F	640 keV	110 min	1.1 mm

A PET scanner uses paired gamma cameras to detect the photons (figure 1.8). The resolution is approximately constant across the imaging field and can achieve a spatial resolution of 4-5mm

in whole body scanners, and 2mm in head scanners with a temporal resolution of approximately a few seconds (Strangman *et al*, 2002). The regional distribution of the tracer in the brain can be followed for periods of minutes to hours after administration of the isotope, as shown in table 1.1. This is one of the reasons that ^{18}F is a popular choice, as its half-life is up to 110 minutes, meaning that multiple scans can be produced with one isotope (Haier *et al*, 1997). One advantage of PET is that the data obtained can be integrated with a CT scan. Therefore clinicians have information on both the structural and the chemical activity within certain regions of the brain (Alkire, 2008). The obvious disadvantage of this type of functional imaging is the need for administering ionising radiation which can equate to a year's permitted exposure with one dose.

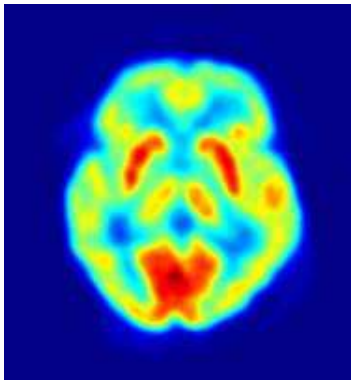


Figure 1.8 An example PET image of the brain (Langner, 2003)

1.2.2.2 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a specific form of MRI that is able to image the haemodynamic changes in the brain (Webster, 1998). The changes in blood flow and blood oxygenation in the brain are closely linked to the neural activity (Roy and Sherrington, 1980); when the nerve cells activate an action potential they increase the consumption of oxygen. BOLD-fMRI (Blood-Oxygen-Level-Dependant fMRI) is the most commonly used fMRI technique and relies on the fact that the oxygenated blood (oxyhaemoglobin) is diamagnetic

compared to the surrounding tissue, and deoxygenated blood (deoxyhaemoglobin) is paramagnetic with respect to the surrounding tissues.

At rest the brain has a normal blood flow consisting of both oxyhaemoglobin and deoxyhaemoglobin. As shown in figure 1.9, there is an initial decrease in the oxyhaemoglobin immediately after neural activity, which is followed by a period of increased blood flow overcompensating for the increased demand required by the neuron. This means that the oxyhaemoglobin increases after neural activity, peaking around 6 seconds after the activity, and then it falls back to baseline.

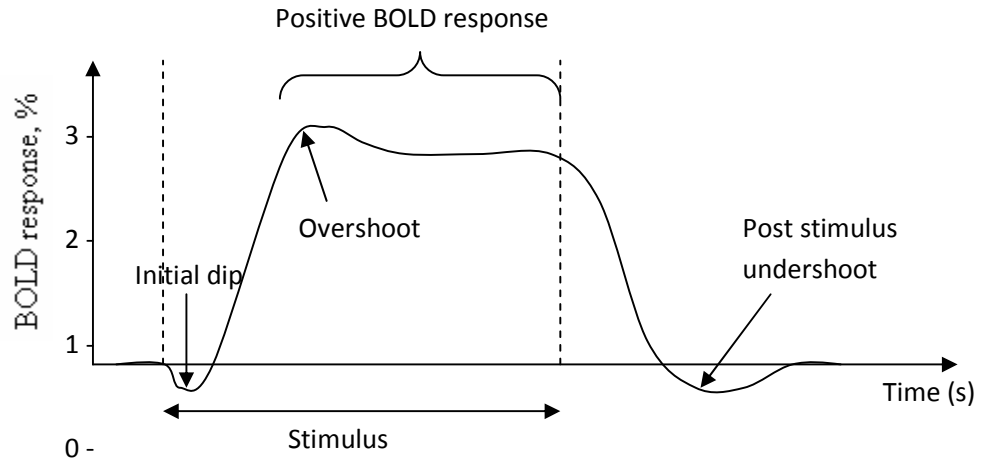


Figure 1.9 BOLD time course during stimulation

Using a 7 Telsa fMRI system the activity can be mapped down to a spatial resolution of 0.5 mm (Li *et al,* 2006). However the temporal resolution is limited by the slow blood flow response, typically a few seconds. Using fMRI it is possible to produce images with a depth sensitivity of up to 2 to 3 cm (Logothetis, 2008).

1.2.2.3 Magnetoencephalography

Magnetoencephalography (MEG) measures the small magnetic fields that are produced by neurons. As previously discussed, neurons communicate information by action potentials that

transmit down the axon to the synaptic cleft where the information is passed to another neuron in the form of graded potentials. MEG works on the principle that many action potentials are active at the same time, acting as a current dipole. This creates a magnetic field (~50μT) which can be detected by sensitive detectors known as SQUIDS (Superconducting QUantum Interference Devices). Commonly used systems have multiple channels, such as the Omega-275 that has 275 SQUIDS across the scalp (CTF Systems, Canada).

One of the main advantages of MEG is its ability to regard the brain and its overlying tissues as a single medium of a constant magnetic permeability (Webster, 1998). This means that it is not influenced by the other tissues, such as the skull or muscle. MEG does not have artefacts due to the scalp contact impedances that are a source of error in other modalities such as electroencephalography (EEG), because the magnetic fields are able to be detected in free space and so the SQUIDS are usually located a few cm away from the scalp surface. MEG has a temporal resolution of less than 1 ms and a spatial resolution of approximately 3 mm (Stufflebeam *et al*, 2009). A disadvantage of MEG is the depth sensitivity. It is reported to detect changes within 1-2 cm of the cortex. MEG also needs a large specialised room and equipment, since the tests need to take place in a magnetic shielded room as the magnetic fields are so small that it is important to ensure there are no outside interferences.

1.2.2.4 Electroencephalography

Electroencephalography (EEG) with evoked potentials describes the measurements of scalp potentials taken to observe signals due to the brain's function as a response to an applied stimulus (Webster, 1998). Measurements are usually in the range of 0.5-100μV at frequencies up to 100 Hz. Voltage potential differences are measured between electrodes placed on the scalp, and as the brain responds to a known stimulus, such as a flash of light in the eye, the electrical activity within the functioning region changes the measured scalp voltage.

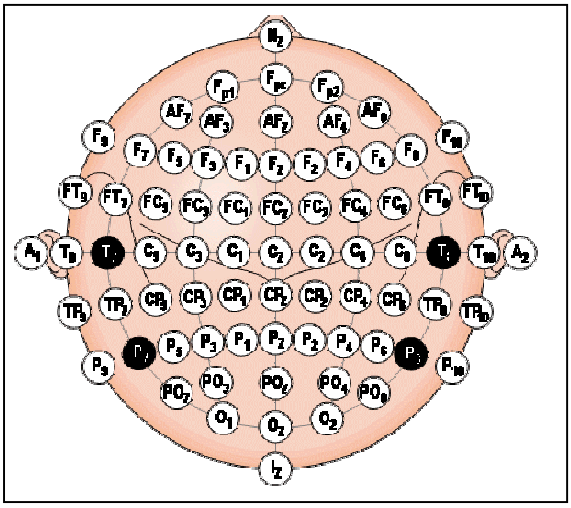


Figure 1.10 The 10-20 system of electrode positions on the scalp.

The electrodes can be placed at any location on the scalp. However a number of standardised configurations have been developed. A commonly used electrode configuration in EEG is the 10-20 system (Regan, 1989), seen in figure 1.10.

To obtain information about the localisation of electrical responses to certain stimuli the raw EEG data must be analysed by sophisticated techniques. Using digital filtering and averaging techniques, over many repeated stimuli, it is possible to filter the signals down to a single event-locked response.

The average signal over many (N) stimuli is:

$$\omega(t) = \frac{1}{N}\sum_{i=1}^{N}\omega_i(t) \tag{1.1}$$

where $\omega(t)$ is the averaged signal, and

$\omega_i(t)$ is the individual signal responses to one stimulus

Unfiltered signals are also recorded and can instantly distinguish between certain states of functionality. For example an awake, alert person has a different EEG signal compared to a sleeping person. Signals are categorised into four wave groups alpha, beta, theta and delta. An

EEG can be carried out to determine the influence of some disorders that can alter the normal functionality of the brain. The main advantage of EEG over fMRI and PET is its speed; at best it can be less than 1 ms. However it has a poor spatial resolution, at best 1-2 cm (Cooper et al, 1980). EEG usually requires repeated stimuli so the signals can be averaged. The depth sensitivity of EEG is up to 4-5 cm within the cortex, which is not ideal as most of the early neural processing happens in the brain stem (Lin *et al*, 2006).

1.2.2.5 Review of modalities

In summary, none of the above techniques can offer the combination of deep brain sensitivity, sub-second temporal resolution, portability and cost effectiveness. Such a combination would be highly desirable. Deep-brain sensitivity would provide the ability to probe some of the key areas in brain processing such as the brain stem. Having sub-second temporal resolution is necessary to study the human brain's bulk synaptic activity for an individual stimulus on short term scales. However, it is also important to obtain data over longer periods to understand the haemodynamic effects associated with stimulus. Therefore a device that could offer both time scales would be beneficial. A portable system would provide the benefit of having functional brain imaging available in intensive care units and operating theatres.

Table 1.2 Summary of the modalities in section 1.2.2

	Temporal Resolution	Spatial Resolution	Depth Sensitivity
fMRI	100 ms to a few seconds	Few mm to 0.5 mm	≈ 2-3 cm[1]
PET	Over seconds	Few mm to 2 mm	N/A
MEG	1 ms to 100 ms	Few cm to 3 mm	≈ 1-2 cm[2]
EEG	1-2 ms to 100 ms	Few cm to 1-2 cm	≈ 4-5 cm[2]

[1] (Sase *et al*, 2001); [2] (Lin *et al*, 2006).

1.2.2.6 Impedance Imaging

EIT is a non-invasive technique that measures the distribution of conductivity within the area of interest (Metherall *et al*, 1996). EIT is already applied routinely in both medical research (Brown *et al*, 1985) and industrial (York, 2001) imaging with sub-second temporal resolution. These impedance measurements are usually designed to interrogate as much of the volume as possible, giving a depth sensitivity of 5-6 cm (Brown, 2003) with a spatial resolution of 7-8 mm based on 546 independent measurements (Wilkinson *et al*, 2006). The use of EIT to measure brain functionality associated with evoked potentials is explored in this thesis as it meets most of the criteria explained in 1.2.2.5; the main description of EIT methods and applications is provided in chapter 2.

1.3 Thesis Outline

Substantial work to develop a new portable EIT brain imaging device has taken place at The University of Manchester (McCann *et* al, 2006; Davidson *et al*, 2010). Thus the motivation of the research presented here is to use the new fEITER system on human volunteers whilst performing evoked potential studies to aid the understanding of the functioning brain. The author carried out an in-depth study of the use of different electrodes, as part of the design and optimisation of fEITER. This thesis analyses data collected using the new fEITER system, and details the safety requirements for this new medical device as well as the local ethics and national safety procedures that had to be in place prior to the trial.

A detailed description of existing EIT systems and the intended medical applications is discussed in chapter 2, along with a detailed look at previous studies that have attempted to understand the complicated electrode contact region as this would influence several design parameters in a new EIT system. The study to understand this contact/skin impedance required the development of safety circuitry to attach a non-medical device to volunteers. Local ethical approval was sought to ensure that the experimental procedures and information provided to the volunteers was ethically sound, as discussed in chapter 3. Once the fEITER hardware and controlling firmware was completed (more details can be found in (Ahsan, 2010) there was need for safety and ethical approval from the Medicines Healthcare Regulatory Agency

(MHRA). The detailed description of this procedure is found in chapter 3, including the rigorous safety tests that had to be performed.

The details of the study on the 'composite' impedance i.e. the impedances associated with a two-electrode-and-tissue system, is described in chapter 4. This chapter describes the changing impedance of three different commercial electrodes over a frequency range, 1-100 kHz and explores some of the factors that may change this impedance, such as incorrect electrode positioning, preparation techniques, length of time electrodes are in place as well as comparing different sites.

Whilst waiting for a notice of no objection from the MHRA the author requested local ethical approval to use the fEITER system on the principal investigators. This enabled reference data to be collected at The University of Manchester; the analyses of these reference tests can be seen in chapter 5. MHRA notice of no objection was granted in July 2009. Chapter 6 explains some of the tests that were undertaken using the fEITER system. Auditory evoked studies were performed in order to identify localised auditory cortex impedance changes. This study was carried out on several volunteers at the University of Manchester and the Manchester Royal Infirmary.

Finally the conclusions of the research presented are discussed in chapter 7 as well as some short- and long-term future work using fEITER. Since this device is in its infancy there are many potential future research projects that can be explored.

Chapter 2 Electrical Impedance Tomography

2.1 Description of EIT

As briefly explained in section 1.2.2.4, EIT is a method of non-invasively imaging the distribution of conductivity within an area of interest. An array of electrodes are positioned around the body, the number of which can vary but usually ranges from 16 to 64 electrodes that can be in a single or multi-planes. In EIT systems that use a single current source for serial injections, separate pairs of electrodes are used for the current injection and voltage measurement, known as tetrapolar measurements. The general set-up of EIT can be seen in figure 2.1.

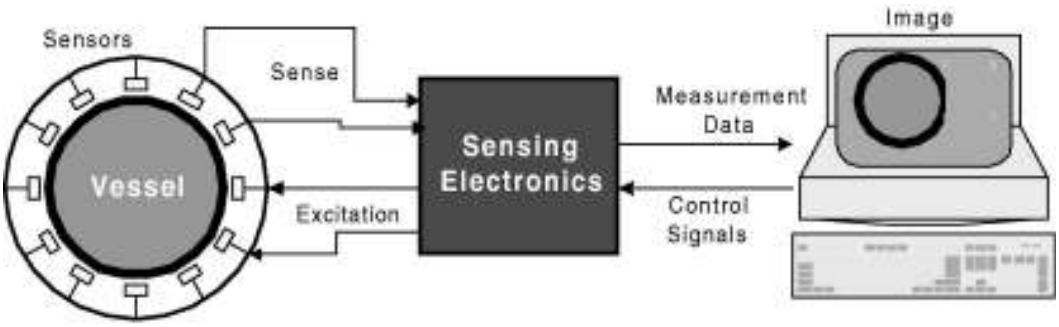


Figure 2.1 General EIT system set-up using an adjacent strategy (York, 2001).

The measurement strategy of the current injection electrodes, known as the current patterns (CPs) (shown in figure 2.2), can influence the quality of the measurements. As a result it is important that the current and voltage measurement electrode configuration is such that it is a 3D multi-plane configuration (Stephenson *et al*, 2008). Choosing an opposite (polar) electrode CP strategy, as opposed to an adjacent electrode CP strategy, improves the spatial resolution

and depth sensitivity (Polydorides and McCann, 2002; Davidson *et al*, 2004). Once voltage measurements are obtained, it is possible to use forward modelling algorithms and advanced data inversion techniques, referred to as 'image reconstruction', to yield images of the conductivity distribution (Polydorides and Lionheart, 2002; Bayford, 2006). Electrical Impedance tomography and Diffuse Optical tomography Reconstruction Software (EIDORS) is a MATLAB based software toolbox and is regarded as one of the best techniques to obtain images (Lionheart *et al*, 2005; Adler and Lionheart, 2006). It was first developed as a 2D reconstruction (Vauhkonen *et al,* 2000) before it was enhanced to produce 3D images (Polydorides and Lionheart, 2002). By having a standardised method of producing images, data produced at different institutes can be directly compared. A new form of standardisation for lung EIT is being developed, called GREIT (Adler *et al*, 2009).

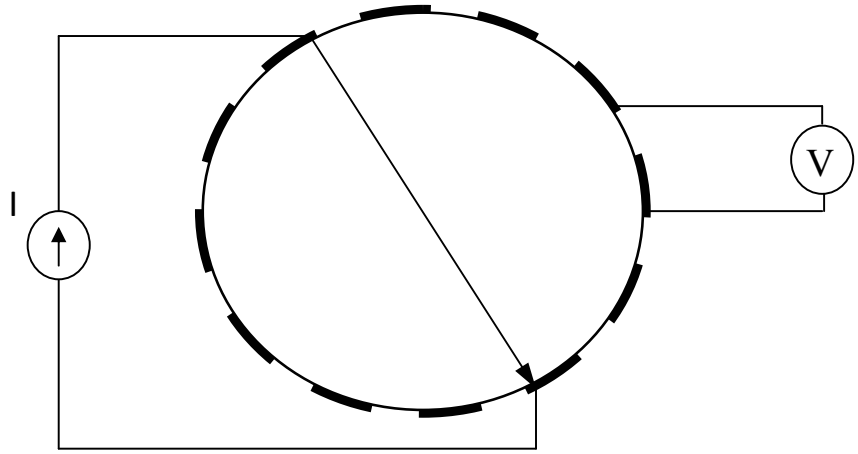


Figure 2.2 Schematic of the opposite strategy current injection on a vessel.

The EIT technique is limited by the fact that current spreads out over the whole subject volume and voltage measurements can be affected by a change of conductivity anywhere in the volume. Therefore EIT is known as a 'soft-field' tomography. Typically, EIT has poorer spatial resolution than PET or fMRI, but a better temporal resolution in comparison. However

the spatial resolution of EIT is variable as it is highly dependent on the current injection patterns and the number of independent voltage measurements made, as well as the SNR of the EIT system (Polydorides and McCann, 2002). EIT has other advantages over existing modalities such as cost and portability, e.g. it is feasible that EIT could be used in GP surgeries or in intensive care units/operating theatres in hospitals in the future.

There are two main areas of application of EIT; industrial process tomography (IPT) and medical tomography. An example of IPT is the imaging of oil, gas and water in pipelines; more details of other areas in IPT are available in (York, 2005). Some key areas of research in medical EIT are discussed in this chapter, and is the main subject of this thesis.

2.2 Some Medical Applications of EIT

2.2.1 Lung Function

As early as 1984 when the Sheffield group developed the first EIT system. Lung function monitoring was seen as an area in which EIT would be able to provide useful information for clinicians. The lungs have large volumes of high resistivity tissues meaning that a change in fluid would result in a large change in impedance within that region. Placing 16 electrodes around the thorax, the early data showed that it was possible to image the lungs, suggesting that it would be possible to image a pulmonary embolism as it would be able to detect changes of fluid volume less than 10 ml (Barber *et al*, 1985).

Since then several groups have explored the possibility of imaging the lungs using the Sheffield system. Several research groups have collected encouraging data on animals using this system (Smulders *et al*, 1993; Hahn *et al*, 1995; Brown *et al*, 1996; Frerichs, 2007). Other examples of lung function monitoring have been published using alternative systems such as the Montreal EIT system (Guardo *et* al, 1991) which produced images of mechanically ventilated dogs (Adler *et al*, 1998) and the Rensselaer system ACT3 (Cook *et al*, 1994) which produced images of mechanically ventilated dogs comparing the lung conductivity over 3-6 hours between healthy lungs and lungs with acute pulmonary edema (Newell *et al*, 1996). Although not conclusive, all of the above the work suggests that it is possible to image large changes in impedances due to perfusion changes.

Other research groups have concentrated on imaging healthy volunteers and comparing the data to patients with diagnosed lung conditions (Holder and Temple, 1993) concluding that only the largest pulmonary ischemia could be detected. One main reason for the reduced spatial resolution is due to motion artefacts caused by respiration, creating problems for image reconstruction. However, a promising technique to remove this error is time-difference EIT of the lungs. Some of these previous studies have been summarised by Frerichs (2000) and Smit *et al* (2005).

Since EIT has a good temporal resolution but a poor spatial resolution, some groups are combining EIT with other modalities with high spatial resolution, such as cone-beam CT (CBCT) (Pengpan *et al*, 2010). This research group applied the method to the thorax where the information of the moving lungs obtained by EIT is fed into the CBCT system to compensate for the motion. Preliminary studies on tanks suggest that the blurring artefacts around a tumour can be reduced by combining these modalities.

The method of combining EIT with other modalities could be a promising research area which would provide more spatial information about the area of interest whilst maintaining a high temporal resolution. Having both of these qualities would prove beneficial for diagnosis and treatment.

2.2.2 Intra-Abdominal Bleeding

Similar techniques to lung function monitoring have been applied to explore the possibility of imaging large changes in the thorax due to internal bleeding. An example of this type of research is being carried out at the University of Florida, USA (Sadleir et al, 2008). This research group uses EIT to monitor patients that have suspected intra-abdominal bleeding. The main objective is to use a limited number of electrodes to produce images of the thorax, so that the patient can remain stationary while the tests are carried out, which is ideal for potential spinal injury patients where it would prove difficult to attach electrodes surrounding the thorax. Their purpose-designed EPack system (Tang *et al*, 2006), uses an injection current of 2 mA at 62.5 kHz. Using a tank of similar dimensions to the average thorax a saline solution of 25 to 200 ml was introduced. Measurements were taken using an 8-electrode hemiarray before and after the introduction of blood-like substitute. Sadleir *et al* concluded that although there

was uncertainty due to the limited number of electrodes it was thought possible to monitor the intraperitonel bleeding. This research is still ongoing.

2.2.3 Gastrointestinal Function

Gastroparesis is a condition whereby the stomach is failing to contract sufficiently to move food out into the small intestine, which is usually due to a damaged vagus nerve. This condition is most common in those that have diabetes and can lead to other medical complications. Currently diagnosis is confirmed by an upper endoscopy or by gamma scintigraphy. The upper endoscopy is unpleasant for the patients and can result in inflammation of the throat. Gamma scintigraphy is a method of highlighting the stomach and the contents by using a radioisotope that emits gamma rays. However the results are not always conclusive. EIT may be an alternative to aid diagnosis for this condition as well as other conditions such as pyloric stenosis in infants (Holder, 1993).

Some of the earliest experiments using EIT to measure gastric emptying were carried out by Avill *et al* (1987). Initially using an abdominal shaped tank, using a balloon containing 5ml saline solution which was introduced into the tank, the data was collected. The results were encouraging and so the study progressed to human volunteers. Each volunteer had balloons inserted into the stomach, lying at the gastro-oesophageal junction. The balloon was filled in steps of 50 ml with air, and measurements were taken at each step. The images showed a good agreement with the expected results (Holder, 1993).

Later studies compared EIT to gamma scintigraphy as a method to confirm the accuracy of the EIT measurements (Wright, 1993; Chang *et al*, 2001). Chang *et al* developed a new EIT system to record the gastric emptying of 20 volunteers with 12 electrodes positioned around the abdomen. The injection current was 4.7 mA at 100 kHz. Volunteers were given a highly conductive test meal and EIT was compared to the scintigraphy results (over 9 minutes of data capture, which included a 1 minute EIT and 8 minutes of scintigraphy). The results were encouraging, with 83.3% agreement between the two measurements. The authors suggested that the difference in the data may be due to the measurement positions, i.e. EIT data collected whilst volunteers were sitting and scintigraphy data collected whilst volunteers were lying down. This research is ongoing.

2.2.4 Breast and Testicular Tumours

Early detection of breast cancer may increase the survival rate amongst patients. Therefore a cheap, portable and accurate detection system would be advantageous for early diagnosis. EIT may offer an alternative to the traditional x-ray mammography, which produces a high rate of false-positive results; up to 22% have been recorded on women in the USA annually screened between the ages of 40-69 (Mandelblatt *et al*, 2009). The x-ray mammography is reported to be uncomfortable, even painful for some patients as the breast has to be compressed to produce clearer images. There is also concern about the effect of repeated exposure to x-rays, which ionise tissues. EIT electrodes could be positioned comfortably around the breast as the patient stands, sits or lies down, and without any radiation hazard.

Several institutes have developed EIT systems to investigate abnormal breast tissue, an example of which was developed at De Montfort University (Wang *et al*, 1998). This is a broadband multi-frequency (1 kHz to 5 MHz) electrical impedance mammography (EIM) system. It uses a maximum of 32 electrodes. The system has been designed to be flexible, using DSP and FPGA technologies it is possible to programme the device in situ. The current amplitude and frequency settings can be changed, enabling the device to interrogate the tissues. The system has a SNR of 40 dB. The system has been tested on a range of phantoms leading to the development and design of new phantom that has multiple layers of different conductivities (Qiao *et al*, 2007).

Another multi-frequency EIT system has been designed and built by engineers at Dartmouth College, Hanover USA (Halter *et al*, 2008). Work was successfully fulfilled to assess the potential of using EIT for breast cancer screening (Halter *et al*, 2004). The system produces broadband signal frequencies up to 10 MHz. Typical results using this system with a phantom made of gelatine that had a conductivity of 2.16 S/m with a 'tumour' positioned in the upper section of the phantom breast of a higher conductivity 5.21 S/m, showed that there was a significant inclusion-to-background ratio thus suggesting electrical impedance spectroscopy (EIS) as a possible method to image breast tumours at these higher frequencies (Halter *et al*, 2005). A trial using a 64 electrode system (made of four rings of 16) was positioned in a customised table, allowing the patient to lie on top of the array of sensors. This procedure was

much more comfortable than the x-ray mammograph. This system has been trialled on 8 patients with known tumours that are having chemotherapy treatment (Hartov *et al*, 2007). The authors reported that the study showed the EIS had good agreement with the pathology assessment in 4 out of 5 cases (80%), meaning that it could have a prospect in clinical use.

A similar area that is currently being investigated is the use of EIS without imaging, which is being used to detect differences in benign and malignant prostate tissues (Halter *et al*, 2008a). The results on freshly excised prostates from 14 men showed significant differences in the conductivity between cancerous and normal connective tissues at frequencies 1 kHz to 1 MHz ($p < 0.01$). This research is ongoing, with the objective of developing a diagnostic tool.

2.3 EIT of the Brain

As discussed in 1.1.2, the functional activity in the brain can be considered on two different timescales. The timescale that is commonly used to inform diagnosis and aid treatment using the previously described functional imaging devices (fMRI, PET etc) is over a few seconds, measuring the haemodynamic effect which typically occurs 5 seconds after a stimulus. However, the faster synaptic responses are measured using other modalities such as EEG and MEG, which typically range from few milliseconds to hundreds of milliseconds.

The theory of using electrical techniques to measure both synaptic and haemodynamic responses has been investigated by several research groups. Experiments involving direct cortical impedance measurements on anaesthetised and unanaesthetised cats that were subjected to auditory and visual stimulus, were reported by researchers at Yale University (Klivington and Galambos, 1967; Klivington and Galambos, 1968; Galambos and Velluti, 1968; Velluti *et al*, 1968; Velluti and Galambos, 1970; Klivington, 1975). These publications report that an evoked resistance shift (ERS) could be measured in conjunction with evoked potentials. When the intensity of the auditory/visual stimuli was varied, the observed ERS appeared to be varying with the evoked potential, showing a decrease of 0.003% in the cortex (Klivington and Galambos, 1967) and a change of 0.03% in the subcortical nuclei (Galambos and Velluti, 1968). However, when they changed other parameters such as brain temperature and depth of anaesthetic there was no correlation between the ERS and the evoked potential. The later stages of the work concluded that the ERS could be attributed to the synaptic

electrical properties (Klivington, 1975). Later work by another research group showed that fast signals could be recorded, using cortical electrodes, over a few tens of milliseconds (Jancke *et al,* 2004). It is these works that form the basis for the hypothesis that EIT could measure bulk synaptic activity from electrodes on the scalp. Certain modalities assume that there is a link between the two timescales, cause and effect. However recent literature has questioned this assumption. Logothetis (2008) comments that the experimental findings in some circumstances are that BOLD fMRI displays haemodynamic reponses but EEG shows no bulk synaptic activity spikes are recorded. This thesis will discuss the measurements obtained using a system (described in section 2.2.1.3) that is capable of collecting sub-second data over a 1-minute period, allowing for both haemodynamic and bulk synaptic analysis.

The first proposal for EIT images of the fast changes in the brain was in 1987 (Holder, 1987). The Sheffield MK1 system was used by the researchers at UCL to monitor brain activity on animals using an adjacent CP strategy with 16 electrodes in direct contact with the cortex. The anaesthetised animals were imaged at a frame rate of 10 images per second using an injection current of 5 mA (pk-pk) at 5 kHz. An ischaemic stroke was induced and the results suggested it was possible to detect an increase in resistance (Holder, 1992).

Since then several groups have developed new EIT systems or modified existing systems to analyse impedance changes on various sites. Reviews of some of these systems can be found in recent papers, such as 'Bioimpedance Tomography (Electrical Impedance Tomography)' (Bayford, 2006) and in PhD theses such as 'Low noise measurement techniques for brain function imaging by electrical impedance tomography' (Rafiei-Naeini, 2008).

Recently, extensive research using EIT for brain imaging application has been carried out in several centres (Holder 2005; Tidswell *et al,* 2001; Bonmassar and Iwaki, 2004; Murrieta-Lee *et al,* 2004). Most notable for functional brain imaging, is the work of the UCL group where animals and human volunteers (including children) have been studied (Holder, 2005). For one study, measurements were made using a modified HP 4284A impedance analyser with a current applied to two diametrically opposed electrodes with the current set between 1 and 2.5 mA at 50 kHz. The remaining electrodes positioned on the head in a modified set-up based on the EEG 10-20 configuration were used to make adjacent voltage pair measurements.

Impedance changes were recorded from 39 human volunteers who were carrying out visual, motor, and somatosensory tasks. Measurements were taken over 6 minutes 15 seconds with a frame rate of 1 every 25 seconds, i.e. 0.04 fps. The visual stimulation was a checkerboard alternating at 8 Hz on a black and white monitor positioned 70 cm from the volunteers. Analysis of the visual stimulus data showed an average change in the conductivity of 0.05% from the baseline impedance, which lasted 6 to 41 seconds post-stimulus in 13 healthy volunteers tested. However, these changes were only seen on a subsection of the electrode combinations, 3% of the total number of measurements (Tidswell *et al,* 2001). Moreover, 18/51 of the data sets that showed the significant impedance changes were not in the expected region. The authors speculated that this may be due to an inaccurate forward model (based on a homogenous sphere) or errors in electrode positioning.

More recently, measurements using EIT and EEG whilst volunteers are exposed to visual evoked stimulus have been carried out (Gilad and Holder, 2009). The use of full-field pattern-reversal black and white checkerboard, reversing at a rate of 4 per second was presented to 7 subjects; totalling 20 individual measurement sets. As expected a distinct EEG visual evoked potential (VEP) is seen peaking at 100ms and 200ms post stimuli. Seven EIT measurements showed a significant resistance decrease, $1.3 \pm 0.3\mu V$, peaking at the appropriate time course of 141 ± 34 ms post stimulus. Further analysis of the data excluded volunteers with strong EEG alpha signals leading to 16 of the data sets having a significant boundary voltage decrease of $0.001 \pm 0.0005\%$ peaking at the same time as the EEG response (Gilad and Holder, 2009). This direct comparison of evoked responses measured by EEG and EIT shows that there is a time correlated link between the measurements, although the percentage change in voltage is lower than the realistic model suggests.

One of the main issues that arise from EIT of the brain is the need to pass current through the skull. The skull has a significantly lower conductivity than the brain (Oostendorp *et al,* 2000; Hoekema *et al,* 2003), meaning that some of the current is diverted through the scalp. A further complication is the cerebral spinal fluid (CSF), which is positioned next to the skull and is highly conductive meaning that the current is shunted around it (Liston *et al*, 2002). More recently, the electrode protocol in brain EIT has been examined as a method of extracting the most information from scalp measurements (Fabrizi *et al*, 2009). The image reconstruction of

several different electrode measurement projections were analysed using the Kung He MK1 system on a realistic tank. The result from these experiments revealed that an adjacent measurement strategy with electrodes positioned sub-occipital produced the best images in terms of localisation error, resolution, image distortion and sensitivity in the region of interest. This publication corroborates the electrode locations for fEITER, as four additional electrodes are positioned sub-occipital, as shown in 2.4.2.

Previously, at The University of Manchester, data has been acquired using an adapted commercial EIT instrument used in combination with a standard Evoked Response (ER) system to monitor functional brain activity on experimenter volunteers (Murrieta-Lee *et al,* 2004; Murrieta-Lee *et al,* 2005; McCann *et al*, 2006). This work used 16 electrodes to achieve a frame rate of approximately 3 frames per second (fps). More details about this system and results can be found in theses (Murrieta-Lee 2001, Polydorides 2001). The encouraging results that were produced from the pilot study led to the development of the new fEITER system. Among these results was the observation that the skull in vivo conductivity is approximately 50mS/m, as opposed to the accepted value of around 6mS/m in the 1990s. This is corroborated by Hoekema *et al* (2003). The higher level of skull conductivity promises significantly better sensitivity in fEITER.

2.4 Functional Electrical Impedance Tomography (fEITER)

The design and development of a new fast, portable, two-unit EIT system was undertaken at the University of Manchester as a continuation from the previous pilot study. The details of the fEITER system are given in this section.

2.4.1 Electrode Contact Impedance

Before the new electrical impedance system (fEITER) was designed and built it was necessary to understand the typical impedance encountered by the injected current. EIT measurements from biological tissues can be better understood by characterizing the effective impedance presented to the instrumentation system by the test subject with the two electrodes attached (Barber and Brown, 1984). It is imperative that there is good electrical contact between the electrodes and the skin, and that their impedance behaviour is well understood (Yang *et al*,

2005). It is known that there are several factors that can contribute to the overall impedance measurements when using surface electrodes (McAdams and Jossinet, 1995; Rosell *et al,* 1988; McAdams *et al,* 1996; Medrano *et al,* 2007). These unknown impedances consist of the electrode capacitive effect, electrode/electrolyte interface and the skin impedances. It is important that each of these areas is considered when taking impedance measurements using surface electrodes (Kolehmainen *et al*, 2008).

Many researchers have attempted to understand the 'contact' regions in the electrode-electrolyte-tissue system (Rosell *et al*, 1988; McAdams *et al,* 1996; Medrano *et al,* 2007; Rahal *et al*, 2009). Tissues are complex structures and their electrical properties display an intricate dependence on the frequency of an applied current (Webster, 1998; Regan, 1989). Placing an electrode and electrolyte gel onto the skin surface creates other unknown impedances. Understanding the combination of these impedances (tissues, electrolyte and electrode) is important when designing a physiological measurement system.

Specifically, several groups have studied impedance values around the contact region, i.e. the impedance that is created at the interface of an individual electrode and the skin. In most cases they have used a special geometry of non-standard electrodes (e.g. Rossell *et al,* 1988). These measurements are referred to as "skin impedances". Other groups have considered what is normally referred to as the "transfer impedance", i.e. the impedance that is inferred by passing a known current between two electrodes in contact with the skin and then making voltage measurements between a different pair of electrodes situated close by, e.g. as reported by the UCL group (Tidswell *et al*, 2001). Others have measured the "tissue impedances" (e.g. Osypka and Gersing, 1995). These are the impedances measured by needle electrodes, inserted into the tissue of interest (i.e. muscle, fat, liver etc). In this thesis, the author considers the "composite impedance" created by two commercial disposable electrodes (with associated gel) in contact with skin, where the composite impedance is that which is presented to a current flow between the two electrodes and/or a voltage measurement system connected between the two electrodes.

Rosell *et* al (1988) studied the skin impedance, by using a specially designed annular electrode. Measurements were made on 10 male subjects aged 19-55 on 10 different locations

on the body. It was found that the range of impedances (for electrodes plus tissue) went from 1MΩ to 100Ω (shown in figure 2.3). The authors noted a few errors in the data, repeat tests at the beginning and end of the tests (with electrodes in same site locations) having sometimes shown differences up to a 20% decrease in impedance. It was suggested that this change was due to the closure of sweat ducts after a cool gel was applied. However Grimnes *et al* (1983) observed similar differences in repeat tests when comparing measurements taken at different times after the gel had been applied, and attributed it to electrolyte penetration. These results imply that the electrolyte gel can reduce the skin impedance by 20% over a given time period.

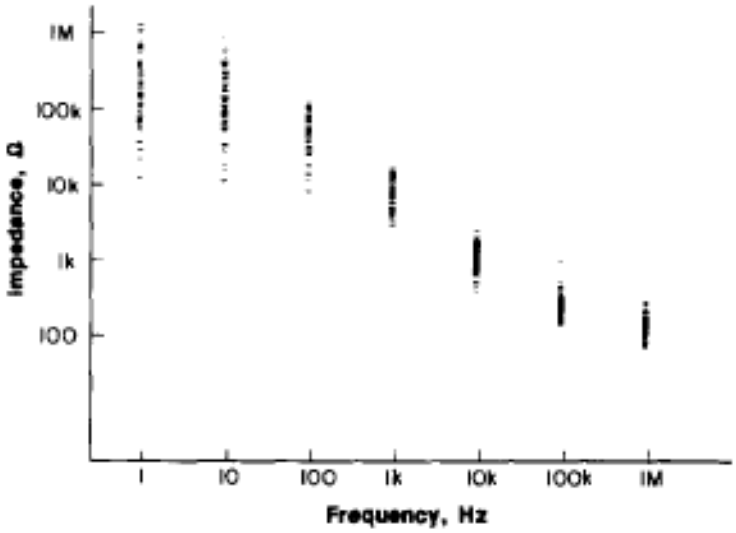


Figure 2.3 A scatter plot of impedance data measured using annular electrodes (Rosell *et al*, 1988).

More recently, similar work has been carried out by Rahal *et al* (2009) using six commercially available electrodes on the dorsal forearm. Impedance measurements were made using a Solartron SI 1260 over the frequency range 10 Hz to 1 MHz with an AC signal of amplitude 10 mV thus limiting the current to less than 50 μA at 1 MHz. Six adults were tested using both two-electrode and four-electrode systems. These approaches mean it is possible to differentiate between the composite impedances (two-electrode) and tissue impedances (four-electrode). The results displayed two electrode types that had the lowest composite impedance up to 1

MHz; the Ambu BRS electrodes which had an impedance of 559 Ω at 100 kHz, and the Kendall ARBO electrodes which had an impedance of 639 Ω at 100 kHz.

An area of concern when trying to design a system that requires many electrodes is the repeatability in position accuracy, in the case of fEITER this will be 32 electrodes placed on the scalp which may lead to significant electrode positioning variability between subjects. The effects of positioning errors have been investigated by Hary *et al* (1987), who looked at the impedance of EMG wire and surface electrodes. Measurements were taken on the legs of 5 subjects, 4 male and 1 female, over a frequency range 50 Hz – 2 kHz. Before the surface electrodes were placed, the site was shaved and cleaned with alcohol before electrolyte gel was applied. The experiments analysed the effects of electrode spacing. Electrodes were parted by 25mm and 50mm, however no changes were seen. When the diameter of the electrodes was changed, the results showed significant impedance changes.

Another area of uncertainty in electrode/contact impedance is the repositioning errors due to the electrodes falling off. This is a particular issue when working with a large number of electrodes for example during EEG. As well as that, there are errors in long term electrode replacement, e.g. during body composition control measurement subjects are tested over weeks. Lozano *et al* (1995) studied the percentage changes when a single electrode is replaced and when the whole set of electrodes were replaced, with results shown in table 2.1.

Table 2.1 The percentage changes when electrodes are replaced. Measured at 8 kHz (Lozano *et al*, 1995).

	One Electrode Replacement Mean ± SD	All Electrode Replacement Mean ± SD
Both arms	2.32 ± 0.01	3.45 ± 0.93
Left arm	3.6 ± 0.1	4.10 ± 0.67
Right arm	1.07 ± 0.34	4.44 ± 0.42
Left side of global	2.15 ± 0.03	3.87 ± 0.83
Control impedance	0.09 ± 0.02	0.11 ± 0.08

The results from the repositioning tests showed impedance changes up to 3.6% when one electrode is replaced, and 4.4% when all electrodes are replaced. Further to this work Soleimani *et al* (2006) investigated the electrode movement issues in EIT. An example of

electrode movement is easily identified in lung EIT. Initially electrodes are uniformly positioned around the thorax. However, breathing causes the electrodes to move and can cause electrodes to fall off (Zhang and Patterson, 2005). This can happen for all forms of medical EIT as they all use surface electrodes. Soleimani *et al* (2006) developed an image reconstruction algorithm to account for electrode movement in the reconstruction. The results showed a better reconstruction (in terms of fewer artefacts) after the algorithm was implemented into the simulated and tank data.

For fEITER it is necessary to understand the composite impedances on the scalp. Ideally, EIT electrodes would produce a low impedance for the current to pass between the system and the subject. However electrode-tissue impedances can dominate the measurements. To obtain accurate EIT images of the subject it is necessary to identify the effects of the electrode contact impedance on the skin. Among other considerations, artefacts created by movement, muscle action and other subject-related conditions have been identified as major influences on the electrode-skin contact properties (e.g. Lozano *et al*, 1995; Zhang and Patterson 2005). If artefacts are not addressed, the contact impedance could be altered which would have an effect on the images produced. These types of error have been noted to be greater when measuring human characteristics compared with non-human subjects (McAdams and Jossinet, 1990). Therefore, when considering a system that is to be used on a human subject, it is essential to know the extent to which the contact impedance can change under certain conditions.

2.5 fEITER

The design and build of fEITER was carried out at the University of Manchester, and system details can be seen in table 2.3. It is a fast, portable system. Designed to have a large number of electrodes (32, based on the 10-20 system, see figure 2.4), fEITER obtains a high number of independent measurements which is desirable for improved spatial resolution. It uses polar current injection, as previously described in section 2.1, which allows for better depth sensitivity, also aided by the use of a 3D measurement strategy which has 20 current projections (CPs), listed in table 2.3.

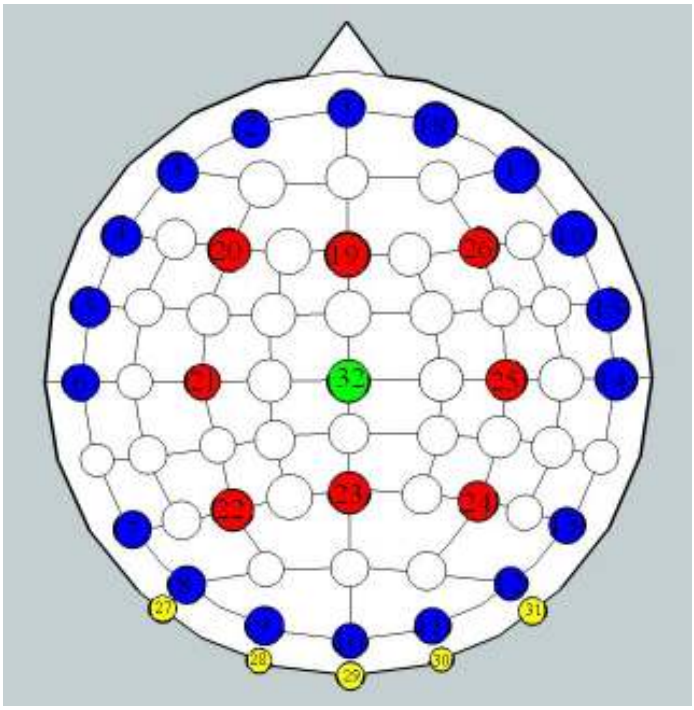


Figure 2.4 The fEITER electrode configuration based on the 10-20 standard set-up.

Table 2.2 A list of the current projections (CPs) used in fEITER, in terms of electrodes numbers.

1-10	6-14	9-18	1-27
2-11	7-13	19-23	1-28
3-12	7-16	20-24	1-29
4-13	8-12	21-25	1-30
5-15	8-17	22-26	1-31

fEITER is capable of providing 100 tomographic frames per second (10 ms temporal resolution). The system has an injected current which is set at a frequency of 10 kHz within firmware and its amplitude is monitored via an active current safety monitoring module

(Ahsan, 2010). The current is set to 1mA pk-pk, which is approximately one third of the permitted level set by BS EN 60601-1:2006 for auxiliary currents at this frequency, as discussed in chapter 3. It is necessary to acquire high precision measurements, i.e. with a high SNR. To obtain accurate information about small impedance changes (1%) within the brain due to visual stimulation, it was suggested that an EIT system would have to have a measurement sensitivity of 80 dB (Polydorides *et al*, 2002; Towers *et al*, 2000). Under tank test conditions fEITER has consistently produced an SNR greater than 80dB at 10 kHz, and further details can be found in chapter 5. This high level of precision is maintained when tests are performed on the head. A comprehensive description of the hardware and firmware can be found in (Ahsan, 2010).

Table 2.3 fEITER system specifications

fEITER System Details	Value
Frame rate	100 fps
Frequency of injected current	10 kHz
Magnitude of current injection	1 mA pk-pk
Number of electrodes	32 (Placed in a 3D array)
Number of current patterns (CPs)	20
Sequence of CPs used	1-30, 1-27, 22-26, 9-18, 7-16, 3-12, 1-28, 8-12, 5-15, 1-29, 4-13, 8-17, 7-13, 20-24, 6-14, 1-31, 1-10, 2-11, 21-25, 19-23
Measurement SNR	Approx. 80dB

fEITER has been designed to be a Class II medical device able to withstand the processes of electrosurgery and defibrillation, in order to allow the use of the device in the operating room. The EIT system comprises of two parts; a headbox unit and a base unit which are shown in figure 2.5.

The headbox unit is a fully electrically floating device measuring approximately 186 mm in width, a total of 313 mm in length and a depth approaching 40 mm. It provides the small sinusoidal currents, digitizes the measured scalp voltages and records their amplitude at 10 kHz by phase-sensitive demodulation. The data is transferred to the base unit. The headbox unit is designed to meet the standard associated with a Type II BF part in accordance with BS EN 60601-1:2006, as described in chapter 3.

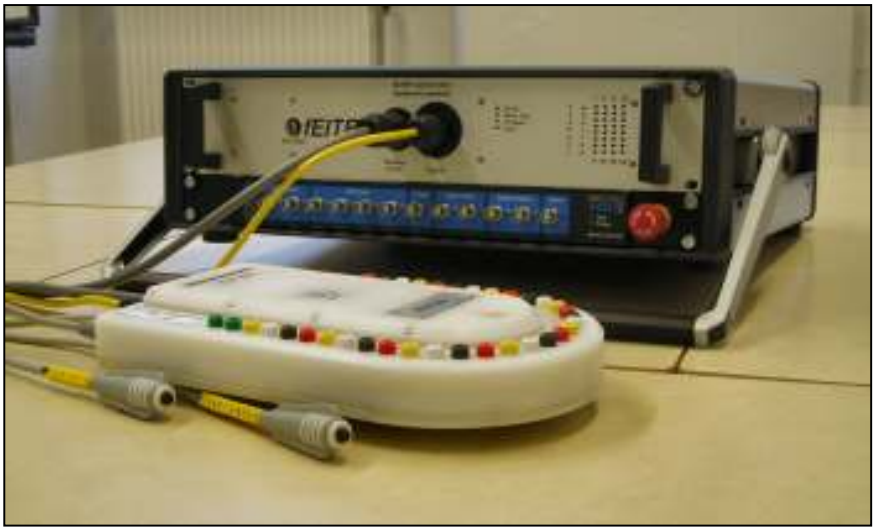


Figure 2.5 A photograph of the fEITER system, including the Base Unit with the stimulus generator, the HeadBox and the independent switches (emergency stop and user input mode control).

The base unit of the EIT system provides interfacing to the headbox unit, data acquisition laptop and the Cambridge Electronic Design (CED) Micro 1401. Interfacing to the laptop and

CED1401 are both galvanically separated from the connection of the base unit to the headbox unit. The electronics of the EIT system base unit is enclosed within a 2U 19" rack mount case with a depth of 363 mm. Both the EIT system base unit and CED1401 are housed in a single commercial 19" case measuring 3U in height and 500 mm in depth. The instrument case houses a medical grade power supply for the EIT sub-system base unit, the CED1401 power supply and the NI DAQ card with power supply. The stimulus generator (CED) uses software known as 'Signal' to deliver a pseudo-random sequence of stimuli events. Details of auditory sequences as discussed in chapter 6.

Figure 2.6 shows a schematic of the complete fEITER system comprising of the 5 major hardware blocks of the system; the selected stimulus device, scalp electrodes, headbox unit, base unit (incorporating stimulus generator, CED 1401) and data capture laptop.

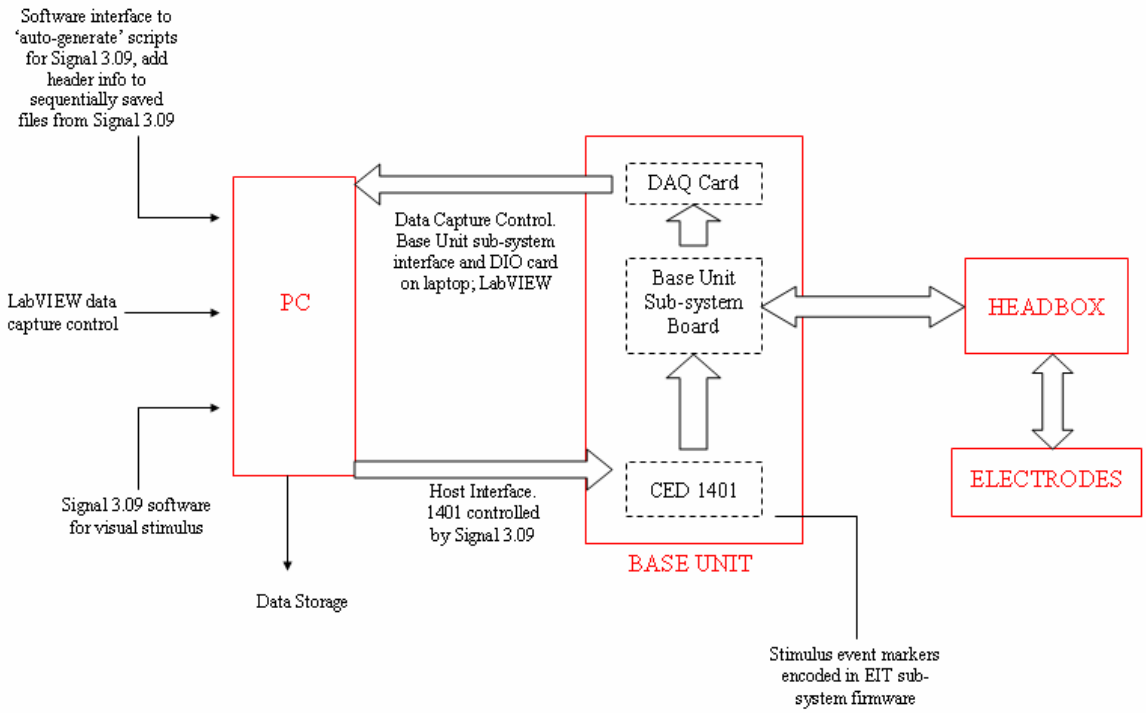


Figure 2.6 Schematic of the fEITER system showing the hardware components and controlling software

The front-end electronics uses a combination of miniature gas discharge tubes, clamping diodes and other components to provide a protection layer against the high currents and voltages that may be present during electrosurgery (ESU). This layer also provides EMC protection. The protection is designed not only to protect the front-end measurement electronics but also to ensure protection of the patient against possible fault conditions potentially giving rise to alternate burn sites during ESU. This provides an auto shut-off of the applied current should the current exceed 99% of 1mA rms.

The key concept of fEITER is to integrate a fast 32-electrode EIT system together with an evoked response system. This will provide the facility to investigate functional brain activity as a consequence of stimulating the brain using auditory stimuli.

Chapter 3 Ethical and Safety Considerations

Electrical equipment in a medical environment is used to aid the diagnosis or treatment of patients. However, all electrical equipment has the potential to cause harm to both patients and staff. For these reasons safety is critical.

3.1 Background

The World Medical Association (WMA) Declaration of Helsinki (DH) is a document that outlines the essential practices and principles that must be followed when conducting medical research involving human volunteers. It was the first document that emphasised the importance of ethics and the need for consent of the volunteers/patients in medical trials. It has been suggested that it was formed to help prevent a repeat of crimes that were committed in Germany in the Second World War (Human and Fluss, 2001). Although the document is not legally binding it does have influence over the practice of medical research within most European countries including the UK. It was formally established at the 1st General Assembly of the WMA in Paris, France in 1947. Since then there have been many additional guidelines introduced as well as several amendments to existing procedures. The most recent amendments were decided at the 59th General Assembly of the WMA in October 2008 in Seoul, South Korea.

Within the UK there are several organisations that monitor research involving human volunteers; these are on a local and national level. Nationally there is the NRES (National Research Ethics Service), which aims to protect the human rights of patients/volunteers as well as the safety, dignity and well-being of each volunteer. Locally, universities and NHS organisations have their own ethical procedures. These usually include a panel of experts from many different disciplines that discuss the proposed study/experiment before determining if

they do or do not want to object to it. In the case of a positive proposal, this will lead to a notice of no objection.

As well as ethical considerations there must be safety considerations, for both patients and staff. All medical devices, including new designs and adaptations of all old devices, must adhere to the relevant British Medical Standards. The Medicines and Healthcare products Regulatory Agency (MHRA) is a UK government agency that attempts to ensure that medicines (such as painkillers) and medical devices (such as infusion pumps) work correctly and are acceptably safe. The MHRA was established in 2003. It combined the functions of previous organisations called the Medical Devices Directorate (MDD) and the Medicines Control Agency (MCA). All new drugs and devices entail an element of risk. The MHRA tries to determine if the benefits of the new drug/device outweigh these risks.

All medical equipment that is intended to be used on people must be fully assessed in terms of risk through a risk management plan (BS EN ISO 14971), and in terms of electrical safety (BS EN ISO 60606-1). It may be necessary to consult and adhere to other British standards depending on the type of device, for example if there are programmable elements within the device it must adhere to the BS EN 60601-4:1997. All of the relevant standards must be taken into account when designing and developing medical electrical equipment, for both research and commercialisation.

3.2 Standards

The safety and ethical considerations for this thesis can be split into two different sections; the composite impedance study (chapter 4) and the fEITER clinical trial (chapters 5 and 6). The composite impedance study used a non-medical commercial product to make the impedance measurements, whilst fEITER was a newly designed medical device that had not been CE marked. However, both of these studies had to adhere to the following standards: BS EN 60601-1; BS EN 14971; BS EN 60601-4.

The British standard 60601-1:2006 is titled “Medical Electrical Equipment; General Requirements for Safety”. This standard ensures that equipment is safe to be used in a clinical setting. It defines the safety limits for many different elements within the device, a few

examples of some of these defined elements being leakage current, movable parts, power supply and markings, to name but a few. The standards define the classification of the device, which can be either Class I or Class II. Class I equipment has a protective earth, meaning that, if the basic insulation between the live and the external conductive components fail, the protective earth will prevent the external conductive components becoming live. Class II equipment also has basic insulation but in addition it has supplementary/double insulation as a further means of protection.

Table 3.1 Definition of applied parts.

Type	Definition
Type CF	Applied part would be in direct conductive contact with the heart. This must be an electrical floating device.
Type BF	Generally for devices that are in conductive contact with the patient for a medium or long time. This must be an electrically floating device.
Type B	Applied part is not in conductive contact with the patient and can be immediately released. This device can be connected to earth.

The standard also defines the classification for each applied part. Table 3.1 shows the different classifications and the definitions. An applied part physically connects the equipment to the patient. In other words it is something that the patients needs to touch or something that can be brought into contact with the patient for the device to carry out its intended function. There is a further extension of this standard that covers information relating to programmable devices: BS EN 60601-1-4 titled 'General Requirements for Safety - Collateral Standard: Programmable Electrical Medical Systems'. This standard refers to the procedures for design and implementation of suitable programmable components within a medical device including the implications of safety for both patients and staff.

BS EN 14971 is a separate standard that covers the risks associated with all medical devices. Titled the 'Application of risk management to medical devices,' the standard gives guidelines on the understanding of risk and hazards that the device may produce. It specifies a process to

aid the manufacturer in identifying the hazards, enabling them to estimate and evaluate the risks associated with each hazard. The standard aims to eliminate all hazards associated with each device; however this is an ideal situation which practically will not be possible. The standard endeavours to reduce these risks, by allowing the manufacturer to quantify each risk associated with all hazards, leading to a comprehensive monitoring system through which these risks may be reduced in the future.

3.3 Effects of Current Applied to the Body

For electricity to have an effect on the human body, through non-invasive means, two main conditions must be satisfied:

An electrical potential difference (or voltage) must be present;

The individual must be part of the electrical circuit, permitting current flow through the body.

It has been shown that current, not voltage, is often the source of injury or death. It takes only a small amount of current to cause major consequences (BS EN 60601-1, 2001). The effect on the body due to current is influenced simply by two main factors; the amount of current and the length of time the current flows. Another factor that is necessary to consider is the current path through the body, i.e. the entrance and exit points of the current. The worst case situation is a path crossing the heart, i.e. arm to arm, or arm to leg. Tables 3.2 and 3.3 show the consequences of current exposure.

Table 3.2 Physiological effect of a current path across the thorax

Physiological Effect	Current (50Hz)
Threshold of perception	0.2 – 0.4 mA
'Let-go' current; cannot be tolerated over 15 minutes	15 – 20 mA
Ventricular fibrillation; respiratory arrest	50 – 100 mA
Serious burns and muscular contraction of such a degree that the thoracic muscles constrict the heart	100 – 250 mA

Table 3.3 Current levels/time required to stop the heart (50Hz)

Current	Time required at current level to stop heart
40 mA	250 ms
100 mA	100 ms
200 mA	50 ms

The limits for auxiliary currents are shown in figure 3.1. As stated fEITER has a current level set at 1 mA peak-to-peak, this equates to 0.35 mA rms. Therefore it is within the recommended limits set by BS EN 60601-1:2006, which states a maximum current of 10 mA at 100 kHz.

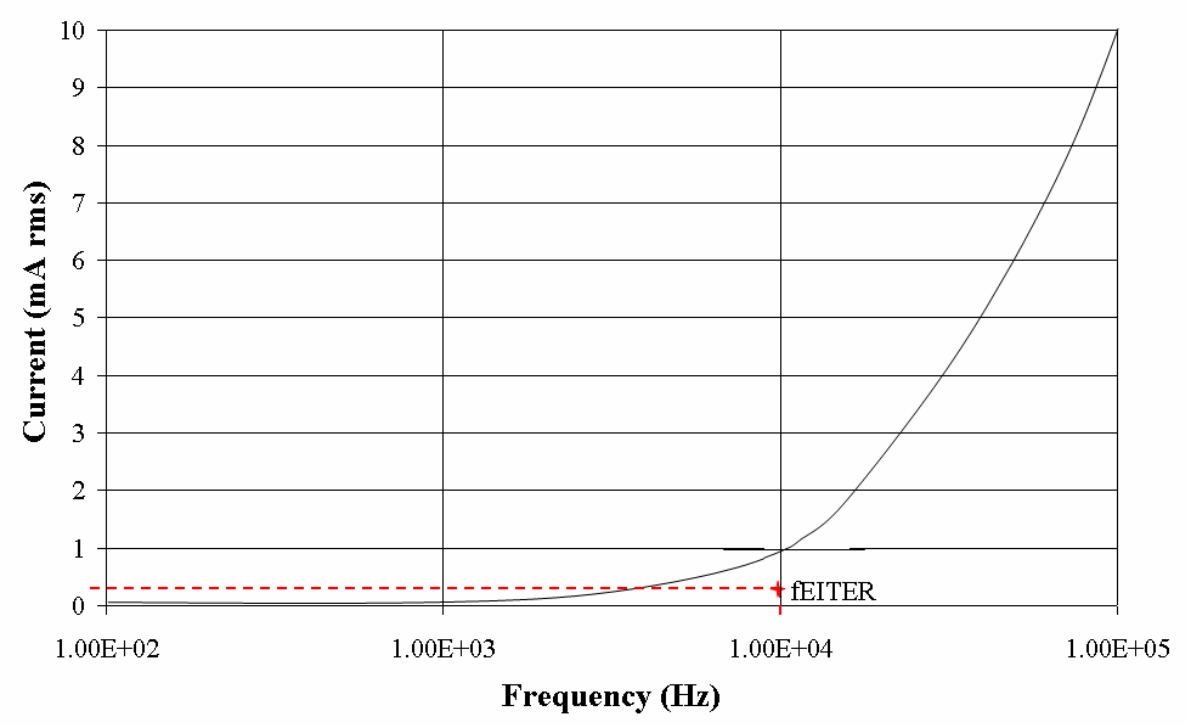


Figure 3.1 Auxiliary current limits as defined by BS EN 60601 as a function of frequency. The current level for fEITER is highlighted.

3.4 Safety Considerations for Composite Impedance Study

To produce the most revealing images from fEITER an area that is critical to understand is the contact region between the system and the human. To carry out tests to determine the composite impedance of the scalp due to two electrodes in contact with the skin located in close proximity to one another, it is necessary to gain university ethical approval. To satisfy the ethical committee, several parameters had to be considered, including the British Safety Standards. The author designed a series of experiments that would be carried out in stages, these are fully explained and results discussed in chapter 4. The ethical application for this study is attached at Appendix II, along with the committee's letter of approval.

Composite impedance (fully defined in chapter 4) measurements were made on several parts of the body, including the head. In common with other work in this field (e.g. Holder *et al,* 2005), an HP 4284A impedance analyser was used to make these measurements. The HP 4284A does not comply with the relevant medical electrical equipment safety standard (BS EN 60601-1, 2006) so the author adopted a unique arrangement designed to offer a similar level of protection to the volunteer to that of a medical device with a type BF applied part (see section 3.4.2).

Under the provisions laid out in the standard for electrical medical equipment BS EN 60601-1, it is not possible to connect a non-medical device to a patient without supplementary safety circuitry. This is a frequent problem in physiological measurement where electrical equipment in patient contact, e.g. a treadmill, has been constructed to a non-medical standard. In some cases, the addition of supplementary devices, most commonly a separating transformer, to non-medical equipment allows the construction of a safe electrical system for medical use. This provides effective isolation of any patient connections from the mains part of the system. Unfortunately, this approach cannot be applied to the HP 4284A as it requires measurement of the F-type patient leakage current, as defined in section 3.4.1. This procedure involves the application of an external mains voltage to the measurement terminals of the HP 4284A, which would be in direct contravention of the manufacturer's instructions.

However, many authors (e.g. Tidswell, Gibson *et al*, 2001; Holder *et al,* 2005; Gabriel *et al*, 1996) have used the HP 4284A directly to make measurements on several parts of the body

including the head, on both adults and children. These were carried out without any additional safety circuitry, however there were no reported adverse affects.

3.4.1 Safety Circuitry

The HP 4284A cannot limit both the voltage and the functional current (i.e. the intentional injected current as apposed to leakage currents) simultaneously. It was decided that the HP 4284A would be set as a constant voltage source of 1 V to make measurements over the frequency range 1 kHz – 100 kHz. Safety circuitry was introduced to ensure that the functional current was limited, meaning that it can protect the volunteers from excess functional currents and leakage currents. Three main areas of fault/hazard had to be considered when designing the circuitry; applied functional current limits, earth leakage limits and the single fault condition from mains supply. A schematic of the safety circuitry can be seen in figure 3.2 and the circuit diagram is shown in figure 3.3.

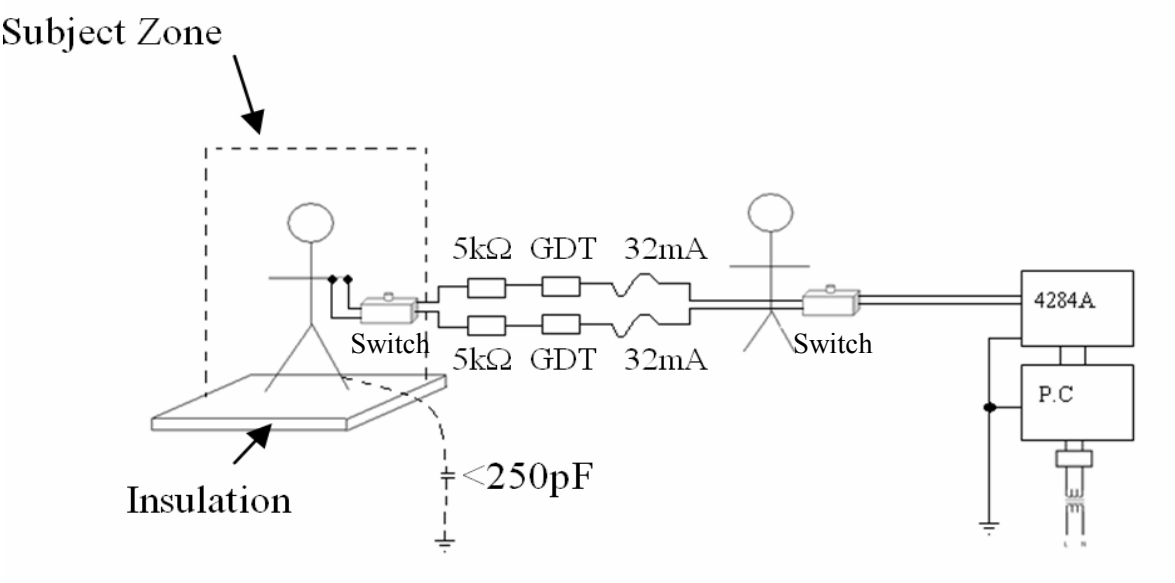


Figure 3.2 Experimental set-up, identifying the subject zone. Note the electrode positions are on the forearm as an example location.

The volunteer is placed within a defined zone (see figure 3.2), with substantial electrical separation from earth. This arrangement provides effective isolation of the volunteer from mains earth in the absence of other connections and eliminates all risk of auxiliary leakage currents. No electrical equipment or conductive structures enter the volunteer zone apart from the measurement leads and electrodes.

The functional current was limited by the source capability of the HP 4284A. This restricted the applied voltage to 2 V rms and the applied current to 20 mA rms, but this may be superimposed on a DC bias of up to 40 V. Under normal circumstances the bias was set at zero. However, should a single fault condition occur it could have increased to a maximum of 40 V. To limit the hazard created from this, each volunteer lead contained a 5 kΩ resistor and an F-type fuse (32mA) for current limiting, as seen in figure 3.3. The loop impedance (greater than 10 kΩ) was sufficient to ensure that any current flow was not dangerous (< 4 mA DC). Although the threshold of perception varies between volunteers, this level of current would be unlikely to produce an unacceptable level of stimulation and would potentially be undetectable to some volunteers. If the volunteer experiences any sensation the pushbutton switch could be released to stop all current flow. The author carried out all the experiments and also had access to a switch to ensure that there was another method of stopping the current.

The fuses operate in conjunction with gas discharge tubes to provide rapid and irreversible disconnection by shunting the current if an unexpectedly large voltage should appear across the volunteer leads under a fault condition. Then the use of gas discharge tubes provides the large over-current necessary for rapid fuse rupture without requiring this current to flow through the volunteer.

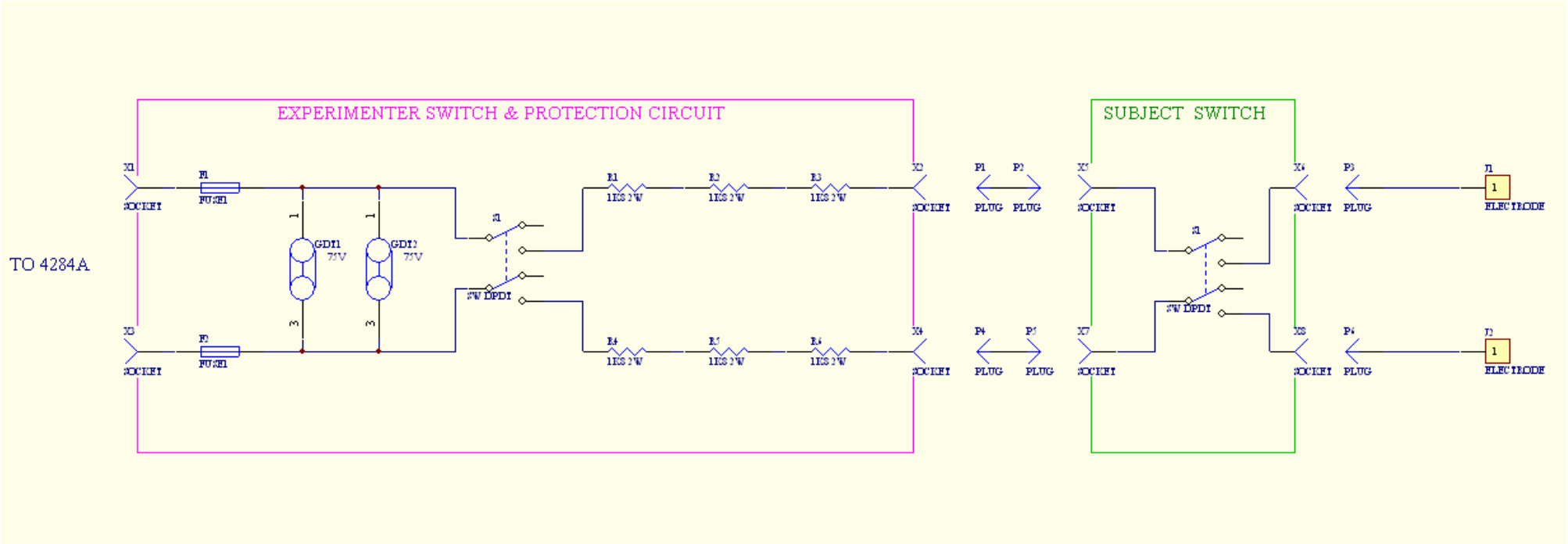


Figure 3.3 The circuit diagram for the additional safety (details of the circuit features are explained in sections 3.4.2 – 3.4.5).

3.4.2 Risk from patient auxiliary current

The medical standard (BS EN 60601-1) defines the limits for functional current (i.e. the applied intentional current), known as patient auxiliary currents. This limit varies depending on the classification of the applied part, as shown in table 3.4. These limits apply to dc and ac waveforms up to 1 kHz. For this experiment the equipment was classified as a type BF applied part, meaning that it may be connected directly to earth via the HP 4284A in this case. Therefore, additional safety circuitry was necessary.

Table 3.4 Allowable limits for patient leakage and patient auxiliary currents. (NC – Normal Condition, SFC – Single Fault Condition). Note all values are rms.

	Type B Applied Parts		Type BF Applied Parts		Type CF Applied Parts	
Leakage Current Type	NC (mA)	SFC (mA)	NC (mA)	SFC (mA)	NC (mA)	SFC (mA)
Earth Leakage (General)	0.5	1	0.5	1	0.5	1
Enclosure Leakage	0.1	0.5	0.1	0.5	0.1	0.5
Patient Leakage (dc)	0.01	0.05	0.01	0.05	0.01	0.05
Patient Leakage (ac)	0.1	0.05	0.1	0.5	0.01	0.05
Patient Leakage (F-Type)	N/A	N/A	N/A	5	N/A	0.05
Patient Auxiliary (dc)	0.01	0.05	0.01	0.05	0.01	0.05
Patient Auxiliary (ac)	0.1	0.5	0.1	0.5	0.01	0.05

Under normal conditions the current was measured to be less than the permissible normal condition auxiliary leakage current in a BF applied part. At these levels the auxiliary currents

were therefore considered non-hazardous. Table 3.5 shows the measured values on a variety of locations on several volunteers. These are samples of the data obtained and are viewed as typical. As shown the data in table 3.5 most of the current levels are within the limits of the standard for leakage currents. None of the volunteers reported any sensation.

Table 3.5 A sample of data showing the current levels measured on the volunteers (10 kHz). The electrodes were positioned in various locations.

Volunteer No.	Electrode Location	Current (mA rms)	Sensation
A	Forearm	0.41	NONE
B	Shin	0.53	NONE
C	Forearm	0.49	NONE
D	Forearm	0.49	NONE
E	Thigh	0.82	NONE
G	Shin	0.52	NONE
F	Forearm	0.72	NONE
A	Head (Side by side)	0.67	NONE
C	Head (Opposite)	1.21	NONE

3.4.3 Risk of discomfort, pain or injury arising from earth leakage

The HP 4284A and its associated PC were powered from a medical-grade isolating transformer but an uninterrupted earth connection was provided so as not to degrade the EMC performance of the devices. This meant that some earth leakage was possible through the EMC filters. To prevent any earth leakage passing through the volunteer, he/she was located on an 8mm thick insulating plate that defines the ‘subject zone’. This zone was kept clear of all electrical equipment and conductive structures apart from the measurement leads.

The experimental setup shown in figure 3.4 was used to test the earth leakage under single fault condition (SFC). To represent the volunteer, a 1kΩ resistor connected to a sheet of aluminium (650 cm^2, approximately the size of a volunteer's feet) was placed on the 8mm dielectric plate. The amount of leakage that would occur if the volunteer was connected to mains 280V (240V +10% as required by BS EN 60601-1) was measured.

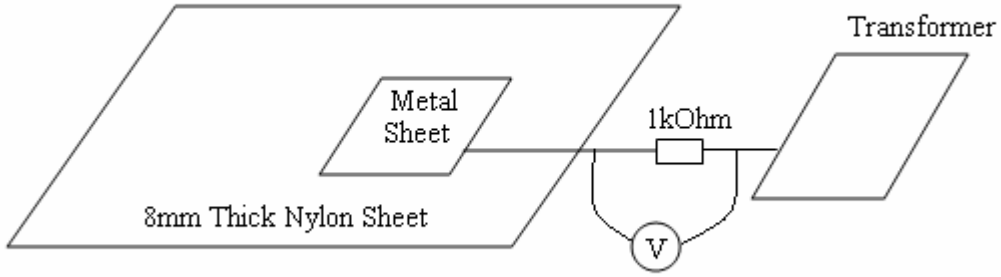


Figure 3.4 (a) The experimental set-up to measure the earth leakage under a SFC.

The average leakage current measured from 5 tests was 18μA rms. This result shows that the earth leakage is compliant with the medical standard 60601-1 for a BF applied part.
The nylon sheet provided an effective isolation of the volunteer from mains earth (250pF estimated maximum leakage capacitance) in the absence of other connections and eliminated all risk of auxiliary leakage currents.

The assumptions in the above analysis are very conservative when considering the earth leakage. The 8mm nylon sheet was the only 'deliberate' dielectric. The actual dielectric thickness is likely to be higher as the nylon plate is on carpet and the volunteer will be wearing shoes.

3.4.4 Risk of electric shock due to a single fault condition

Under a fault condition, mains voltage could appear on the HP 4284A terminals, either differentially or as a common-mode voltage with respect to earth. For common mode, the current flowing through the volunteer (patient leakage current) was limited to an estimated 18 μA rms by the low capacitance path to earth, as explained in section 3.4.3.

As previously explained, to address the possibility of an excessive differential voltage appearing across the volunteer leads, each lead is fitted with a 32 mA F-type fuse and a 5 kΩ resistor in series. The gas discharge tubes and fuses were experimentally tested using the same set-up shown in figure 3.4 with safety circuitry positioned between the 'volunteer' (1 kΩ resistor) and the transformer. Additionally, an oscilloscope was used to monitor the voltage. The measured voltage reached 53 V before the clamping took effect, reducing the voltage over a 1kΩ load to 3.38 Vrms, providing sufficient over-current for extremely rapid (300 μs) fuse rupture.

Further protection from electric shock is provided by a medical grade separating transformer which is used to power the HP 4284A and associated PC. This experimental arrangement achieves volunteer protection without interruption of the earth connection, ensuring that the electrical safety and EMC performance of these devices are not compromised.

3.4.5 University Ethics

Once the author was satisfied with the experimental set-up and design, it was necessary to prepare the appropriate documentation for the local ethics committee. As explained in section 3.1, when designing experiments which are to be carried out on human volunteers it is essential to adhere to all the relevant safety standards and the local and national ethical standard. For this study it was necessary to obtain a 'notice of no objection' from the university ethics committee.

The volunteer consent form, information sheet and questionnaire are shown in appendix III. The information sheet includes a brief overview of the experiments and the potential implications to the wider project, fEITER. It was also important to inform the volunteers of the hazards that may be present whilst participating in this experiment and these were carefully explained to ensure that all volunteers understood their ability to remove themselves from the experiments without any consequences. A detailed risk assessment of all the possible hazards and their associated risks was included in the ethics application, including the potential for allergic reactions to the electrodes, the possibility of abrasion due to prolonged wear of electrodes as well as details of the electrical hazards (under normal condition and single fault conditions).

The study to understand the composite impedance was designed to be a 3-stage experiment. The preliminary test was presented using the experimental set-up described in section 3.4.1.

However, this was carried out on the forearm only. The experiment was designed to study several different electrode types (ECG and EEG disposable electrodes). The preliminary test required an ethics application and 'notice of no objection'. Stage 2 was to make measurements on the shin and thigh, then stage 3 incorporates measurements on the scalp. Each stage required a new ethics application. The ethics applications included a detailed report of the previous experiments and the volunteer's feedback of the experiments and the applied current. Each ethics application requires a meeting with the ethics committee to discuss the proposed experiment before the committee decides if the experiments are ethically sound.

3.5 Safety and Ethical Considerations for fEITER

fEITER was designed to investigate the possibility of imaging functional brain activity in response to stimuli. This technique uses EIT to measure the variation of the electrical properties of the tissues within the head in response to various stimuli. All of the design and build elements were made to adhere to the British safety standards described in section 3.2. Apart from the presentation of stimuli, fEITER is no different from earlier studies in this field when considering risk and safety (Holder *et al*, 2005). The testing of fEITER requires a two-stage clinical trial; stage A involves volunteers from the development team, who will remain awake; stage B involves anaesthetised patients recruited at Manchester Royal Infirmary. To perform a clinical trial with non-CE marked equipment it is essential to have completed applications to the NRES (ethics) and MHRA (device safety) and obtained a 'notice of no objection' from both. Research projects that are carried out within a single entity do not have to apply for 'notice of no objection' from the MHRA; it is expected that they are developed with the relevant standards leading to clinical trials that require approval from the local ethics committee. However, since the clinical trial was to be held at Manchester Royal Infirmary (a separate legal entity), and the device was funded by a Wellcome Trust translation award (i.e. the aim was commercialisation and therefore CE marking), it was deemed necessary to apply to the MHRA.

The author coordinated the preparation of documentation for the MHRA application and participated in the safety testing of the device. The author also participated in designing the experimental protocols for the evoked response studies and in the experiments for the clinical trial stage A.

The application process for the MHRA is a relatively new procedure and this was the first time that a group within the Faculty of Engineering and Physical Sciences at the University of Manchester had carried it out. The general application requirements include a detailed document, known as PCA2, which included a comprehensive description of the functionality and inherent safety features of the device. In addition, the application included a separate Technical File that included details of the risk management file, safety testing and the verification and validation processes.

The following is a list of all the elements that were included in the MHRA application. Some of these are explained in more detail in this section. A copy of the MHRA application (PCA1, PCA2, NRES, patient information sheets and consent forms) can be seen in appendix IV.

- PCA1 – Notification
- PCA2 – Documentation
- General Information
- Investigation Parameters and Design
- Data Collection/Analysis/Statistics
- Device Details
- Technical File
- Risk Management File
- Circuit/Device Details (including all component data sheets)
- Firmware Verification and Validation
- Compliance to Relevant Standards
- Safety Testing (including independent validation)

- NRES (National Research Ethics Service)
- Patient Information Sheets
- Patient Consent Forms

As defined by BS EN 60601-1:2006 an EIT system is a Class II medical device. This means that the equipment is protected against electric shock by double or reinforced insulation, rather than having accessible conductive parts that are connected to a protective earth conductor. fEITER has been designed to withstand the processes of electrosurgery and defibrillation, in order to allow the use of the device in the operating room. The applied part, known as the HeadBox, is classified as type BF, which means that it is protected by means of an isolating supply. This is provided by the galvanic separation interface which allows connection to both the CED 1401 and a data collection laptop without the need for external separation devices. The schematic below (figure 3.4) shows two examples of an F type applied part, as defined by the standard.

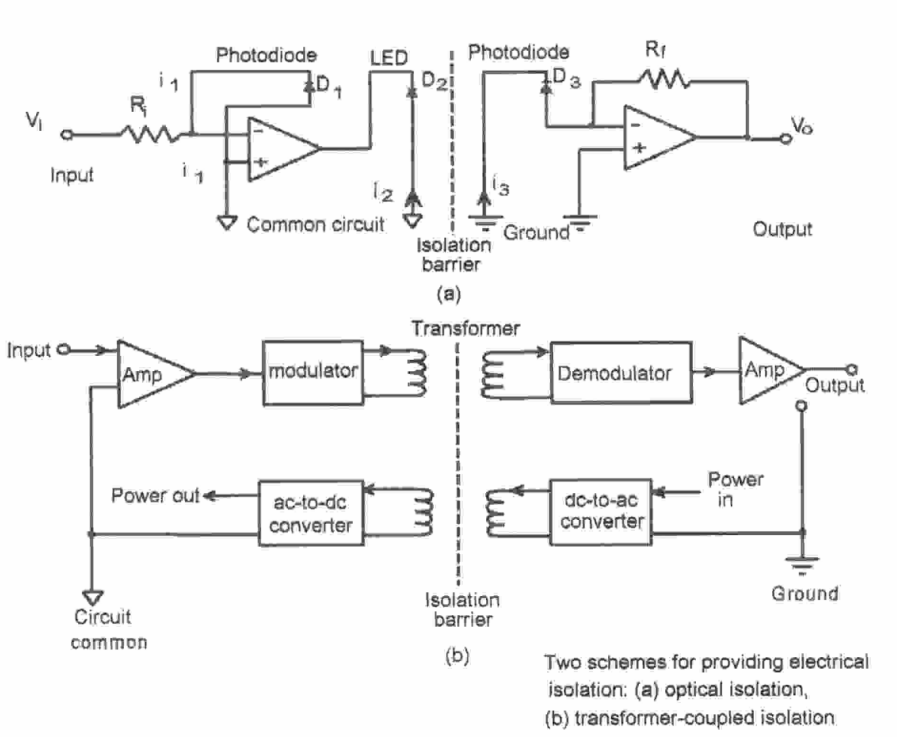


Figure 3.4 Examples of methods of isolation defined by BS EN 60601-1:2006 (Image taken from standard).

The applied part in fEITER is a fully floating device, as there is galvanic isolation in the base unit between the applied part and the data acquisition laptop and the stimulus generator (CED1401). The front end electronics uses a combination of miniature gas discharge tubes, clamping diodes and other components to provide a protection layer against the high currents and voltages that may be present during electrosurgery (ESU). This layer also provides EMC protection.

The frequency of the injected current is set at 10 kHz within firmware and its amplitude is fixed in hardware at 1mA pk-pk, approximately one third of the permitted level set by BS EN 60601-1:2006 for auxiliary currents at this frequency. The current waveform is monitored in firmware in terms of its amplitude, frequency and shape, to provide active current protection in compliance with the standard. The speed of the current shut-off should it exceed 1mA rms, has been tested and found to occur within 4µs. The details of the firmware can be found in (Ahsan, 2010). It was a requirement of the MHRA application that all firmware was both verified and validated. The verification process is a systematic internal check by the developers to ensure that the firmware is correctly controlling all the required states. The validation process must be carried out by an independent expert to ensure that the developers have not overlooked any area. An independent expert must provide a report to state the objective evidence that the specified requirements are met.

Similar to the composite impedance study, there is an emergency stop which is independent of firmware, to disable the applied current. This can be enabled by either the intervention of the clinical team or (in the case of awake volunteers) by the volunteer/patient. For the case of intervention by the clinical team, there are two emergency stops via red push-button switches that are clearly visible on the front of the headbox unit and base unit. The headbox emergency switch is firmware controlled and stops the current injection through the 32 electrodes, resulting in the headbox going into a ‘fault’ state, which continues until the switch is pressed and held for 5 seconds, thus restarting the headbox. The base unit emergency switch stops all power from mains, cutting power to the EIT system, including the headbox, base unit and 1401 stimulus generator. In the case of intervention by the volunteer, the emergency stop feature is controlled directly by using a hand-held push-button switch. This is firmware controlled and stops the current injection to the headbox and switches the headbox into a ‘fault’ state.

The only point of contact to the patient is through the CE-marked ZipPrep EEG electrodes, supplied by Aspect Medical Systems, Inc. ZipPrep means zero preparation, in that they are directly applied to the volunteer without prior preparation of the skin, describing its main advantage over other electrodes. ZipPrep electrodes have small 'tines' on the underneath of the electrode plate, shown in chapter 4, providing a less resistive passage for current without the need for abrasion.

The base unit of the fEITER system provides the interface between the headbox, data acquisition laptop and the stimulus generator (CED1401). Interfacing to the laptop and CED1401 are both galvanically separated from the connection of the base unit to the headbox unit. The galvanic isolation complies with BS EN 60601-1:2006. The electronics of the EIT sub-system base unit is enclosed within a 2U 19" rack mount case with a depth of 363 mm. Both the EIT sub-system base unit and CED1401 are housed in a single commercial 19" case measuring 3U in height and 500 mm in depth (Schroff, Comptec desk top case). Internal communication wiring between the CED 1401 and the EIT sub-system base unit is routed within the rear of the instrument case. The instrument case also houses a medical grade power supply for the base unit, the CED1401 power supply and the NI DAQ card.

3.5.1 Safety (MHRA)

Safety testing for the MHRA application was similar to the firmware testing in that the system had to be tested 'in house' before a qualified external specialist performed the same tests on the device to ensure it complied with all the safety aspects of the standards (BS EN 60601-1:2006). The main purpose of safety testing is to ensure the safety of the patient/volunteer and the staff operating the device. Therefore safety testing is an essential component of the fEITER design; it is during the safety tests that potential hazards may be identified. If hazards were identified during these tests it would have been possible to modify the safety features to eliminate or reduce the risk.

Measurements of the various leakage currents that may arise in clinical use, under both normal and single fault conditions, were carried out. These are required type tests for manufacturers of medical electrical equipment under test methods and conditions defined in Clause 8 of BS EN 60601-1:2006. The tests are intended to identify potentially unsafe conditions.

Most of the tests have to be performed under normal condition (NC) and single fault condition (SFC). However to ensure a high standard of safety the tests performed under normal condition are completed with the mains supply in normal and reversed polarity.

There are several safety tests that need to be completed to satisfy the MHRA. As defined by BS EN 60601-1 the leakage current limits at 10 kHz are 1 mA rms. A table of limits can be seen in section 3.4. The tests include the following:

1. Measurement of earth leakage current. The current flowing through the medical device to the protective earth.

2. Measurement of enclosure leakage current. The current that flows if a person comes into contact with the enclosure (or any part not intended for treatment or care).

3. Measurement of patient leakage current. This is any leakage that flows from an applied part via the patient to earth or flowing from the patient via an applied part to earth.

4. Dielectric withstand: a high voltage is applied between insulated parts to be sure insulation will withstand the high voltage for a specified time.

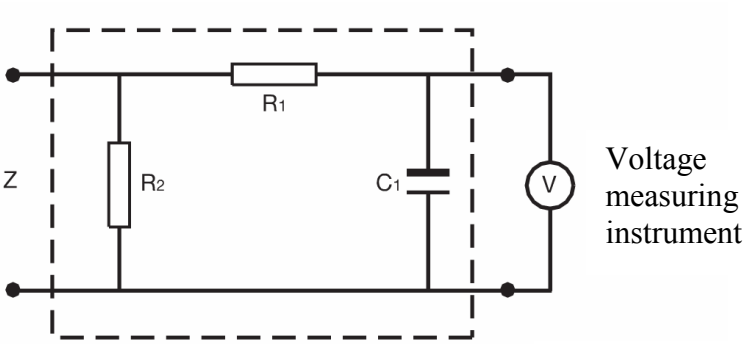
5. Measurement of residual voltage. This is the voltage present on the mains input 1 second after the plug is disconnected from the line.

6. Measurement of power consumption. This is a steady state test to measure the input of the device at the rated voltage, ensuring that it does not exceed more than 10% of its input voltage at operating settings.

The test procedures follow the requirements of the standard (clause 8.7 in BS EN 60601-1). The measurements are performed at 110% of rated mains voltage for the equipment under test (EUT), i.e. in this case 264 Volts RMS. The tests variously involve one or two independent sources of this voltage, each referred to the local ground plane. Most of the leakage tests require the use of a measurement device, the schematic circuit of which is shown in figure 3.5 (b). This will be referred to below by the symbol used by the standard, shown in figure 3.5 (a). The applied part within the fEITER system consists of the headbox,

touch proof leads and electrodes. The schematic for the applied part is depicted by the figure shown in figure 3.5 (c).

Figure 3.5 (a) The BS symbol for the measuring device.



R_1 = 10 kΩ ±5% I)
R_2 = 1 kΩ ±5% I)
C_1= 0.015 µF±5%

Where,

I) Non-inductive components

II) Impedance > Impedance of measured circuit (Z)

Figure 3.5 (b) Schematic of the measuring device (MD) used in the leakage tests

Figure 3.5 (c) Schematic representation of the applied part.

Most tests involve insertion of a defined MD into the circuit before cycling through all modes of operation / configurations and are necessarily performed with limited contact with the EUT whilst energized as this may change the leakage behaviour. For fEITER 'all modes' includes power up, measurement only (voltage measurements are performed on all channels but without current injection), EIT mode and fault mode.

The earth leakage tests are the sum of all the leakages in the devices in all modes. This measures the current flowing back to ground through the earth line, shown in figure 3.6. Under normal conditions this means that S1 is closed and S5 is normal mains supply before reversing the polarity of the supply.

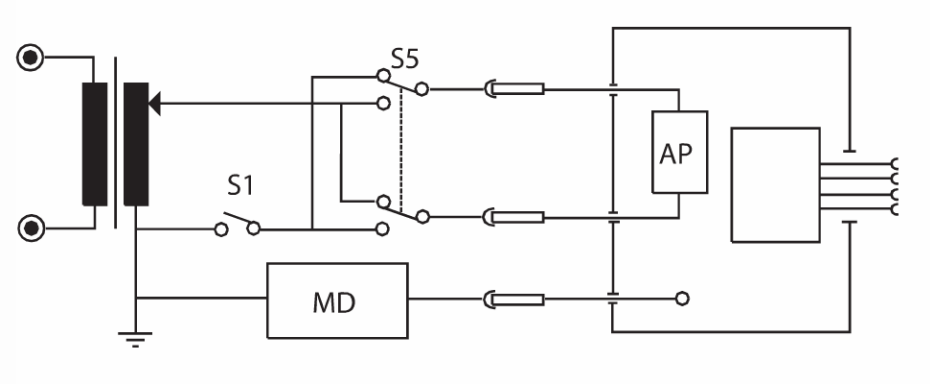


Figure 3.6 The Test circuit for the earth leakage tests.

For SFC the switch S1 is opened and the mains supply is normal then reversed. The standard specifies that this test is made with open and closed neutral under all possible combinations of reversed line (S5), grounded functional earth terminal, and grounded patient leads. The various combinations result in 16 different conditions to be tested, if the equipment has a functional earth and an applied part.

The enclosure leakage current is measured to assess the current to which a person would be exposed when in contact with the enclosure. The test circuit can be seen in figure 3.7, showing that the leakage currents are measured between the earth and each part of the enclosure that is not protectively earthed. This test is done under NC, which means that S1 and S8 are closed whilst S5 the mains supply is normal then reversed. Under SFC two tests are carried out with the mains supply normal and reversed. One is with S1 open and S8 closed, i.e. single fault with supply open, and the other test is with S8 open and S1 closed, i.e. the single fault earth open.

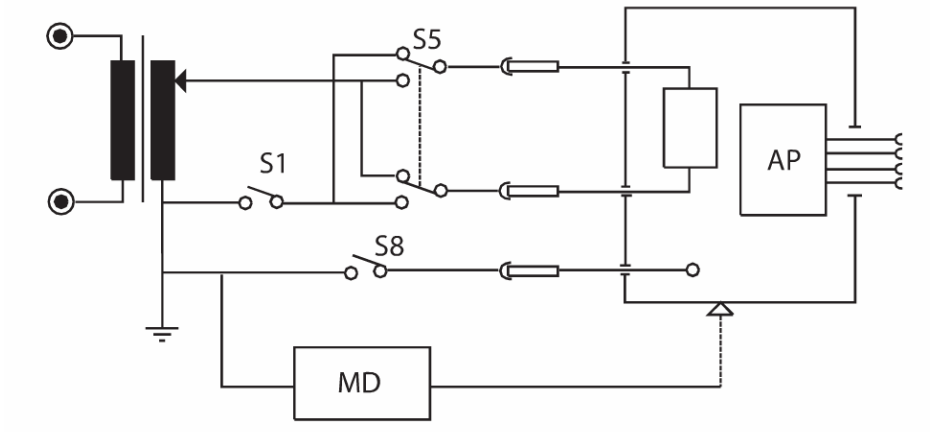


Figure 3.7 Test circuit for enclosure leakage tests.

The patient leakage tests measure any leakage that flows from an applied part via the patient to earth or flowing from the patient via an applied part to earth. This is a crucial test for fEITER as the patient connections have deliberately low impedances, and so it is important that the device is within the limits for the type BF patient leakage. There are several tests that have to be completed for the patient leakage tests, mainly due to the large number of electrode connections to the patient. It is only necessary to measure the patient leakage to each applied part for type CF tests. Although fEITER was deemed a BF applied part it was possible to perform the tests to ensure that it complied with the limits for a CF device (ensuring extra protection). Therefore all the channels were measured under normal and reverse mains supply under NC, SFC with the supply open (S1 open) and SFC with the earth open (S8 open).

There are several other tests that are required to be performed for the patient leakage tests. It is necessary to measure the total leakage to ground from all of the leads tied together. This simulates what happens when all of the leads are in contact with a patient and the patient touches a grounded object, as shown in figure 3.8.

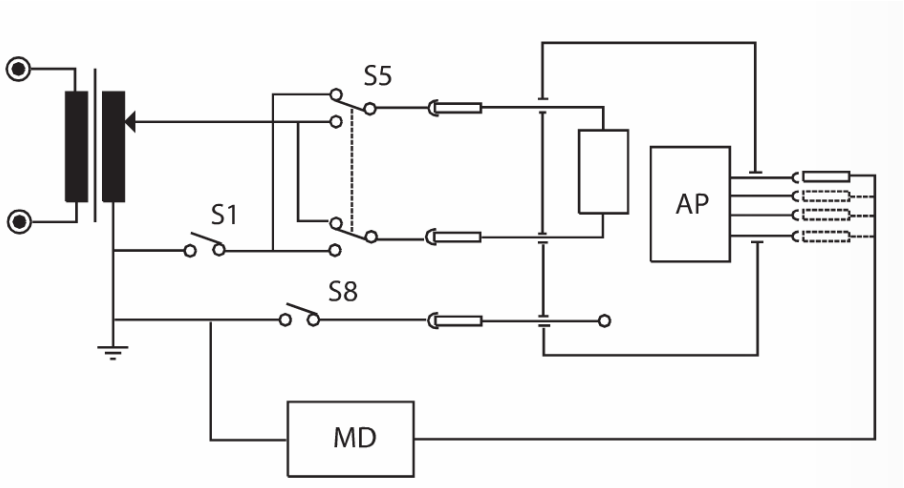


Figure 3.8 The test circuit for patient leakage current with all electrode connections tied together.

The patient auxiliary leakage currents were measured to ensure that under all conditions, including mains reversal and SFC, the leakage was within the limits as stated in table 3.4.

Figure 3.9 shows the test circuit for the patient auxiliary tests. All combinations of electrode leads were tested for normal and reverse mains supply (S5), under NC, SFC with supply open (S1 open) and with earth open (S8 open).

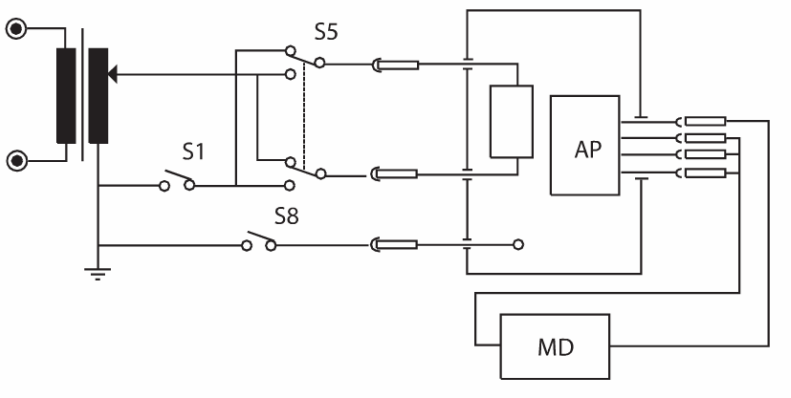


Figure 3.9 Test circuit for the patient auxiliary tests. Note that fEITER has 32 channels to be tested.

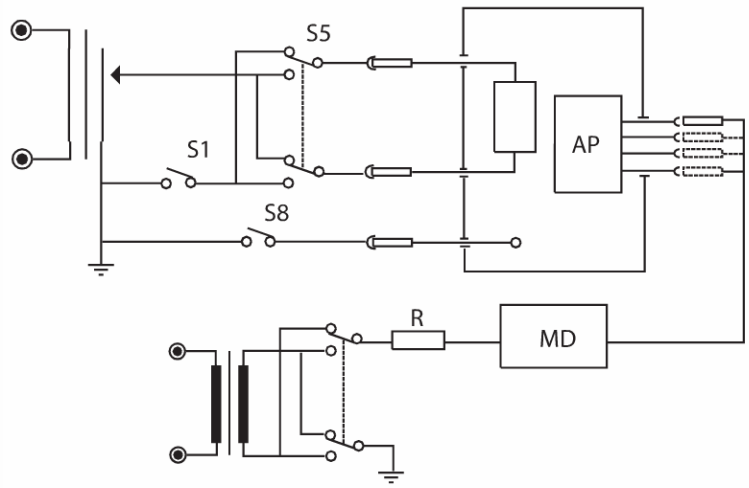


Figure 3.10 Schematic circuit diagram for patient leakage tests (F-Type).

The mains input voltage is applied to the patient connection (however this is current limited by the resistor, R) to simulate a worst case situation. Once again this test must be completed with the normal and reversed mains for S5, and the mains on the applied part. The tests are completed for NC, SFC with supply open (S1 open) and SFC with earth open (S8 open).

The dielectric withstand test is performed to test the strength of the insulation when a high voltage is applied. If a high voltage was accidently applied to either the headbox or the base unit it is important to know that the insulation barrier can withstand the voltage. Under normal circumstances this would be classed as destructive testing; since fEITER was a unique instrument the whole system was not tested in this way. However, the test was carried out on the data transfer and the power leads. The cables were tested up to 3000V and remained intact throughout the duration of the tests.

3.5.2 Outcome

The MHRA application took 12 months to complete, including the 60 days that it takes for the MHRA to respond to the application. The application is submitted in paper format; it must include 8 copies of PCA1, PCA2 and Technical File, which totalled 48 kg of boxed documents. There are two independent reviewers; one technical and one medical. Each of the reviewers are able to ask questions to the manufacturer within 30 days of receiving the application. These questions were answered and returned within a week. From this point the reviewers have another 23 days to review the application and meet to discuss their opinions.

The MHRA application for the clinical trial using fEITER was given 'notice of no objection' on the 22nd of July 2009.

3.5.3 University Ethics

Prior to receiving the outcome from the MHRA the fEITER system was taken to the local university ethics committee, described in section 3.4.5. This preliminary research proposal was presented with the aim of performing experiments on the two principal investigators, using an experimental range of auditory stimulus (varying the tone duration, frequency, number of stimuli per minute, inter-stimulus interval and loudness level). It was proposed that measurements would be taken using fEITER. The main aim was to enable the author to complete a preliminary study of auditory stimulus (the results are shown in chapters 5 and 6) before using a preferred auditory stimulus on a larger number of volunteers upon receiving MHRA notice of no objection. The preferred stimuli would be chosen based on the largest changes in EIT measurements.

This preliminary research project was granted ethical approval in July 2009. The work was carried out at the University of Manchester with several different auditory stimuli in order to

establish the stimuli that resulted in the largest changes. The details of this application can be seen in appendix V and the details of the experiments can be seen in chapters 5 and 6.

3.6 Summary

The safety tests for the study to understand the composite impedance were carried out and the system complies with the British safety standard 60601-1:2006. The initial university ethics application regarding the composite impedance was submitted for tests on the forearm, and was given 'notice of no objection'. These initial tests proved to be successful in measuring the composite impedance without causing any adverse reactions in the volunteers. Further applications to the university ethics for tests on the shin, thigh and scalp were presented (applications included the results from the previous experiments with the details of the volunteers' comments about sensation). All applications were given 'notice of no objection', meaning that several tests to understand the composite impedances using three different electrode types were able to be measured on the forearm, shin, thigh and scalp. The details of these experiments are in chapter 4.

The process to use an experimental research device, fEITER, in tests on human volunteers meant that the "manufacturer" (The University of Manchester) had to ensure that the device met all British safety standards. This meant adhering to BS EN 60601-1:2006 amongst other safety standards and submitting an application to the MHRA. The MHRA submission is a lengthy, complicated procedure that required many different areas to be examined before the project was given 'notice of no objection'. The details of the safety tests are given in this chapter. However, there is a significant area of the standard that has not been tested on fEITER. These are the destructive tests. The destructive tests laid out by BS EN 60601-1 include drop tests, water ingress tests, pressure tests, full dielectric withstand tests, and more. It was not possible to fully complete all of these tests because fEITER is a unique system (i.e. there was only a single unit manufactured). The clinical trial to be carried out using fEITER was a proof of concept experiment. If the tests reveal a positive outcome some of the future work will have to include destructive tests on samples of the device. The application to the MHRA included the PCA1, PCA2 and Technical File. After 60 days the MHRA gave 'notice of no objection' and the clinical trial was able to begin, as discussed in chapters 5 and 6. The ethical application for fEITER was submitted to the NRES, the application and the response given was included in the MHRA documentation. The NRES also gave the clinical trial 'notice of no objection'.

Chapter 4 Composite Impedance

4.1 Importance of Understanding Composite Impedance

An electrode is an electrical conductor that is used to make contact with a non-metallic part of a circuit. In this case it is used to connect to a subject's skin. There are two types of electrodes, polarisable and non-polarisable. A perfectly polarisable electrode would mean that no charge crosses the electrode-electrolyte interface. This type of electrode would behave like a capacitor. A perfectly non-polarisable electrode is one that allows current to pass freely across the interface requiring no energy (Webster, 1998). Examples of electrodes that behave as close as possible to the perfectly polarisable electrodes are those made of noble metals, such as platinum. Conversely electrodes made of silver/silver chloride (Ag/AgCl) are the closest to perfectly non-polarisable electrodes (Geddes *et al*, 1969). These electrodes still have a small capacitive barrier at the surface of the skin which contributes to some of the unknown contact impedance. For EIT it is essential that electrodes allow the current to pass through as freely as possible.

The electrode-electrolyte interface has an effect on the impedance values recorded when examining skin impedance using surface electrodes (McAdams *et al*, 1995a). There is a separation of charge at the electrode-electrolyte interface resulting in an electric double layer (Webster, 1998). This is where one type of charge is dominant on the surface of the electrode and the opposite charge is distributed in the immediately adjacent electrolyte. A potential difference is created between these two layers, known as the half-cell potential. Each electrode has a half-cell potential that is determined by the metal of the electrode, the concentration of the ions in the solution, and temperature. The potential difference affects the performance of the electrode, thus affecting the impedance. The half-cell potential of the standard hydrogen electrode has been set to zero, relative to which Ag/AgCl has a half-cell potential of 0.223 V. This low potential is another reason for choosing Ag/AgCl electrodes for this study. Another important area to consider when a current is passed between the

electrode and the electrolyte is the polarization. The presence of a current alters the half-cell potential by changing the resistance of the electrolyte thus resulting in a voltage drop; the current also changes the distribution of ions at the interface as well as changing the energy. It has been reported that Ag/AgCl electrodes have a low and stable potential when in contact with the chloride gel (Janz and Ives, 1968), reinforcing the choice of Ag/AgCl for this study.

The underlying tissues have different resistivity values due to the variability of ion concentration within the tissues (Martini, 2004; Bayford, 2006), as discussed in chapter 1. The stratum corneum is the most resistive tissue and can create a capacitive effect between the electrodes and the skin causing some unknown impedance values.

The study in this chapter addresses the measurement of the combined impedance of all these areas. In all cases the "composite impedance" of a two-electrode system is reported, i.e. the total impedance of the system comprising two identical electrodes, between which current is passed, and the associated tissue. Therefore, the reported values include the internal impedances between each electrode plate and its electrolyte gel, the impedance of the gel, the impedance of the region where the gel is in intimate contact with the tissues, the stratum corneum, and the impedance of the bulk tissues through which current is passed.

4.1.1 Electrode

Different manufacturers produce electrodes that are suitable for different parts of the anatomy. The experimental study presented here compares the composite impedance characteristics of a standard commercial EEG electrode (ZipPrep™, Aspect Medical Systems Inc.) and two standard ECG electrodes (Kendall ARBO®, Tyco Healthcare UK Ltd; Red Dot™, 3M Inc.) applied to different sites on the body.

ZipPrep electrodes are currently used in conjunction with other Aspect Medical Systems devices for monitoring depth of anaesthesia, as well as with other brain monitoring devices. They are claimed to have very low contact impedance due to the development of the Velcro-like tines, figure 4.1 (a). (ZipPrep electrodes cost approximately £2.40 each).

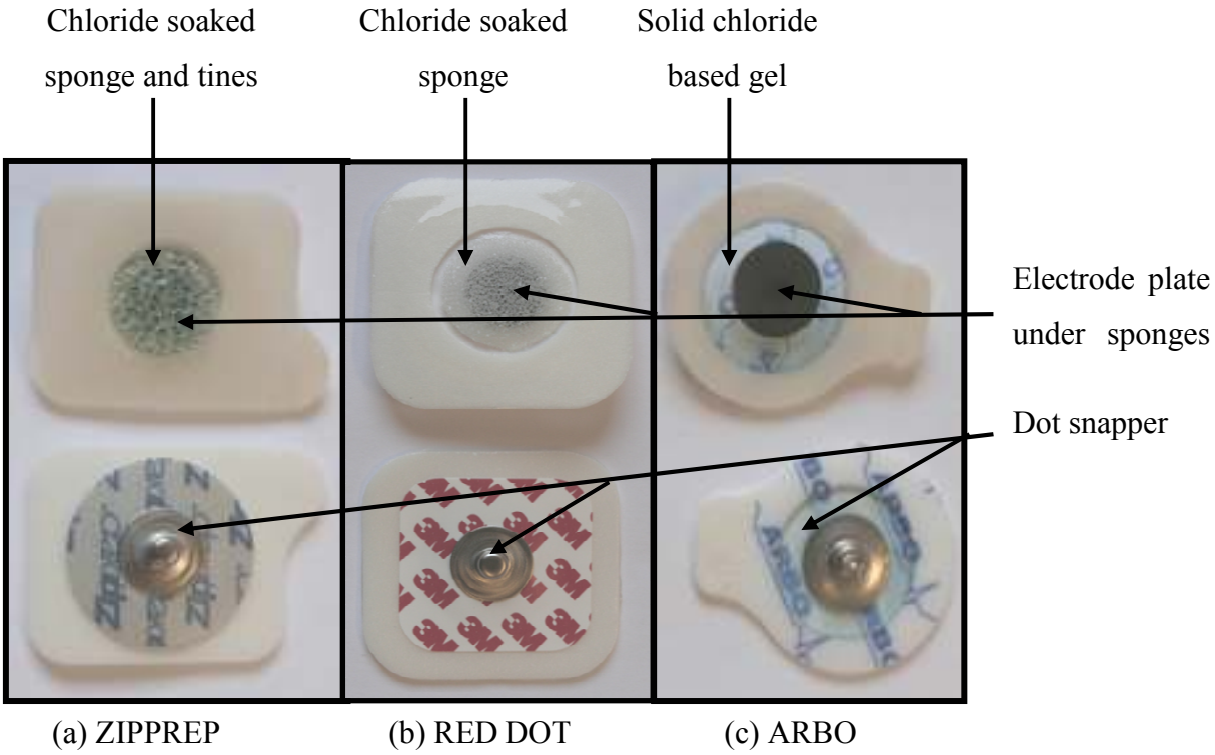


Figure 4.1 Photographs and description of electrodes

Red Dot electrodes have a chloride-based gel within a sponge underneath the electrode plate, and their design is relatively simplistic compared to the ZipPrep electrodes, figure 4.1 (b). This simplicity is reflected in the cost, the ZipPrep electrodes are approximately 10 times the price of Red Dot electrodes. Red Dot electrodes are commonly used for ECG measurement. Due to frequent use in a medical environment they were chosen to be tested alongside the EEG electrodes.

ARBO electrodes have two major differences compared to the ZipPrep and Red Dot electrodes: the overall size of the electrode pad is smaller, resulting in easier removal and they have a solid gel instead of a gel-soaked pad, figure 4.1 (c). These disposable electrodes are used frequently for neuro-feedback (EEG) and occasionally for bio-feedback (ECG and EMG) measurements.

4.2 Methodology

Composite impedance measurements are to be made on several parts of the body, including the head. As discussed in chapter 3, the HP 4284A does not comply with the relevant medical electrical equipment safety standard (BS EN 60601-1: 2006) so a unique arrangement was designed to offer a similar level of protection to the subject to that of a medical device with a type BF applied part. The subject is placed within a defined zone (see figure 3.2), with substantial electrical separation from earth.

Each of the two electrodes is applied to the same body part (e.g. limb, scalp) to localise the applied current. This prevents differential current flow across large regions, especially the chest. Both the experimenter and the subject have to depress double-pole pushbutton switches (momentary) to connect the subject to the HP 4284A, which allows either party to immediately interrupt the current flow if necessary. These switches provide more than 250 V of isolation and so they will remain effective under any foreseeable fault condition.

4.2.1 Calibration Tests

The HP 4284A has the ability to null out the impedance of test fixtures. However, the impedance of the safety circuitry is greater than the normal limit, so the effectiveness of the nulling procedure was verified experimentally. Calibration tests were carried out using a variety of resistor and capacitor values, in both series and parallel networks. In each case nulling was carried out prior to measurement of the RC network. This was done by introducing an RC network at the end of the circuit, in place of human tissue and electrodes. Figure 4.2 shows measurements of a RC series network (430 Ω, 10 nF) with and without the inclusion of safety circuitry in the test fixture. These values were chosen as they are representative of the impedances reported in the literature (Webster, 1998).

The difference between the ‘with safety circuitry’ and ‘without safety circuitry’ is displayed as the residual impedance i.e. the difference in impedance at each frequency (figure 4.2). Based on the predicted values calculated from the formula below, the impedance measurements from the RC network display are accurate. The residual difference between the ‘with’ and ‘without’ safety circuitry is greatest at the lower frequencies with the smallest difference at the highest frequencies (approximately 10Ω at 100 kHz).

$$Z = \sqrt{R^2 + X^2}$$

(4.1)

where,

$$X = \frac{1}{j\omega C} = \frac{1}{2\pi f C}$$

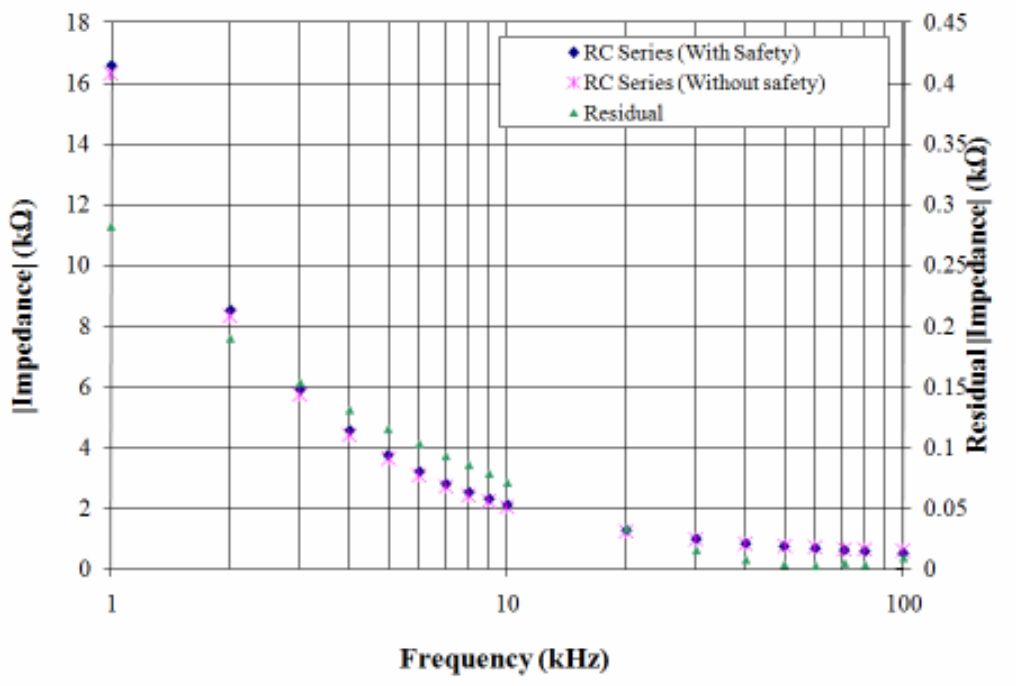


Figure 4.2 Measured impedance of RC series network when placed in the measurement location, when all safety circuitry is in place ('With Safety') and with no safety circuitry between the impedance analyser and the RC network ('Without Safety'). The secondary axis shows the residual impedance between the measured results with and without the safety circuitry.

Additional experiments were carried out using biological tissues to further ensure that the calibration of the system would be accurate on more realistic tissues. A banana was used as it is a common substitute for human skin (e.g. Holder, 1992). The banana (10cm length and 3cm diameter) had ZipPrep electrodes attached at either end, and attached to the HP 4284A via the previously described safety circuitry, as seen in figure 4.3. Impedance measurements were taken over the frequency range 1 kHz to 100 kHz. Then a 1cm^2 section of the banana was removed and filled with 2.5ml saline solution of conductivity 500 µS/cm. Then the

impedance was measured, 0.5ml of saline solution was removed and the measurements repeated. This was repeated so that there was 2ml and 1.5ml of remaining saline solution (figure 4.4).

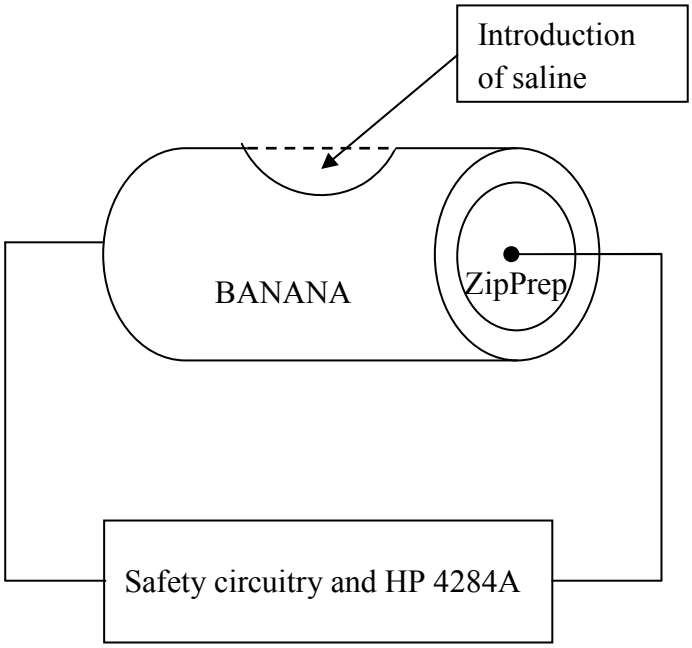


Figure 4.3 Schematic of the experimental procedure to measure the impedance of a banana over frequency range 1 kHz to 100 kHz using the HP 4284A.

As shown in figure 4.4 the impedance decreases over the frequency range, ranging from a maximum of 7.5 kΩ at 1 kHz to a minimum of 1.1 kΩ at 100 kHz. The removal of a $1cm^2$ section and introduction of 2.5 ml of saline solution lowers the impedance across the frequency range. The impedance monotonically decreases at each frequency with the removal of the saline.

As shown by the secondary axis the residual difference is plotted; this is difference between the 100% banana and each of the saline stages. It shows that the difference in impedance between 100% banana and the introduction of saline is approximately 600Ω at 1kHz. This residual difference decreases with frequency.

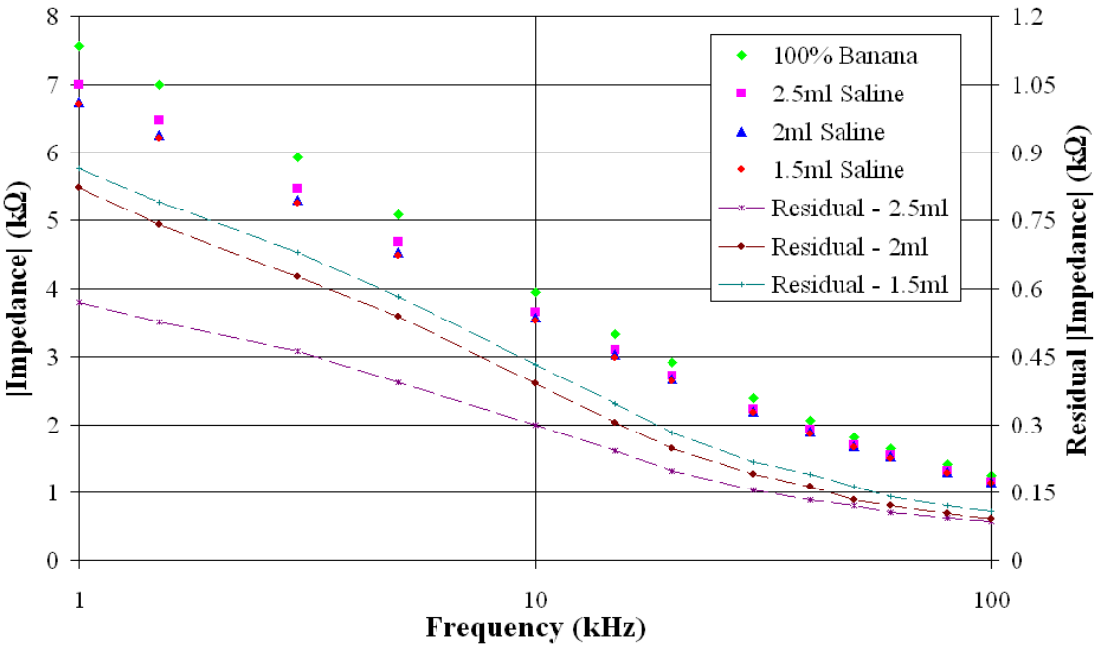


Figure 4.4 Measured impedance of banana and saline solution with all the safety circuitry in place. The secondary axis shows the residual impedance between the banana only results with the reduction in saline solution.

This section shows that the safety circuitry and nulling procedure of the system has been tested successfully using RC networks and biological tissues. The results show that the system can null out the safety circuitry and the results of measuring the impedance of the RC networks and the banana are as expected.

All subsequent results reported in this chapter are stated as total composite impedance (or resistance and reactance as stated) of two electrodes plus tissue, with the effect of the safety circuitry and test fixture removed by the nulling procedure.

4.2.2 Current Analysis Measurements

The HP 4284A was operated as a constant 1 Vrms voltage source. The measurements were then based on the resulting current level. Typical values were 0.7 mA rms at 10 kHz on the forehead, 0.6 mA rms on the forearm, 0.5 mA rms on the shin and 0.8 mA rms on the thigh. This level of current applied to the subjects is below the permissible maximum as defined by the medical electrical equipment standard at 10 kHz (1 mA rms), as discussed in chapter 3. It was noted that no subject reported experiencing any sensation during the application of the current.

4.3 Results

Measurements were made on 10 healthy volunteers (age range 24-53 years). Various sites were tested, including the scalp, shin and forearm. Prior to placing the electrodes the site was left unprepared. In each test, 20 repeat measurements were made within a few seconds at each frequency. The results reported, in all cases, are the mean value and standard error at each frequency.

As discussed in chapter 3, all the volunteers gave informed consent to a protocol approved by the University of Manchester research ethics committee (Application references: 06241, 07185 and 09107).

4.3.1 Forearm and Shin Measurements

Electrodes were firmly positioned and placed 2.8 cm apart (as measured between the centres of the electrode plates) on the posterior forearm. Figure 4.5 shows the variation of total impedance magnitude with frequency, using ZipPrep electrodes shown. The individual components resistance and reactance, can be seen in figures 4.6 and 4.7.

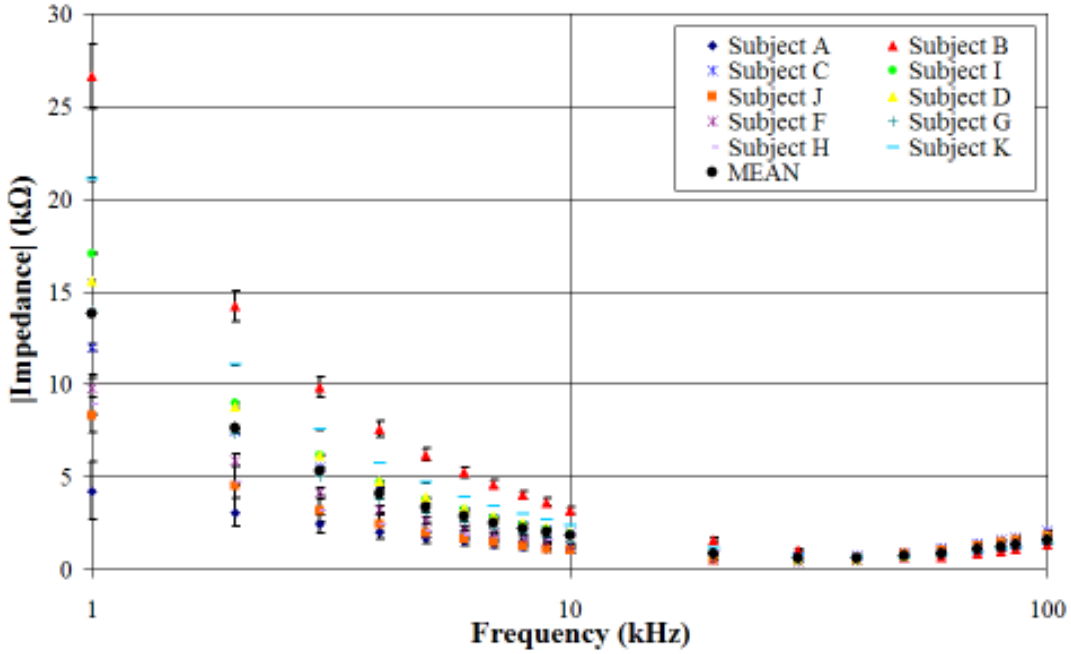


Figure 4.5 Impedance magnitude measurements on the forearm using ZipPrep electrodes.

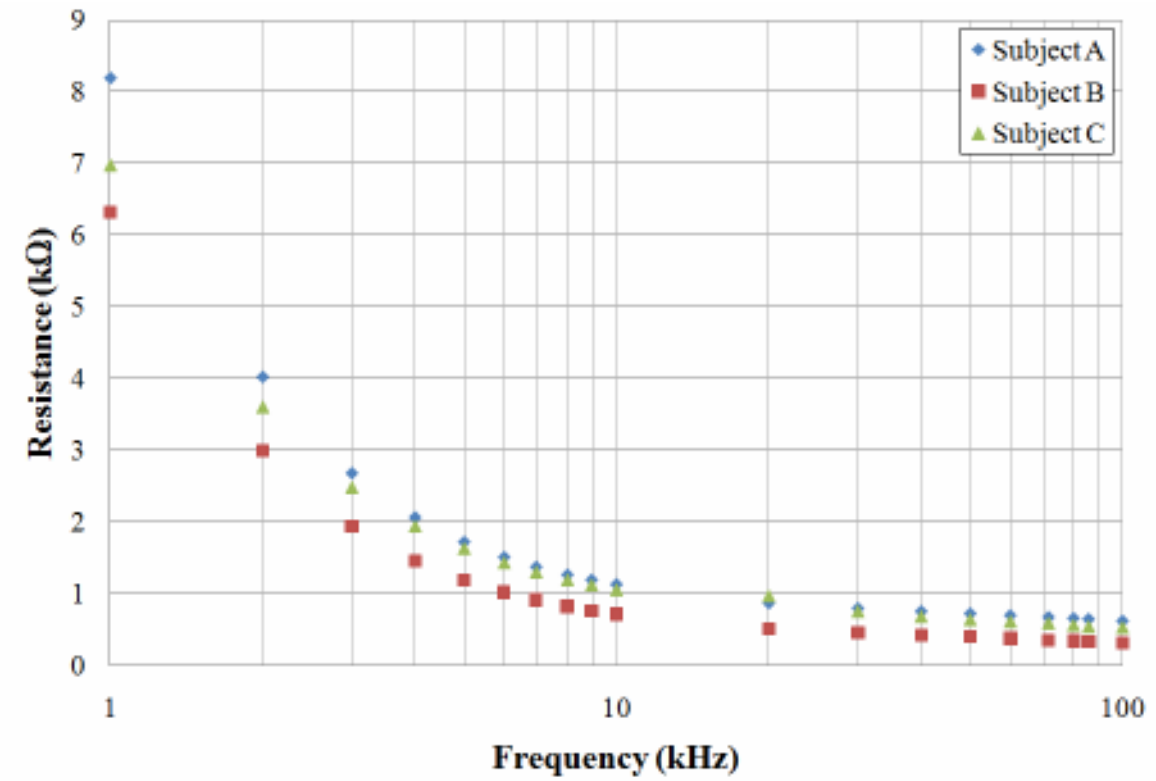


Figure 4.6 Typical measurements of the resistive component over the frequency range, 1 kHz to 100 kHz.

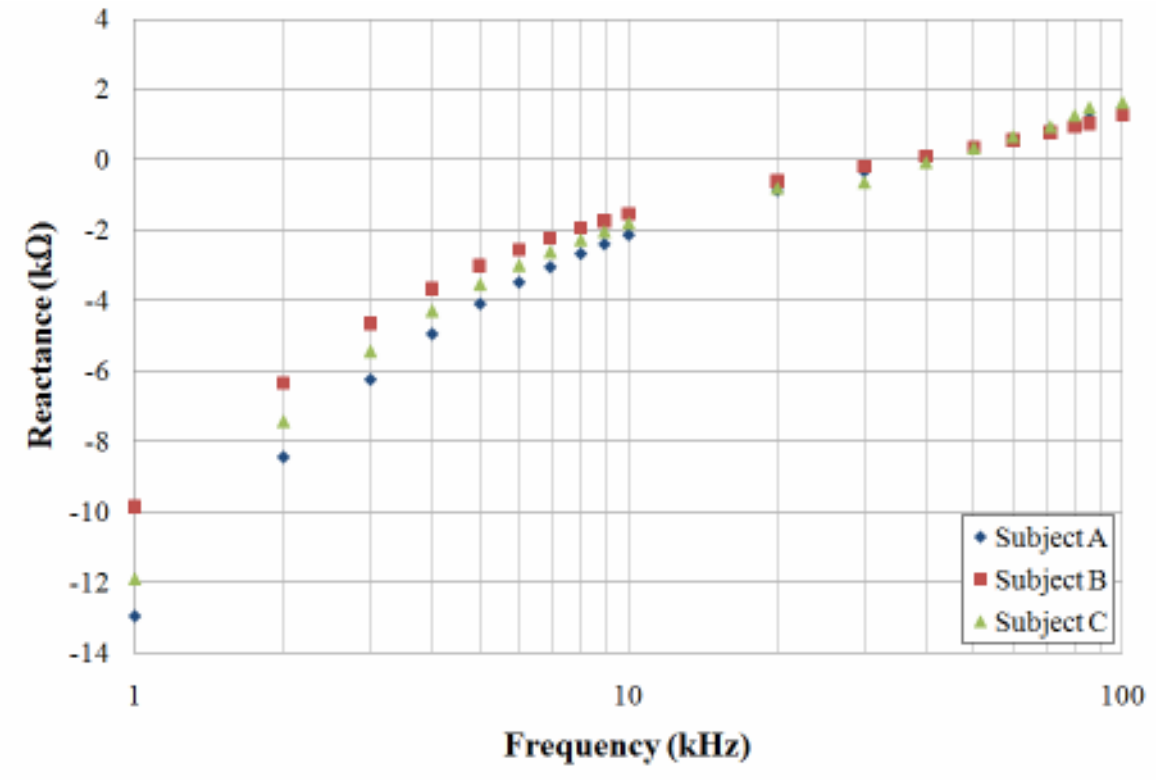


Figure 4.7 Typical measurements of the reactive component over the frequency range.

As shown in figure 4.6 the real component of the composite impedance falls monotonically over the frequency range. The variability between subjects is only slight but they all display a similar pattern over the frequency range. However, the reactive component of the composite impedance (figure 4.7) shows a monotonical increase over the frequency range. It can be seen that at 40 kHz the reactance becomes positive.

These results (figures 4.6. and 4.7) are typical of all the data sets obtained in this chapter. All display a monitonical decrease in resistance and a monitonical increase of reactance with the latter changing to positive at approximately 30-40 kHz. For the purpose of this thesis it was decided to only display the magnitude of the impedance in the future discussions below.

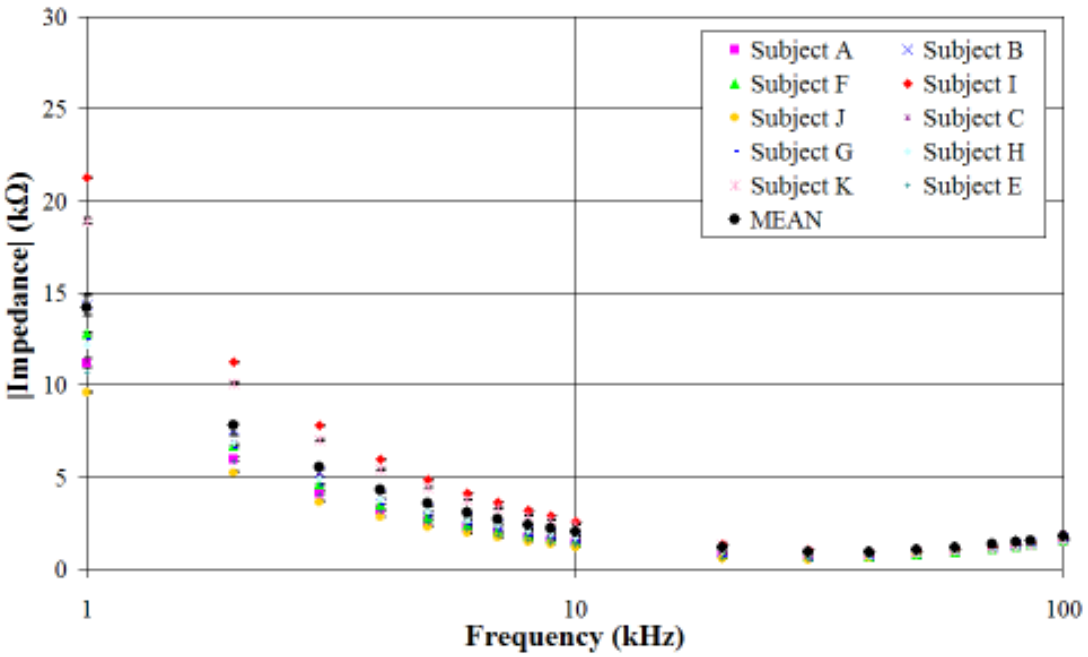


Figure 4.8 Impedance magnitude measurements on the forearm using Red Dot electrodes.

The data points are presented for all subjects at each frequency. The circular black data points show, for each frequency, the mean value over all subjects. Representative data (subjects C and F) are given in Table 4.1. In all cases, the ZipPrep electrodes show an impedance equal to or less than the impedance observed using the Red Dots. The individual component analysis for the Red Dot and ARBO electrodes show similar responses to the ZipPrep electrodes shown in figures 4.6 and 4.7. The resistive component continues to fall across the frequency range whilst the reactive component shows a change to positive at approximately 30 kHz.

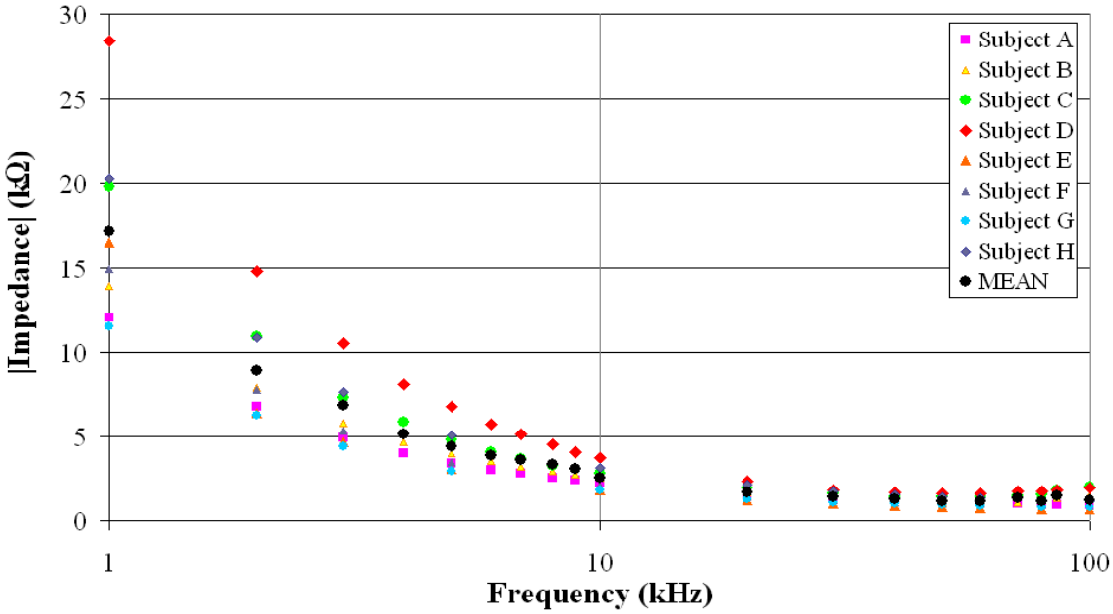


Figure 4.9 Impedance magnitude measurements on the forearm using ARBO electrodes.

Similar measurements were taken on the shin, using ZipPrep electrodes (figure 4.10) and Red Dot electrodes (figure 4.11). Electrodes were firmly positioned and placed 2.8 cm apart (as measured between the centres of the electrode plates) on the anterior shin. The site was unprepared before the electrodes were positioned.

Over the frequency range the shin data shows a similar impedance response to that of the forearm data. There is a larger range of variability at 1 kHz using the ZipPrep electrodes, ranging from 19.12 kΩ to 2.21 kΩ compared to the Red Dot electrodes which range from 17.56 kΩ to 10.95 kΩ. Both sets of data appear to coincide at the higher frequencies, greater than 10 kHz. The mean values, over all subjects, for ZipPrep are 1.93 kΩ at 10 kHz and 1.49 at 100 kHz; Red Dot electrodes yield values of, 1.64 kΩ at 10 kHz and 1.21 kΩ at 100 kHz respectively.

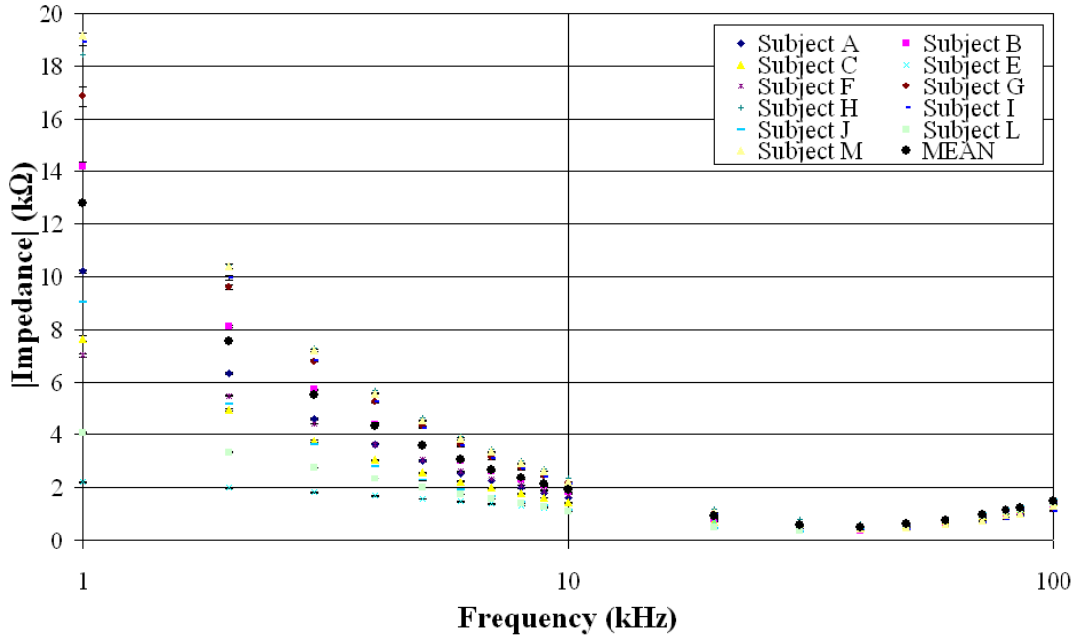


Figure 4.10 Impedance magnitude measurements on the shin using ZipPrep electrodes.

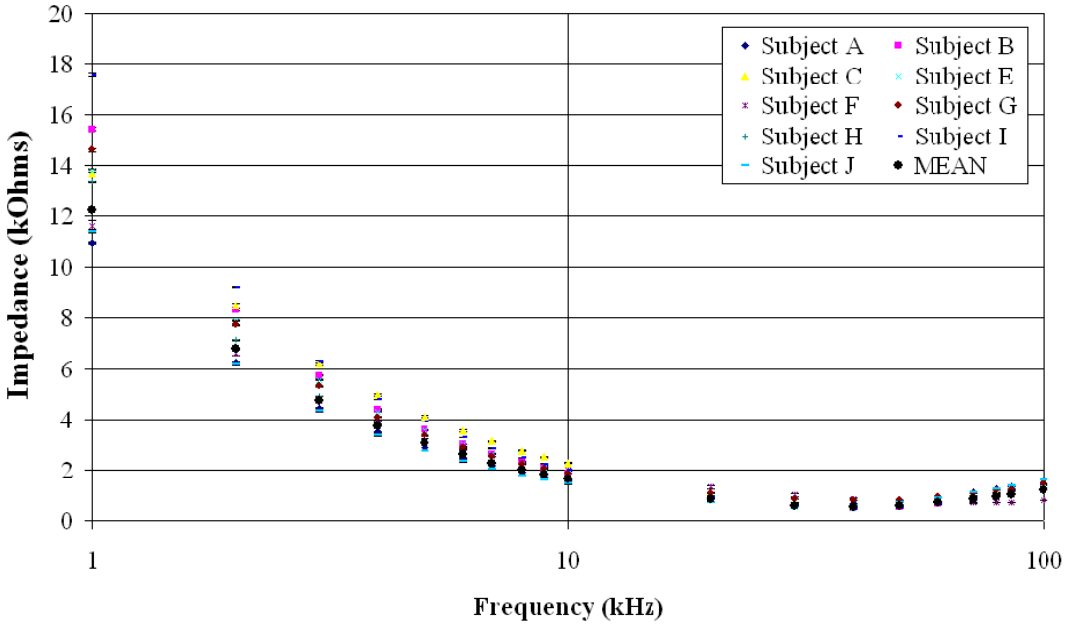


Figure 4.11 Impedance magnitude measurements on the shin using Red Dot electrodes.

Table 4.1 Comparison of data from two volunteers using two electrode types on the forearm and the shin. Data shown are based on 20 repeats at each frequency. The table shows the mean value of total impedance in kΩ and in brackets, the sample standard deviation in Ω.

Subject	Loc-ation	1kHz		10kHz		100kHz	
		ZipPrep	Red Dot	ZipPrep	Red Dot	ZipPrep	Red Dot
C	Arm	12.0 (745)	12.0 (900)	1.9 (46)	1.9 (73)	2.0 (14)	2.0 (62)
	Shin	7.7 (408)	13.0 (520)	1.4 (25)	2.2 (89)	1.4 (6)	1.4 (20)
F	Arm	10.0 (615)	13.0 (365)	1.3 (70)	1.5 (31)	1.6 (8)	1.6 (2)
	Shin	7.0 (298)	23.0 (998)	1.7 (38)	4.0 (416)	1.2 (37)	1.6 (25)

There is a marked improvement in repeatability (i.e. reduced sample standard deviation, SD) between subjects as frequency increases, for Red Dot and ZipPrep electrode types. At 10 kHz the shin data show better repeatability when using the ZipPrep electrodes compared to the Red Dot electrodes; the ZipPreps have a standard deviation of around 30 Ω, compared to at least 100Ω for the Red Dots. The data were seen to coincide better between subjects at 40 kHz in all measurements, irrespective of which electrodes were used. However, the Red Dot electrodes show better consistency between subjects in the lower frequency range (<10 kHz). When considering the repeatability between subjects the data suggest that the composite impedance is more consistent above 10 kHz.

Additional systematic considerations of parameters that may affect measurements are presented in section 4.3.3 onwards.

4.3.2 Scalp Measurements

Initial investigations on the scalp considered the ability to drive current using the two different electrode types, Red Dot and ZipPrep electrodes. The placement of the electrodes was based on the conventional EEG Ten-Twenty system (see chapter 2). In the work presented here, electrode pairs were placed in four measurement configurations on the scalp, as shown in figure 4.12, chosen to represent all possible combinations of contact type:

- two non- hirsute sites
- two hirsute sites

- one hirsute and one non-hirsute

These combinations of sites are expected to aid the understanding of the relative composite impedances arising when electrodes are positioned side-by-side versus opposite locations the head.

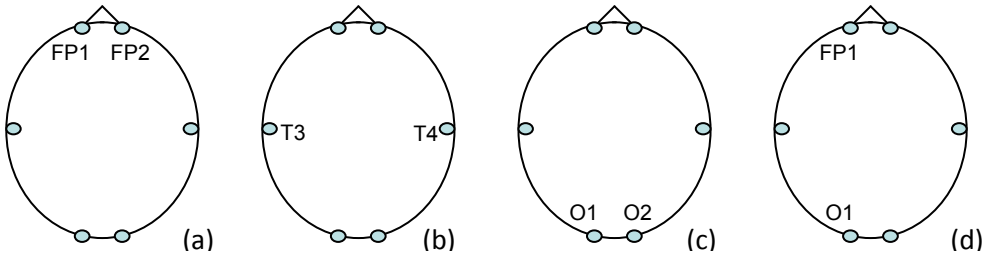


Figure 4.12 Measurement electrode configurations; (a)Forehead – FP1 and FP2; (b) Opposite (side to side) – T3 and T4; (c) Rear – O1 and O2; (d) Opposite (front to rear) – FP1 and O1.

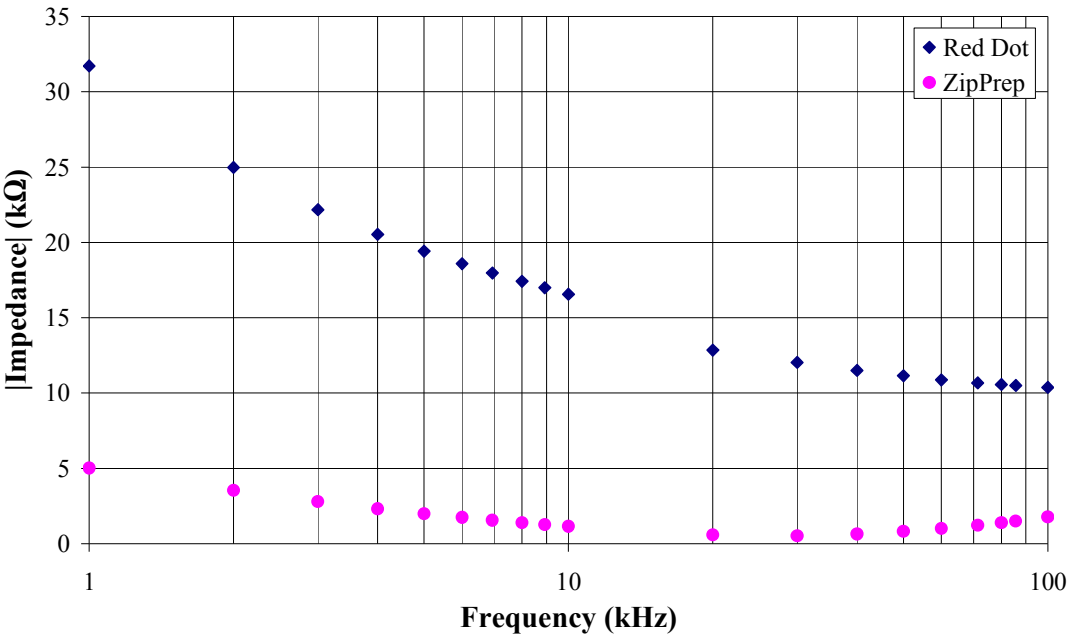


Figure 4.13 Composite impedance measurements made on the forehead of subject A, at FP1 and FP2, comparing the Red Dot and ZipPrep electrodes.

The Red Dot electrodes yielded much higher impedances throughout the frequency range compared to the ZipPreps, as shown in figure 4.13. This resulted in smaller currents being driven into the head: for the Red Dots to deliver the same amount of current as the ZipPreps, the required drive voltage is much higher. The Red Dot electrodes yield composite impedance values of 31.7 kΩ, 16.6 kΩ and 10.4 kΩ at 1 kHz, 10 kHz and 100 kHz respectively, compared to the ZipPrep electrodes, which gave 5.02 kΩ, 1.15 kΩ and 1.79 kΩ, respectively, at the same frequencies.

Figure 4.14 shows that, when using ZipPrep electrodes at FP1 and FP2, subject A exhibited the highest values in the sample, with mean value 3270 + j745 Ω at 1kHz, falling to a minimum of 730 - j80 Ω at 30 kHz, and rising to 417 - j1680 Ω at 100 kHz. For the case of adjacent electrodes figure 4.14 shows there is a range in the data of 3.6 kΩ at 1 kHz and a range of 800 Ω at 100 kHz. The data almost coincide at 30 kHz, with a small difference of less than 50 Ω between the minimum and maximum impedances at that frequency.

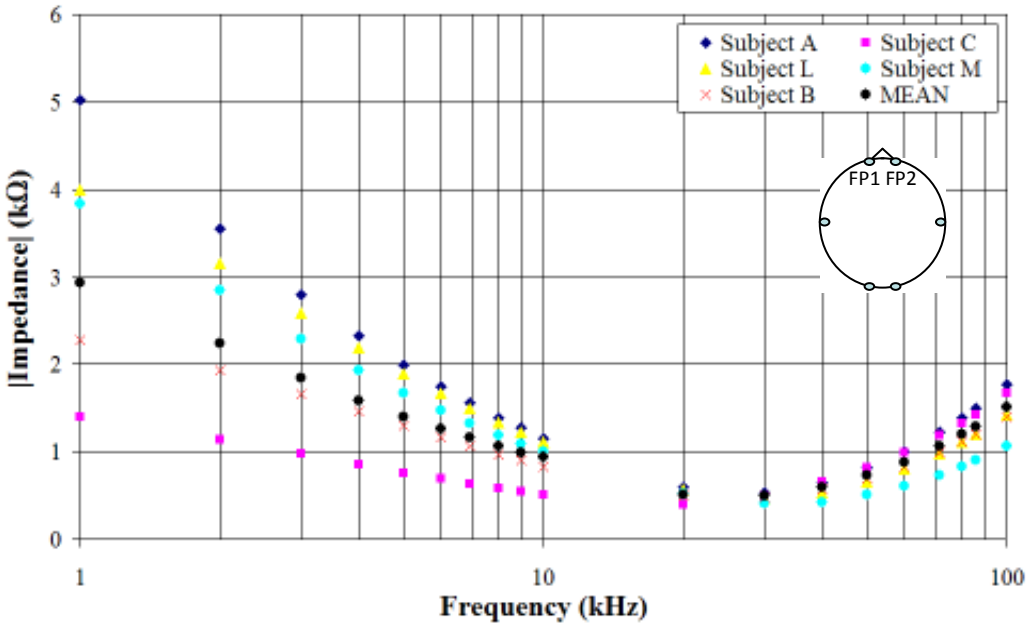


Figure 4.14 Composite impedance measurements from five subjects using ZipPrep electrodes at FP1 and FP2.

Similar variations are generally observed to occur for all electrode locations on the scalp, as for electrodes placed on nearly diametrically opposite positions, FP1 and O1, on the scalp. For the case where the electrodes are on opposite sides of the head, as shown in figure 4.15, the variation at 1 kHz is much greater (9.1 kΩ), and much smaller (200 Ω) at 100 kHz. The data coincide better at a higher frequency, 100 kHz, compared to the case where electrodes are adjacent. Alternative adjacent sites (O1 and O2) and opposite sites (T3 and T4) yielded similar trends as shown in figure 4.15 and 4.16. There is a minimum impedance value that can be observed at 30 to 40 kHz using the ZipPrep electrodes on the scalp, which is clearly visible in all the figures.

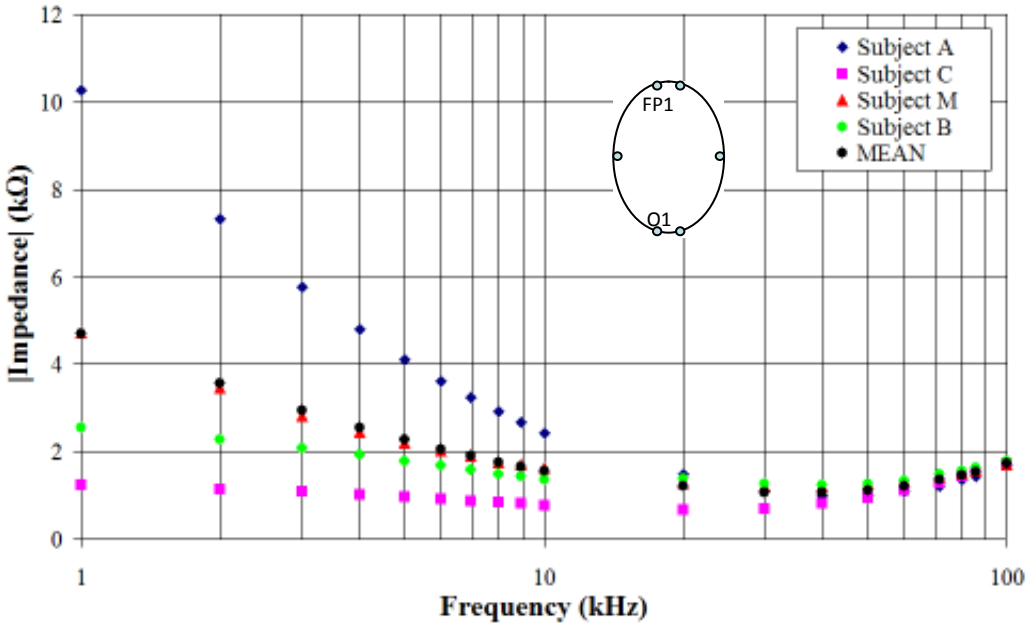


Figure 4.15 Composite impedance measurements from four subjects using ZipPrep electrodes at FP1 & O1.

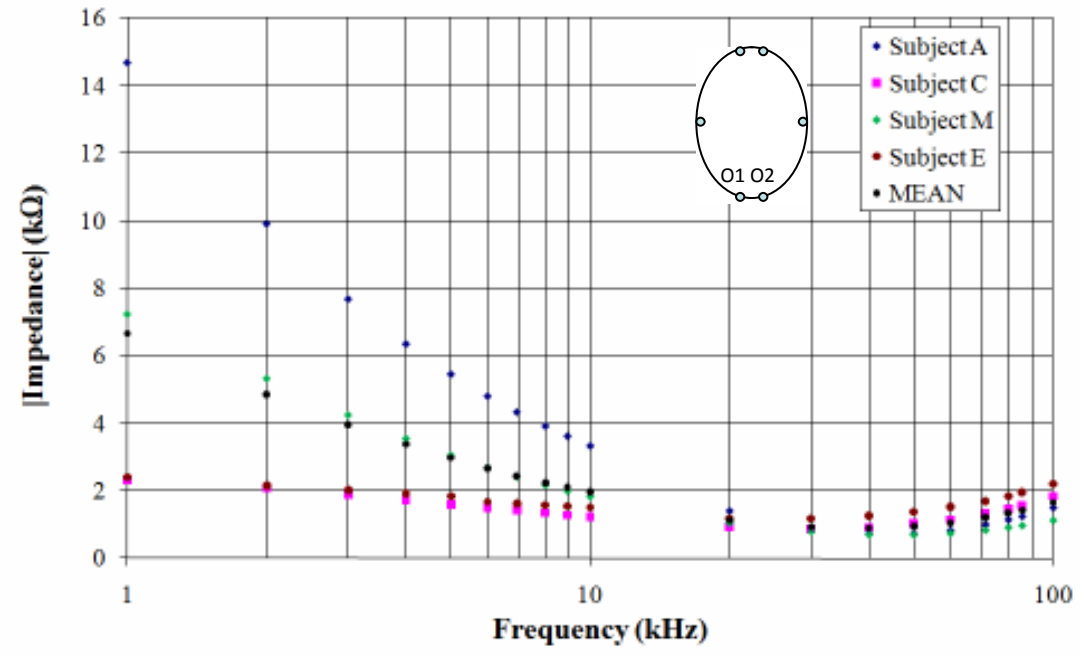


Figure 4.16 Composite impedance measurements from four subjects using ZipPrep electrodes at O1 & O2.

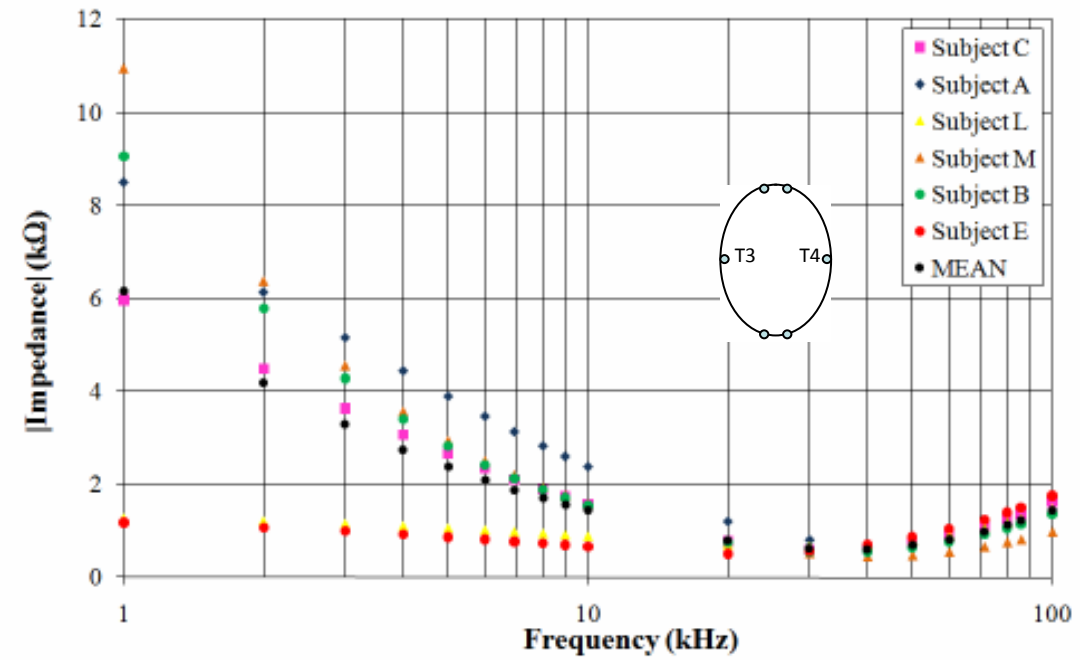


Figure 4.17 Composite impedance measurements from six subjects using ZipPrep electrodes at T3 & T4.

The observations from the ZipPrep data on the scalp are noticeably different to the results obtained from the Red Dot electrodes, shown in figures 4.18 and 4.19. Figure 4.18 shows

that, when using Red Dot electrodes at FP1 and FP2, subject A gives the highest values, which is 26.5 kΩ greater at 1 kHz compared to the mean value using ZipPrep electrodes. This difference in the composite impedance can be seen throughout the frequency range. At 10 kHz the difference is 15.4 kΩ and at 100 kHz the difference is 8.6 kΩ. Unlike the ZipPreps the Red Dot electrodes do not appear to yield a minimum impedance on any of the scalp sites.

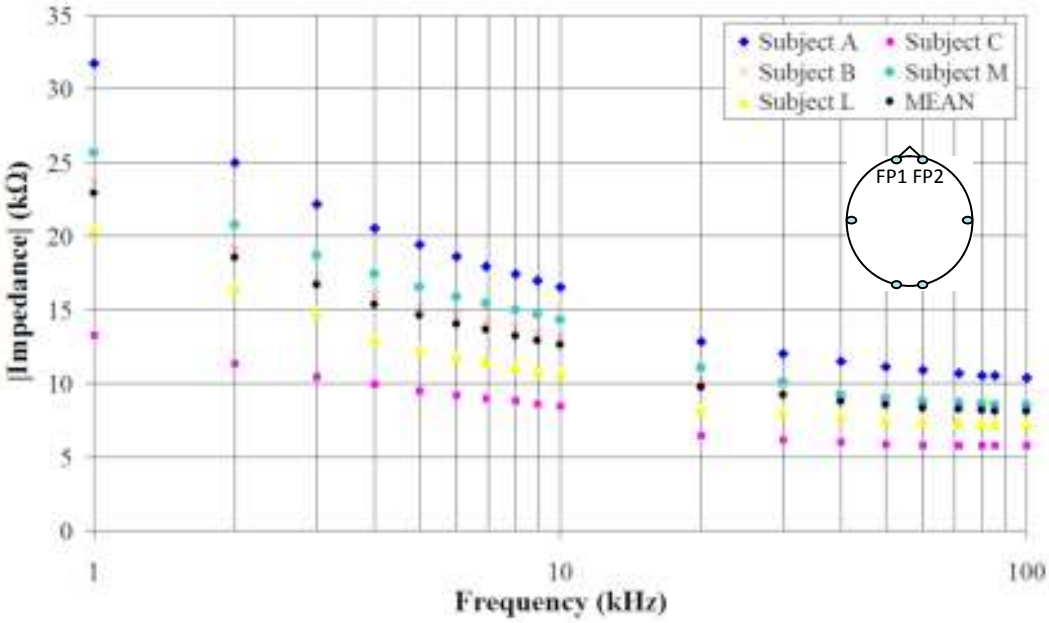


Figure 4.18 Composite impedance measurements from five subjects using Red Dot electrodes at FP1 and FP2.

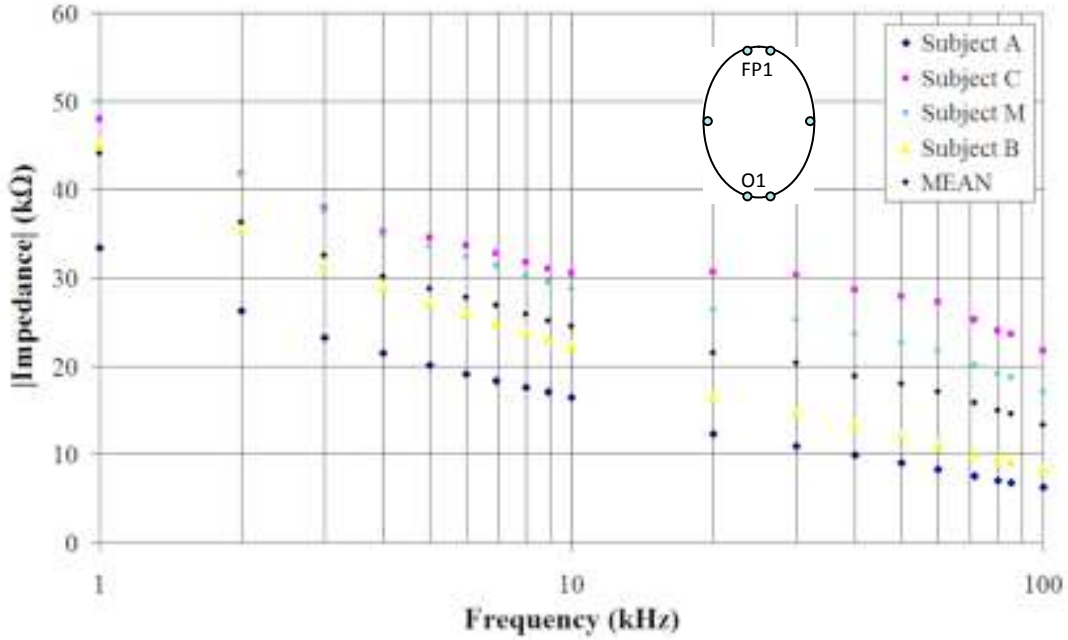


Figure 4.19 Composite impedance measurements from five subjects using Red Dot electrodes at FP1 & O1.

4.4 Time Dependence

During certain measurement processes, electrodes may be left on patients or volunteers for an extended period of time, e.g. >1 hour for typical EEG recordings (Tallgren *et al*, 2004) or haemodialysis (Lonzano *et al,* 1995). The temporal stability of the composite impedance was therefore measured for a similar forearm location to that used in section 4.3.1. Electrodes were placed on the forearm and left in position throughout the experiment. The sites were unprepared before the electrodes were positioned. Figure 4.20 shows measurements taken at 30-minute intervals over a 2-hour period using ZipPrep electrodes.

The composite impedance values monotonically decrease over time at the lower frequencies, below 10 kHz, on all electrodes types. As common with the previous plots in this chapter, there is a minimum in composite impedance at around 40 kHz, which is stable throughout the duration of the experiment, i.e. the impedance does not decrease over time for frequencies greater than 40 kHz.

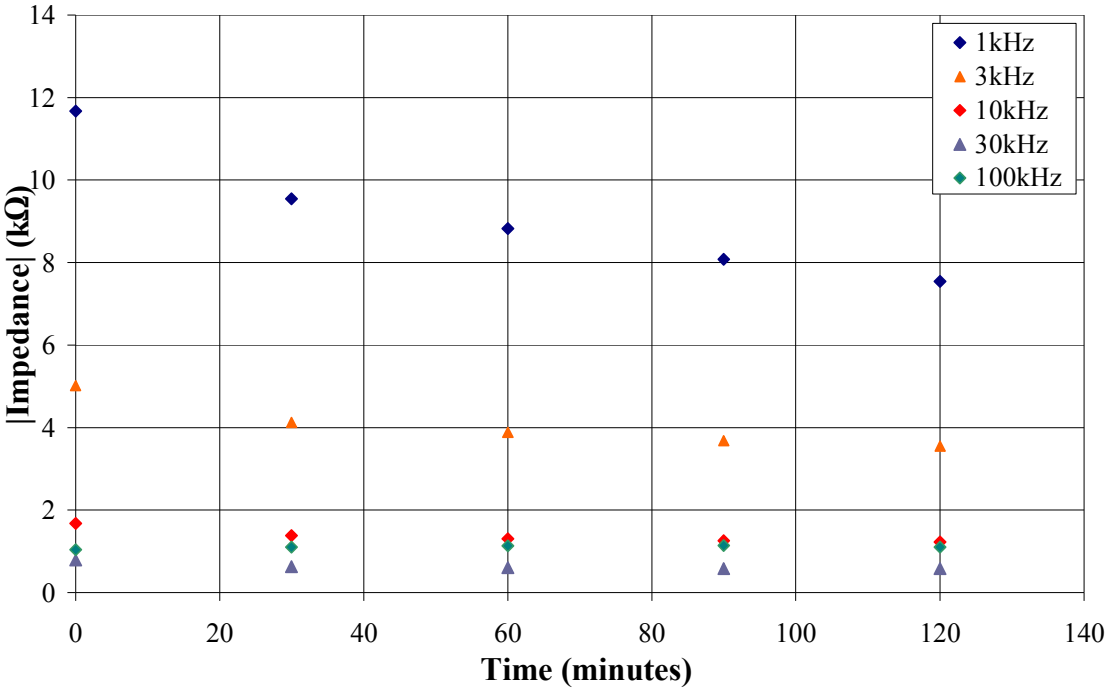


Figure 4.20 Composite impedance measurements using ZipPrep electrodes over an extended period of time on the forearm.

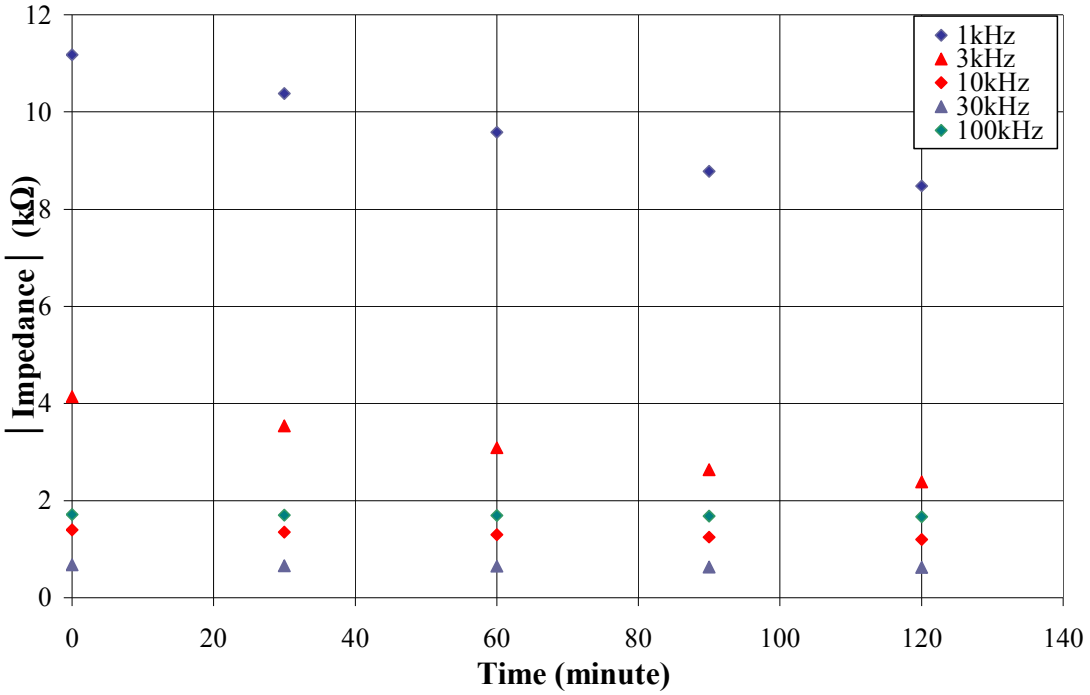


Figure 4.21 Composite impedance measurements using Red Dot electrodes over an extended period of time on the forearm.

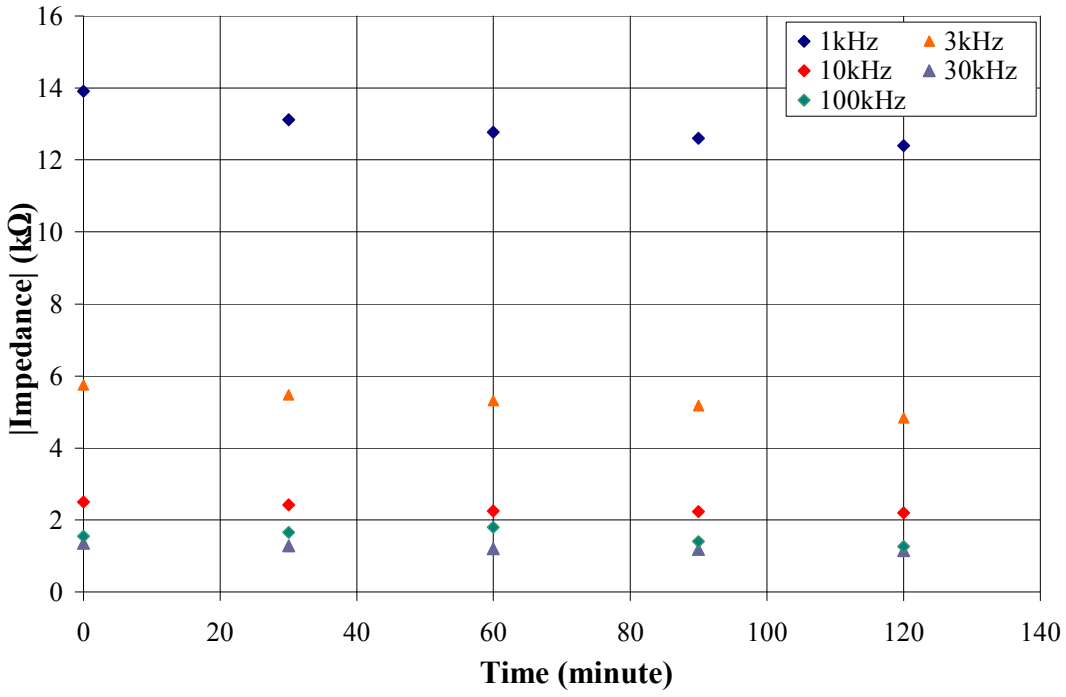


Figure 4.22 Composite impedance measurements using ARBO electrodes over an extended period of time on the forearm.

Similar to the ZipPrep electrodes the composite impedance when using Red Dot electrode decreases over time. At 1 kHz the composite impedance is 11.18 kΩ at 0 minutes, compared to 8.48 kΩ at 120 minutes, a decrease of 24%.

The ARBO electrodes also show a decrease over time. However the percentage decrease is not as great as that of the ZipPrep or Red Dot electrodes. At 1 kHz at time 0 minutes, the composite impedance is 13.91 kΩ, whereas at 120 minutes it is 12.4 kΩ, a change of 10.8%.

The largest change in impedance over time can be seen on the ZipPrep electrodes at 1 kHz; at time 0 minutes the composite impedance is 11.67 kΩ compared to 7.54 kΩ at 120 minutes, a decrease of 35%. At 10 kHz at time 0 minutes the composite impedance is 1.68 kΩ, and at 120 minutes there is a decrease of 27%. However at 100 kHz at time 0 minutes the composite impedance is 1.25 kΩ, increasing slightly at 120 minutes to 1.32 kΩ, a change in composite impedance of +700Ω. To further understand the changes in the impedance magnitude the individual component analysis is shown in figures 4.23 and 4.24.

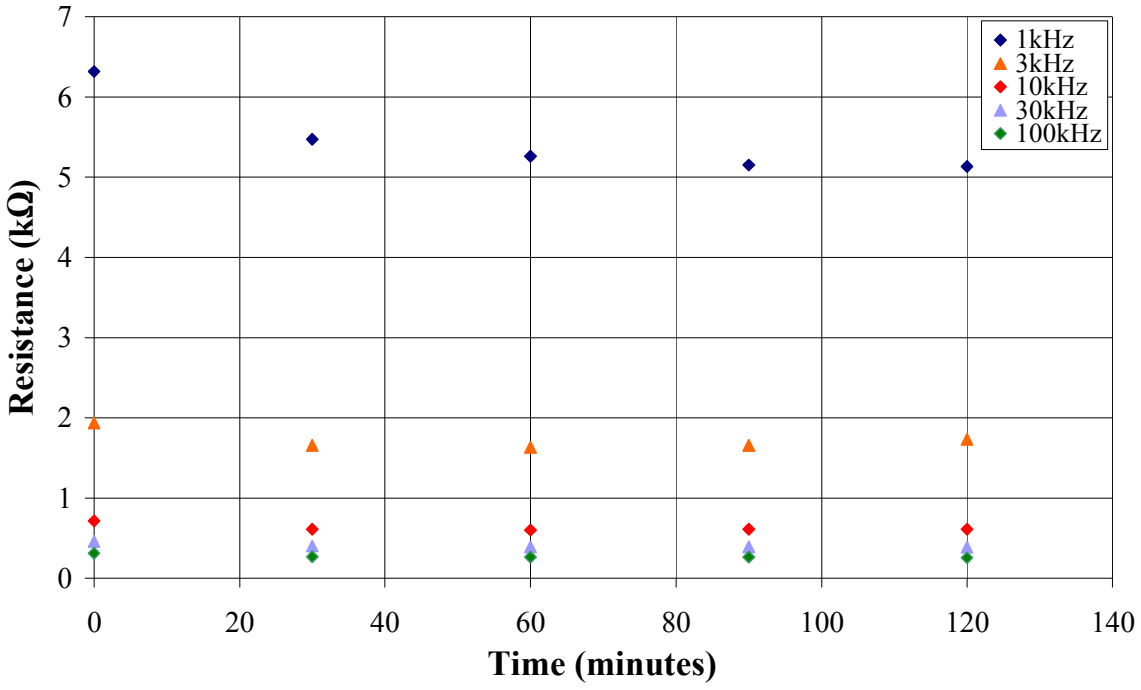


Figure 4.23 Resistive component measurements using ZipPrep electrodes over an extended period of time on the forearm.

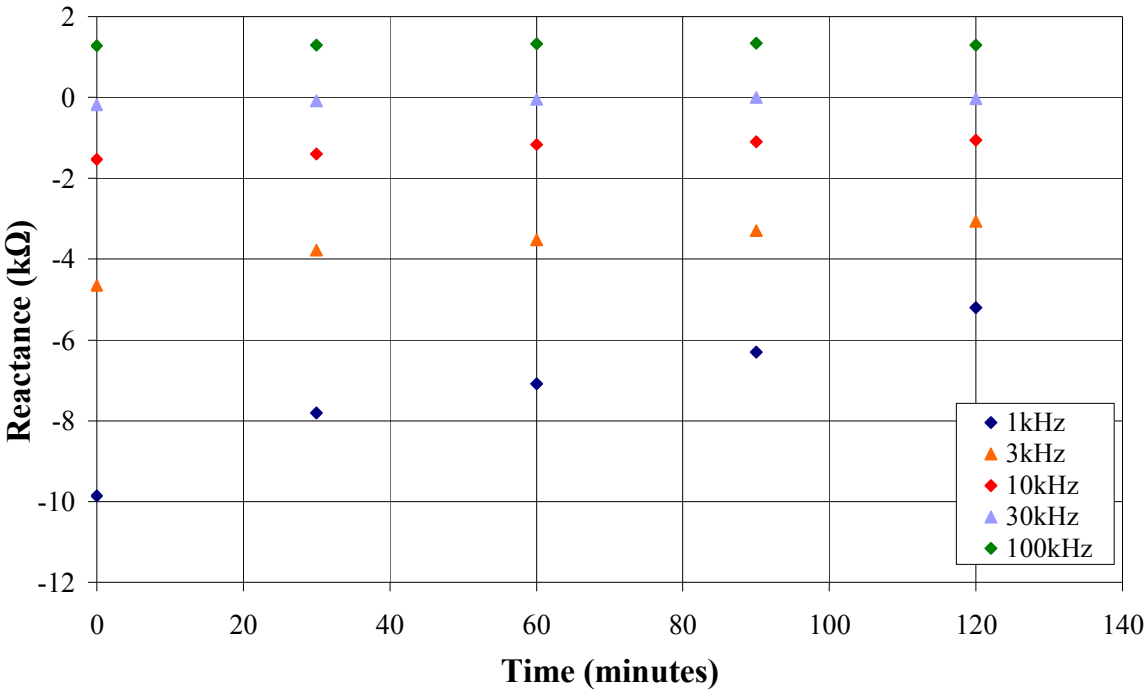


Figure 4.24 Reactive component measurements using ZipPrep electrodes over an extended period of time on the forearm.

The general trend shows that the resistance decreases with time whereas the reactance increases with time, over the frequency range, as previously discussed. Similar to the impedance magnitude, shown in figure 4.20, the resistance decreases significantly over time at the lower frequencies (less than 10 kHz) and only varies slightly with time at 100 kHz (approximately 60Ω). Although the initial decrease in resistance at 1 kHz over the first 30 minutes is relatively large (approximately 845Ω) it stabilises over the next 90 minutes, only decreasing by 340Ω. The reactive component (figure 4.24) increases substantially with time for the lower frequencies (less than 10 kHz) and has a minimal increase at 100 kHz (22Ω). At 1 kHz the reactance continues to increase over time. At time 0 minutes the reactance is -9.86 kΩ, increasing by 2.05 kΩ at 30 minutes, increasing by 720 Ω at 60 minutes, increasing by 780 Ω at 90 minutes and finally increases by 1.10 kΩ by 120 minutes. This means that, between the initial measurement (0 minutes) to the final measurement (120 minutes), there was an increase in reactance of 4.66 kΩ, i.e. nearly a 50% change.

The equation (4.1) shows the relationship between the resistance and the reactance in the impedance magnitude. From this equation and the data presented in figure 4.23 and 4.24 it is

possible to determine that the change in reactance is the dominant feature in reducing the impedance magnitude over time, as seen in figure 4.20.

4.5 Preparation Techniques

It is common practice during bio-feedback measurements such as EEG and ECG to prepare the skin before placing the electrodes. This is usually done by cleaning the site with alcohol, followed by shaving and abrading the area (McCann ed, 2008). The number of electrodes that can be placed on the scalp in EEG can vary from 32 to over 64 electrodes. If each area has to be rigorously prepared it can take a long time to get the subject/patient ready for measurements and it is unpleasant for those needing a full set of EEG electrodes. This section will show results using the previously described setup with different preparation techniques.

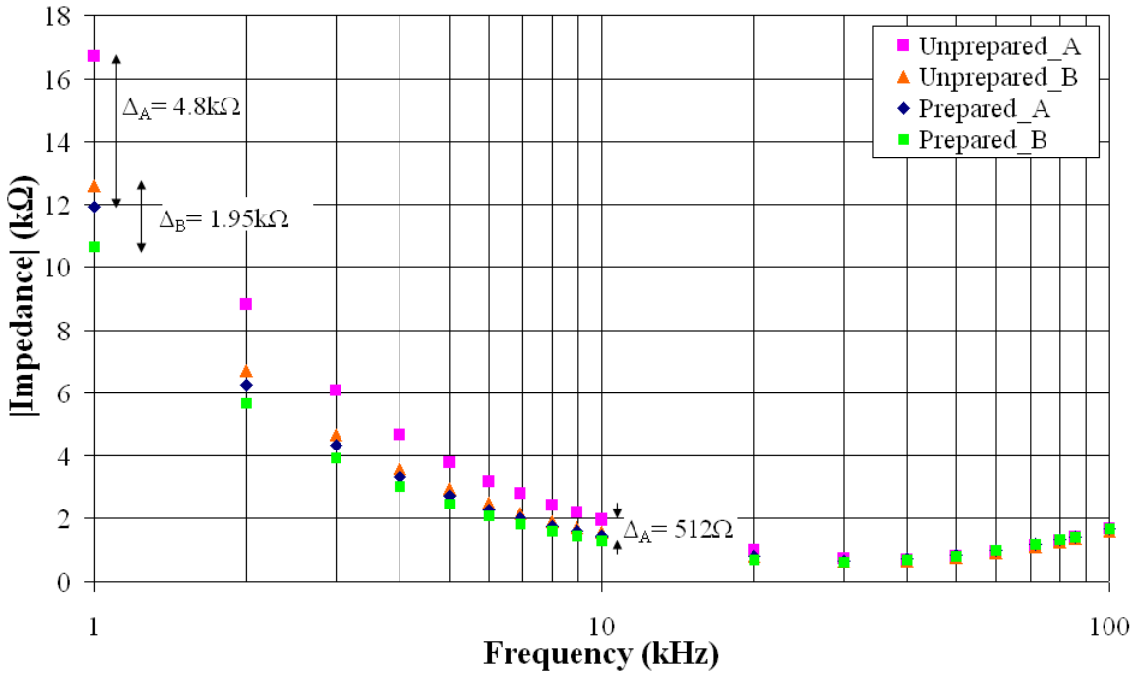


Figure 4.25 Composite impedance measurements of two subjects using ZipPrep electrodes before and after abrasion.

At an area on the anterior forearm, composite impedance measurements were taken without any site preparation. The electrodes were then removed before the area was cleaned with alcohol and abraded for a few seconds using coarse tissue paper as an abrasion pad. New

electrodes were then applied. The results (figure 4.25) show a large reduction in impedance at the lower frequencies, 1-10 kHz as shown in table 4.2.

Table 4.2 Comparison of composite impedance with unprepared and prepared skin on two subjects at selected frequencies.

	Subject A			Subject B		
	Unprepared	Prepared	Difference	Unprepared	Prepared	Difference
1 kHz	16.7 kΩ	11.89 kΩ	4.8 kΩ	12.6 kΩ	10.65 kΩ	1.95 kΩ
10 kHz	1.97 kΩ	1.45 kΩ	520 Ω	1.55 kΩ	1.3 kΩ	250 Ω
100 kHz	1.68 kΩ	1.67 kΩ	10 Ω	1.61 kΩ	1.6 kΩ	10 Ω

An alternative method of preparing the skin is by gently removing the upper layers of the skin by placing an adhesive tape over the area and gently removing it to remove dead skin cells that stick to the tape (Yamamoto and Yamamoto, 1975). This experiment was carried out as a potential option for skin preparation on patients that may not be able to have harsh abrasion, for example neonatal babies.

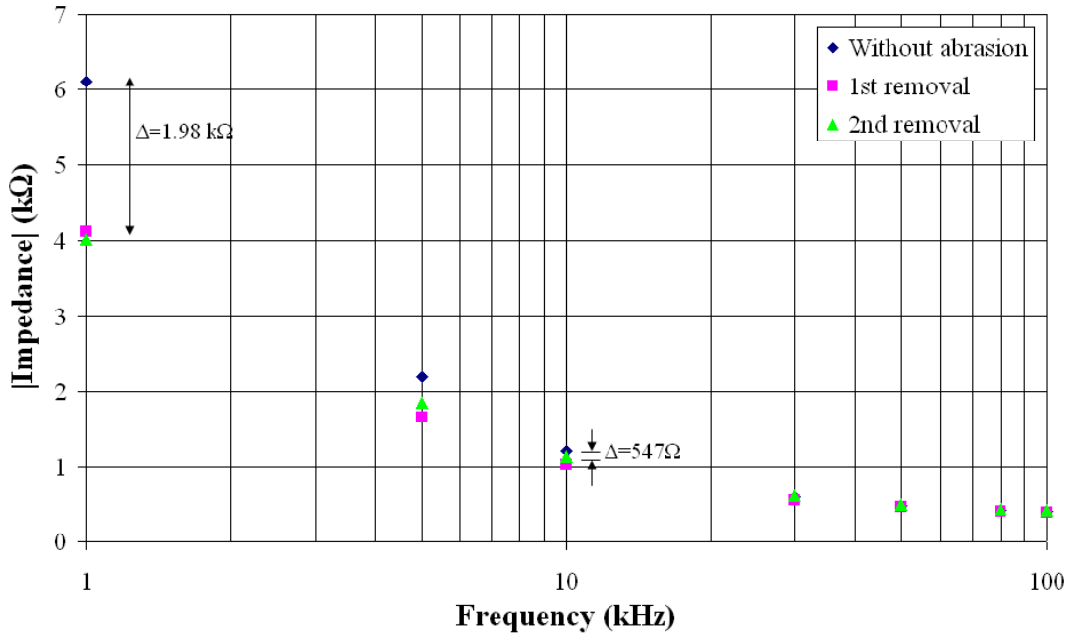


Figure 4.26 Composite impedance measurements using ZipPrep electrodes with removal of stratum corneum by adhesive tape.

Figure 4.26 shows the composite impedance changes associated with the removal of the upper layers of the skin, namely the stratum corneum. Measurements were taken on the forearm without preparation, shown by the blue diamond points. Measurements after the adhesive tape was placed on the skin to remove dead skin cells, are shown by the pink

squares. The change in impedance before and after removal is 1.98 kΩ at 1 kHz, 547Ω at10 kHz and 13Ω at 100 kHz. The second adhesive removal shows a slight decrease in the composite impedance at the frequencies less than 10 kHz. However these changes are not as great as the first removal.

4.6 Separation of Electrodes

The distance between the two electrodes was varied in an attempt to understand the impedance contributions from the skin and the underlying tissues. Previous studies have looked at the spatial variability in the 10-20 montage (Towle *et al*, 1993; Khosla *et al*, 1999) and reported 3D measurement variability between subjects as great as 5mm, and as much as 7.7mm between different sessions. Therefore, it is important to know if these separations change the composite impedance.

Electrodes were placed side by side (with adhesive pads touching) on the forearm, then one electrode was removed and repositioned at various separations (measured between the edges of the adhesive pads). Tests were carried out using the ZipPrep electrodes (typical results are shown in figure 4.27 – 4.29) and the Red Dot electrodes (typical results are shown in figure 4.30 – 4.32).

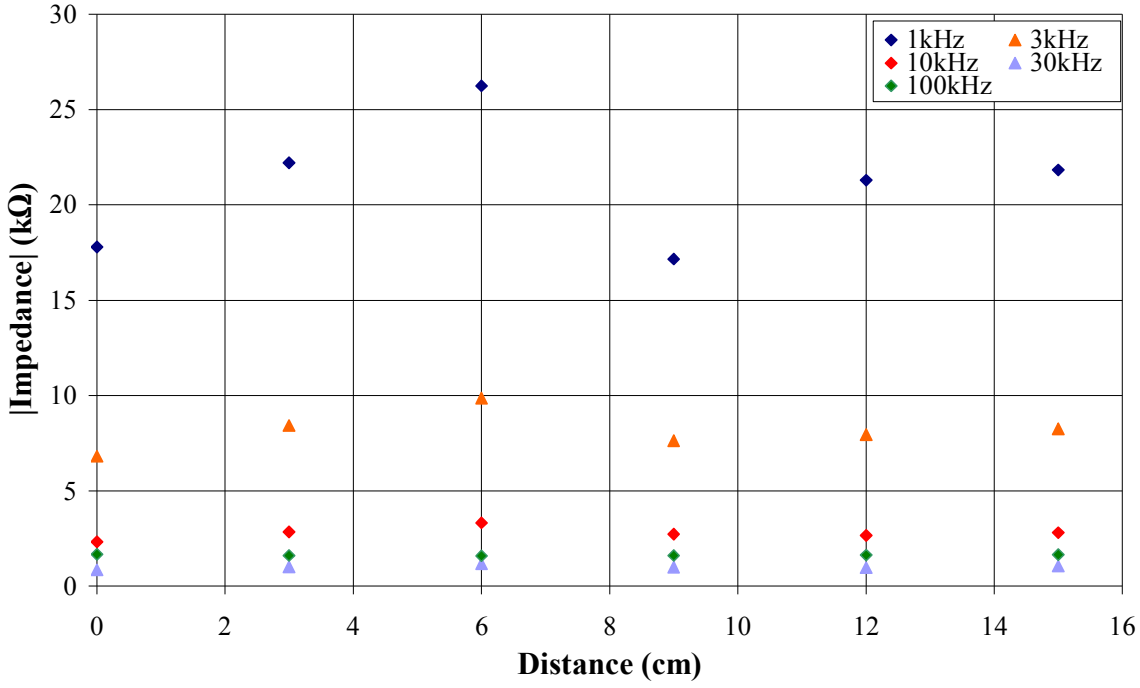


Figure 4.27 Impedance measurements on subject A using ZipPrep electrodes with varying distance between the electrodes.

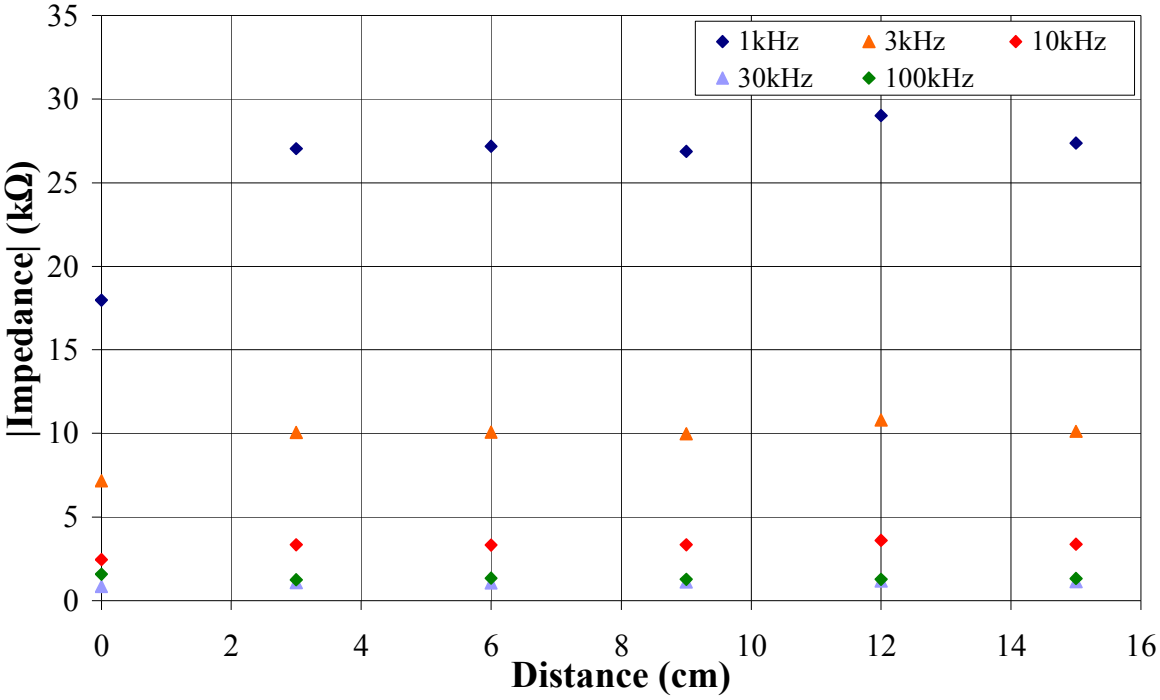


Figure 4.28 Impedance measurements on subject B using ZipPrep electrodes with varying distance between the electrodes.

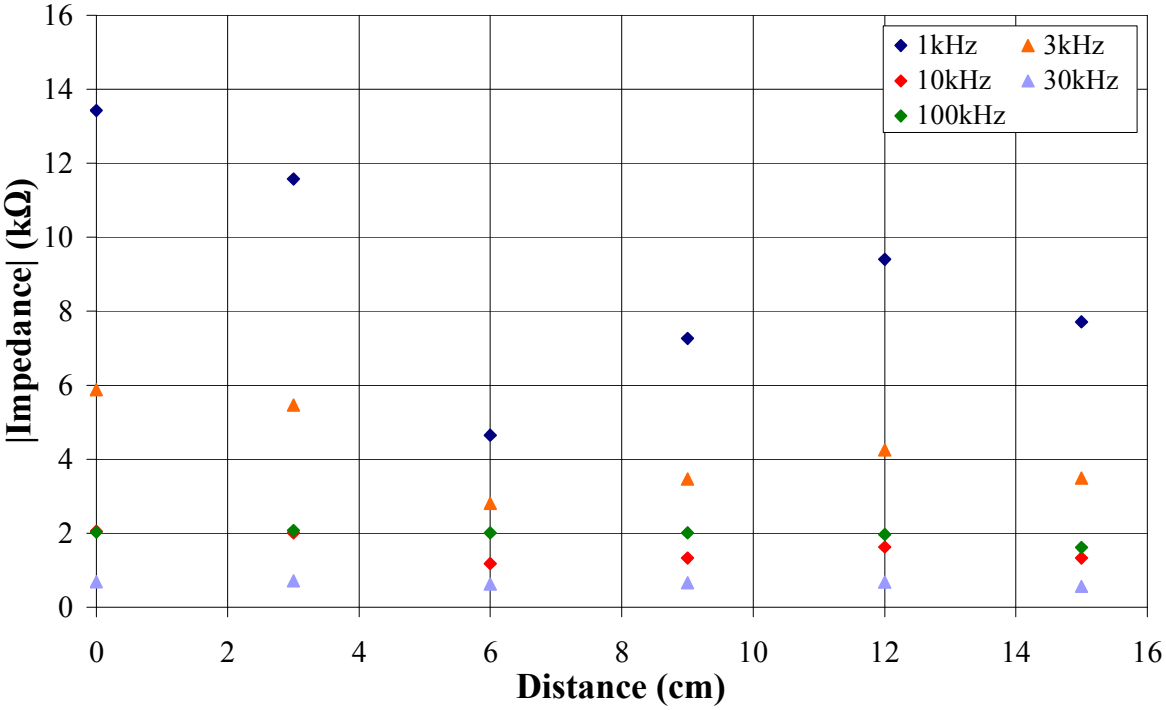


Figure 4.29 Impedance measurements on subject C using ZipPrep electrodes with varying distance between the electrodes.

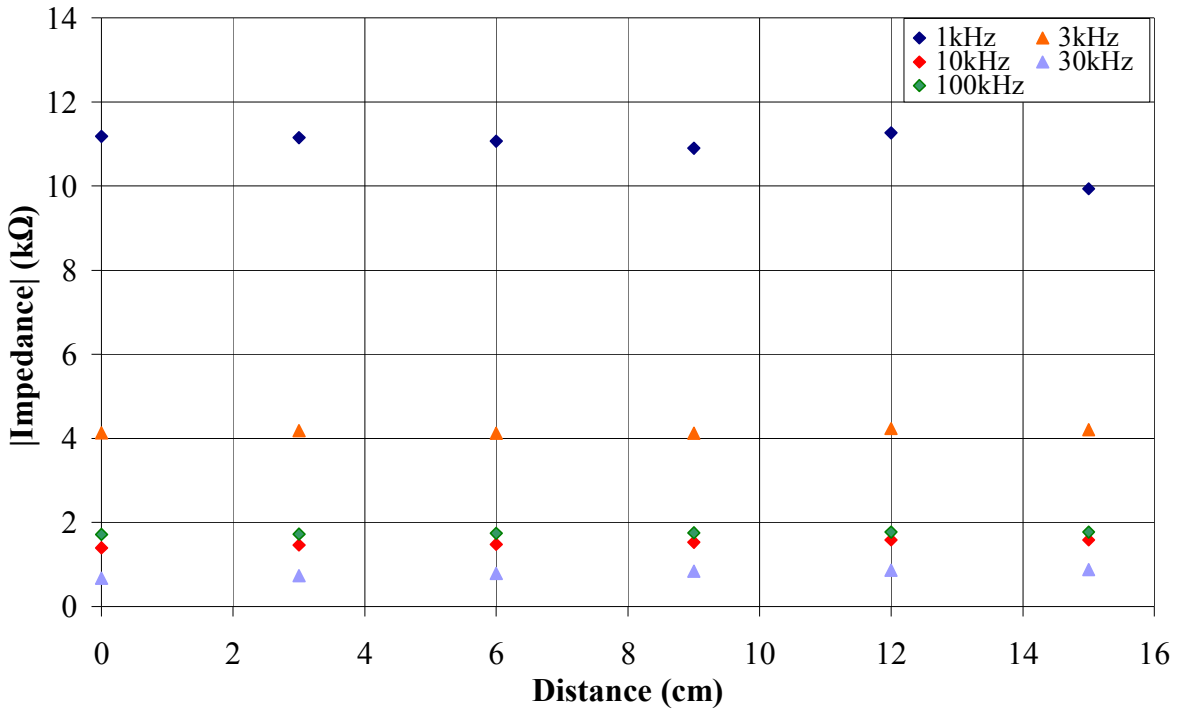


Figure 4.30 Impedance measurements on subject A using Red Dot electrodes with varying distance between the electrodes.

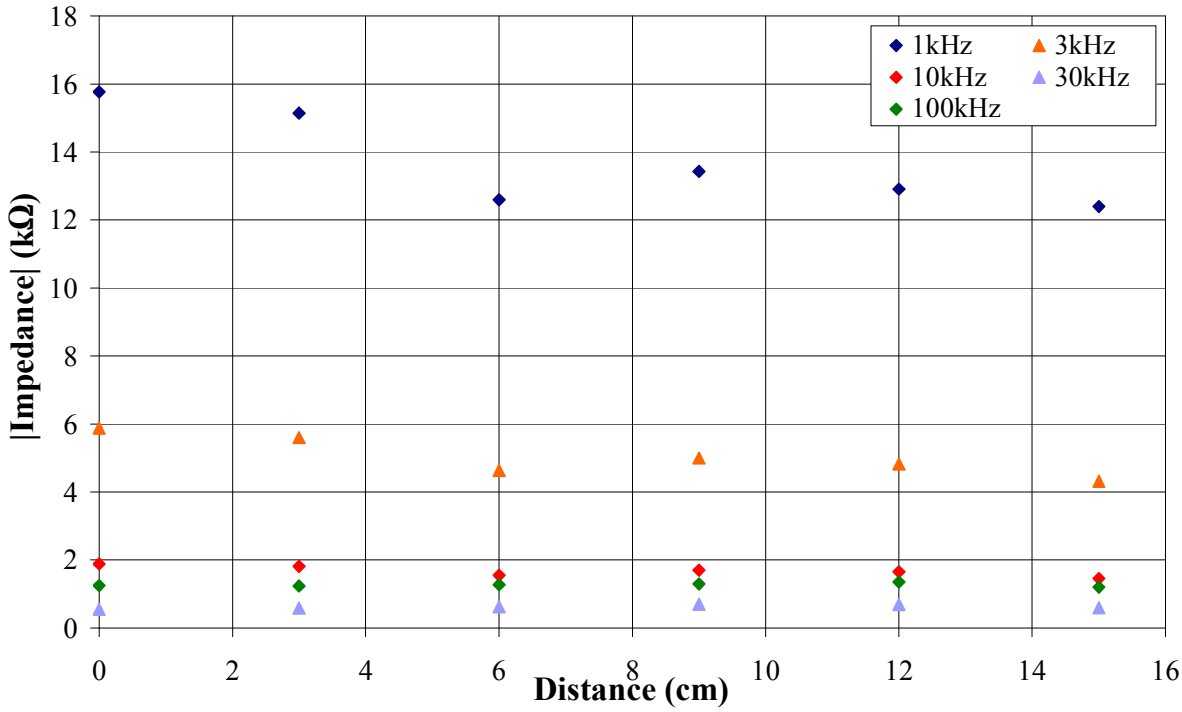


Figure 4.31 Impedance measurements on subject B using Red Dot electrodes with varying distance between the electrodes.

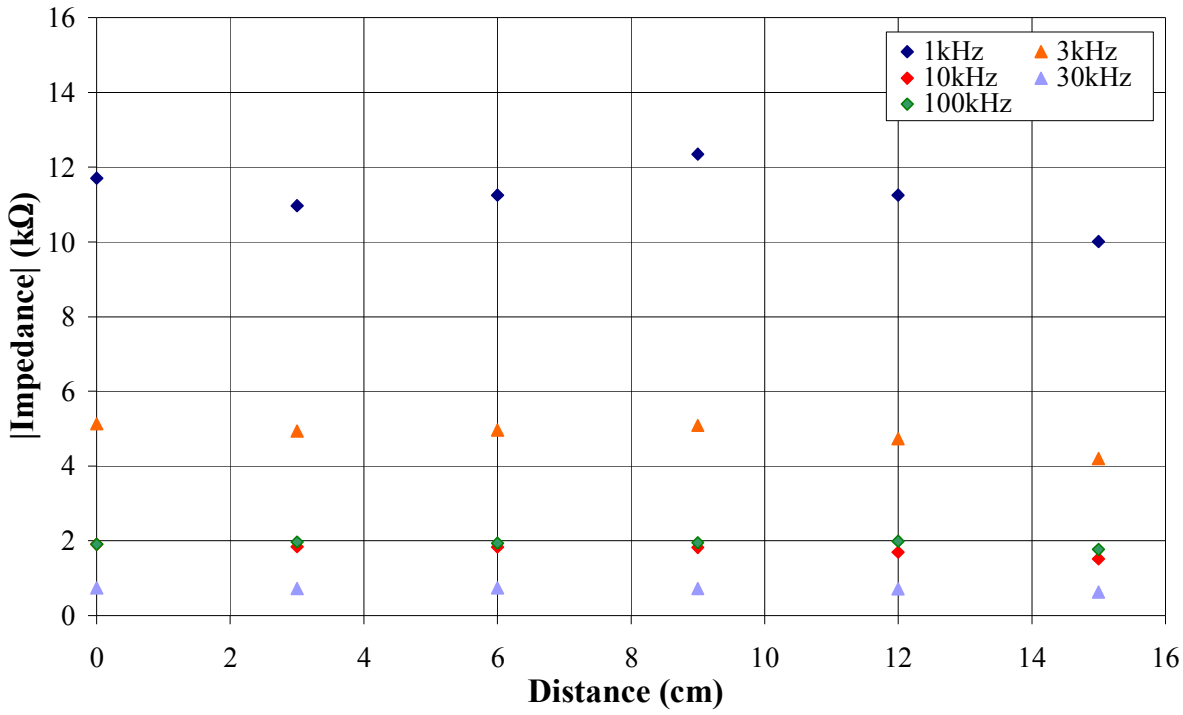


Figure 4.32 Impedance measurements on subject C using Red Dot electrodes with varying distance between the electrodes.

Figures 4.27 – 4.29 display the variation of composite impedance values with separation of ZipPrep electrodes on the forearm. They show a high variability at 1 kHz across all subjects, with all subjects having a similar maximum change of approximately 9 kΩ. There is a minimum amount of variability in the impedance at 40-60 kHz. At 10 kHz the impedance is 2.31 kΩ when the electrodes are together, compared to 2.8 kΩ when they are 15 cm apart, which is an impedance change of approximately 500 Ω.

With the Red Dot data, shown in figures 4.30 – 4.32, there is not a large variability at the lower frequencies. The largest individual variation can be seen on subject B at 1 kHz, showing a change of 3.17 kΩ, whereas the other subjects show maximum variability of 1-2 kΩ. There is a noted minimum in the composite impedance which is stable with varying distance, at 30-50 kHz, a slightly lower frequency than the ZipPrep electrodes. At 10 kHz the impedance is 1.39 kΩ when electrodes are adjacent, compared to 1.58 kΩ at 15 cm apart, which is an impedance change of approximately 200 Ω.

Tables 4.3 and 4.4 show the resistive and reactive components of the impedance magnitude for the measurements made using ZipPrep electrodes on subject A. The results are typical for all subjects. The resistance initially decreases at 3 cm apart for lower frequencies (less than 10 kHz) before increasing until reaching a distance of 12 cm where it decreases again. At the higher frequencies it does not vary severely, with the maximum increase of 280Ω (at 30 kHz) between electrodes side by side and 6 am apart. A similar trend can be seen in the reactive component, with the lower frequencies measuring the largest variability. It is also noted that there is a similar trend with the data at a distance of 6 cm, showing that there is a decrease in reactance followed by a rise at 9 cm before it finally decreases at 12 and 15 cm apart.

Table 4.3 Measured resistance (kΩ) at particular frequencies with respect to an increasing distance between the two electrodes (subject A using ZipPrep electrodes).

Separation (cm)	1kHz	3kHz	10kHz	30kHz	100kHz
0	8.19	2.69	1.14	0.81	0.63
3	5.78	2.29	1.20	0.88	0.69
6	6.03	2.49	1.33	1.09	0.87
9	7.16	3.06	1.31	0.89	0.68
12	5.16	2.06	1.15	0.88	0.69
15	5.49	2.23	1.24	0.95	0.75

Table 4.4 Measured reactance (kΩ) at particular frequencies with respect to an increasing distance between the two electrodes (subject A using ZipPrep electrodes), where a negative value indicates that the impedance lags the resistance, and a positive value indicates that the total impedance leads the resistance.

Separation (cm)	1kHz	3kHz	10kHz	30kHz	100kHz
0	-12.95	-6.23	-2.12	-0.31	1.49
3	-21.51	-8.21	-2.62	-0.48	1.44
6	-25.87	-9.69	-3.08	-0.76	-0.29
9	-14.93	-6.91	-2.41	-0.44	1.45
12	-20.69	-7.72	-2.43	-0.42	1.47
15	-21.10	-7.98	-2.54	-0.46	1.46

4.7 Muscular Movement

Electromyography (EMG) is a method of measuring the electrical potential changes that are present under muscular contractions/relaxation (Merletti and Parker, 2004), and is usually measured by needle electrodes. Typical signals are usually 0.1–5 mV at dc – 10 kHz (Webster, 1998).

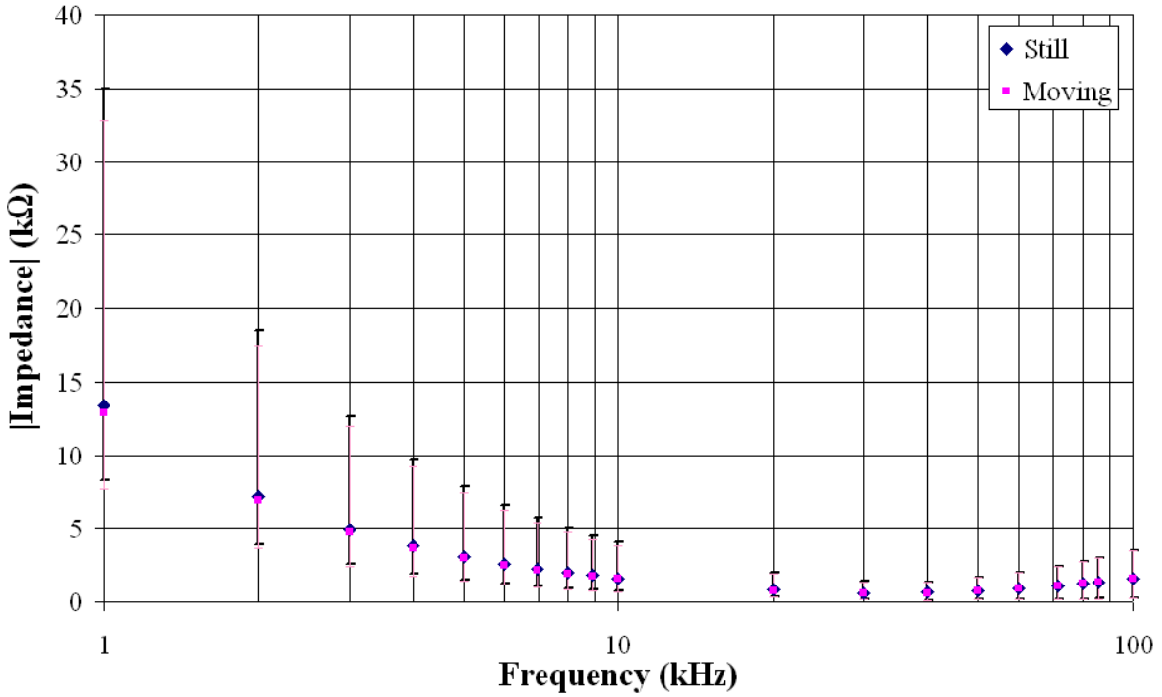


Figure 4.33 Mean impedance measurements (for all subjects) comparing 'static hand' and 'moving hand' using ZipPrep electrodes. Y-axis bars show the range of data points across all subjects for both still and moving.

The previous results discussed in this chapter assume that the impedance changes are not related to muscle movement. This section will attempt to identify the changes in impedance associated with muscle movement over the frequency range, 1-100 kHz. Subjects were asked to clench and relax their hand throughout the experiment. As shown in figure 4.33 there is no significant difference in the mean of the two conditions; static and moving. The composite impedance at all frequencies is within similar ranges, illustrating that at these frequencies is not influenced by the muscular movement.

Table 4.5 The P Value calculated using a rank correlation test, to determine if there is a significance difference between the data when the subject is moving their hand, compared with remaining static. Significance level is $p<0.01$.

Freq	P Value
1	0.000
2	0.000
3	0.000
4	0.000
5	0.000
6	0.000
7	0.000
8	0.000
9	0.000
10	0.000
20	0.000
30	0.000
40	0.000
50	0.000
60	0.000
70	0.004
80	0.588*
90	0.022*
100	0.0025

The above table shows the p-value for each of the frequencies, comparing the significance of the differences between the data for motion and static conditions. The P-Value was calculated using a non-parametric test, since it is not known if the data is normally distributed. Non-parametric tests assume less about the data. The non-parametric test used was a Kendall Tau Rank Correlation Test, with a null hypothesis of no correlation between data. The table shows that the data are correlated throughout most of the frequency range (1 kHz – 670 kHz and 100 kHz). However 80 and 90 kHz (*) are greater than the significance level, meaning that it is not possible to conclusively dismiss the null hypothesis. This means that when a subject is moving the composite impedance measured is not affected by the 'additional' EMG voltage changes below a measurement frequency of 70 kHz.

4.8 Discussion

This chapter has explored the composite impedance of three disposable electrode types, the ZipPrep, the Red Dot and the ARBO electrodes over a frequency range 1 – 100 kHz. The main aim was to inform the design of a new portable brain imaging device using EIT. The data has considerable relevance to EIT system design, in terms of the necessary current drive and voltage measurement design conditions.

Before the tests were carried out, on informed volunteers, the bespoke safety circuitry was rigorously tested to ensure it was not contributing to the measurements. As described in section 4.2.1, tests were performed on inanimate objects and the measurements from the RC networks matched the calculated results. The calibration tests provided good validation of the nulling procedure which was adopted to negate the impedances due to the safety circuitry.

Prior to the scalp tests, composite impedance measurements on the forearm and shin measurements were prepared. These results showed some evidence of a minimum composite impedance value at a frequency of 30-40 kHz, for all electrode types. However the ZipPrep electrodes have a greater variability between subjects at lower frequencies, less than 10 kHz. Compared to the Red Dot electrodes on the forearm, the ARBO electrodes have a greater variability between subjects across the frequency range (seen in the figures in section 4.3.1). The inter-subject variability is greater in the ZipPreps across the whole frequency range compared to the Red Dot electrodes. However, above 10 kHz all sets of electrodes display an excellent short term repeatability ($p<0.01$; calculated using rank correlation statistics).

Figure 4.27 shows the individual components of the resistance and the reactance that result in the impedance magnitude (4.2) for a typical set of forearm data.

$$Z = R + jX$$

$$\therefore |Z| = \sqrt{R^2 + X^2} \tag{4.2}$$

Between 40-50 kHz the reactive component is negligible meaning, that the impedance is dominated by the resistive component. However above 50 kHz the reactive component becomes the most dominant feature in the impedance, causing a slight increase in impedance at the highest frequencies.

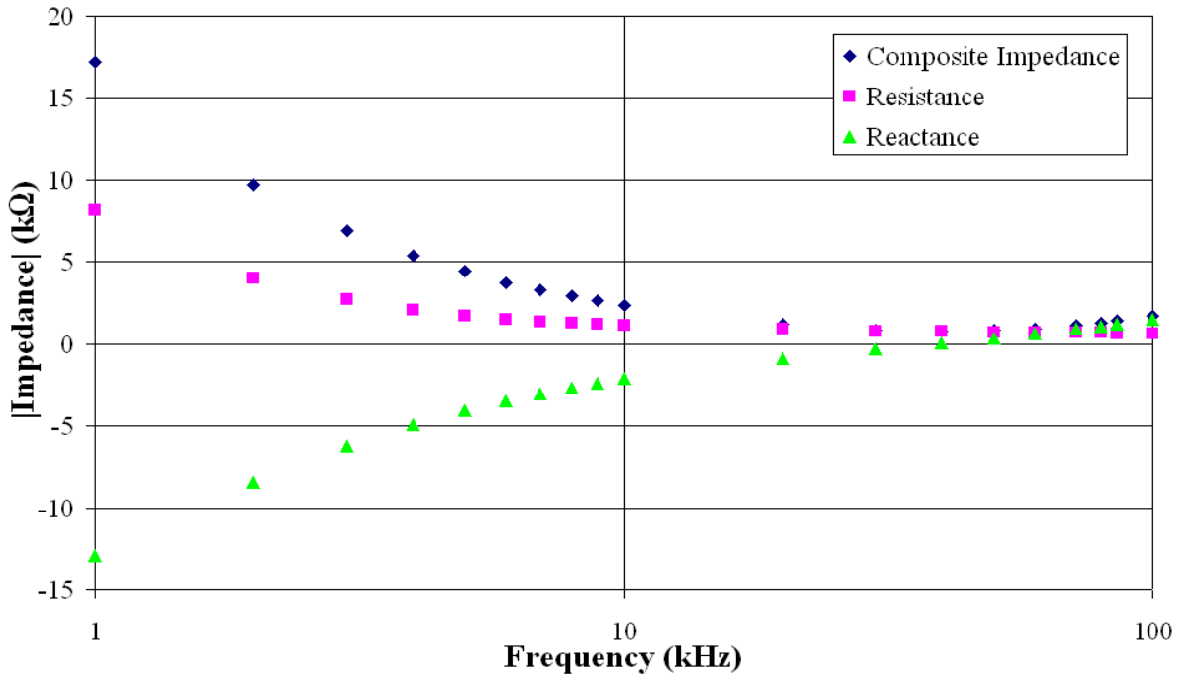


Figure 4.34 Total impedance measurements and the measured resistance and reactance components, using ZipPrep electrodes on subject A.

Similar to the forearm, the shin data also show minimum composite impedance at 30-40 kHz when using the Red Dot and ZipPrep electrodes. The variability between subjects is also greater on the ZipPrep than the Red Dot at lower frequencies, less than 10 kHz. However, for a single subject, the short term repeatability with ZipPreps is improved compared to the forearm data. Representative example data from subject C, forearm, are 2.23 kΩ (SD 50Ω) within twenty repeats, compared to 1.61 kΩ (SD 40Ω) for subject C on the forearm (measurements made over 30 seconds). Overall, the composite impedance results on the forearm and shin display a similar trend across the frequency range for all electrodes types.

Analysis of the time dependence study shows that, with time, there was a decrease in composite impedance below 10 kHz. Previous studies have speculated that this is due to the absorption of the electrolyte gel into the skin, decreasing the resistance of the stratum corneum (Webster, 1998). As the stratum corneum is the most resistive layer of the skin, being primarily composed of dead cells, the absorption of the electrolyte gel would be

expected to decrease the resistance, thus reducing the composite impedance. An earlier study hypothesised that the initial application of the electrodes with the electrolyte gel causes the closure of localised sweat ducts due to the temperature of the gel being lower than body temperature (Grimnes, 1983). The data presented in section 4.1.1, show that there is a noticeable reduction in composite impedance over time at the lower frequencies, less than 20 kHz. This effect was more pronounced with certain electrode types. The theory that the electrolyte gel is absorbed by the stratum corneum may explain the differences between the electrode types. Each type of electrode has a different type of contact region , i.e. the ZipPreps have gel-soaked sponges with penetrating tines, the Red Dots have gel-soaked sponges, and the ARBOs have a solid gel. At 1 kHz the ZipPrep composite impedance reduced by 35%, compared to the Red Dot which reduced by 24% and the ARBOs by 10.8%. It is possible that the tines of the ZipPrep electrodes aid the absorption of the electrolyte gel into the stratum corneum. In contrast, the solid gel in the ARBO is less absorbed and may only be affected by the initial closure of the local sweat ducts and reopening over time as the area warms, explaining the reduced drop in impedance over time. The impedance values do not display large temporal variations above about 20 kHz for any of the electrode types.

The placement of the electrodes is paramount in EIT, in terms of both accurate positioning and electrode contact. Successful image reconstruction from EIT data requires accurate definition of the electrode positions. Based on the 10-20 set-up the author estimates that electrodes could be incorrectly positioned by a maximum of 0.5cm; this estimation is based on many hours of practice in electrode placement. The experiments in section 4.6 show the composite impedance varying with distance. Red Dot electrodes, across the frequency range, give a reasonably consistent impedance. The largest individual variation can be seen on subject B at 1 kHz, showing a change of 3.17 kΩ, whereas the other subjects show maximum variability of 1-2 kΩ. The equivalent data with ZipPrep electrodes suggests that the higher frequencies, greater than 30 kHz, would provide a consistent composite impedance over all locations.

Another area that was considered in this chapter was the preparation technique. Currently clinical professionals are asked to clean the site with alcohol before abrading the area, along with shaving if possible (McCann ed, 2008). However in a busy working environment, with 32 electrodes to fit to the scalp these preparations are difficult. The method of abrasion can vary dramatically from a light rub with an alcohol wipe to a more vigorous rub with coarse

tissue paper. The amount of abrasion necessary to see a change in the composite impedance is described in section 4.3.4. It was noted that at low frequencies, less than 10 kHz, it was possible to reduce the composite impedance by a maximum of 31% by gentle removal of the stratum corneum using adhesive tape. This result was similar to the more aggressive form of abrasion using coarse paper, where a maximum change of 28% in composite impedance was seen at 1 kHz. This more gentle approach would be preferable when preparing the skin on neonatal babies, as well as other patients that required multiple site preparations. The measurements in section 4.3.4 suggest that preparation does not significantly influence the composite impedance at high frequencies, above 30 kHz. At 100 kHz all subject measurements had a reduction in composite impedance, after abrasion, of less than 50Ω.

The study on the scalp showed that there were differences in the data found on the hirsute sites compared to the non-hirsute sites, as shown in table 4.6. At lower frequencies the hirsute sites give composite impedance which is significantly greater than on non-hirsute sites. At higher frequencies there are some slight differences, however the effect is reduced.

Table 4.6 The mean composite impedance for the different electrode sites on the scalp, showing a distinct difference in the data at 1 kHz between the hirsute sites (O1 & O2) compared to the non-hirsute sites (FP1 & FP2) using ZipPrep electrodes.

	1 kHz	10 kHz	100 kHz
O1 & O2	7.22 kΩ	1.75 kΩ	1.11 kΩ
FP1 & FP2	3.8 kΩ	0.98 kΩ	1.06 kΩ
FP1 & O1	4.73 kΩ	1.58 kΩ	1.72 kΩ
T3 & T4	6.16 kΩ	1.56 kΩ	1.44 kΩ

The composite impedance had a pronounced minimum as a function of frequency for the ZipPrep electrodes on the scalp. This was more evident than in the forearm and shin data. However, this effect was not seen on the Red Dot electrode scalp data. It may be that the overall larger impedance on the scalp using these electrodes prevented any subtle effect being observed. At 10kHz the ZipPrep electrodes yielded a mean composite impedance of 980 Ω compared to Red Dot electrodes which yield a composite impedance of 12.6 kΩ. This implies that, to drive a given amount of current through the head with Red Dot electrodes, a voltage 13 times greater is required than in the case for ZipPreps.

In general, it is possible to model the observed composite impedance by using a simple RCL series system in parallel with a resistor, as shown in figure 4.35. Table 4.7 shows the best fit values that were found to reproduce the measurements made on representative subjects. Figure 4.36 shows the fit obtained using the theoretical circuit (figure 4.35) for one subject, as an example.

Table 4.7 Electrical equivalent model for the composite impedance.

Subject	R1 (kΩ)	C (nF)	L (mH)	R2 (Ω)
A	8.5	13	2.8	500
L	5.8	12	2.4	500
M	6.0	14	1.9	400
B	3.0	15	3.0	500

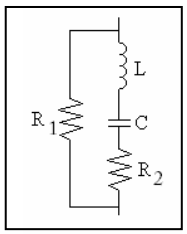


Figure 4.35 Simple equivalent circuit to model the impedances at FP1 and FP2 using ZipPrep electrodes.

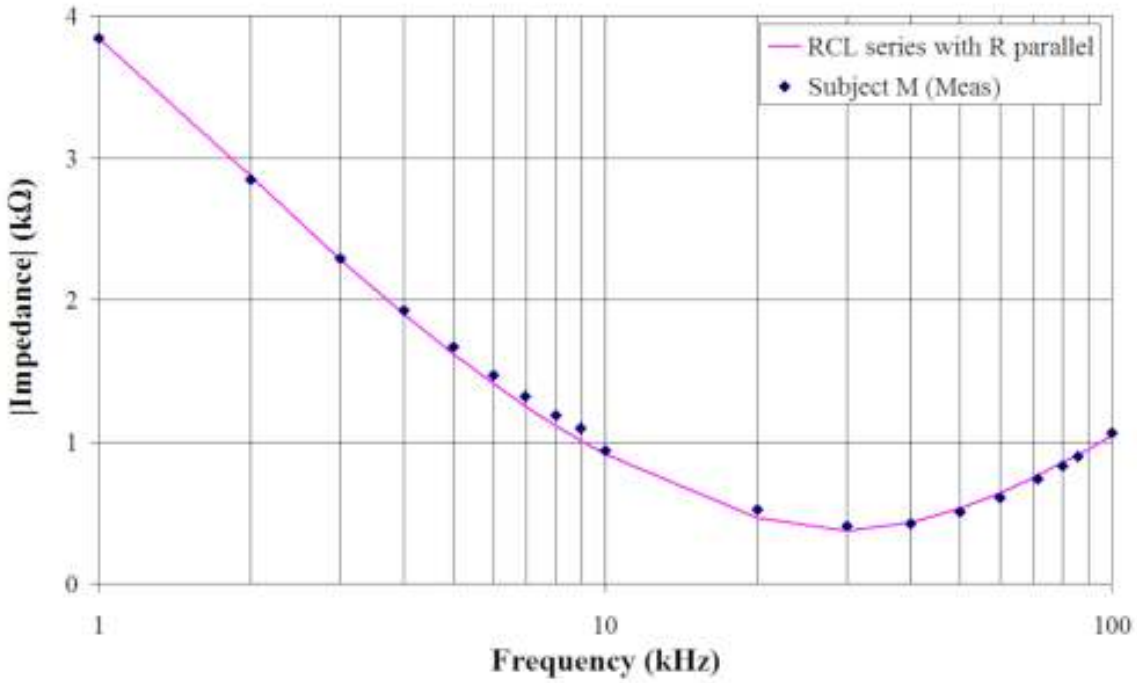


Figure 4.36 Typical measured impedance using ZipPrep electrodes on the forehead, at FP1 and FP2, and a plot of the calculated impedance using the best-fit parameters for the circuit shown in figure 4.35.

The same circuit can be used as an approximate model for the Red Dot electrodes. However, the necessary value of R_2 has to be much larger to fit the higher measured impedance, and the quality of fit is poor (shown in figure 4.37 based on values in table 4.8).

Table 4.8 Electrical equivalent model for the total impedance at FP1 and FP2 using Red Dot electrodes.

Subject	R1 (kΩ)	C (nF)	L (mH)	R2 (kΩ)
A	38	0.8	5	16
C	15	1.4	0.9	10

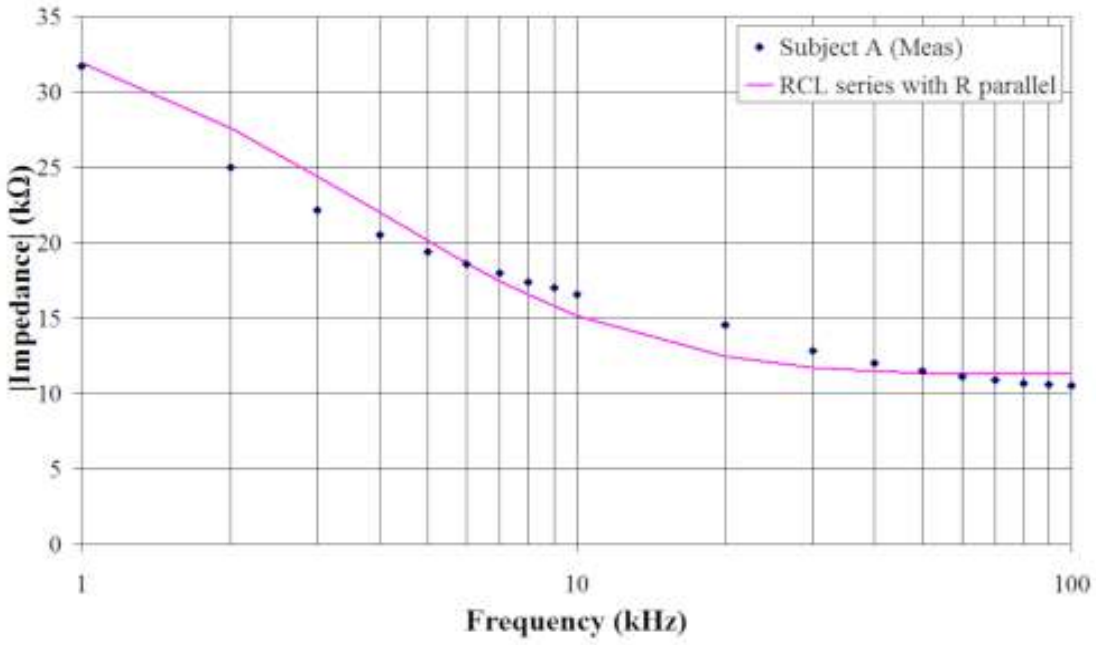


Figure 4.37 Typical measured impedance using Red Dot electrodes on the forehead, at FP1 and FP2, and a plot of the calculated data using the best-fit parameters for the circuit shown in figure 4.35.

Ideally an EIT system would encounter a low composite impedance for current injection, as it can be implemented with moderate output impedance (1 MHz) of the current source circuit (McEwan *et al*, 2007). Additionally, a large composite impedance would induce a large

common-mode signal at the input voltage measurements which have limited common-mode rejection capability at higher frequencies (>100 kHz). For EIT on the scalp, ZipPrep electrodes show marked advantages in the comparisons presented here. In general for all electrodes at frequencies in the range of 1 kHz to a few kHz, the composite impedance is much larger than for frequencies greater than 10 kHz.

The composite impedance measurements discussed in this chapter using ZipPrep, Red Dot and ARBO are unique i.e. the author is not aware of any equivalent data in the literature. A general conclusion is that the composite impedance is at a minimum between 30-50 kHz for all types of electrodes at all locations. Therefore, to ensure stable composite impedance, the data suggests that EIT should best be performed at a frequency around 40 kHz. If electrodes are to be placed on the head, the author suggests that ZipPrep electrodes are used as the impedances are lower, thus leading to better quality of data resulting in greater image resolution.

Chapter 5 fEITER – Non-Stimulus Study

The fEITER system was tested on two tanks, one cylindrical and the other a more realistic head-shaped container, to understand the overall performance of the system. The test parameters of fEITER were defined in terms of measured SNR at the high EIT frame rate (100 fps), and the ability to distinguish objects of varying conductivity and size at an array of locations both near to and far away from the measurement electrodes. Once these parameters had been defined it was possible to begin the preliminary tests on informed volunteers. This chapter describes and analyses the data from phantoms and from volunteer tests without stimulus.

5.1 Tank Tests

The tank tests described in this section are measurements of a 'realistic' head phantom. The outer surface of the tank is a hollowed-out mannequin head. Thirty-two holes were made at the positions defined by the 10-20 electrode montage, and one for the reference electrode placed on the mastoid under the left ear. ZipPrep electrodes were placed on the tank as these showed the lowest composite impedance on the scalp as discussed in chapter 4, and therefore were to be used during the human tests. A photograph of the head phantom can be seen in figure 5.1. The head circumference, measured at 52 cm, is slightly smaller than that of the average adult, which is 55.9 cm for a man and 54.5 cm for a woman (Ormeci *et al*, 1997). The conductivity of the saline solution in the tank was measured at 500 μScm^{-1} by a conductivity probe. This value of conductivity was set as it is approximately the lowest conductivity of tissues in the head, based on a measured range from 0.5 $mScm^{-1}$ to 15.38 $mScm^{-1}$ (Bonovas *et al,* 2001).

Figure 5.1 Photographs of the head phantom used for fEITER tank tests.

The measured voltages from fEITER can be expressed as the real (I) or imaginary (Q) voltage components or the magnitude and phase of the signal, which can be calculated from these measurements. All results discussed in this chapter are the magnitude of the signal, which was chosen as the method of standardising the data plots. An example of a typical EIT data plot is known as a 'u-curve' due to the pattern the voltages produce against their serial measurement number (measurement index), when using a cylindrical tank and the standard polar current pattern. Since the aim of fEITER is to interrogate as much of the brain as possible, the current injection strategy for fEITER has been designed to be a 3D strategy. The signals from fEITER therefore form complicated 'u-curves' as seen in figure 5.2.

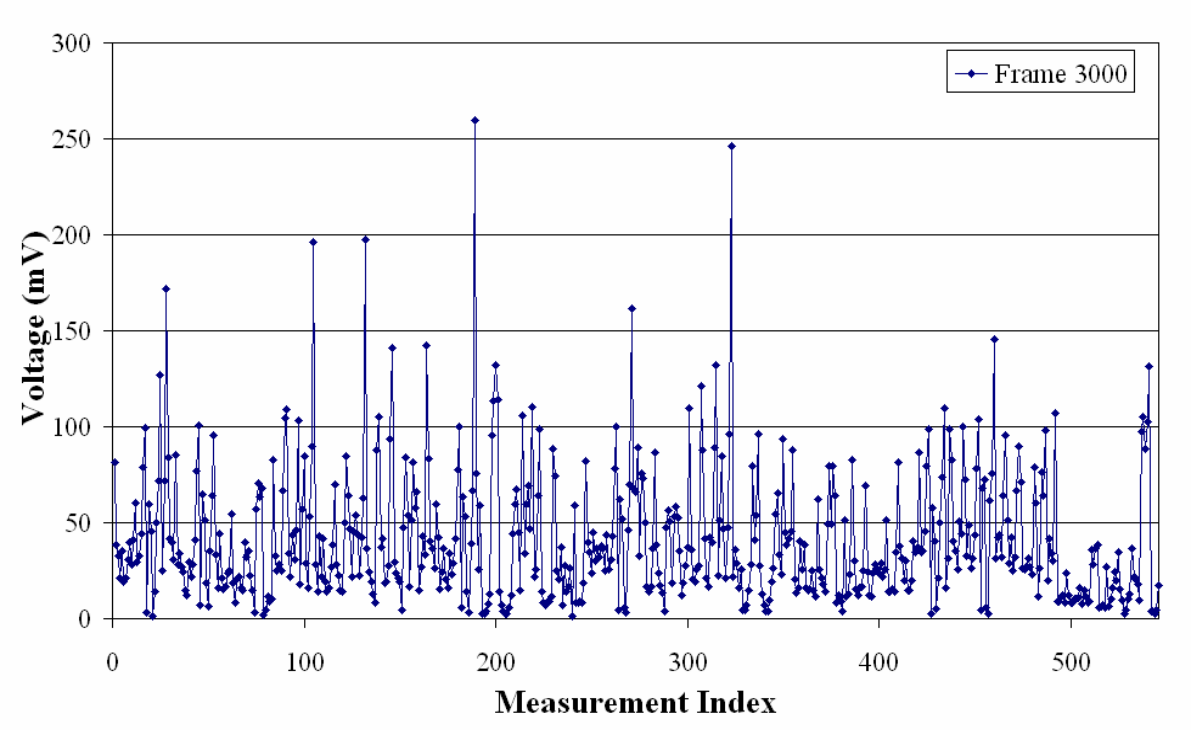


Figure 5.2 Voltage signal magnitudes (peak to peak) versus the measurement index for a head phantom, for frame 3000 in a 1-minute data capture.

The measured voltage signal is influenced by the current pattern (CP) and the voltage measurement site (MS). For example, in the plot above measurement index 201 refers to CP 8-12 and MS 10-11. The MS is spatially adjacent to one of the current injection electrodes, therefore a large voltage is measured compared to measurement index 245 which is CP 5-15 and MS 30-31, where the CP electrodes and the MS electrodes are far away from each another. This means that the measurement electrodes closer to the current injection electrodes will have a greater sensitivity to any localised changes of impedance. The electrode locations that have greater sensitivity to changes of impedance in given regions will be exploited throughout the data analysis in chapters 5 and 6.

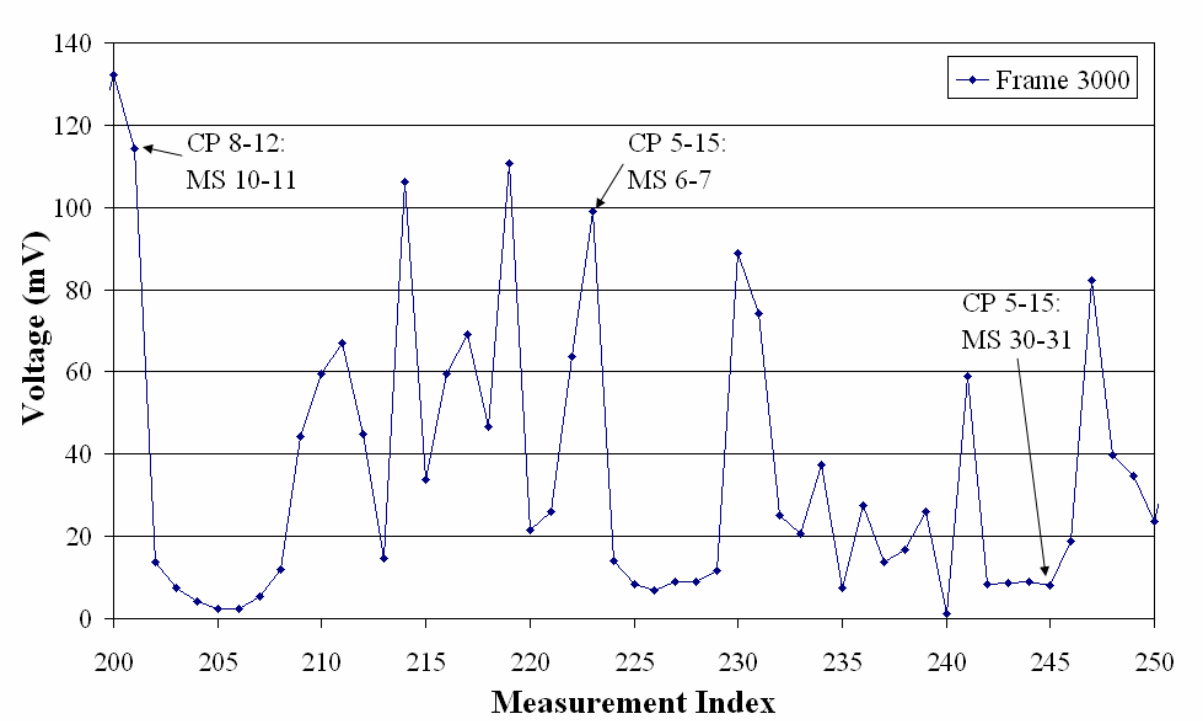


Figure 5.3 Selection of data from figure 5.2, showing only measurement indices from 200 to 250. Some of the corresponding CP electrodes and MS electrodes are identified.

Considering fEITER's performance one important aspect to define is the repeatability between frames within the one minute data capture period. Since there is no change in the conductivity of the solution in the phantom, there should be very little variability between frames and any variability that is observed is an estimate of the system's measurement precision and hence its total noise. Figure 5.4 shows 100 frames of voltage data (from frame

3000 to 3099) where all the u-curves of each frame are overlaid on each other. The precision of these data is discussed below.

Figure 5.4 also compares these data with the predicted voltage as calculated using EIDORS (Polydorides and Lionheart, 2002), as discussed in chapter 2. EIDORS calculates the boundary voltages based on the geometrical model which, in this case is based on a hemisphere. It also takes account of the electrode position, the conductivity distribution within the object of interest (in this case set at 500 µScm-1), the current pattern and the amplitude of the injection current (1 mA pk-pk).

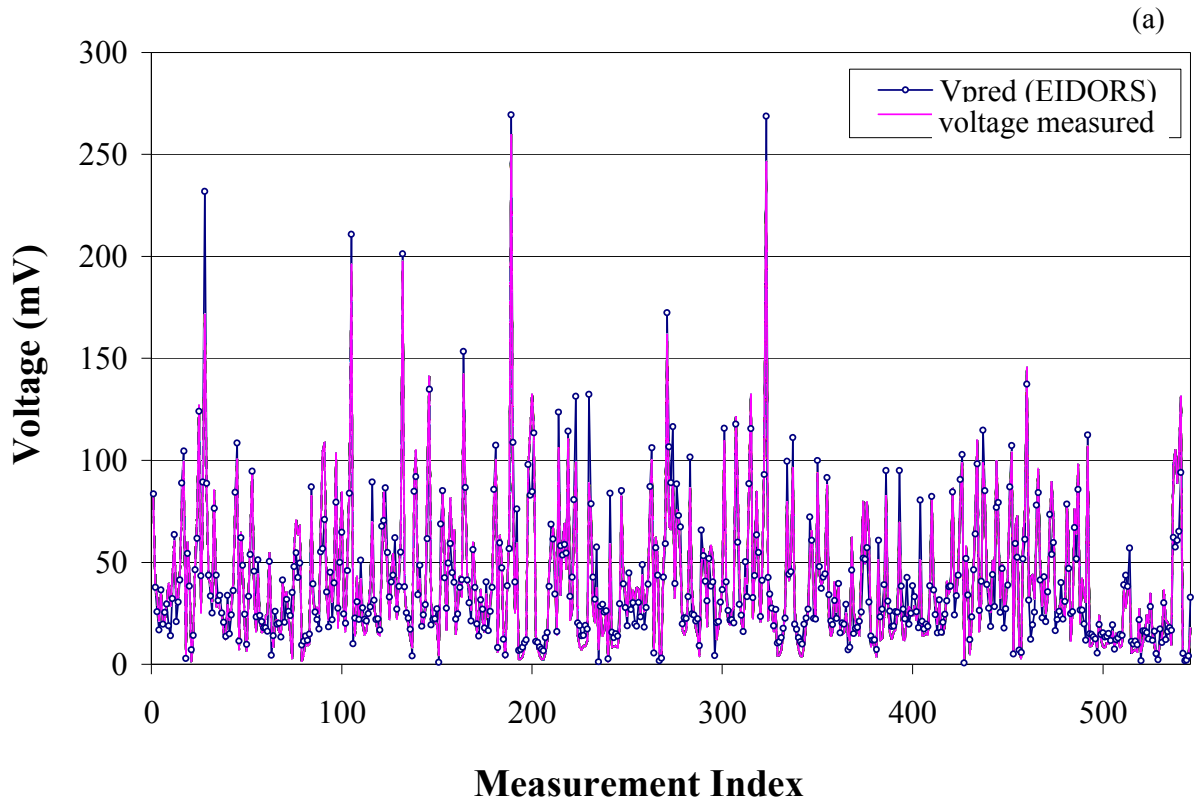


Figure 5.4 Measured data from a head tank test showing 100 frames overlaid on each other, compared to the predicted EIDORS voltages **(a)** All 546 measurements per frame.

(b)

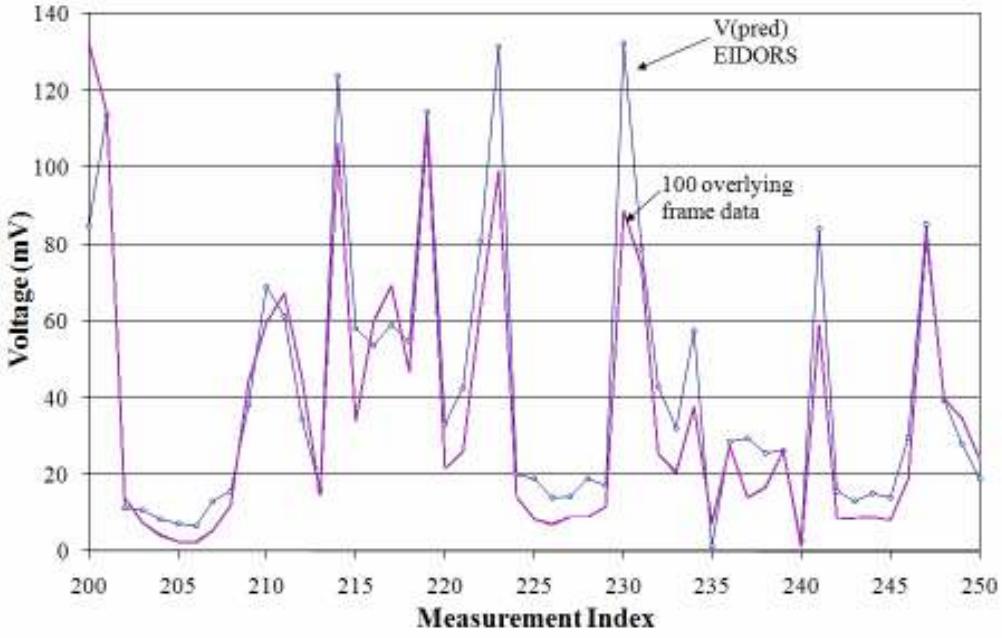


Figure 5.4 Measured data from a head tank test showing 100 frames overlaid on each other, compared to the predicted EIDORS voltages **(b)** 50 measurements, in more detail.

The predicted values for the data in figure 5.4 are comparable to the measured data in terms of the voltage amplitude and the location of the peaks and troughs. There are slight discrepancies due to the mismatch of the EIDORS geometrical model with the head-shaped tank. Another area that is not accurately modelled is the electrodes, which have been modelled as squares as this provides a more uniform tetrahedral mesh throughout the geometric model.

For each measurement index, the standard deviation (equation 5.1) was calculated over 100 frames, to further understand the repeatability and precision of fEITER between frames.

$$SD_j = \sqrt{\frac{\sum_{i=1}^{\eta}(x_i - \bar{x})^2}{(\eta - 1)}} \qquad (5.1)$$

where SD_j is the standard deviation of measurement index$_j$, calculated for η frames of data, x_i is the measurement with index j in the ith frame of data, $\overline{x}$ is the mean value of the measurement with index j for all η frames.

The mean of the standard deviation over all measurement indices is marked on figure 5.6; this is defined by

$$\overline{SD} = \frac{1}{m}\sum_{j=1}^{m} SD_j \tag{5.2}$$

where m is the number of measurement indices i.e. 546.

As highlighted in figure 5.5 there are two distinct outlying sets of data. The upper set are all from measurement electrodes 18-19, whilst the lower set are all from measurement electrodes 16-17. It was noted that this was due to poor electrode contact on the tank, thus the bias of these measurement electrodes was removed by calculating the mean of the standard deviation of the remaining voltages (i.e. voltage measurement from all electrodes apart from CP and MS that use electrodes 18, 19, 16 and 17). The value of outliers was deducted from the mean to give a bias correct value. Figure 5.6 shows the bias-corrected plot of the standard deviation, with the mean value of the standard deviation (over all measurement indices) marked.

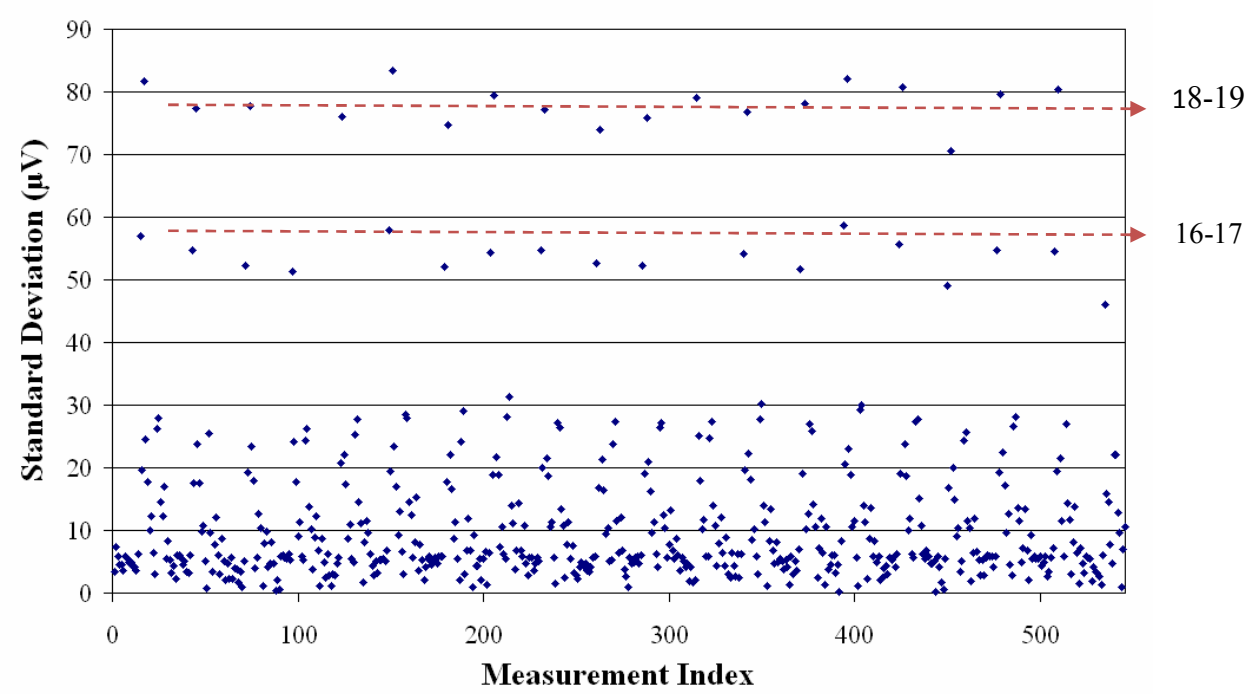


Figure 5.5 The standard deviation for all measurement indices calculated for 100 consecutive frames, from frame 3000 to 3099. Note the two distinct sets of outliers; these are associated with measurement electrodes 16-17 and 18-19.

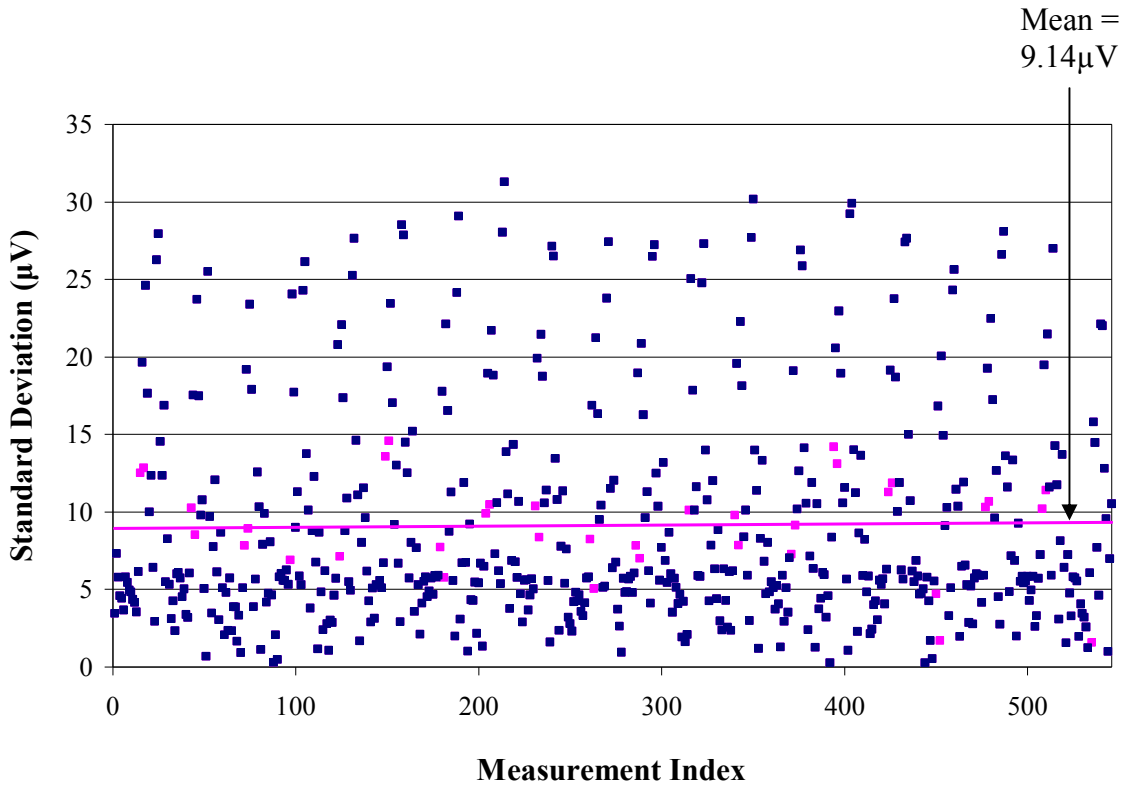


Figure 5.6 The bias-corrected standard deviation plot with the repositioned points identified as pink; the new mean value of the standard deviation is highlighted which includes the new bias-corrected data and the original voltage measurements.

The above tank test results show excellent noise performance at this frame rate. This offers an excellent opportunity for brain function imaging at the sub-second timescale. Figure 5.7 shows the SNR of the same 100 frames that have previously been discussed. The number of measurements greater than 80 dB is 109, and the average is 72.2 dB. For each measurement index, the SNR is calculated by the following equation:

$$SNR = 20log\left(\frac{\bar{x}}{SD}\right) \tag{5.3}$$

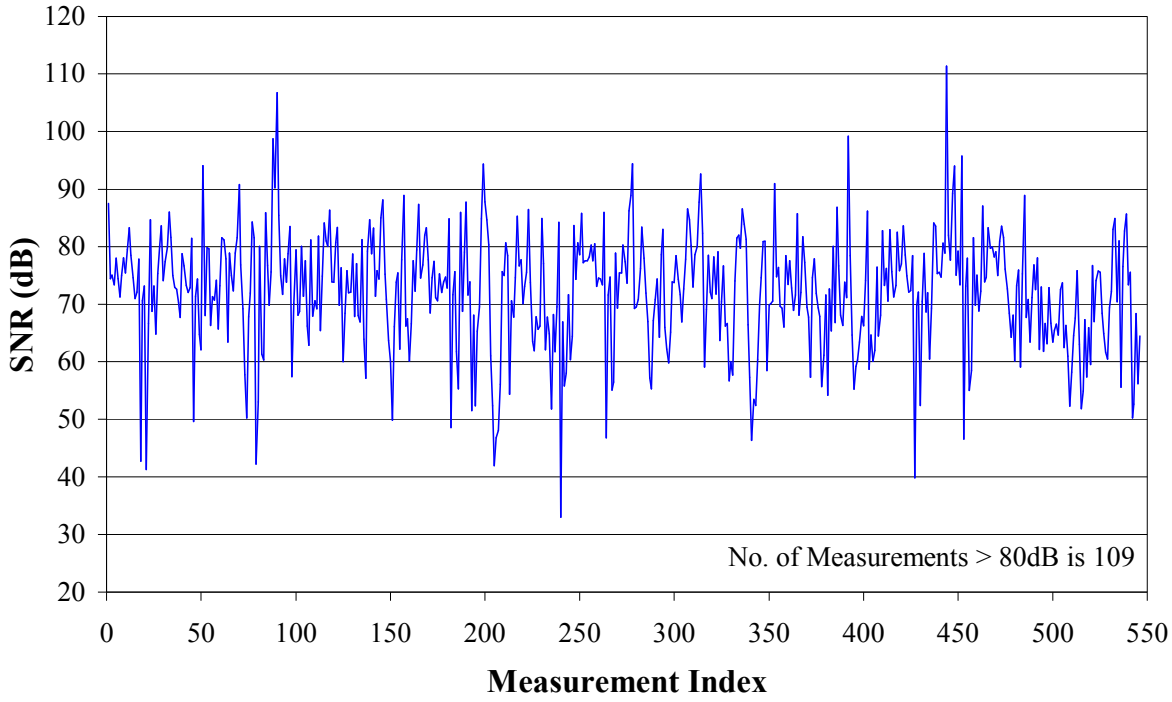


Figure 5.7 SNR for each measurement index over 100 frames (from 3000-3099).

A repeat test was completed after the electrodes on the tank were repaired. The standard deviation and SNR for the same procedure but with a fixed tank can be seen in figure 5.8 and 5.9. The results show a similar SNR; the mean SNR from test 1 (with electrode contact issues shown in figure 5.7) is 72.2dB; whilst the mean from test 2 (repeat test with resolved electrode contact shown in figure 5.9) is 70.5dB. The number of measurements greater than 80 dB is 76. The standard deviation does not display any distinct variability with particular electrodes, implying that the tank repair was successful and therefore the results are a true reflection of the systems capability.

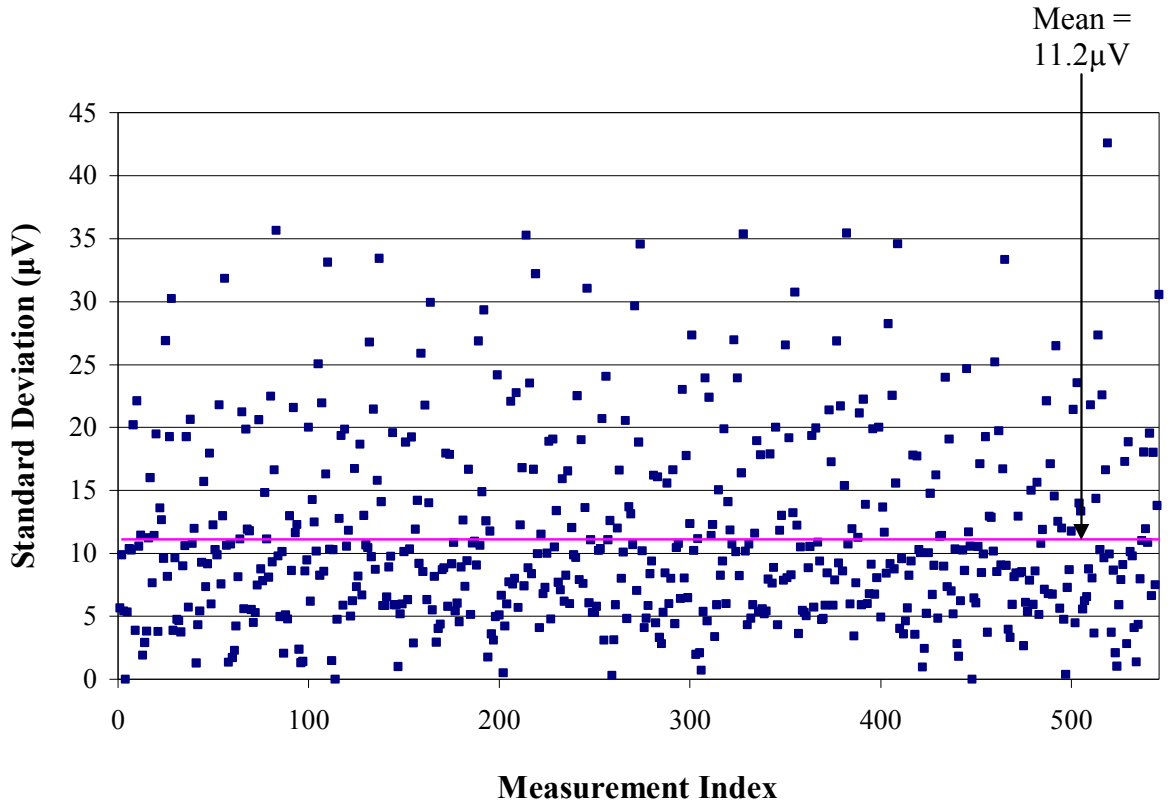


Figure 5.8 The standard deviation plot; the new mean value of the standard deviation is highlighted.

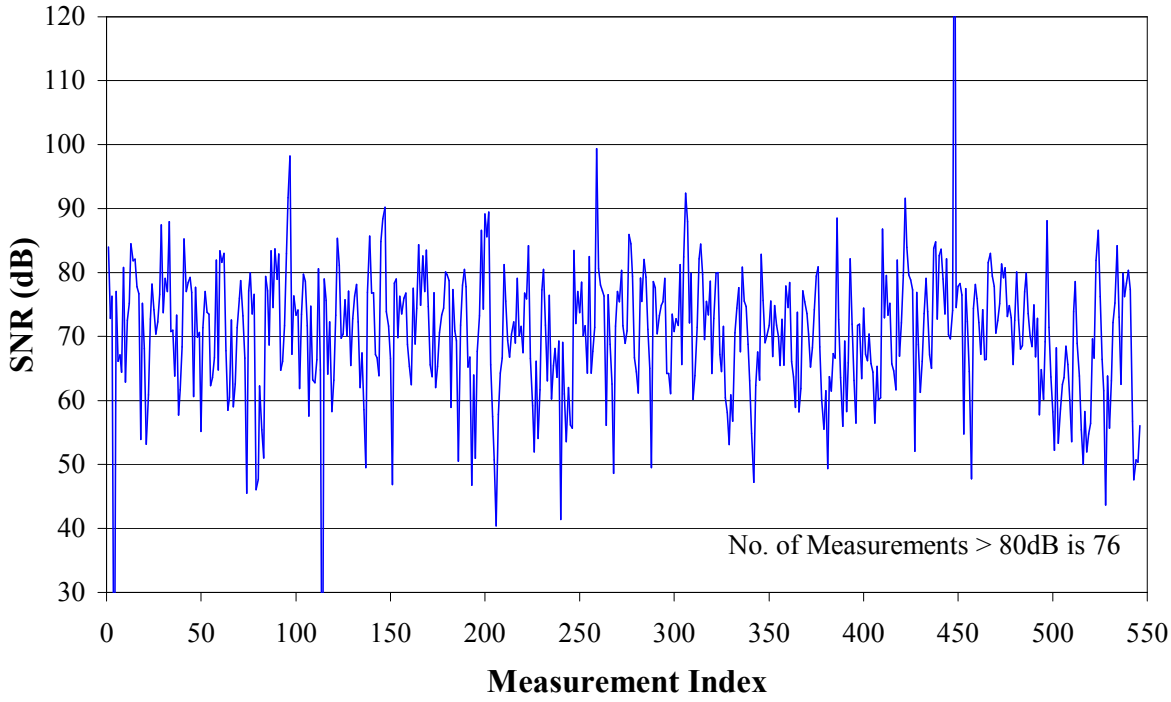


Figure 5.9 The SNR for each measurement index over 100 frames (from 3000-3099).

Further in-depth tank test analysis has been carried out by Ahsan (2010), on both a cylindrical tank and the realistic head phantom used in this section. FEITER showed an average SNR of 75.4 dB for the 546 measurements calculated over all 5998 frames when

using a cylindrical tank filled with saline at 500 μScm-1 (Ahsan, 2010). To the best of the author's knowledge, a system of this frame rate at this SNR is a unique combination compared to other studies in the literature.

5.2 First Human Experiments

5.2.1 Experimental Set-up

Having obtained the appropriate ethical and regulatory approvals as discussed in chapter 3, initial tests were able to be started on two informed volunteers. The experiments discussed in this chapter do not involve a neural stimulus, in order to understand the baseline and background signals before a stimulus is applied.

The ZipPrep electrodes were chosen to be used on the scalp due to the results discussed in chapter 4. These were attached to the volunteers in the bespoke set-up based on the 10-20 system. The current patterns and measurement sites as described in chapter 2 remain the same throughout the data presented in this chapter unless stated otherwise. Each volunteer was asked to sit silently with their eyes closed whilst holding the emergency current cut-off switch described in chapter 3. This could be used at any time during the experiments if the volunteer was feeling uncomfortable or had any sensation. A photograph of the system set-up and electrode montage on a volunteer can be seen in figure 5.10. Once electrodes were positioned, self-adhesive bandaging was placed around the volunteer's head to ensure that the electrodes were in contact with the scalp at all times. As described in chapter 4, the electrodes were attached without prior skin preparation.

(a) (b)

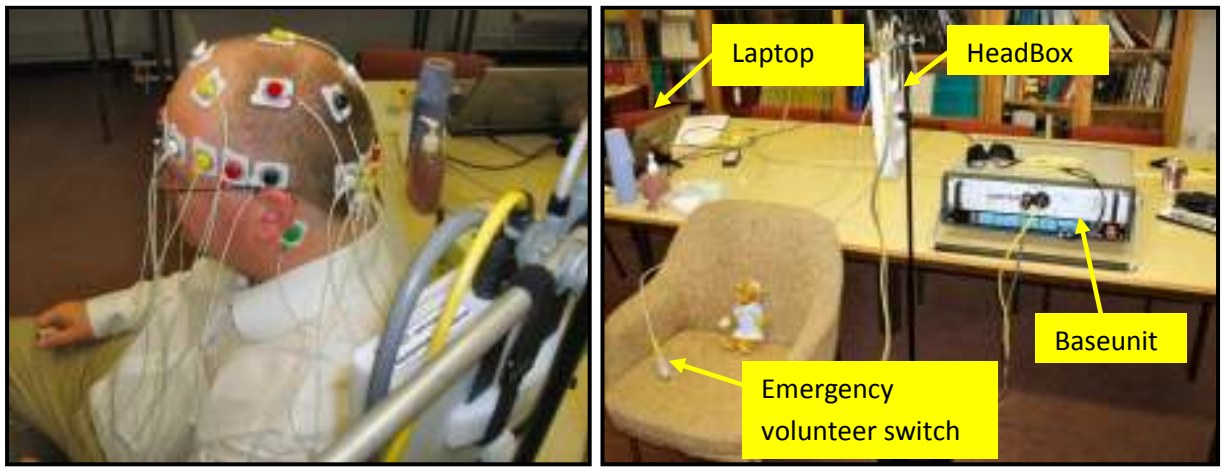


Figure 5.10 Initial experimental set-up (a) electrode montage on a volunteer and (b) the system set-up.

5.2.2 fEITER With No Current

As previously described the fEITER signal frequency is 10 kHz. Comparing this to EEG signal frequencies (dc-150 Hz) it is anticipated that fEITER will not be sensitive to the scalp voltages measured in EEG. However it is important to fully understand the measurements recorded by fEITER. This section describes the use of fEITER with the current off (i.e. voltage measurements only, effectively meaning it is an EEG device operating at 10 kHz). Figure 5.11 shows a time-based plot of the voltages (difference voltage based on formula below) measured when there was no current on, for two sites. Comparing this to figure 5.13, which shows the same sites but when a visual stimulus was shown to the volunteer, and still with no current, the results appear to be similar. The detailed analysis of the rear sites (over the visual cortex) can be seen in figures 5.15 and 5.16.

$$V_D(t) = V(t) - \bar{V} \tag{5.1}$$

Where $\bar{V}$ is the mean voltage between time (T1) and time (T2).

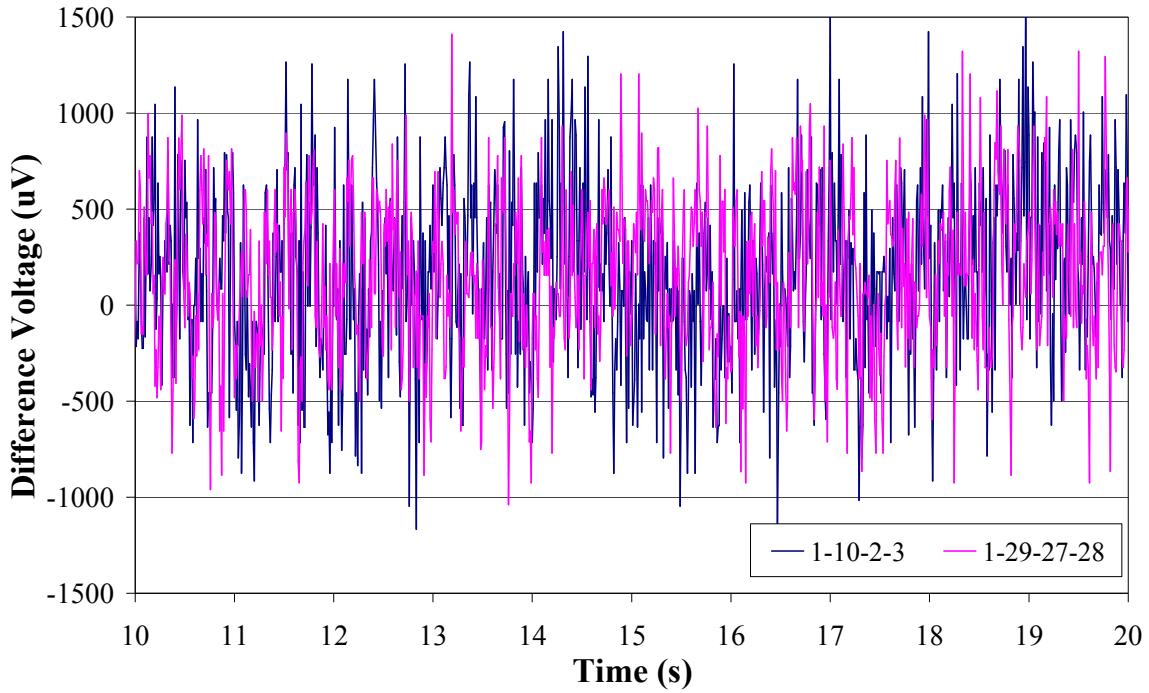


Figure 5.11 The difference voltage $V_D(t)$ between 0.01 seconds and 0.1 seconds measured whilst there was no applied current and no applied stimulus.

Using the data in figure 5.11, the SNR has been calculated, and shown in figure 5.12 for all measurement indices. This shows an average of 42.2 dB, which is lower than the tank test data.

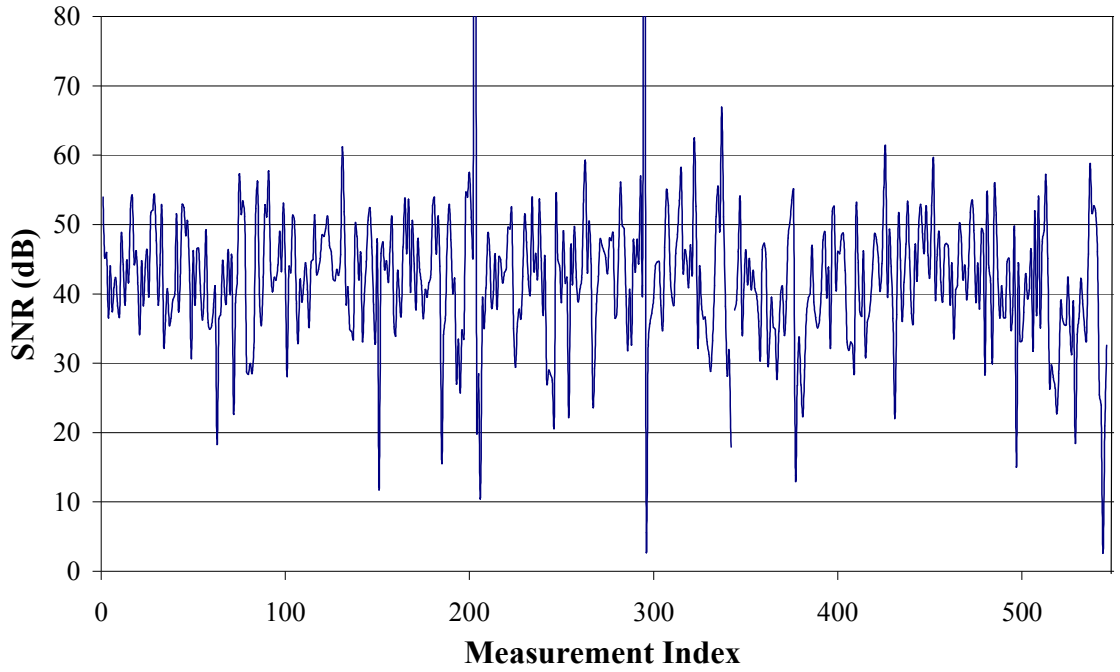


Figure 5.12 SNR for each measurement index over 100 frames (from 3000-3099).

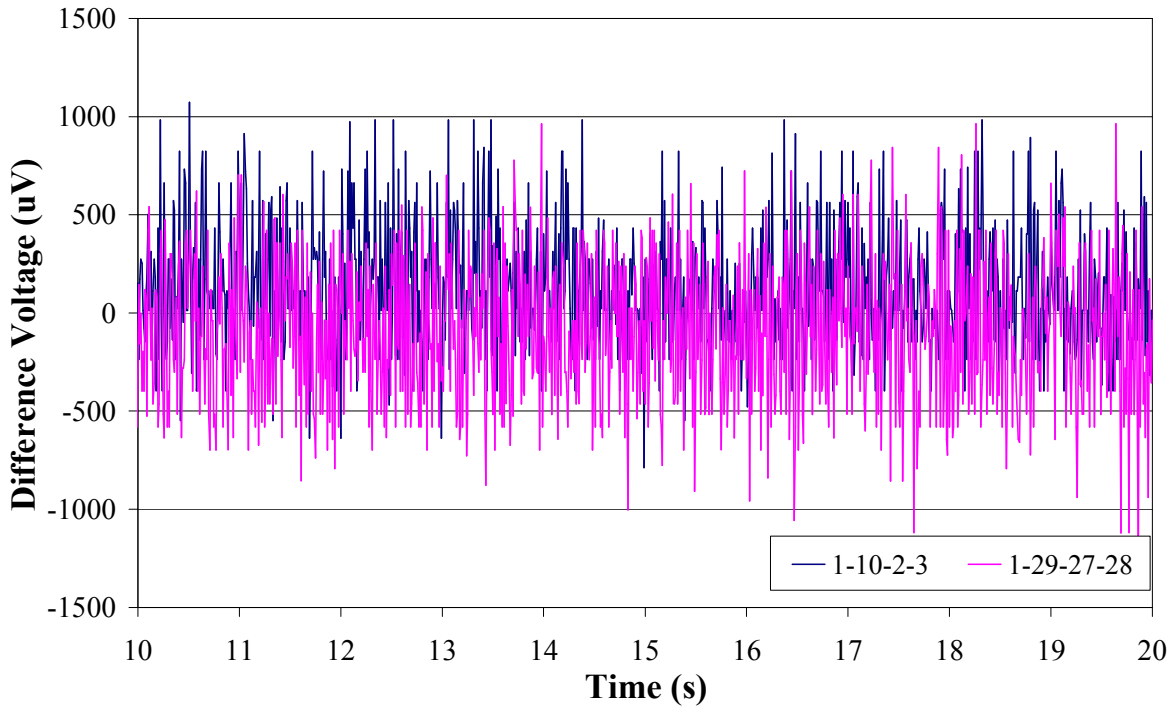


Figure 5.13 The difference voltage, $V_D(t)$, between 0.01 seconds and 0.1 seconds. This is data without current but applying visual stimulus (50 ms flash) to the volunteer every 2 seconds throughout the minute.

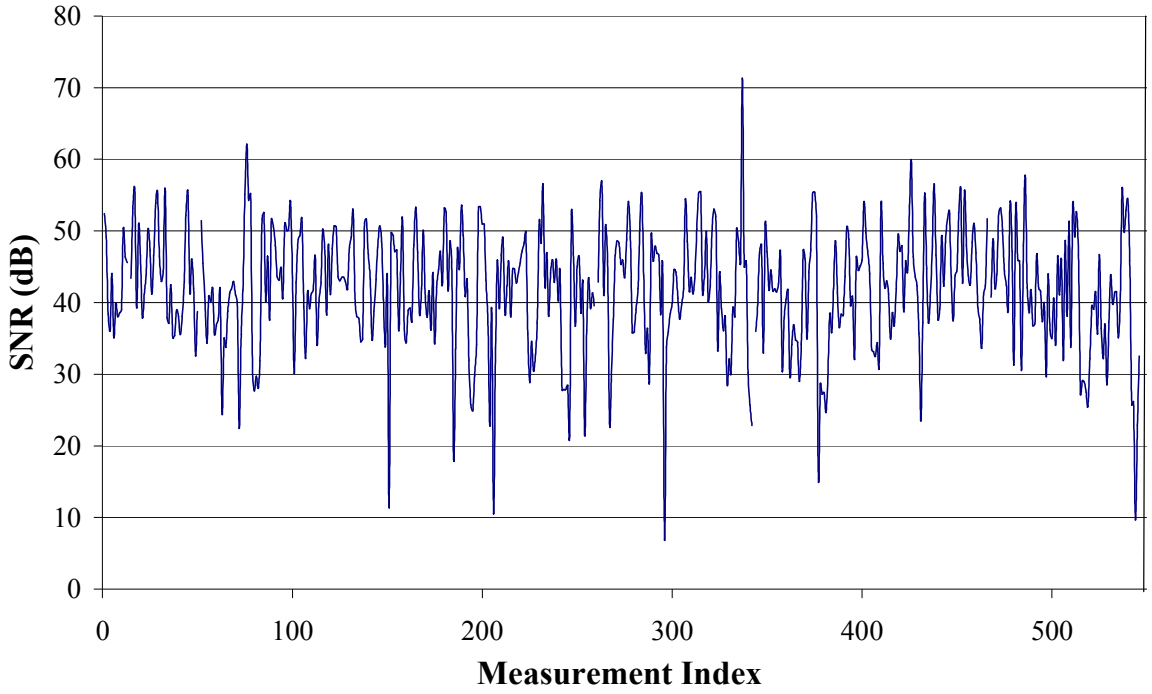


Figure 5.14 SNR for each measurement index over 100 frames (from 3000-3099) .

Figures 5.13 and 5.14 shows the difference voltage measurements (without applied current) when the subject was exposed to visual stimulus every 2 seconds throughout the measurement. The average SNR over all the measurement indices is similar to the test performed without stimulus (average SNR is 42.1 dB).

Table 5.1 shows the p value which was calculated to compare the two sets of data; with stimulus and without stimulus. The paired t-test was performed (shown in equation 5.4) for all the frames in the one minute data capture. The t-test compares two groups of data and calculates the difference between each set of pairs. The test assumes that the differences in population follow normal distribution. The results in table 5.1 are typical example of the p values calculated from the stimulus verses non-stimulus data. The significance level was set at 1% (i.e. $p<0.01$). All of the data rejected the null hypothesis that they were from different data sets. This implies that there is no difference between these data (i.e. without current application) when the subject is exposed to visual stimulus or is under reference no-stimulus conditions.

Table 5.1 Statistics of voltage data using fEITER without applied current; comparing the frames with stimulus and without stimulus. Significance level is set at $p<0.01$.

Frame Number	f_3000	f_3001	f_3002	f_3003	f_3004	f_3005	f_3006	f_3007	f_3008	f_3009
P-Value	1.01E-16	1.39E-16	3.41E-17	1.20E-16	1.36E-19	4.19E-17	4.95E-18	1.11E-17	3.04E-18	1.16E-16

$$t = \frac{\sum d}{\sqrt{\frac{n(\sum d^2) - (\sum d)^2}{n-1}}} \tag{5.4}$$

where, t = paired t-test.

Although the results in table 5.1 show there is no discernible difference between the non-stimulus data and the stimulus data, further detailed analysis was performed. Figure 5.15 shows the details of the rear sites and figure 5.16 shows a section of the same data over a shorter time frame. Since these sites are on the rear they are near the visual cortex which would have the greatest sensitivity to voltage changes related to the visual stimulus.

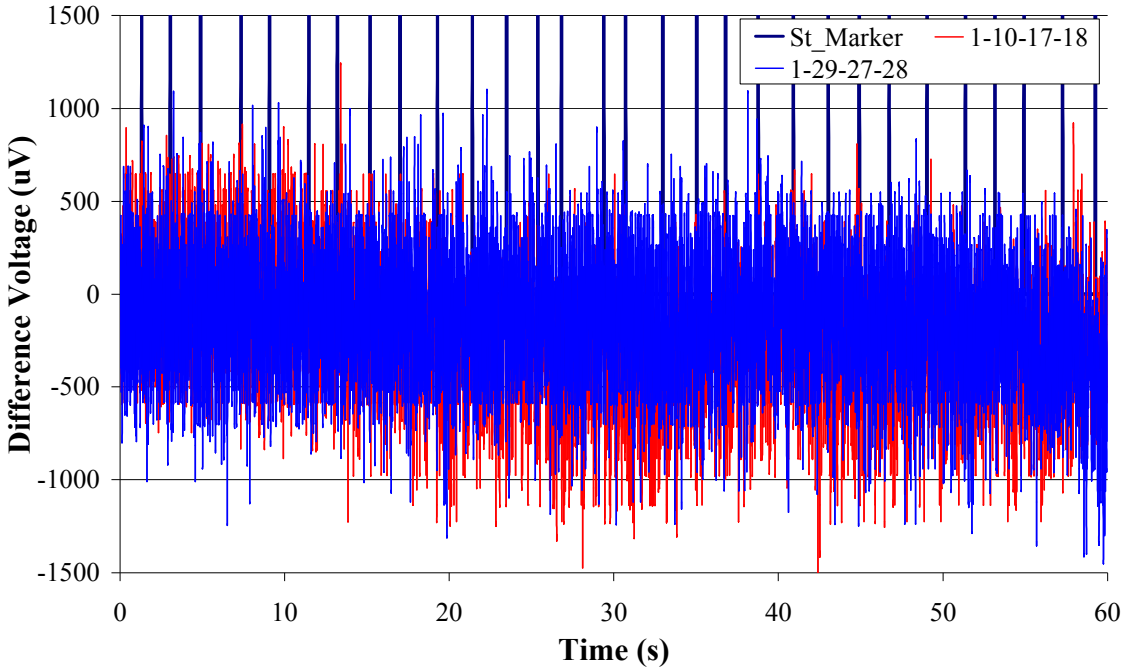


Figure 5.15 The difference voltage, $V_D(t)$, between 0.01 and 0.1 seconds, showing example sites only, when there is no applied current and the volunteer is presented with visual stimulus. St Marker is the rising edge of the stimulus encrypted into the data stream.

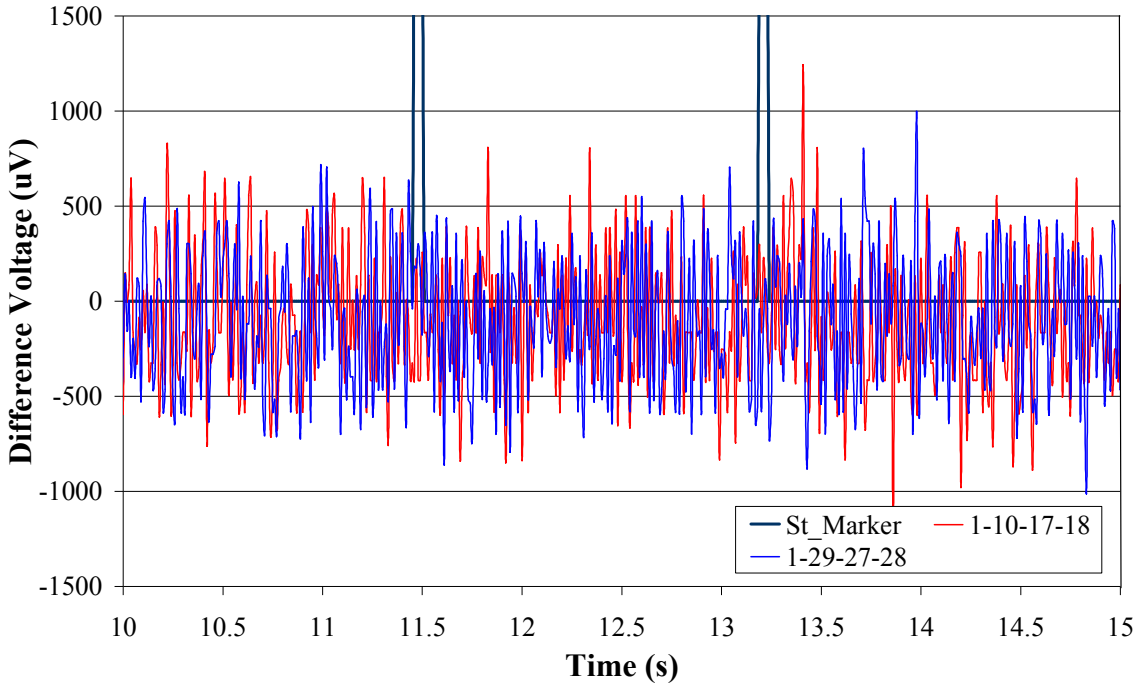


Figure 5.16 A more detailed view of figure 5.11, showing the difference voltage ,$V_D(t)$, over a period of 5 seconds.

Data from sites expected to show sensitivity to visual sites was averaged to test whether there was a voltage change similar to EEG with respect to the stimuli, as shown in figure 5.17. The data was averaged using the formula below (5.5).

$$V_A(t) = \frac{\sum V_n}{n} \tag{5.5}$$

where V_n is the voltage measurements 250 ms pre-stimulus and 750 ms post stimulus and n is the number of stimuli.

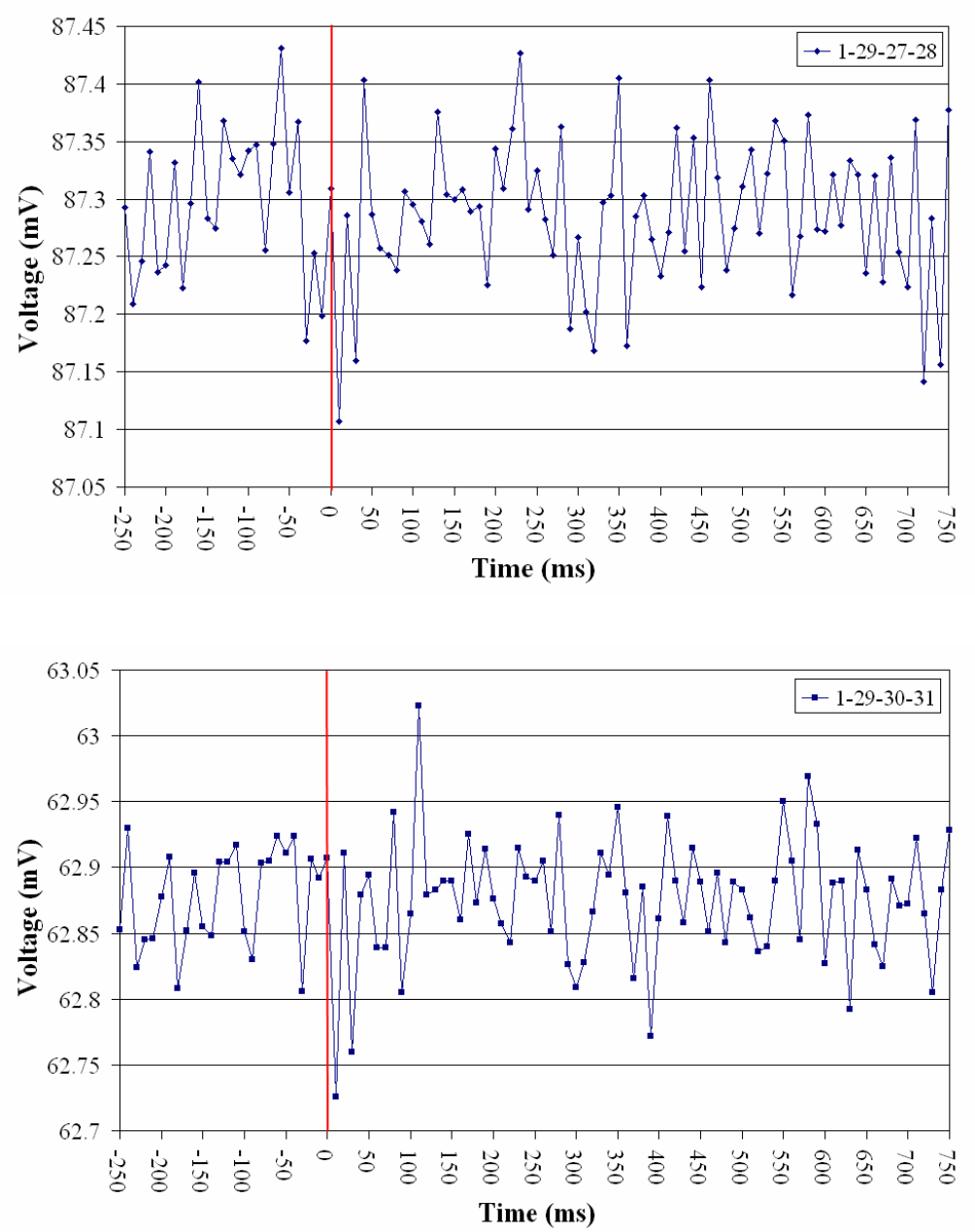


Figure 5.17 Averaged data for 22 stimuli for the period 250 ms pre-stimulus and 750 ms post-stimulus (a) shows CP 1-29 and MS 27-28, left rear position and (b) shows CP 1-29 and MS 30-31, right rear position.

5.2.3 fEITER Current On

The applied current was set at 1 mA pk-pk and a reference data set was captured (i.e no stimulus was applied to the volunteer). The experiments took place in a darkened room, the volunteer and experimenter were quiet throughout the tests, and the volunteer's eyes were closed throughout. The results from these tests were checked in bespoke MATLAB codes to ensure that all the electrodes were able to inject current and take voltage measurements. Comparisons are made between human data and the EIDORS model, which is based on a hemisphere using 1 mA pk-pk and 500 μScm^{-1} for the homogenous conductivity. Since the head is not hemispherical nor of constant homogenous conductivity, the main aim of this comparison is to identify that peaks and troughs occur in similar locations, as the amplitudes are expected to be substantially different.

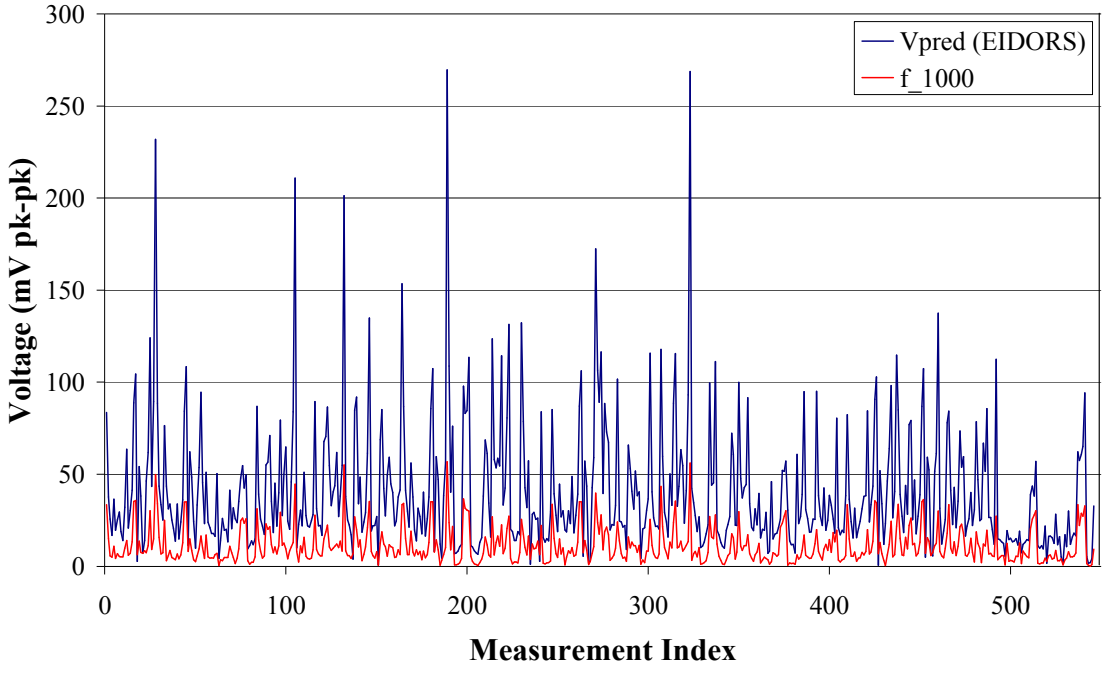


Figure 5.18 A typical comparison of a volunteer data set (frame 1000) compared to the predicted measurements.

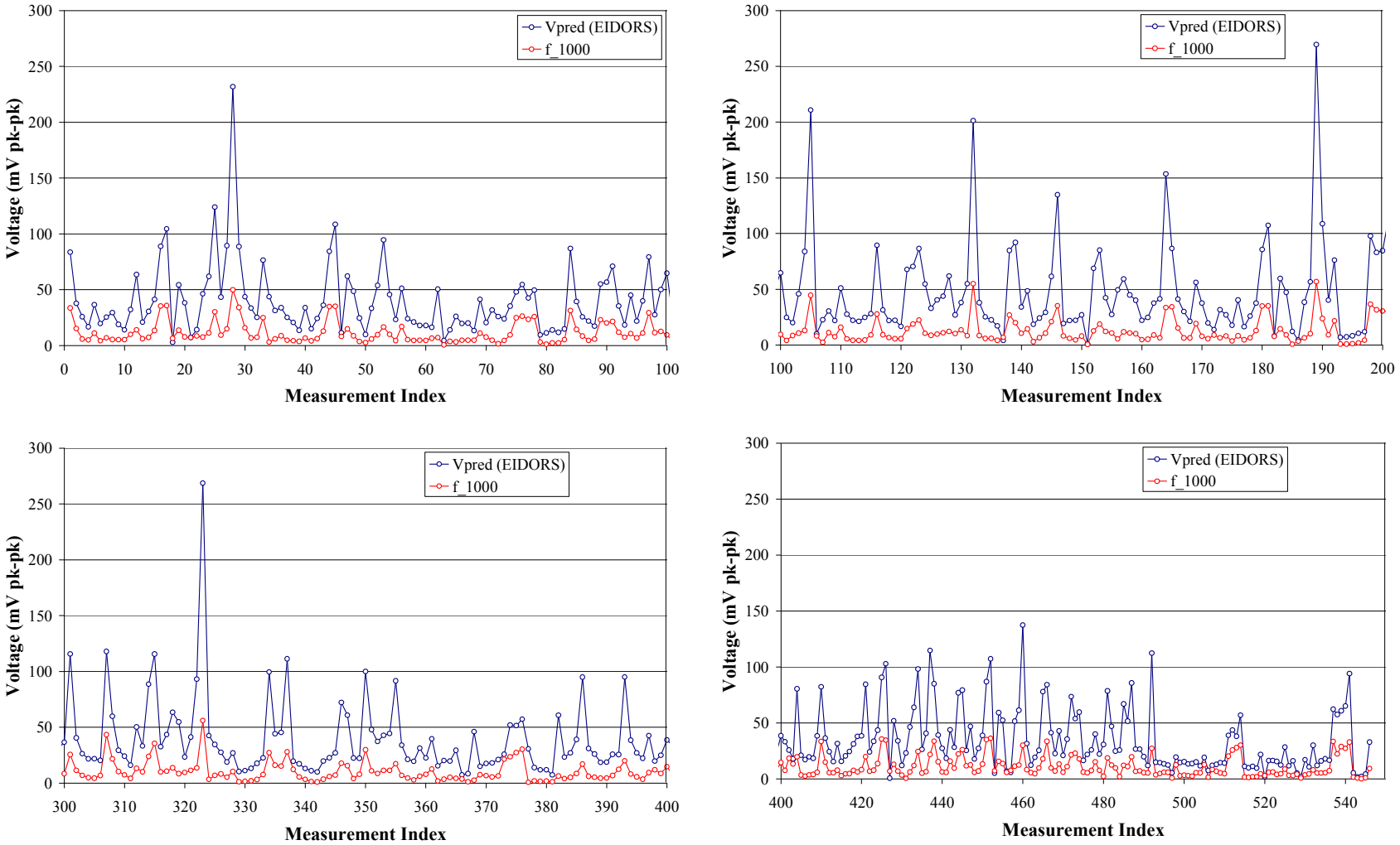


Figure 5.19 The same data as figure 5.14, showing more detail of the peaks and troughs, in blocks of 100-150 measurements.

Figures 5.18 and 5.19 show that the peaks and troughs of the predicted and measured data have similar trends throughout the measurement index. This is a typical example of data taken from the volunteers and clearly shows large differences in the voltage amplitude due to the inaccurate representation of the actual system. The EIDORS model needs to be adapted to include a more realistic geometrical model, conductivity distributions and electrode positioning. Nevertheless, from this initial analysis it is possible to conclude that the fEITER system is operating in a qualitatively functionally correct manner.

5.2.3.1 Data Analysis

Figure 5.20 shows the voltage measurements at one particular site (CP 1-10, MS 2-3) on the forehead over one minute. Figure 5.21 shows 10 seconds of voltage measurements from (a) forehead, (b) rear, (c) left side and (d) right side of the head. All of these plots show a 'saw tooth' signal. In this set of data it has a rate of 72 peaks in a minute. The sites around the head do not appear to have topographical differences. However there may be more subtle changes at less than 100ms temporal resolution seen in figure 5.21.

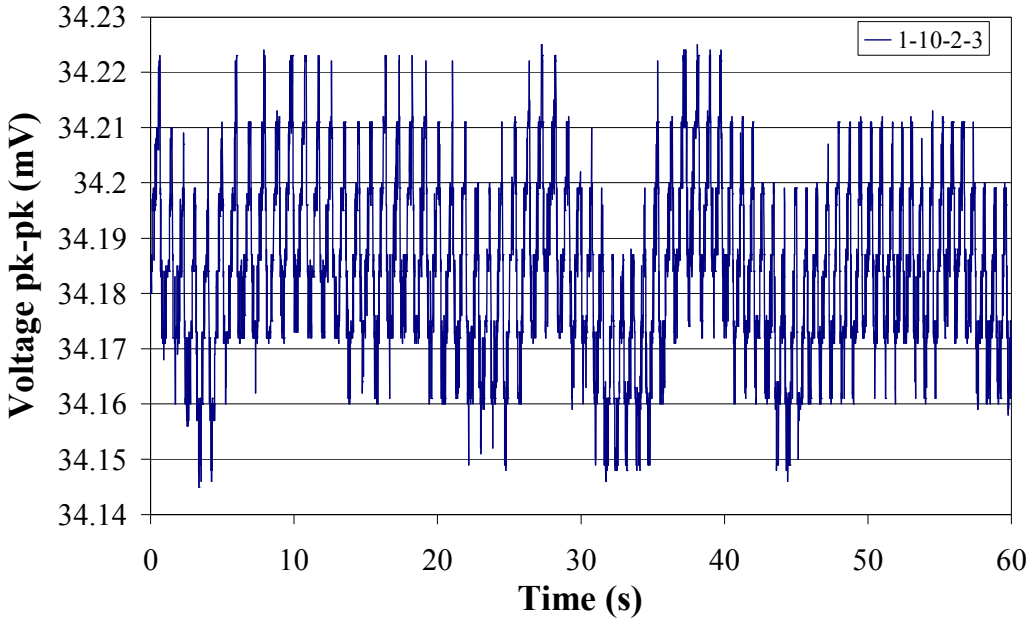


Figure 5.20 Time based plot of the voltage measurements on the forehead over one minute.

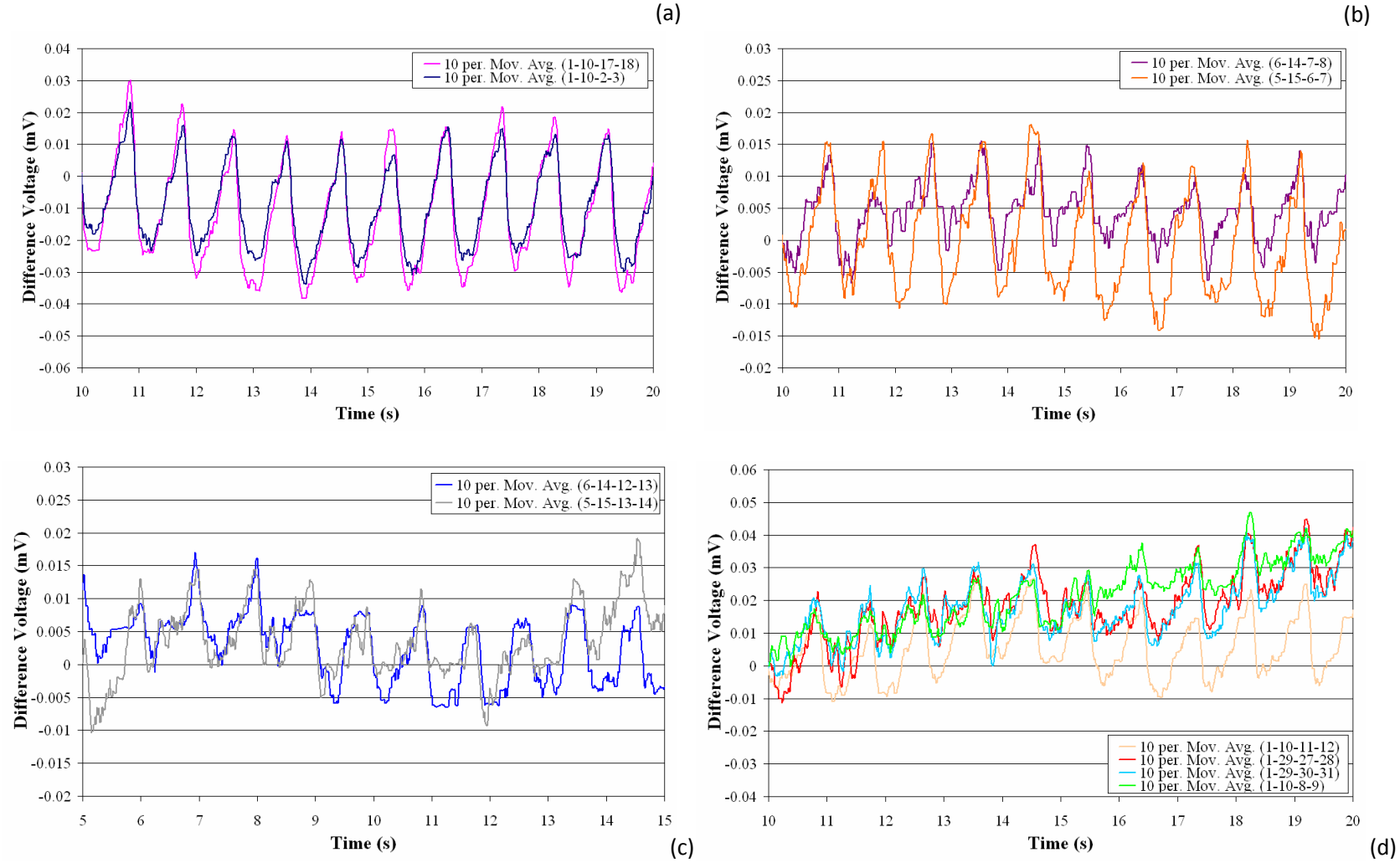


Figure 5.21 The difference voltage measurements, $V_D(t)$, between 9.9 seconds and 10 seconds. Each point in each trace is the moving average of 10 data points, i.e. they all show the measurements with a temporal resolution of 100 ms. (a) forehead (b) left side (c) right side and (d) rear difference voltage measurements.

Since the ‘saw tooth’ has a rate similar to the resting heart rate of the individual tested further tests and analysis of the data was planned in order to confirm this. An ECG is a measurement of the electrical conduction produced within the heart (Martini, 2004). The basic wave can be split into three main sections; PR interval, QRS interval and the ST interval (shown in figure 5.22). Each section represents a different electrophysiological event. The P wave is the first of the electrical changes that occur. It represents the depolarization of both atria. Following this is the QRS complex; all of the changes in this section represent ventricular depolarization. Usually composed within the QRS complex there are two or more waves, usually easily seen are the Q, R and S waves. The T wave is the final section in the ECG wave, representing ventricular repolarisation.

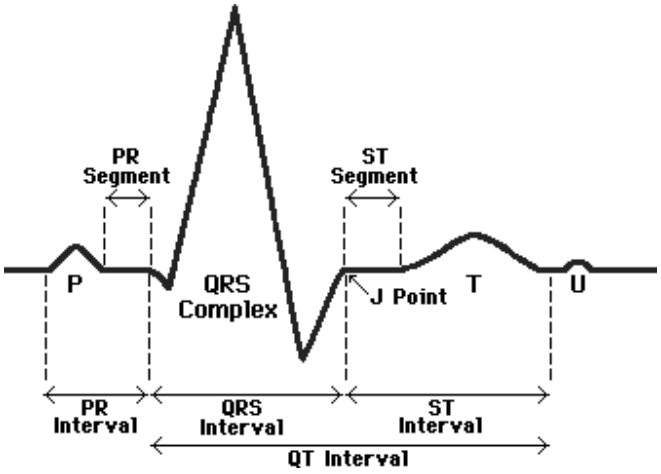


Figure 5.22 A typical ECG signal with the common waves identified.

The above paragraph (including figure 5.22) is a description of the typical results measured from an ECG monitor on the chest. The influences of ECG signals in the EEG measurements have been reported in the literature (e.g. Barlow *et al,* 1980; Harke *et al,* 1999). These signals reported are surface electrical ‘break through’ potentials on the scalp.

In order to understand more about the ‘saw tooth’ signal observed in figure 5.21 an ECG monitor was attached to the volunteer using a wireless chest strap. Tests were carried out to ensure there was no interference to the fEITER data. Once the volunteer was

comfortably seated with their eyes closed in a quiet room, the ECG monitor and fEITER data capture began, seen in figure 5.23.

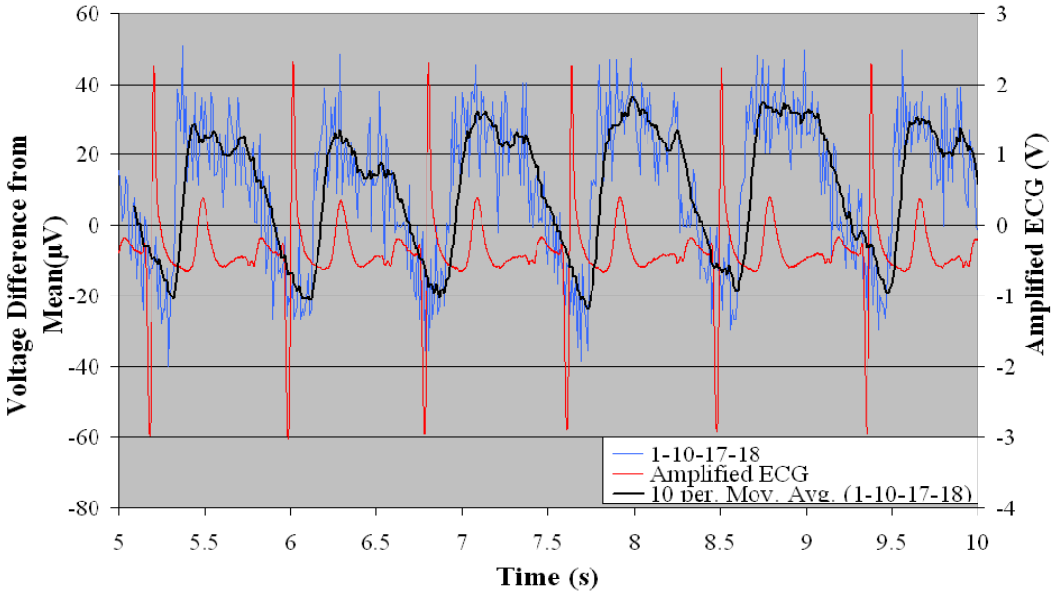


Figure 5.23 A comparison of the measured ECG data (red trace) and the measured fEITER data (raw data shown by blue trace, 10 point moving average of raw data shown by black trace) on the forehead over a 5 second period.

Figure 5.23 shows a sample of the typical data measured from the volunteers, displaying both the ECG and fEITER data. The ECG trace clearly shows the QRS complex followed by the T wave. Each data point for the moving average of the fEITER data (black trace) has been calculated using the formula (5.6). This is a moving average resulting in the unweighted mean based on the previous 10 data points of the raw EIT data (blue trace). Figure 5.23 shows that the volunteer has a resting heart rate of 72 bpm (beats per minute) as shown by the ECG trace (red trace). The frequency of the 'saw tooth' is the same, with 72 peaks per minute, and is shown to be time-locked to the ECG data.

$$x_i = x - \left(\frac{y_n + y_{n-1} + ... + y_{n-10}}{10} \right) \tag{5.6}$$

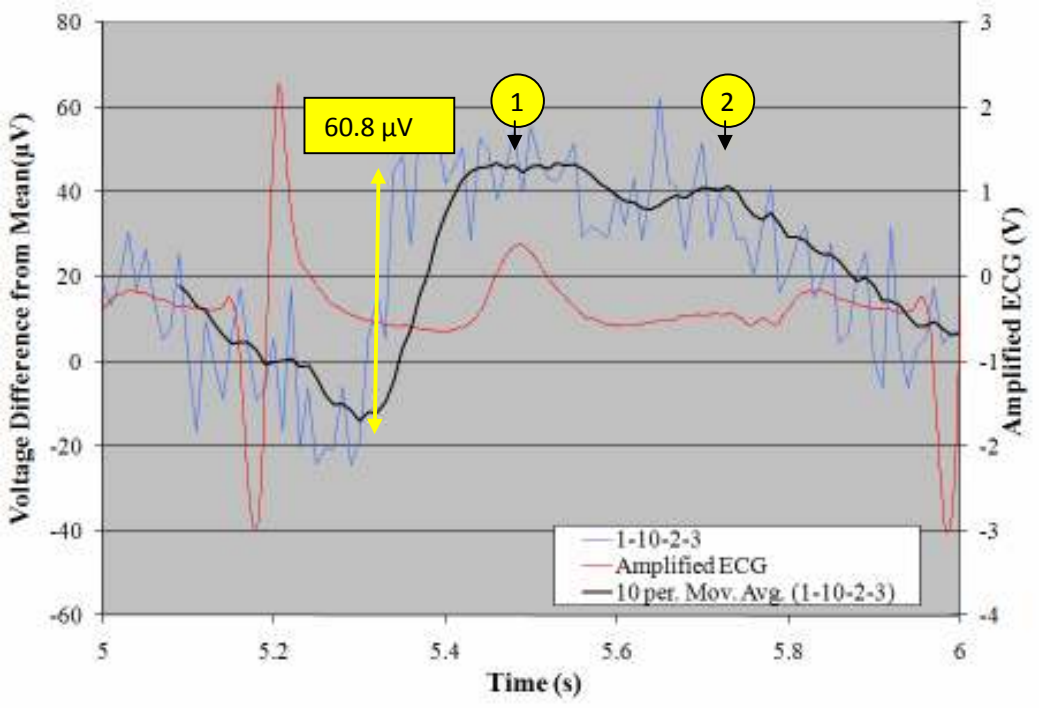


Figure 5.24 Forehead data over 1 second (taken from same data as figure 5.18), showing one cycle of the pulsatile effects.

One cycle of the ECG and EIT data are shown in figure 5.24. It shows that the peak-to-peak change in voltage takes 120 ms, peaking at 60.8 µV. Identified are two distinct peaks (labelled 1 and 2). Both peaks appear to be a regular feature in the data (see figure 5.23). The second peak occurs 550 ms after the peak of the ECG R wave. This second peak on the EIT data is 260 ms after the peak of the ECG T wave. Based on these measured times it is possible to hypothesise, that the first peak (1) is related to the peak of the R wave and the second peak (2) is related to the peak of the T wave (see discussion).

From the set of data shown in figure 5.23 the approximate latencies between the peak of the R wave to the peak of the 'saw tooth' for each cycle have been calculated and are given in table 5.2.

Table 5.2 Approximate times of ECG peak and EIT peak (raw and averaged) for each cycle and the latencies between each ECG peak and the following EIT peak. Data measured from subject A.

ECG Peak (s)	EIT Peak (s)	Averaged EIT Peak (s)	DIFFERENCE (ms) EIT Peak : ECG Peak	DIFFERENCE (ms) Averaged EIT Peak : ECG Peak
5.2	5.41	5.37	170	210
6.02	6.28	6.2	180	260
6.81	6.94	7.09	280	130
7.64	7.97	7.8	160	330
8.51	8.65	8.74	230	140
9.38	9.6	9.56	180	220
		MEAN	200	215

The plot was split into individual ECG cycles for analysis; each cycle is a complete cardiac wave i.e. from P wave to T wave. The peak of the ECG is defined as the peak of the R wave, whilst the EIT peak is defined as the largest positive voltage change in the data. The latencies displayed in table 5.2 are the time between the ECG peak and the EIT peak. This analysis was completed separately for the raw data and the cumulative moving average data.

The EIT data measured at different locations on the scalp are shown in figure 5.25. From these plots the latency values between the EIT (in that location) and ECG data were compared. The mean latency (averaged across 6 cycles) for each location was calculated and is shown in table 5.3. Further analysis was conducted using all of the EIT data captured from one volunteer to understand the differences between the peaks of the EIT data at a different locations on the head. The results from this showed that there was no topographical difference. All latencies were approximately 200 ms.

Table 5.3 Mean latencies (averaged over 6 cycles) from the plots in figure 5.25.

Site Location	Mean Latency (Raw EIT Data)
Forehead	158 ms
Rear	230 ms
Left Hand Side	247 ms
Right Hand Side	187 ms

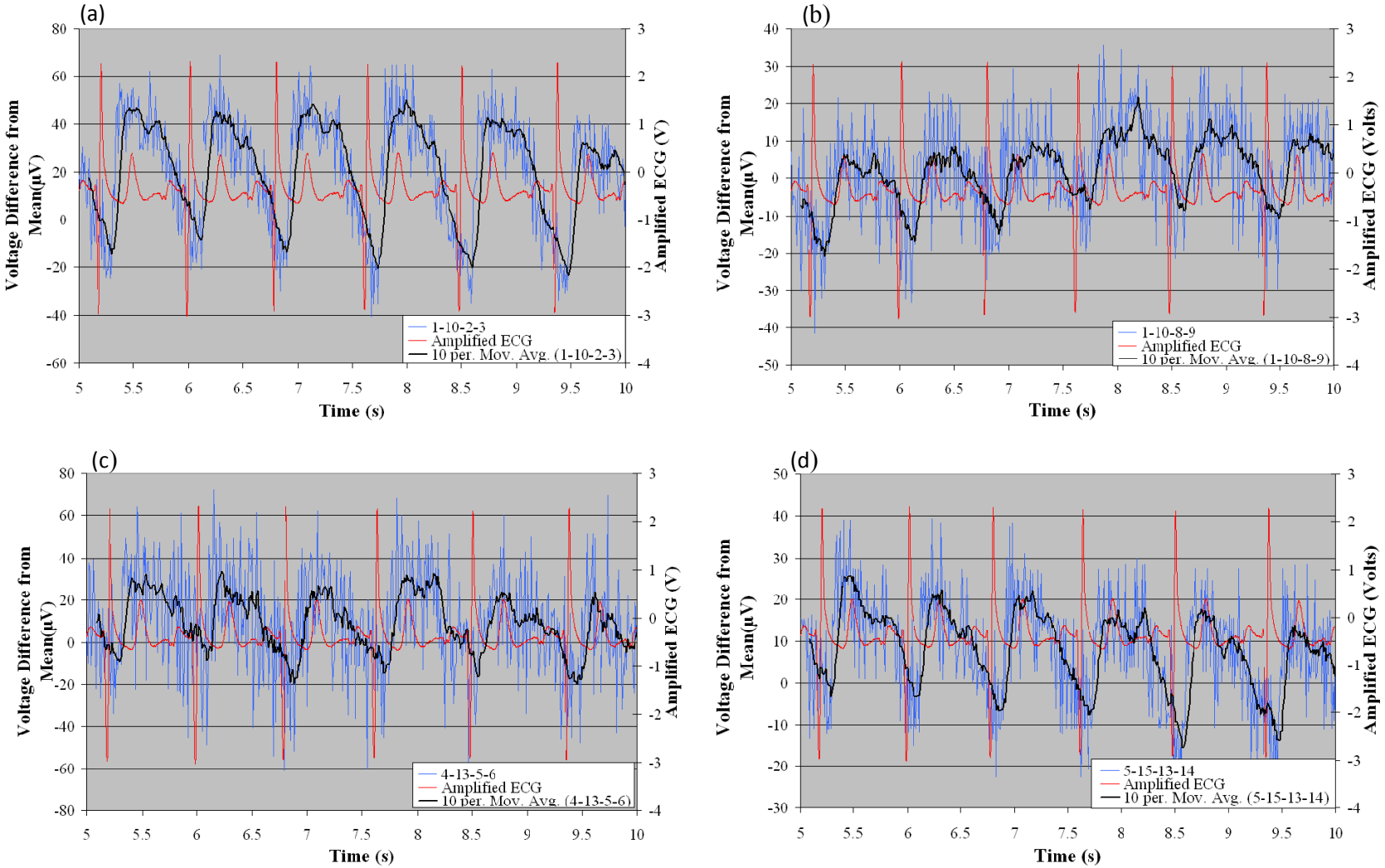


Figure 5.25 The 'saw tooth' with the overlaid measured ECG data; (a) forehead, (b) rear, (c) left hemisphere and (d) right hemisphere.

5.3 Valsalva Manoeuvre

The valsalva manoeuvre was performed on both volunteers as a method of understanding further the saw tooth fEITER data. The valsalva technique is usually performed to release pressure in ears but is also carried out in a clinical setting as a method of understanding more about the cardiac output. The manoeuvre is performed by forcefully exhaling against a closed mouth and nose for a few seconds, effectively closing the Glottis (windpipe). This changes the pressure within the thorax (Stewart *et al*, 2004), causing a rise in blood pressure followed by a reduction in arterial pressure and causing a change in heart rate. Figure 5.26 shows the fEITER data for a forehead site throughout the one minute of capture. At 12.5 seconds the valsalva manoeuvre began, concluding at 27 seconds. The largest changes can be attributed to movement. This was confirmed by some movement tests without performing the valsalva manoeuvre. In-depth analysis of the pre- and post-valsalva periods can be carried out using figures 5.27 to 5.28 respectively.

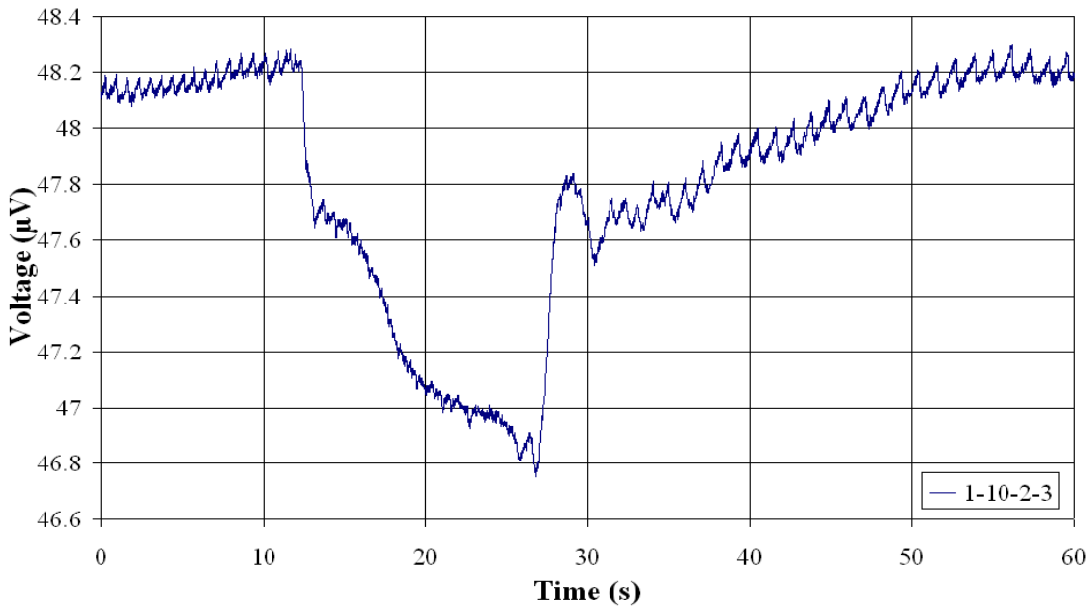


Figure 5.26 Measured EIT data on the forehead whilst the valsalva manoeuvre is preformed, beginning at 12.5 seconds and finishing at 27 seconds.

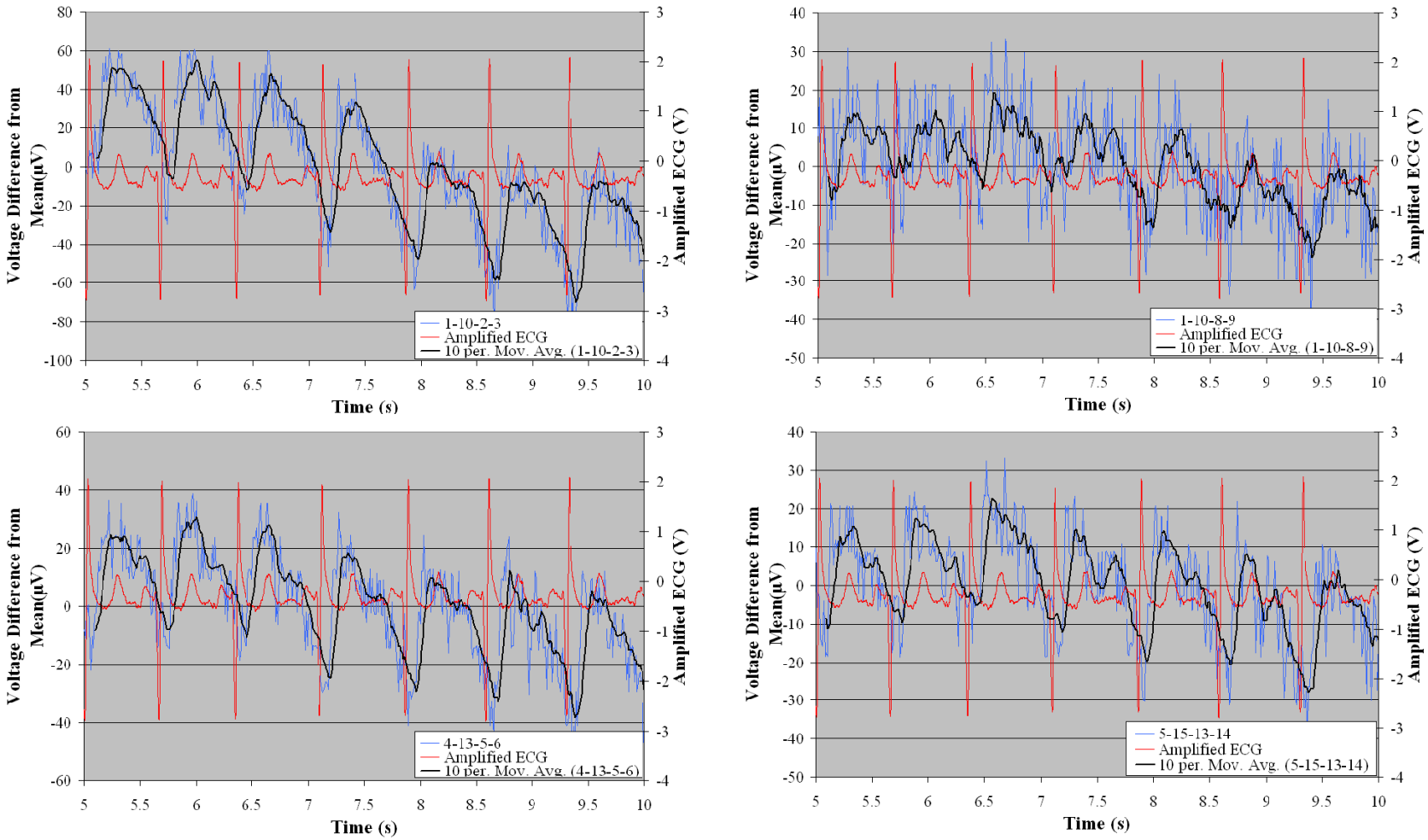


Figure 5.27 Pre-valsalva topographical view; (a) forehead, (b) rear, (c) left hemisphere and (d) right hemisphere.

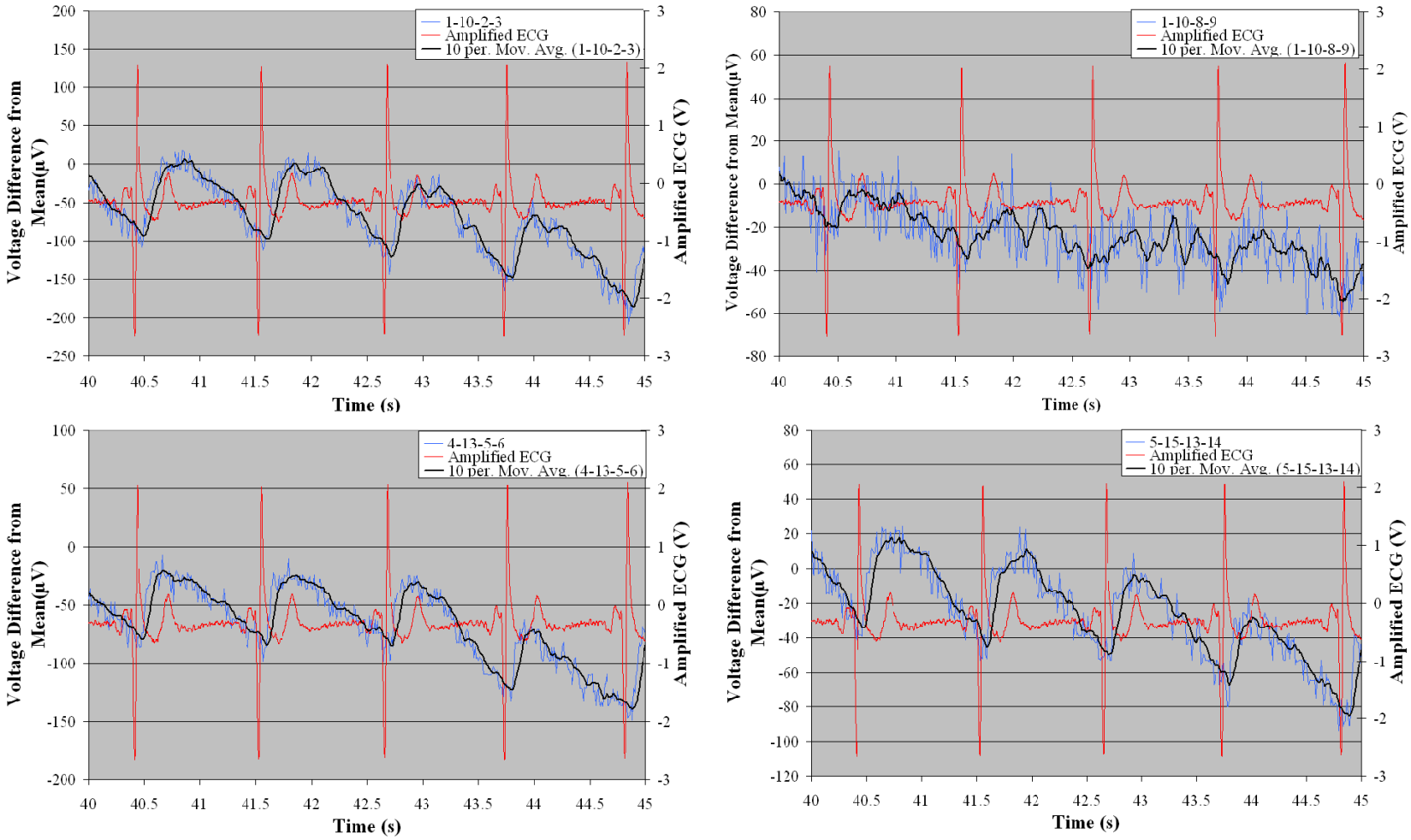


Figure 5.28 Post-valsalva topographical view; (a) forehead, (b) rear, (c) left hemisphere and (d) right hemisphere.

The main comparisons that can be analysed from the data in figures 5.27 (pre-valsalva) and 5.28 (post-valsalva) are the frequency of the cycles and the change in amplitude of the data. The pre-valsalva data (figure 5.27) show a heart rate of 84 beats per minute. This is more than a third more than the post-valsalva (figure 5.28), which has a heart rate of 60 beats per minute.

The ECG data for pre-valsalva data shows that a peak-to-peak (Q wave peak to R wave peak) amplitude of 4.7 V. This value is similar to the post-valsalva ECG data, which has a peak-to-peak amplitude of 4.5 V. If the EIT forehead data, pre- and post-valsalva, is compared it shows that the pre-valsalva data has a peak-to-peak amplitude of 53.9μV whereas post-valsalva it has an amplitude of 92.8μV. The table below shows the maximum voltage changes in the EIT data pre- and post-valsalva for the other sites plotted in figures 5.27 and 5.28.

Table 5.4 The voltage amplitude (peak-to-peak) for pre- and post-valsalva averaged over several cycles.

Location	Pre-Valsalva Voltage Amplitude (μV) (Mean of 7 pulses)	Post-Valsalva Voltage Amplitude (μV) (Mean of 5 pulses)
Forehead	53.9	92.8
Rear	22.0	22.8
Left Hand Side	34.0	56.0
Right Hand Side	29.1	47.5

5.4 Discussion

This chapter discusses the initial application of fEITER, beginning with tank tests before progressing to human tests. The tests using the realistic head-phantom tank show that the fEITER system is operating qualitatively correctly, with all 20 current projections matching the predicted EIDORS 'u-curves'. Any slight discrepancies between the measured data and the predicted data are attributed to errors in the geometrical model and discrepancies in electrode positions between the model and reality, and their size. The repeatability across frames was analysed using the head-phantom, resulting in a mean standard deviation of 11.2 μV. The SNR was calculated for all measurement indices, showing that 76 measurements had SNR greater than 80dB. To the best of the author's knowledge, the combination of the

temporal resolution (100 fps) and the above SNR means that fEITER is the best-resolved medical EIT instrument in the literature, in terms of both SNR and time. This means fEITER has the potential to provide uniquely fast and precise measurements on human volunteers.

The first experiments on human volunteers are described in section 5.2. Initially fEITER was used as a passive voltage measurement device, which is similar to EEG devices although fEITER operates at 10 kHz, which is significantly higher than the low frequency EEG experiments. It is important to ensure that the results obtained by fEITER are different from those obtained in EEG studies. Tests were carried out using fEITER without current injection. The data shown in section 5.2.2, described a series of tests carried out comparing reference and stimulus data. The results from these tests showed no evidence of a change in voltage time-locked to the stimulus (for either single trial or averaged stimuli tests). Data from non-stimulus and stimulus experiments were statistically compared using a pair t-test. The results rejected the null hypothesis that the data were from different sets ($p<0.01$). Therefore it is possible to conclude that the results of fEITER at 10 kHz will be different to those obtained in EEG.

The following sets of tests reported (section 5.2.3) were performed with the applied current (1mA peak-to-peak). The tests (without stimulus) showed a 'saw tooth' curve present on all measurement sites across the head. After simultaneously measuring the ECG and fEITER data it was possible to conclude that the saw-tooth pulses are related to the ECG. Furthermore analysis showed that the latency between the peak of the ECG R wave and the peak of the EIT data was approximately 200 ms. The QRS complex (which peaks with the R wave) represents the contraction of the ventricles. It is during this process that the blood is pushed into the aorta. This equates to an increase in pressure (systole pressure). As described in chapter 1, the blood from the aorta flows straight into the arch which leads to the left and right common external and internal arteries and the vertebral artery, therefore transportation of blood to the brain is fast. The cycles in the EIT data appear to represent impedance changes due to the introduction of oxygenated blood into the head, as can be concluded from their close cyclical relationship to the ECG data.

Discussion with other researchers and an extensive literature search into similar data captured on the head uncovered the technique of rheoencephalography (REG), a method of measuring blood flow in the brain. It uses surface electrodes on the scalp to measure electrical impedance as an indirect measure of flow. There have been several reports in the literature

using REG on animals and humans (Bodo, 2010a) which have confirmed relationships between the measured REG and the cerebral blood flow (CBF), carotid flow (CF) and the intra-cranial pressure (ICP). The impedance changes can be measured on all parts of the body (shown in figure 5.29).

Figure 5.29 Comparison of several measurements between different body sites on body; the EEG and REG locations are FP1 and Cz (EKG – electrocardiograph). (Bodo, 2010b)

The impedance measurements on different body sites show changes that are related to the cardiac output. As seen in figure 5.29, a comparison of measurements taken on one subject shows large response on the head. Bodo *et al* (1998) has reported that changes in the REG signal can be attributed to certain conditions, shown in figure 5.30. He reports that the rise time of the signal is significantly correlated to the age of the subject. The REG rise time and the time difference between the REG peak and the ECG R wave peak both increase with age; an example of this is seen in figure 5.30.

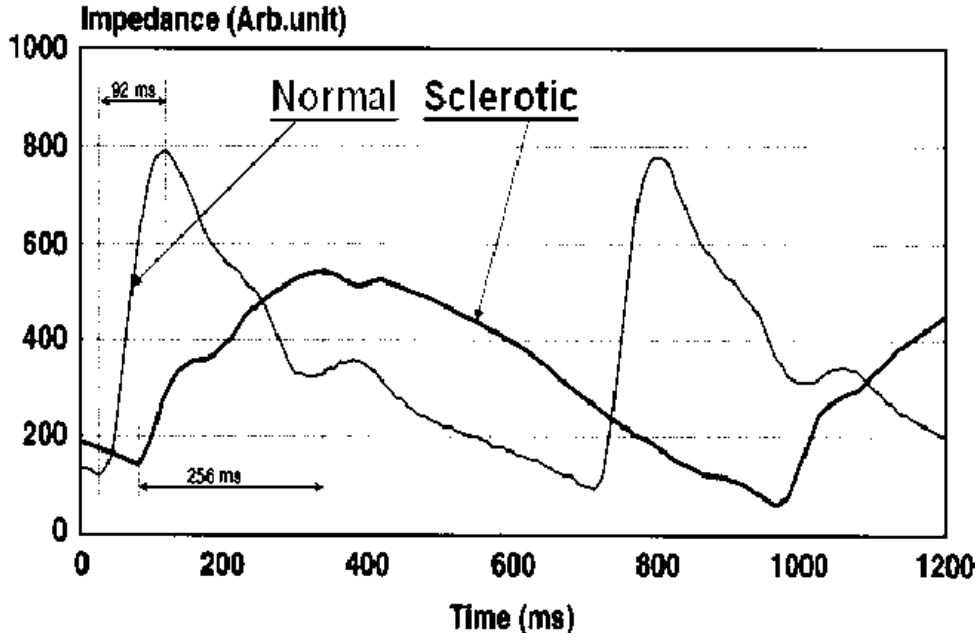


Figure 5.30 Comparison of REG signal from a normal and an aged sclerotic response (Bodo, 2010b).

The sensitivity of fEITER to the cerebrovascular effects is demonstrated in this chapter. The author suggests that it is possible to use fEITER to investigate certain cerebrovascular conditions. However, further research into the relationship between the REG saw-tooth voltage changes and the haemodynamic changes within the brain must be explored. REG is used to measure the changes of blood flow and pressure in the brain. However it is not used for imaging. Since fEITER has a high temporal resolution and uses a 3D strategy to take measurements sensitive to the whole of the brain, it would be more sensitive to changes in blood flow. fEITER may be used to take similar impedance measurements but additionally could be used to produce 3D images. Furthermore it may aid fast and easy diagnosis of conditions such as stroke or arteriosclerosis.

Chapter 6 Auditory Evoked Stimulus

6.1 Auditory Evoked Potentials (AEP)

The use of auditory evoked potentials also known as auditory event-related potentials (ERPs) as measured by EEG, is a well established technique within clinical testing (Halliday, 1993). The technique aims to measure the neural auditory pathways from the early brain stem responses through to the primary and secondary auditory cortex responses. These areas are shown in figure 1.7 and in more detail, in figure 6.1.

As discussed in chapter 1, EEG is a method of recording electrical brain signals from the scalp. However the raw data obtained are a very coarse measure of electrical brain activity. From this it is difficult to assess the highly specific neural response processes such as those occurring in the areas within the auditory cortex. To analyse these EEG signals it is necessary to use averaging and filtering techniques to be able to focus on the response due to the known applied auditory stimulus.

An auditory stimulus is a sound wave that is transmitted through the air, and into the ear canal causing the ear drum to vibrate. The sound waves then move through to the cochlea, seen in figure 6.1, and from here the pressure waves vibrate particular fibres along the length of the tubes. The pressure wave will only vibrate those fibres that resonant at that particular frequency (highlighted as low and high frequencies in the cochlea). If the fibres vibrate an electrical signal is transmitted down the vestibulocochlear nerve to the brain stem. It is within the brain stem that the initial interpretation of the signals is performed, described in EEG measurements as the fast latency responses in the literature (Martin *et al,* 2007). From there the signal is transmitted to the auditory cortices (Brodmann areas 41 and 42), known in EEG measurements as the middle and late latency responses.

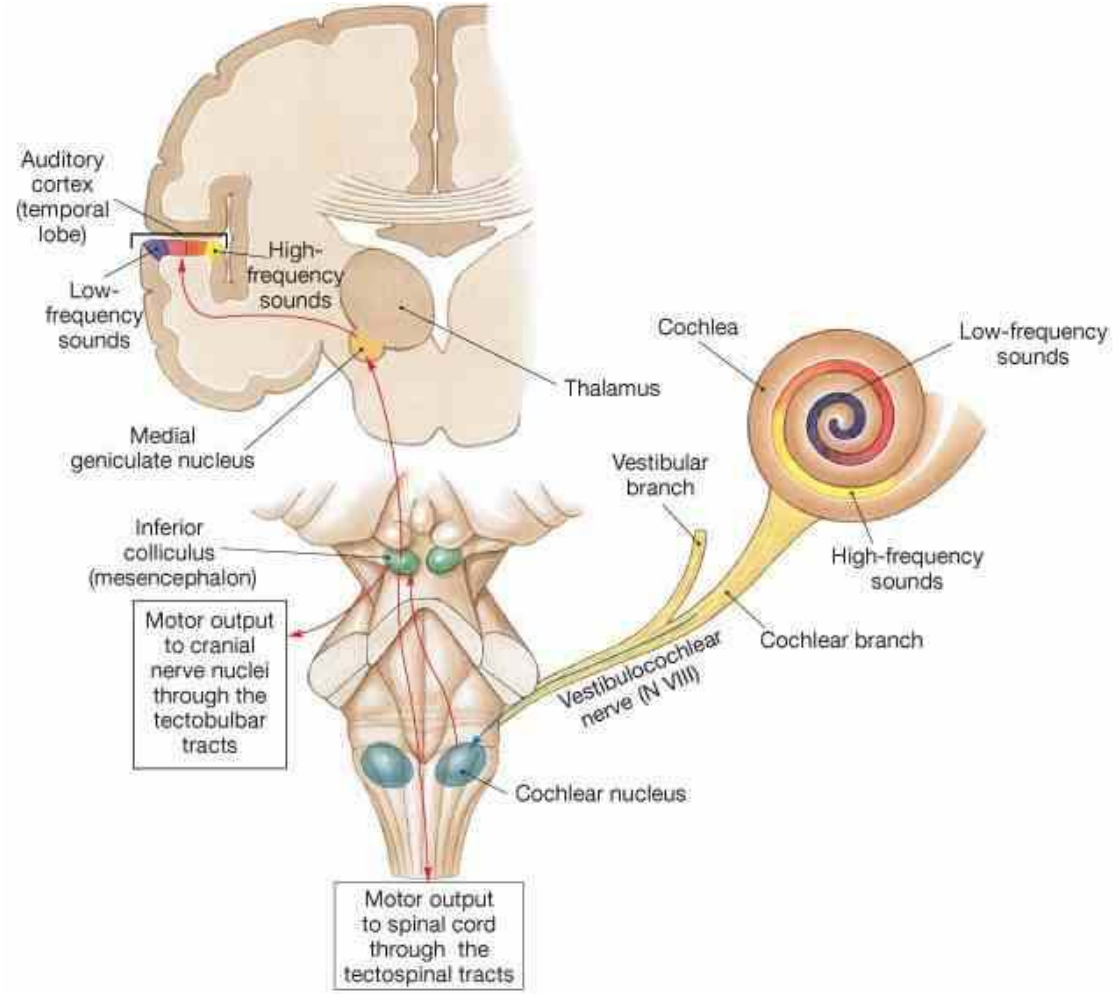


Figure 6.1 A schematic of the pathway for auditory sensations (Martini, 2004)

Before computers aided the analysis process, Davis (1939) discovered the auditory P_1-N_1-P_2 complex (P1≈50 ms; N1≈100 ms; P2≈200 ms after stimulus) which is still used as a method of providing information about the processing of sound in the cortex (Lightfoot and Kennedy, 2006). The time from the onset of the auditory stimulus to the EEG measurement (i.e. latency) can be seen in table 6.1.

Table 6.1 List of anatomy with the associated auditory evoked response latency (Martin *et al*, 2007)

ANATOMY	LATENCY
Cochlear	First (0-5 ms)
Brainstem	Fast (2-20 ms)
Early cortical	Middle (10-100 ms)
Cortical	Slow (50-300 ms)

The use of averaging to obtain a clearer signal was first performed on awake volunteers using auditory evoked potentials in 1964 by a group at the Burden Neurological Institute, Bristol (Walter *et al*, 1964). They used a click, followed by a target visual stimulus 500 or 1000 ms later. The results were averaged and cross-correlated to help with the analysis process. The authors were able to measure voltage changes that correlated with the combined auditory and visual stimulus.

Since then the use of AEPs has been developed over many years, leading to recommended parameters that are used to help ensure a successful AEP recording (shown in table 6.2).

Table 6.2 Summary of recommended parameters for measurement of the P1-N1-P2 complex, adapted from Martin *et al,* 2007.

Subject	State	Awake and quiet
	Eyes	Open
	Condition	Attend or ignore conditions
Stimuli	Frequency	250 – 4000 Hz tone bursts
	Plateau times	20 ms or more
	Inter-onset interval	1-2 seconds
	Intensity	60 – 80 dB SPL
Recordings	Analysis time	Pre-stimulus: 100 ms Post-stimulus: 700 ms
	Number of trials/average	50-100
	Replications	At least 2
	Artefact rejection	±100 μV
	EEG filters	1-30 Hz

The objective of the work described in this chapter is to perform auditory evoked tests under defined conditions, using the fEITER system as the measurement and stimulus device. To the best of the author's knowledge, the use of EIT on the scalp whilst the volunteer is subjected to auditory stimulus is unique. As the amplitude of the EEG AEP results are usually small (up to 10μV peak to peak) and only provide information about the auditory cortices, it is hoped that using EIT will give a greater sensitivity to deep brainstem processing as well as the ability to record responses from single trials (i.e. no averaging would be required).

6.2 Auditory Startle Response (ASR)

An AEP can be masked by the auditory startle reflex (ASR) which is a measure of the brainstem response to an unexpected auditory stimulus, as well as a motor component from facial grimacing, neck flexion and shoulder activity (Bakker *et al*, 2009). ASR is typically measured by EMG techniques, and is used as a method of determining neurological diseases such as acoustic nerve tumours (Freye, 2005) and neurological conditions such as schizophrenia (Ward, 1996).

6.2.1 Methodology

To measure ASR a 'party popper' was used as an auditory startle stimulus. To integrate the 'popper' signal into the fEITER data stream required modification of the fEITER system. Since fEITER has an integrated CED 1401, the auditory startle stimulus tests were carried out using a sound-sensitive circuit board, where the digital signal from the output of an ADC was fed into the digital input on the 1401. From this it was possible to set a threshold on the 1401 so that it was triggered when the auditory intensity was approximately 60 dB. This set-up was tested using an oscilloscope to ensure that the threshold settings were working and accurate, as seen in figure 6.2. The 'popper' was measured to have a maximum sound level greater than 80 dB, as measured by a sound level meter, and a duration of greater than 300 ms, reflecting its broadband frequency range.

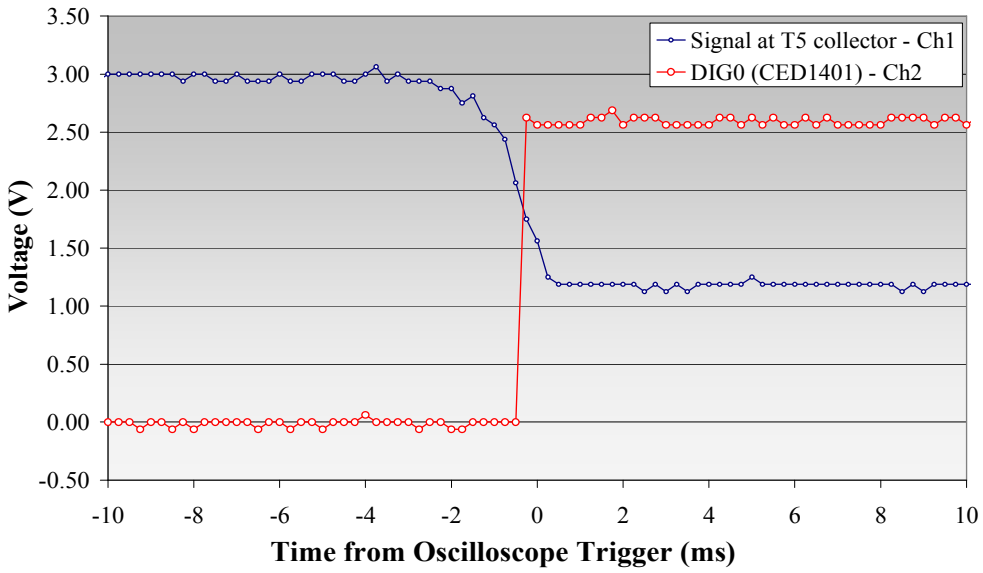


Figure 6.2 Comparison of signals from sound detector circuit and CED output

ZipPrep electrodes were placed on the volunteer's scalp, in the montage shown in figure 2.4. The room was darkened and the volunteer was asked to close their eyes 5 minutes before the experiments to ensure that they were fully dark adapted. The volunteer and experimenter were silent throughout the tests. A 'party popper' was released at a random time during the EIT data capture, at a time unknown to the volunteer. Subject A was not informed that a party popper would be used, but was informed that there would be a surprise at some point. Subject B was informed that a party popper would be used.

Electrode measurement pairs 26-27 and 31-32 are significantly far away from one another. These voltages are discounted in the analysis process as the measurement includes a large unknown area. Unlike adjacent electrodes it would be difficult to conclude that a voltage change measured by these electrodes (26-27 and 31-32) were due to impedance changes in specific cortical areas such as Brodmann areas 41 and 42.

Prior to tests the subjects were asked about their general hearing levels. Subject A is profoundly deaf in their left ear whilst subject B has a perforated left ear drum. Although these are not ideal reference cases the ethical approval was only granted for the principal investigators of the fEITER project to be volunteers.

6.2.2 Results from Subject B

The unexpected auditory stimulus was applied several times during one experimental session. A session would consist of several experiments including references, as well as various visual and auditory stimuli. Table 6.3 shows the times that the poppers were applied for subject B.

Table 6.3 The corresponding experiment and popper release time.

Experiment number	EIT time when popper was applied (seconds)	Time of experiment (24 hour)
3	30	11:09
5	30	11:12
6	10	11:15
16	30	11:38
18	20 and 40	11:46
19	20 and 40	11:51

A representative example (experiment number 3), obtained whilst capturing EIT data and a releasing a 'party popper', is analysed in this section. The popper was released and its auditory signal encrypted into the data stream at 30.01 seconds. Figure 6.4 shows the raw voltage magnitudes (normalised to the applied current) for a data frame at times 50 ms, 100 ms and 150 ms after the onset of stimulus.

Each frame of data ('U' curves) is compared to calculate the difference in voltage, $V_D(t)$, between the time defined by the onset of stimulus (30.01 seconds into the one minute data capture) and 50 ms later, as well the difference between stimulus onset and 100 ms, and stimulus onset and 150 ms. The values of the difference voltage can be seen in figure 6.3. The largest changes between the onset of stimulus at time 0 seconds (30.01 seconds) and 50ms, 100ms and 150ms after stimuli are highlighted on the plot and the details can be seen in table 6.4. As seen from figure 6.3 there are a number of voltage changes that occur at 100 and 150 ms after the onset of stimulus. These are spread across the whole range of measurement index, suggesting a voltage change across the whole of the scalp.

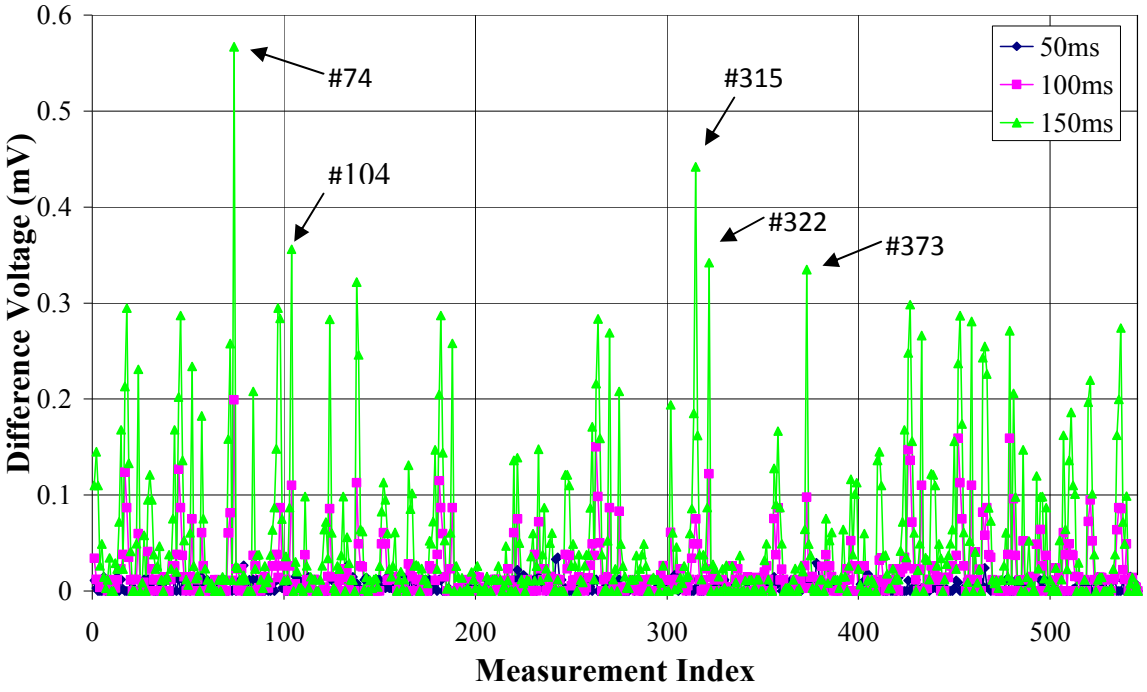


Figure 6.3 Magnitude of the difference voltage, $V_D(t)$, between the onset of stimulus and 50 ms post stimulus (blue trace), 100 ms post stimulus (pink trace) and 150 ms post stimulus (green trace). The largest 5 changes are highlighted on the plots above with the corresponding measurement index.

Table 6.4 Table of the largest 5 changes after the onset of stimulus.

Measurement Index	Current Pattern and Measurement Pair	Changes in voltage, μV (150 ms post stimulus)
74	22-26 18-19	567
104	8-17 18-19	356
315	9-18 25-26	442
322	8-17 25-26	342
373	20-24 18-19	335

6.2.2.1 Topographical Analysis

The previous analysis (figure 6.3) suggested that the voltage changes that occurred 150 ms after the onset of stimulus were across the whole of the scalp. This section analyses the measurements at several sites on the scalp. Samples of data for measurement sites using CP 6-14 are shown in figures 6.4 (experiment 3), 6.5 (experiment 5) and 6.6 (experiment 6).

These figures (6.4 – 6.6) show a voltage change at all measurement sites at the time of the popper release. The amplitude of these changes varies depending on the location. For experiment 3, the forehead has voltage changes of 100μV whereas the rear has voltage changes of 50 μV. Most of the measurements show a return to the pre-stimulus base line after a few seconds post stimuli.

Each of the plots were measured approximately 3 minutes apart. If the amplitude of the stimulus-locked voltage change is compared between experiments it is possible to see habituation in the signals. MS on the rear of the head (9-10 and 10-11) at 11:09 (experiment 3) show large changes of 50 μV and 70 μV; whilst at 11:12 and 11:15 there are no obvious changes on the rear. At time 11:09 the forehead MS, 1-2 and 17-18, shows a voltage change of 100 μV and 150 μV respectively. However, 6 minutes later (figure 6.6) the changes are similar for MS 1-2 at 100 μV but reduced for MS 17-18 to 45 μV.

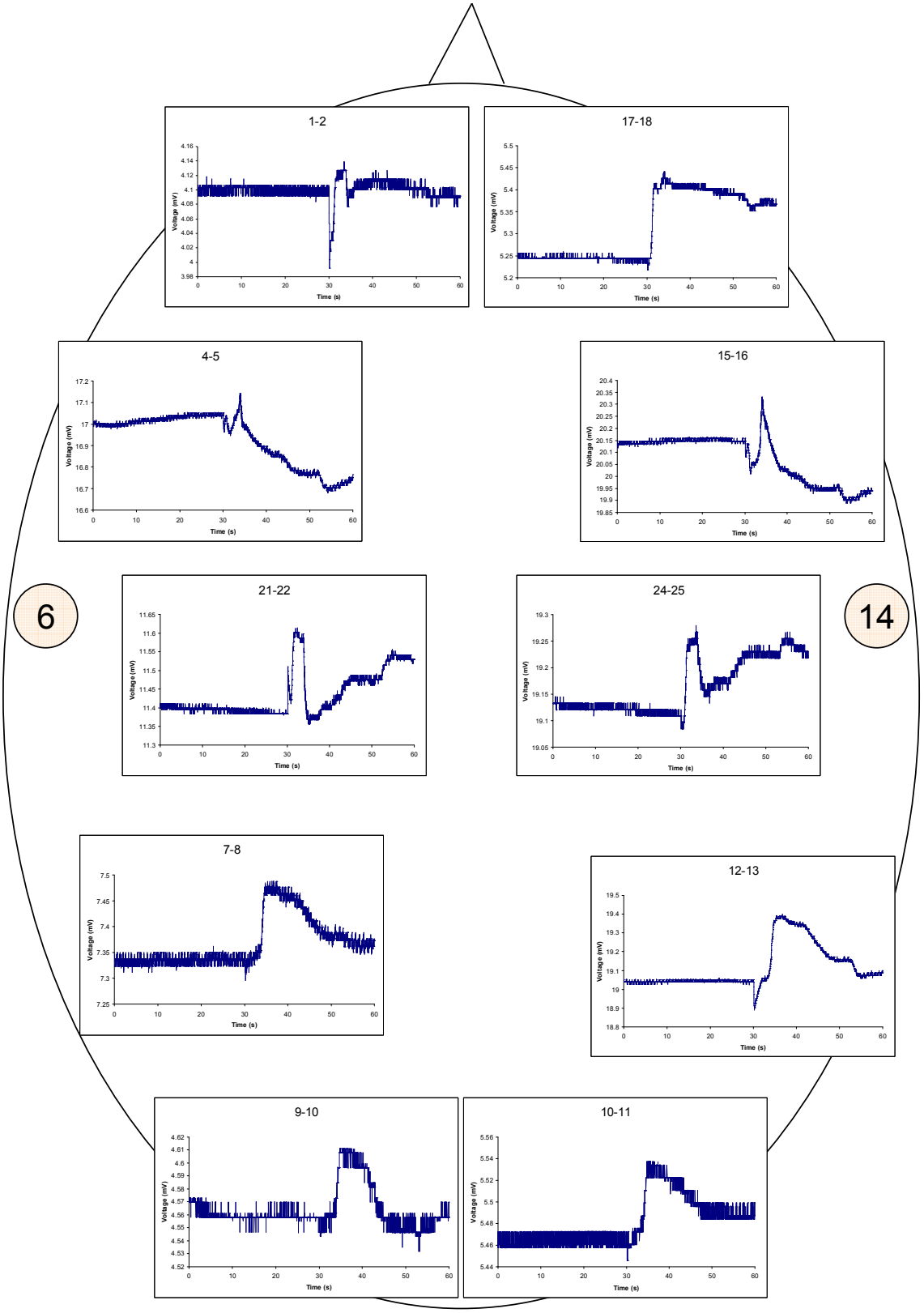


Figure 6.4 Topographic view of party popper experiment at time 11:09. Labelled are the CP sites 6-14. The stimulus was applied at 30.01 seconds into EIT data.

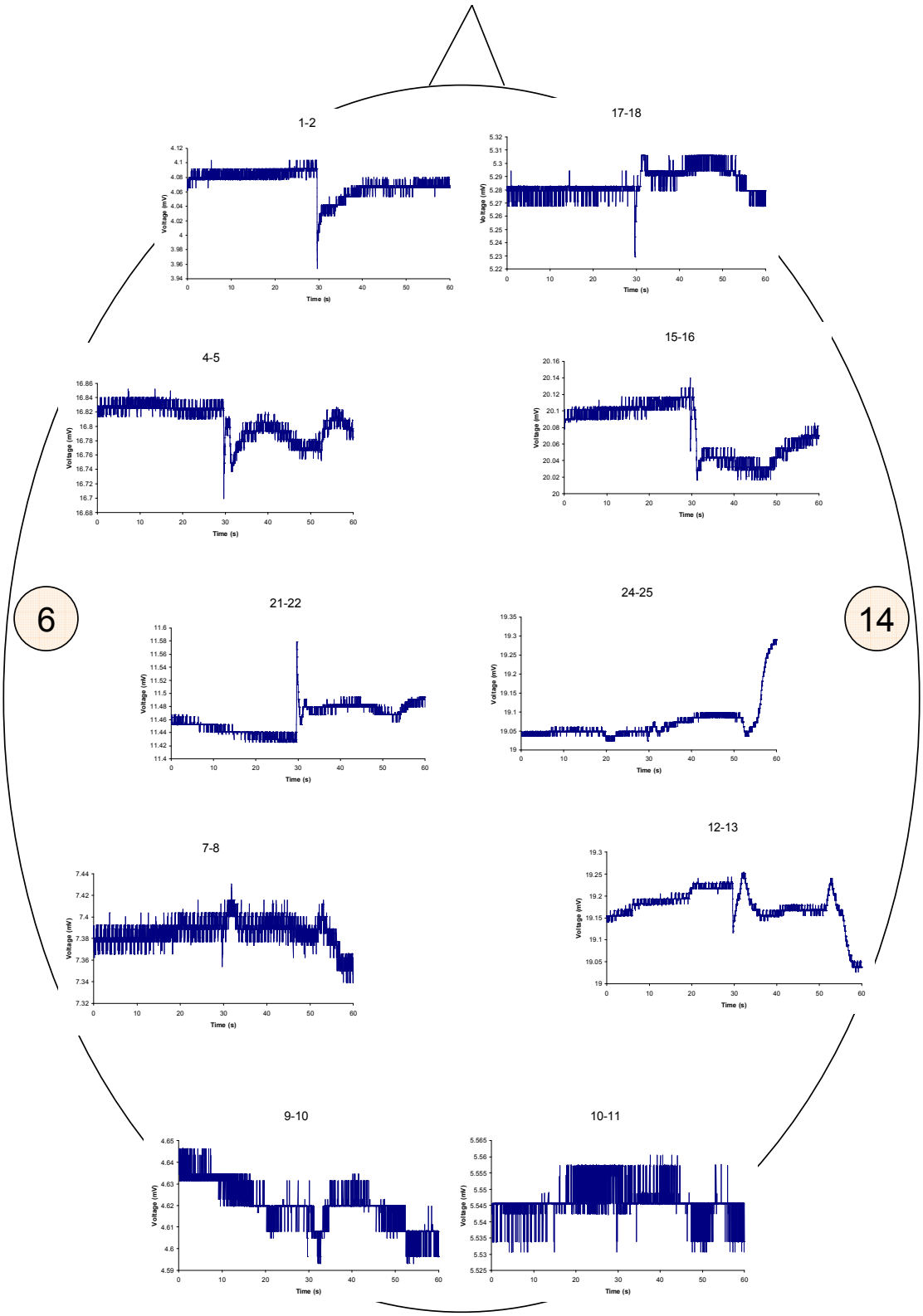


Figure 6.5 Topographic view of party popper experiment at time 11:12. Labelled are the CP sites 6-14. The stimulus was applied at 29.53 seconds into EIT data.

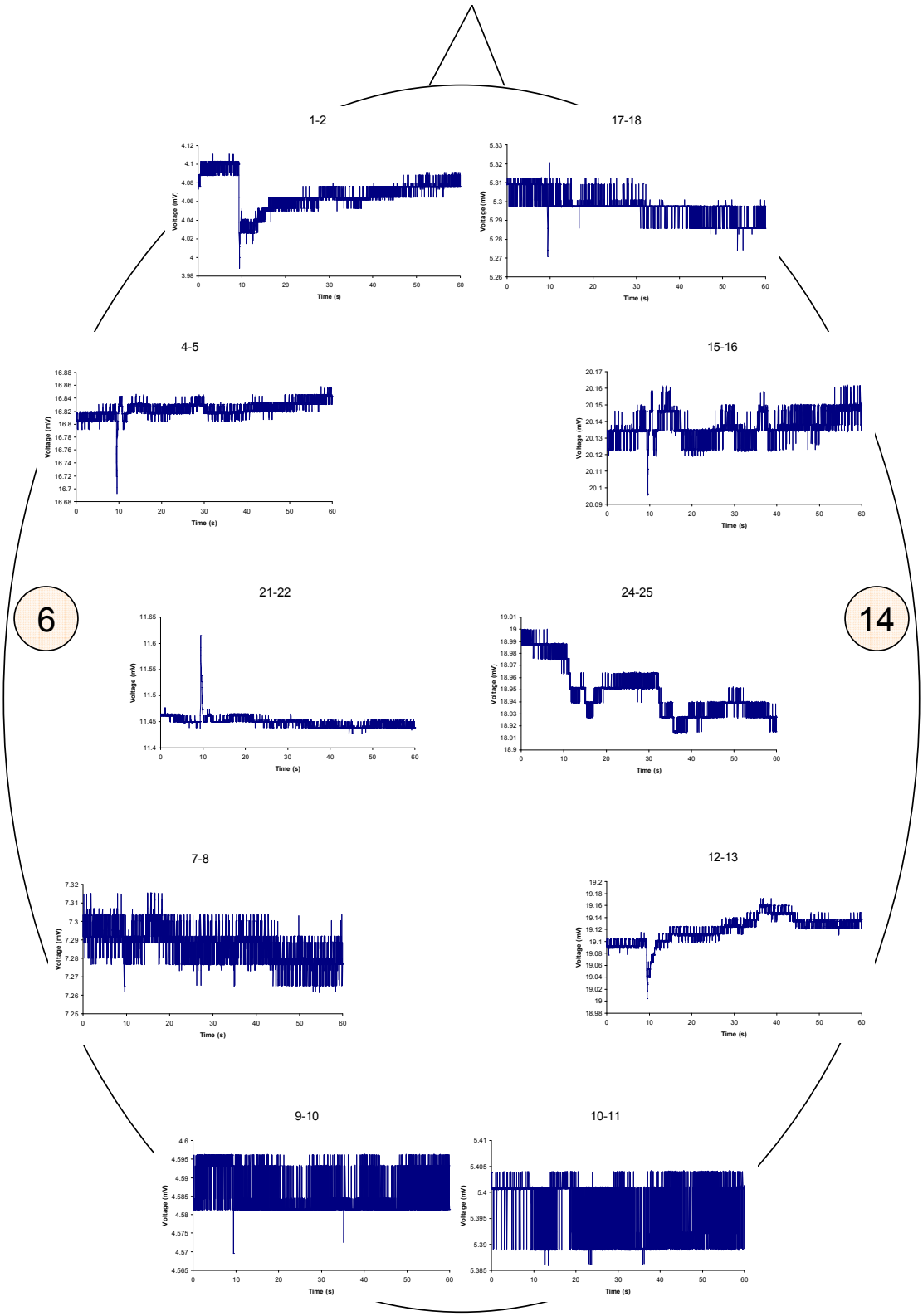


Figure 6.6 Topographic view of party popper experiment at time 11:15. Labelled are the CP sites 6-14. The stimulus was applied at 9.33 seconds into EIT data.

6.2.2.2 Individual Auditory Measurement Sites

As discussed in section 6.2.2.1 there are topographical differences in the measured voltage that occur across most sites on the head when an unexpected auditory stimulus is released. However, since this is an auditory stimulus it is expected that there will be changes over the auditory cortex sites. The analysis for this section is with reference to figure 2.4 for electrode sites 5, 6, 7, 13, 14, 15 on the lower ring and 21, 22, 24, 25 on the upper ring.

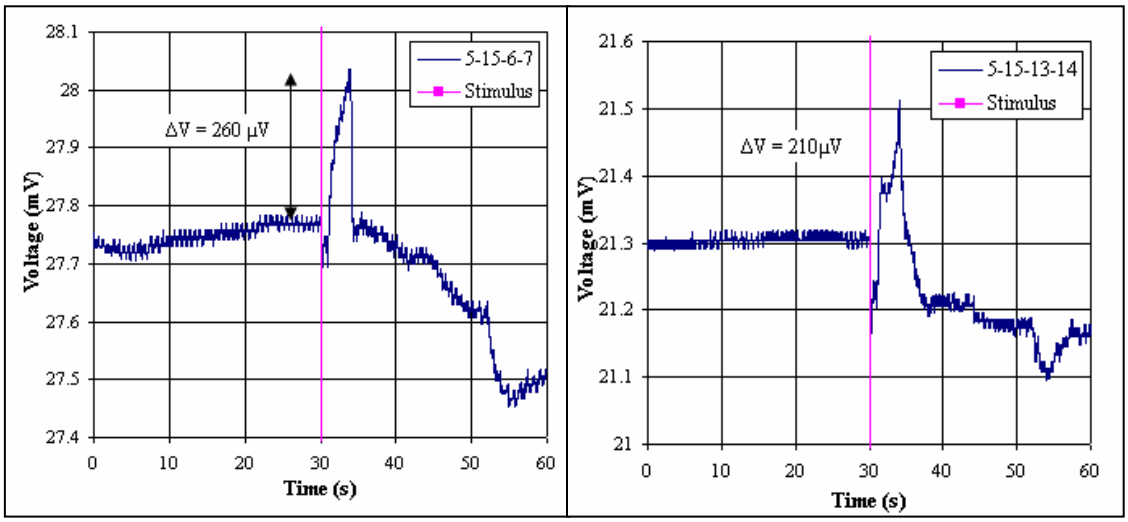


Figure 6.7 Measured voltage over 60 seconds of data capture from CP 5-15 and MS (a) 6-7 (left hemisphere auditory cortex) and (b) 13-14 (right hemisphere auditory cortex).

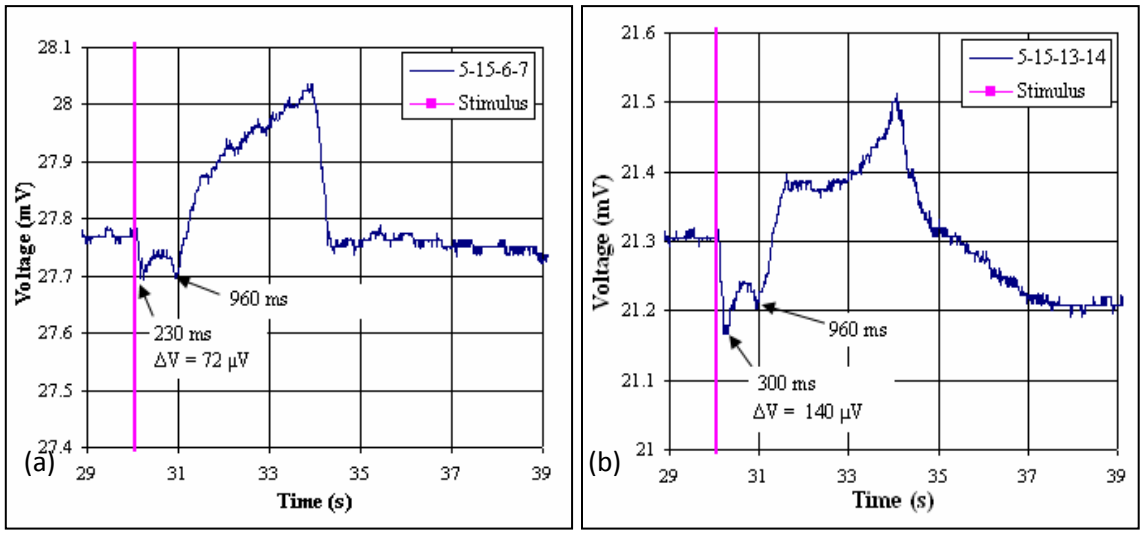


Figure 6.8 A more detailed view of part of figure 6.8. Plots show EIT data over 10 seconds for MS (a) 6-7 and (b) 13-14.

Figures 6.7 and 6.8 show data from the experiment 3 for the left hand side (LHS) and right hand side (RHS) scalp measurements close to the auditory cortices. In terms of amplitude of the voltage change and latency post stimulus, both the LHS and RHS show a similar measured response. There is a fast response that occurs at 230 ms (LHS) and 300 ms (RHS) with a secondary peak at 960 ms for both sides. There is a slower response which peaks at 3.93 seconds (LHS) and 4.05 seconds (RHS) with voltage changes of 260 µV and 210 µV respectively. The recovery to a baseline, seen in figure 6.8, takes between 4-7 seconds after the onset of stimulus. However it is not as stable as the data prior to the stimulus.

6.2.3 Results from Subject A

Further data reported in this section has been taken from a second volunteer (subject A). The same set-up and experimental procedure as described in section 6.2.1 was maintained, except that the party popper stimulus was not encrypted into the data stream thus leading to an estimation of the time of release. Figures 6.9 and 6.10 show the frontal CP-MS, 1-10-2-3 and the rear CP-MS, 1-30-28-29. The frontal and rear EIT measurements are similar between subjects, both have a fast voltage change time-locked to the stimuli before the voltage stabilises after a few seconds.

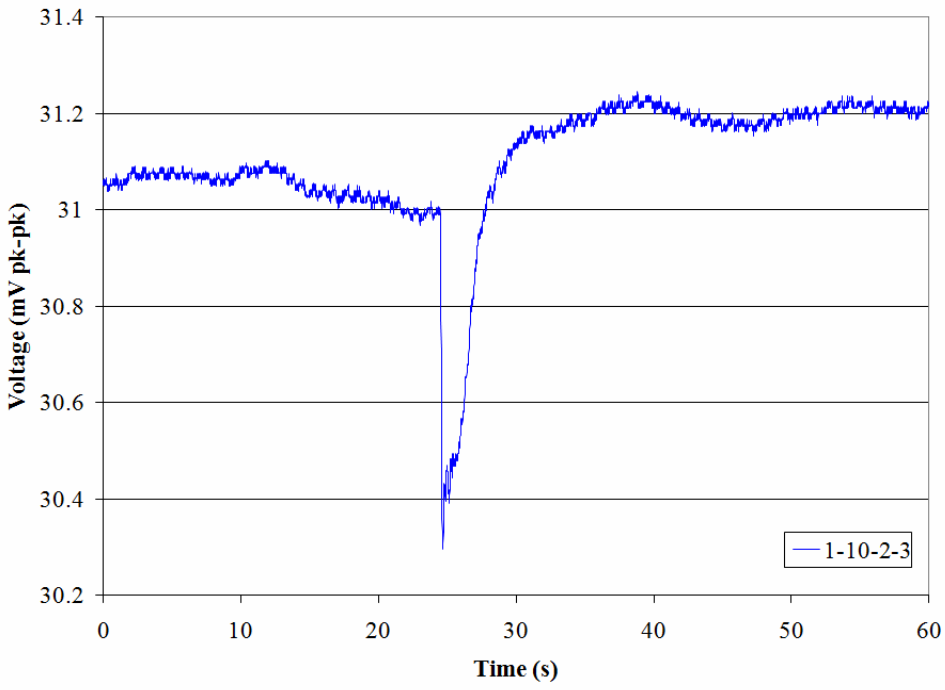


Figure 6.9 fEITER data measured from subject A; Forehead sites CP 1-10, MS 2-3.

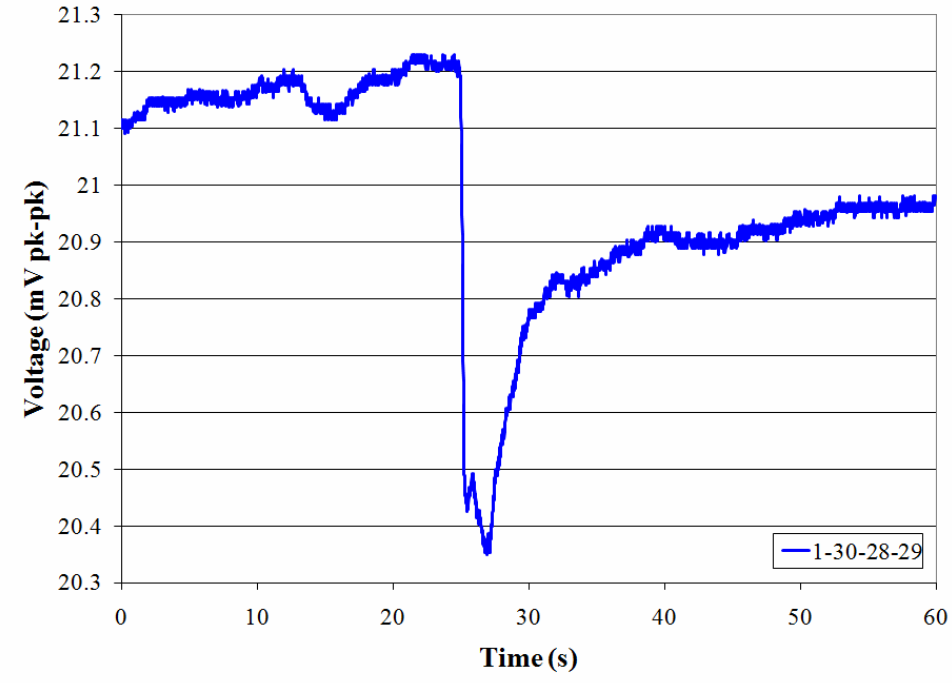


Figure 6.10 fEITER data measured from subject A; Forehead sites CP 1-30, MS 28-29.

Figure 6.11 shows the response of subject A to the unexpected auditory stimulus for the LHS and RHS auditory cortex scalp measurements. The volunteer has a severe hearing impairment in the left ear, and as shown the plots below there is a significant contralateral difference in the data.

Further analysis of the asymmetry is shown in figure 6.12. It shows the difference voltage, $V_D(t)$, with respect to the average between 24.0 seconds and 24.1 seconds. The plot shows voltage difference measurements from CP 21-25, MS 5-6 (LHS) and MS 13-14 (RHS). Both data sets follow a similar trend with an initial peak at 70ms (LHS) and 68ms (RHS), and a second peak at 1.08 seconds (LHS) and 1.13 seconds (RHS). However the amplitude of the voltage change is significantly different with the LHS having a maximum change of 160 μV and the RHS a maximum change of 350 μV.

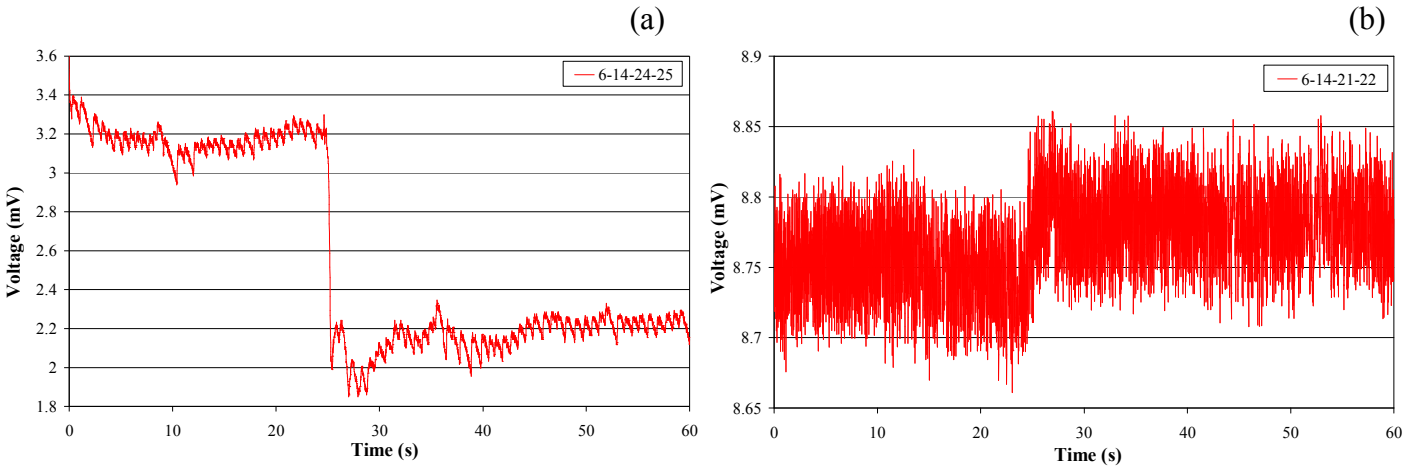


Figure 6.11 The contralateral differences in the data captured with an auditory startle response at approximately 24.5 seconds; (a) LHS and (b) RHS.

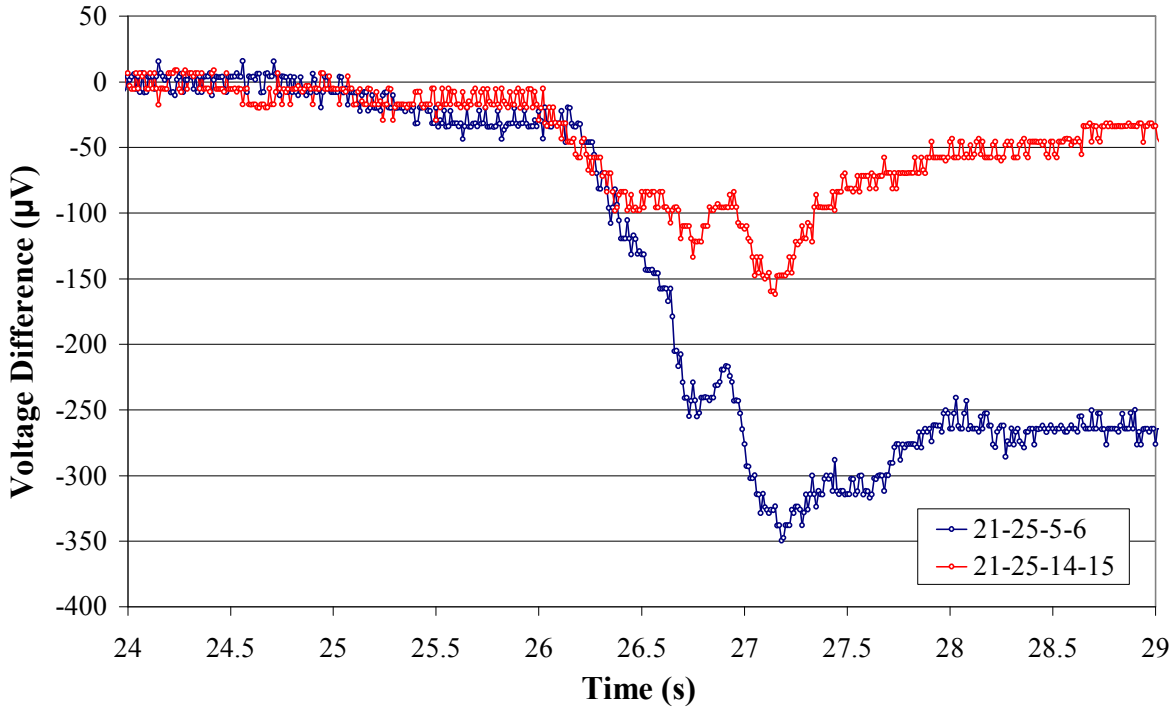


Figure 6.12 Voltage difference, $V_D(t)$, over 5 seconds from CP 21-25 and LHS MS 5-6 (red trace) and RHS MS 14-15 (blue trace).

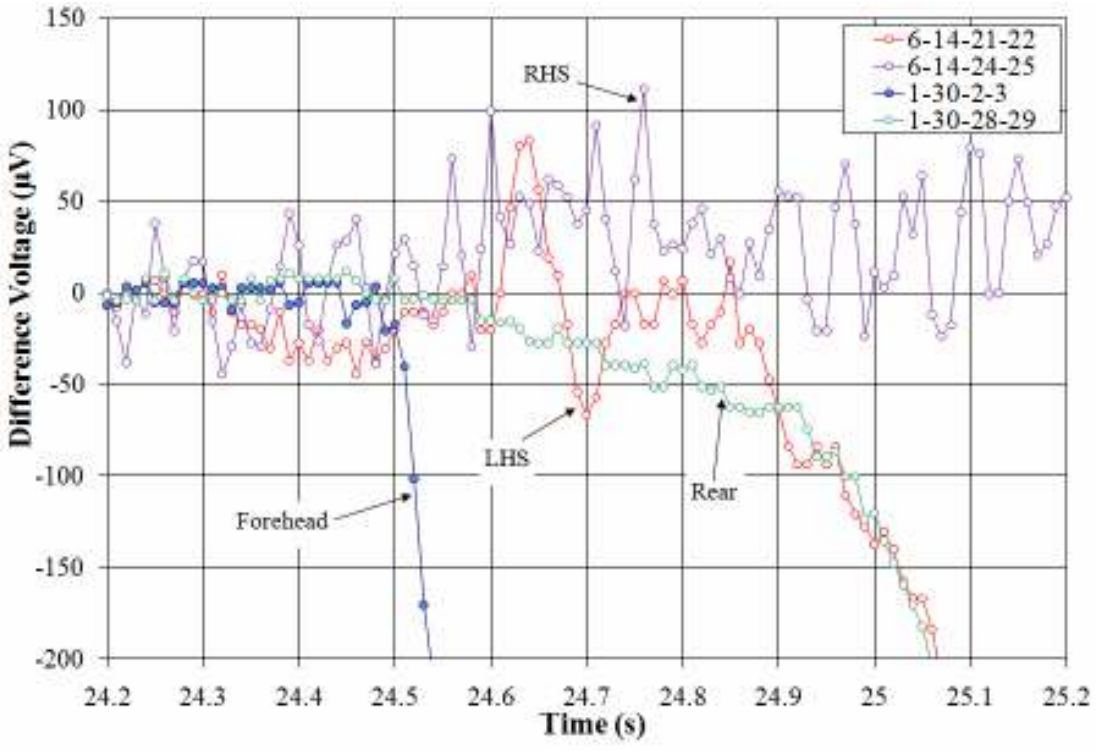


Figure 6.13 Time based plot of the voltage differences, $V_D(t)$, between the post-stimulus voltage changes and the pre-stimulus average.

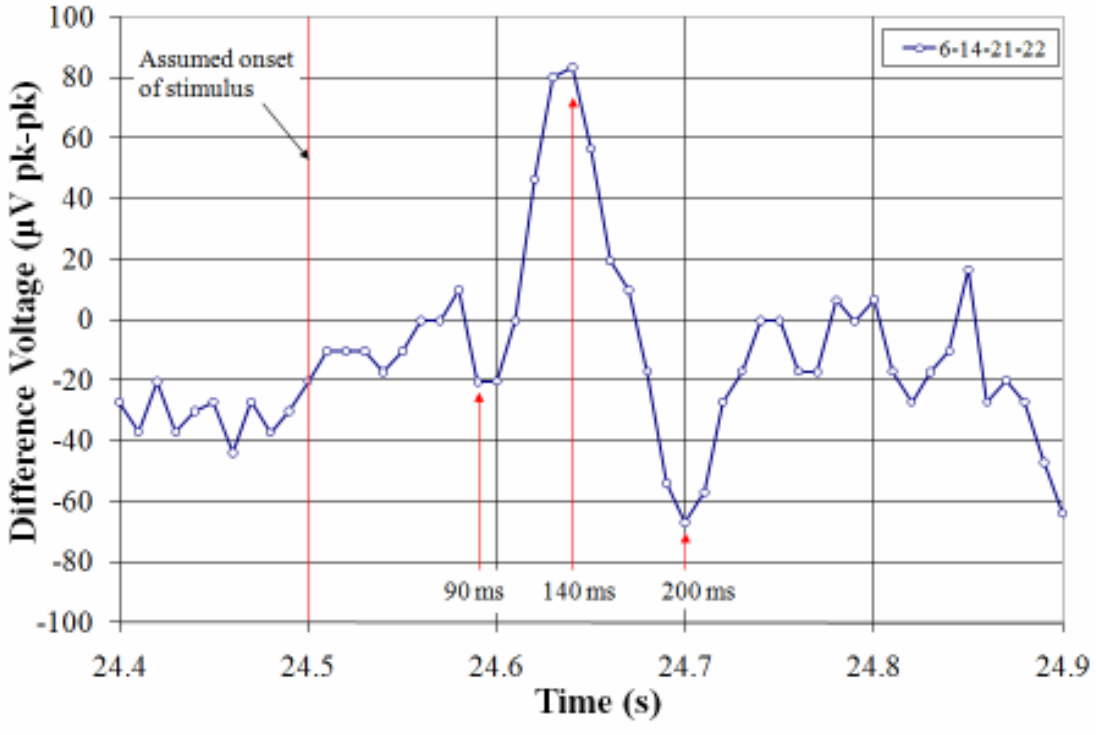


Figure 6.14 Detailed section of voltage measurement CP-MS, 6-14-21-22, from figure 6.13.

Figures 6.13 and 6.14 show the measured voltage difference, $V_D(t)$, with respect to the average between 24.2 and 24.3 seconds. Based on the first obvious voltage changes in the data it is estimated that the stimulus was released at 24.5 seconds. As seen in figure 6.13 the first voltage changes occurs on the forehead, peaking at 522 μV at 170 ms post stimulus. The rear site has a voltage change peaking at 720 ms with a voltage change of 560 μV and the left auditory sites peak at 860 ms with a voltage change of 1.2 mV. Figure 6.14 shows a detailed time based plot of the initial voltage changes that occur over the left auditory cortex. There are two distinct peaks after the onset of stimulus; a voltage change of 110 μV at 140 ms followed by a peak of 40 μV at 200 ms.

6.3 Controlled Auditory Tests

Further experiments were designed to elicit responses associated with the AEP rather than ASR. This section describes the use of controlled-exposure auditory tests that were carried out on two subjects. However, only data from subject A will be analysed in this section. Since subject A has a known hearing impairment if the data in this section is as a result of physiological (neural of haemodynamic) changes it should produce asymmetrical measurements. The results were used to select the auditory stimulus that produced the largest voltage change, for the fEITER phase 1 project (described in chapter 3). All of the results presented are typical examples of the data measured on both subjects.

6.3.1 Methodology

The experiments were carried out in a quiet, darkened room. The volunteer was asked to keep their eyes open throughout the experiments. Two sets of headphones were used; inner-ear Shure headphones and large cup TDH-49P headphones which were placed over the inner-ear headphones. The inner-ear headphones were used to present the auditory stimulus and the TDH headphones were used to deliver white noise for some experiments (throughout the analysis section, it is assumed that no white noise is presented, unless stated otherwise). In all cases, the headphones remained in situ.

Based on the literature on AEP studies measured by EEG (Burkard *et al*, 2007), the controlled stimulus was designed to comply with standard practices. The standard tone bursts for AEP tests in EEG are a set of tone bursts lasting for duration 20 ms or more, over a frequency range of 250 Hz - 4 kHz. The intervals between tones are usually randomised. The

tone loudness level is between 60-80 dB SPL. From these standards a set of controlled auditory tests were designed, as shown in table 6.5.

Table 6.5 Description of the different controlled auditory sequences.

Sequence No.		Frequency (Hz)	Duration of tone (ms)	Voltage (pk-pk amplitude mV)
1		1000	50	11 tones then repeated; 100-500mV (40mV increasing amplitudes)
2		2500	50	11 tones then repeated; 100-500mV (40mV increasing amplitudes)
3		2500	50	Randomised voltages then repeated: 260, 380, 140, 220, 100, 340, 500, 420, 180, 300, 460, 220, 100, 340, 380, 140, 460, 260, 420, 300, 500 and 180
4		1000	50	Randomised voltages then repeated: 260, 380, 140, 220, 100, 340, 500, 420, 180, 300, 460, 220, 100, 340, 380, 140, 460, 260, 420, 300, 500 and 180
5	Standard	22 tones at 2500	50	500 mV
	Deviant	4 tones at 500	100	500 mV
6	Standard	22 tones at 500	50	500 mV
	Deviant	4 tones at 2500	100	500 mV

The variation of loudness level of the tones for sequence files 1 and 2, is shown in figure 6.15. The peak-to-peak voltage amplitude (supplied to the earphones) increased sequentially for 11 tone bursts and was then repeated, giving a total of 22 tone bursts within the minute of

data capture. These tones were calibrated using a Bruel and Kjaer audiometer. The results of the calibration are shown in figure 6.16.

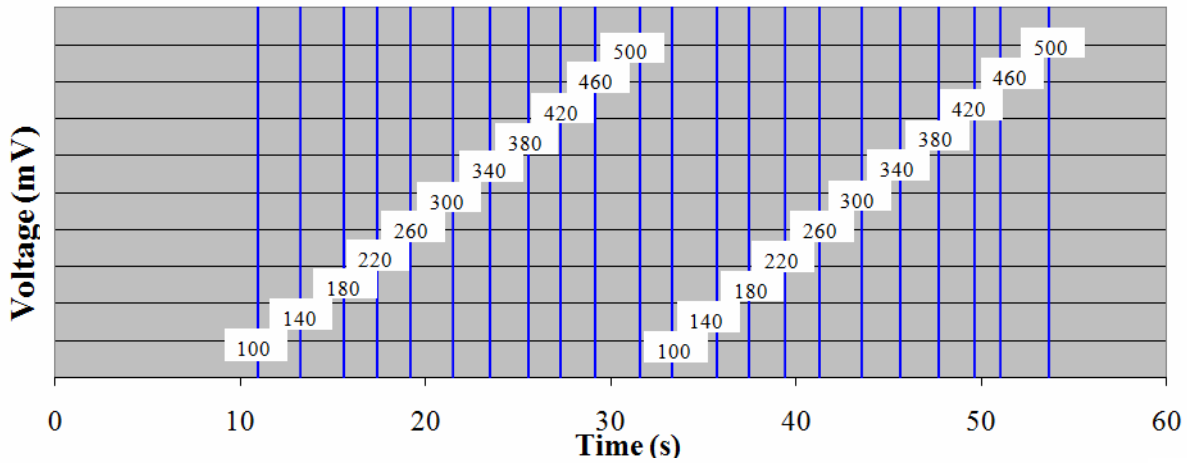


Figure 6.15 An example stimulus file that was used for the controlled auditory stimulus. The labels are in mV.

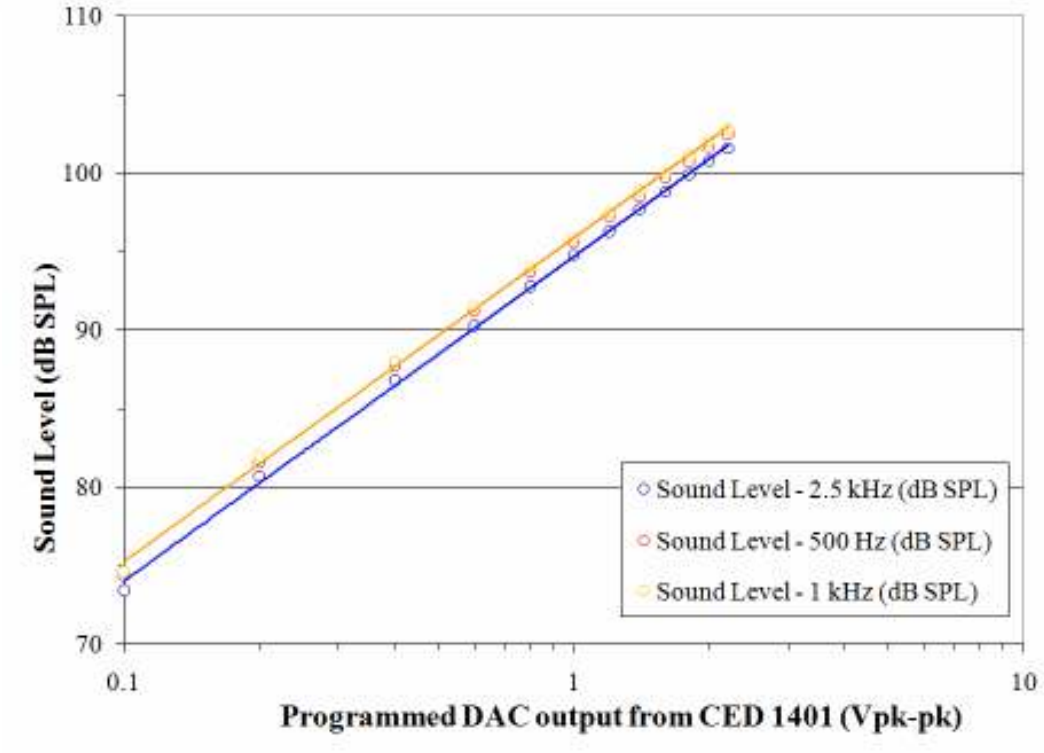


Figure 6.16 The measured loudness levels for the different tone bursts as calibrated by the Bruel and Kjaer audiometer.

The calibration curve shown in figure 6.16 enable the prediction of the loudness levels for the auditory stimulus presented to the volunteers. For sequences 1 and 2, detailed in figure 6.15, the loudness level ranges from 75 – 89 dB for sequence 1 and 73 – 87 dB for sequence 2.

As previously explained the TDH headphones are used to supply white noise. This is a method of ensuring that no inadvertent ambient noise was able to be heard whilst data capture was carried out. Comparisons were made between the experiments with and without white noise when no other auditory stimulus was applied. The results of these tests are shown in table 6.6. It confirms the absence of response to white noise.

Table 6.6 Comparison of the reference data with and without white noise. Significance level is $p<0.01$.

CP-MS	Mean Impedance (kΩ) – No White Noise	Mean Impedance (kΩ) – White Noise	P-Value
1-10-2-3	33.1	33.0	0.005
1-29-27-28	21.9	21.8	0.00
5-15-6-7	28.3	28.2	0.00
5-15-13-14	27.4	27.3	0.00

6.3.2

6.3.3 Data Analysis

The data analysis in this section is from subject A. However similar data were measured from subject B. The analysis of individual raw voltage measurements, selected to be sensitive to the auditory cortices, did not show any significant voltage changes with respect to the stimulus for sequence 1. Examples of those data for MS on the LHS and RHS can be seen in figures 6.17 and 6.18.

Over the minute of EIT data capture there is a drift in the baseline voltage from approximately 13.55 mV to 13.49 mV, a change of 60μV. This magnitude of drift is common on most of the data, including the reference data (without stimulus). It is thought that the drift is due to a combination of effects, it could be caused by slight volunteer movement causing a change in the stresses on the electrode connections and therefore a change in total impedance as well as the possibility is that a drop in impedance over time could be due to the electrolyte penetrating the stratum corneum, as discussed in chapter 4. The above figure shows the rate

of change of impedance is approximately 0.4% per minute, comparing this to the data in section 4.4. Subject A shows the rate of change of impedance is approximately 0.3% per minute (calculated over all measurements in 120 minutes; the first 20 minutes shows a larger rate of change).

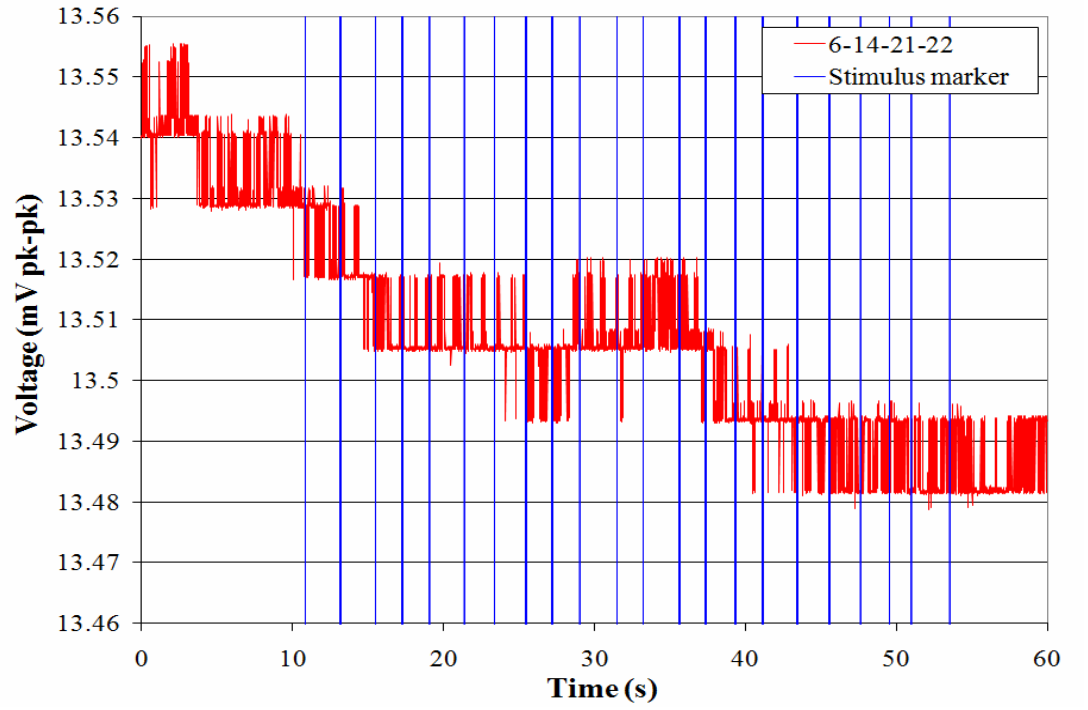


Figure 6.17 Voltage measurements from the left side (sequence file 1 with white noise).

The randomised voltage sequences (3 and 4) and the oddball sequences (5 and 6) produce similar data to sequence 1; i.e. there are no significant voltage changes time-locked to the stimulus on the raw voltage data. However, sequence 2 shows large voltage changes for some of the tone bursts within the minute time-locked to the stimuli. Sequence 2 is set at 2.5 kHz with tone burst duration of 50 ms, separated by approximately 2 seconds.

The measurements from subject B using sequence 2 displayed a similar response. However, the majority of measurements are symmetrical. The other sequences shown in table 6.5 do not elicit a measurable response.

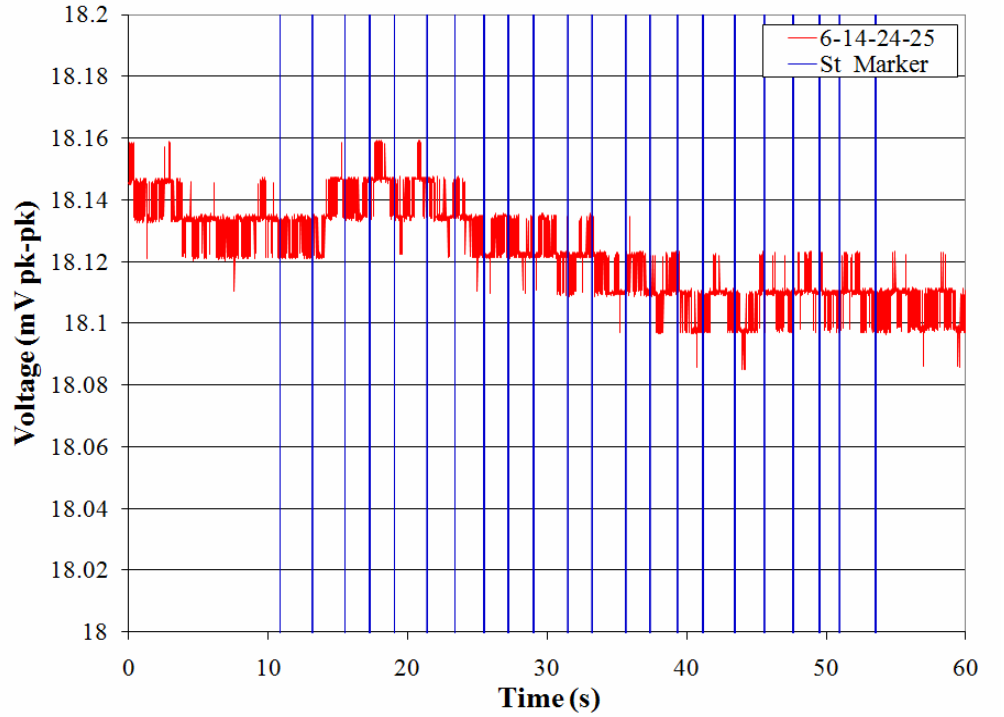


Figure 6.18 Voltage measurements from the right side (sequence file 1 with white noise).

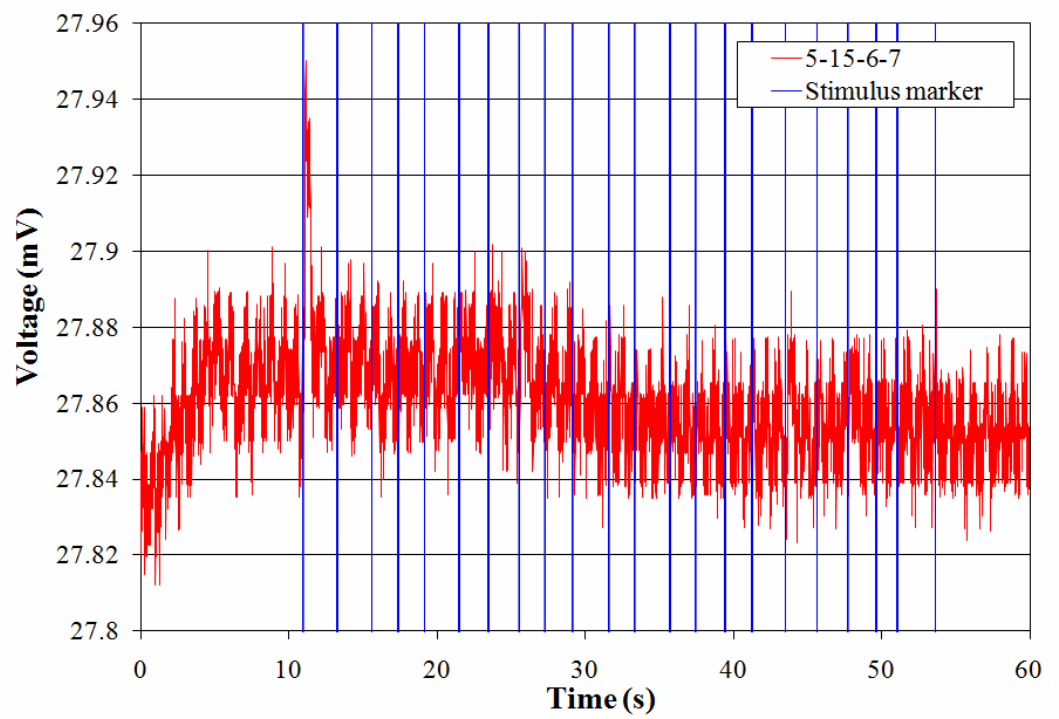


Figure 6.19 Voltage measurements from the left side (sequence file 2 with white noise).

The data measurements shown in figures 6.19 and 6.20 are the equivalent data to those in figures 6.17 and 6.18. However these are measurements using sequence 2. There is a large voltage change for the first stimulus on the LHS, and there is no obvious change on the RHS.

As described in the previous section 6.2, the volunteer has substantially reduced hearing in the left ear thus a contralaterally weighted response is expected.

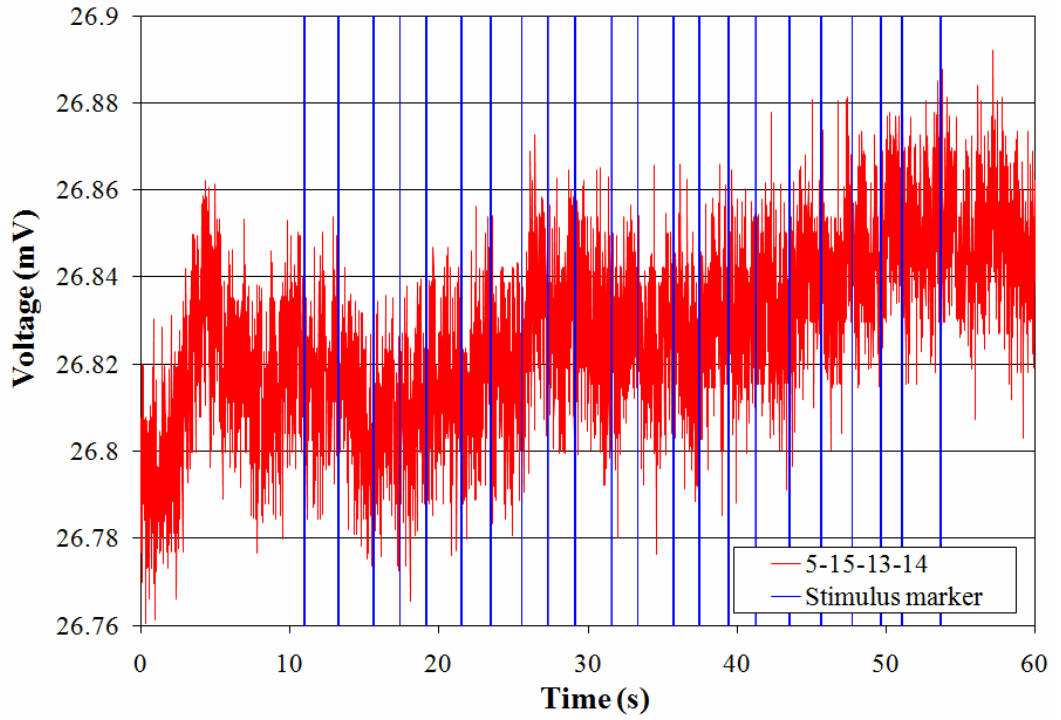


Figure 6.20 Voltage measurements from the right side (sequence file 2 with white noise).

Further analysis of the experiments carried out on subject A using sequence 2 is shown in tables 6.7 (without white noise) and 6.8 (with white noise). Both tables consider the first 11 stimuli and the voltage difference, $V_D(t)$, (with respect to the voltage at time of stimulus onset) at set time intervals post-stimulus (i.e. for stimulus number 1 the voltage difference at 50 ms, 100 ms, 150 ms after the stimulus time of 10.94 seconds). This analysis was performed for the entire range of measurement index. However, the largest 5 voltage changes for each stimulus are tabulated, and the corresponding CP and MS are identified.

The majority of the largest voltage changes have been produced from the frontal sites or those over the auditory regions (as shown in table 5.7 and 5.8). Since the auditory cortices are of most interest in these experiments, the stimuli numbers 2 and 10 for experiments without white noise were further analysed (chosen as four out of five of the largest voltage changes were located over the auditory cortices). Figure 6.21 shows the difference voltages for the whole range of measurement index at 50ms, 100 ms and 150 ms post stimulus number 2 (shown in table 6.7). Figure 6.22 shows the difference voltages for the measurement index at 50ms, 100ms and 150ms after stimulus number 10 (shown in table 6.7).

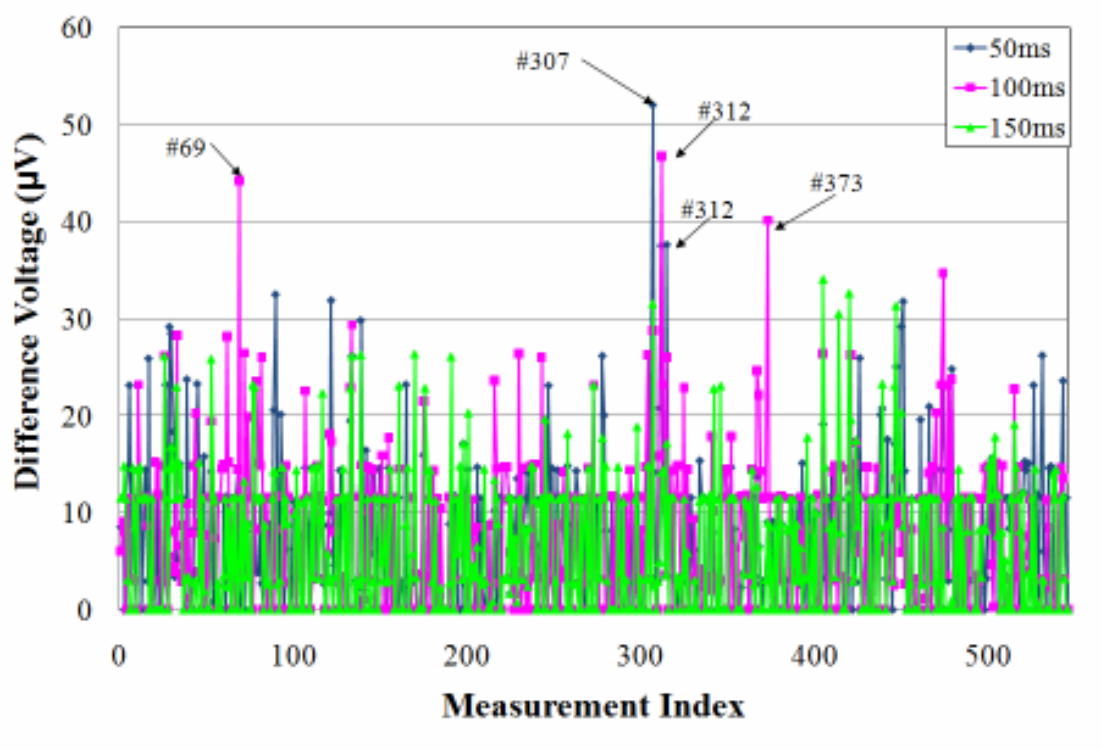


Figure 6.21 Difference voltage, $V_D(t)$, between the onset of stimulus at 13.21 seconds and 50ms, 100ms and 150ms after stimulus number 2 (without white noise). The largest 5 changes are labelled, with the corresponding measurement index named.

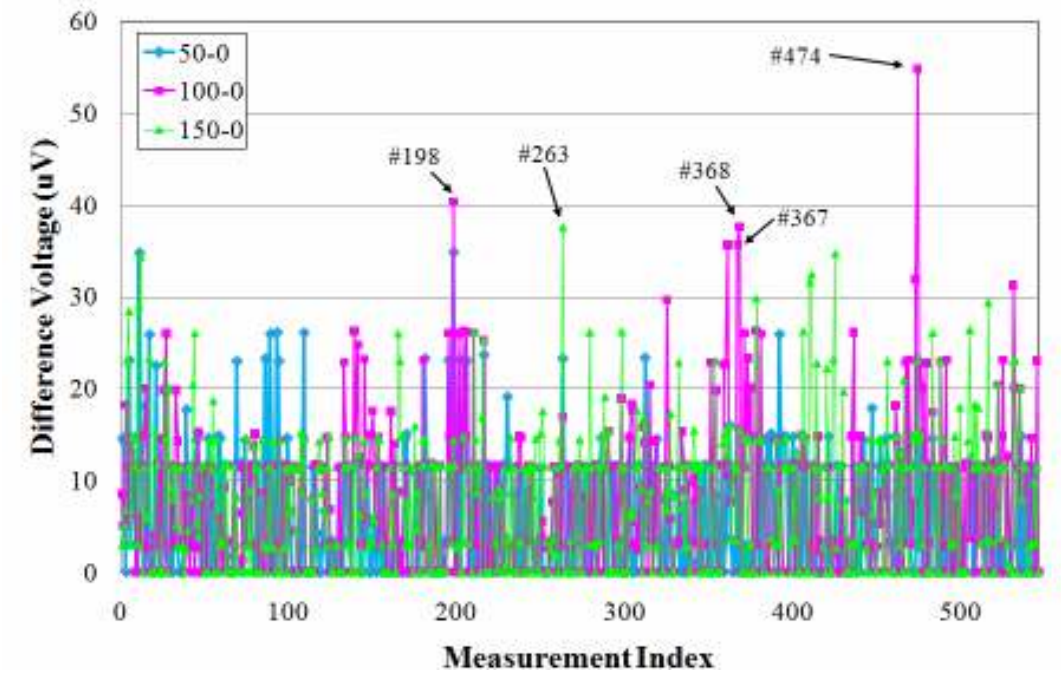


Figure 6.22 Difference voltage, $V_D(t)$, between the onset of stimulus at 29.09 seconds and 50ms, 100ms and 150ms after stimulus number 10 (without white noise). The largest 5 changes are labelled with the corresponding measurement index.

Table 6.7 The largest 5 voltage changes in the experiments without white noise for the first 11 stimuli for sequence 2.

Stimulus No.	Time post stimulus	Measurement Index	Voltage Difference (μV)	Current Injection & Measurement Pair
1	150	181	49.19	1-28 18-19
	150	426	49.19	1-31 18-19
	150	17	49.18	1-30 18-19
	100	17	49.18	1-30 18-19
	50	122	46.30	7-16 14-15
2	50	307	51.99	8-17 6-7
	100	312	46.68	8-17 13-14
	100	69	44.20	22-26 13-14
	100	373	40.14	20-24 18-19
	50	312	37.51	8-17 13-14
3	150	180	52.13	1-28 18-19
	150	97	51.88	9-18 16-17
	150	451	49.20	1-10 17-18
	50	474	49.20	2-11 13-14
	150	263	46.53	1-29 18-19
4	100	69	52.54	22-26 13-14
	100	74	49.20	22-26 18-19
	100	68	40.58	22-26 12-13
	100	62	40.00	22-26 6-7
	50	474	37.64	2-11 12-13
5	50	97	51.88	9-18 16-17
	50	94	37.69	9-18 13-14
	100	97	37.57	9-18 16-17
	150	279	34.61	4-13 7-8
	100	94	34.48	9-18 13-14
6	100	315	51.98	8-17 18-19
	100	263	51.85	1-29 18-19
	100	45	49.19	1-27 18-19
	100	466	49.16	2-11 3-4
	50	175	48.15	1-28 12-13
7	150	201	49.20	8-12 13-14
	50	446	43.68	1-10 12-13
	50	247	40.68	1-29 2-3
	50	261	40.42	1-29 16-17
	150	124	37.72	7-16 18-19
8	100	45	49.19	1-27 18-19
	100	181	37.56	1-28 19-20
	100	263	34.89	1-29 19-20
	50	106	33.97	9-18 27-28
	100/150	298	33.48	4-13 28-29
9	150	447	49.19	1-10 13-14
	50	466	49.16	2-11 3-4
	150	74	46.44	22-26 18-19
	50	1	46.18	1-30 2-3
	100	94	44.10	9-18 13-14
10	100	474	54.81	2-11 13-14
	100	198	40.35	8-12 6-7
	100	368	37.66	20-24 13-14
	150	263	37.56	1-29 18-19
	100	367	35.72	20-24 12-13
11	100	17	49.18	1-30 18-19
	150	368	46.67	20-24 13-14
	50	273	43.45	1-29 30-31
	100	452	42.87	1-10 18-19
	50	29	40. 69	1-27 2-3

Key: Forehead sites
Above auditory cortical regions
Rear sites

Table 6.8 The largest 5 voltage changes in the experiments with white noise for the first 11 stimuli for sequence 2.

Stimulus No.	Time post stimulus	Measurement Index	Voltage Difference (μV)	Current Injection & Measurement Pair
1	50	425	95.63	1-31 17-18
	50	452	75.00	1-10 18-19
	50	44	72.42	1-27 17-18
	50	180	72.42	1-28 17-18
	50	466	70.31	2-11 3-4
2	100	181	49.17	1-28 18-19
	100	263	49.17	1-29 18-19
	100	146	40.33	3-12 13-14
	100	452	39.98	1-10 18-19
	100	466	39.67	2-11 3-4
3	100	514	60.72	21-25 27-28
	100	426	51.65	1-31 18-19
	100	11	49.20	1-30 12-13
	150	45	46.67	1-27 18-19
	100	94	46.16	9-18 13-14
4	50	438	57.92	1-10 2-3
	50	451	49.20	1-10 17-18
	50	165	49.19	1-28 2-3
	50	514	46.92	21-25 27-28
	50	351	46.57	7-13 27-28
5	50	262	72.42	1-29 17-18
	50	425	72.42	1-31 17-18
	50	29	72.37	1-27 2-3
	50	97	67.46	9-18 16-17
	50	44	63.56	1-27 17-18
6	150	425	60.81	1-31 17-18
	150	373	58.42	20-24 18-19
	150	198	58.28	8-12 6-7
	150	307	51.82	8-17 6-7
	50	179	51.81	1-28 16-17
7	100	94	49.20	9-18 13-14
	100	181	49.17	1-28 18-19
	50	452	49.17	1-30 18-19
	100	17	49.16	1-10 18-19
	100	466	49.13	2-11 3-4
8	150	315	58.21	8-17 18-19
	150	69	57.67	22-26 13-14
	50	69	52.27	22-26 13-14
	150	532	52.03	19-23 13-14
	150	97	51.70	9-18 16-17
9	50	466	56.34	2-11 3-4
	150	165	49.19	1-28 2-3
	50	367	48.61	20-24 12-13
	50	373	46.76	20-24 18-19
	50	45	46.68	1-27 18-19
10	150	12	49.19	1-30 13-14
	150	45	49.17	1-27 18-19
	50	452	46.69	1-10 18-19
	150	452	46.69	1-10 18-19
	150	181	46.68	1-28 18-19
11	150	466	49.13	2-11 3-4
	100	532	40.44	19-23 13-14
	50	263	40.00	1-29 18-19
	150	139	37.70	3-12 4-5
	150	510	37.65	21-25 19-20

The same auditory stimulus was applied (sequence 2) to the volunteer which white noise was supplied to the outer headphones. The results are shown in table 6.8. Stimulus number 8 resulted in three auditory sites within the largest voltage changes. The difference voltage at times 50 ms, 100 ms and 150 ms are shown in figure 6.23.

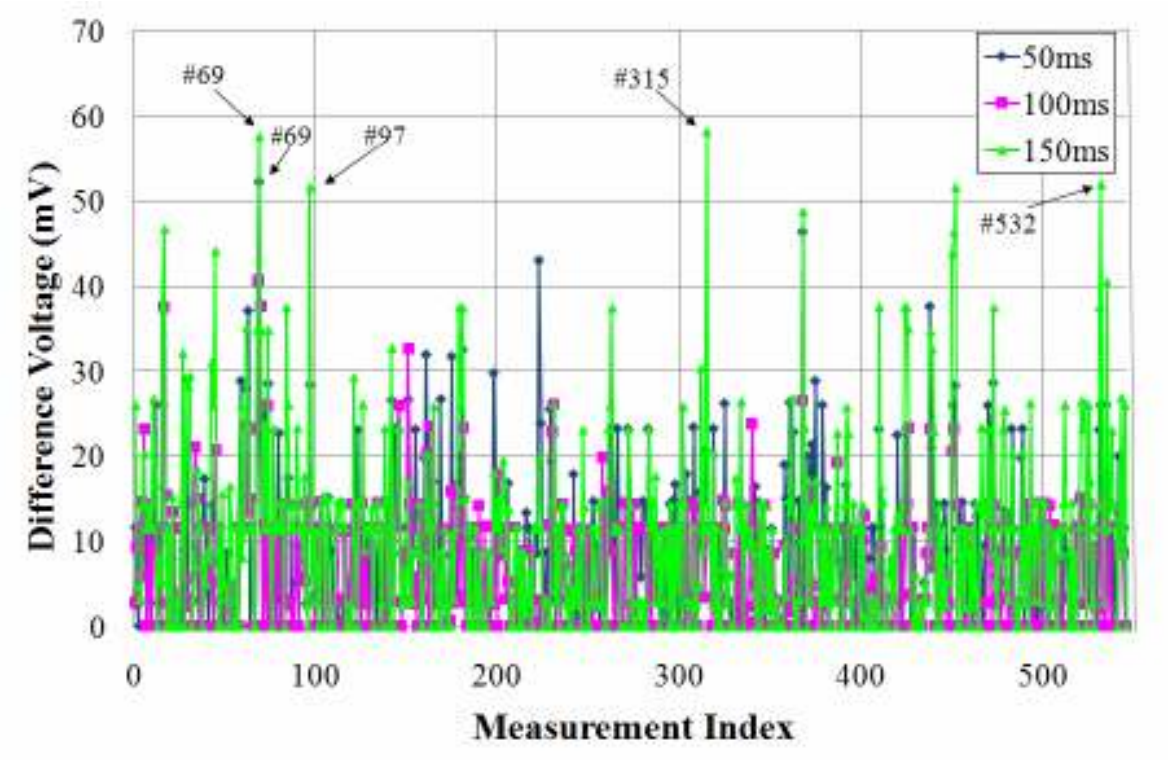


Figure 6.23 Difference voltage, $V_D(t)$, between the onset of stimulus at 25.54 and 50ms, 100ms and 150ms after stimulus number 10 (with white noise) for stimulus 8 in table 6.8. The largest 5 changes are labelled with the corresponding measurement index.

The experiments with white noise produced the majority of largest voltage changes over the auditory cortices after stimulus 8, with these changes measured over the right hand side of the cerebral hemisphere. Figure 6.23 shows the measurement index for 50, 100 and 150 ms post-stimulus.

Comparing the measurement index plots from the experiments with and without white noise, there are some notable differences. The example with white noise, figure 6.23, has many larger voltage changes at 150 ms compared to the 50 ms and 100 ms data. Figure 6.21 shows the experiment without white noise; this has a few changes at 50 ms and 100 ms but the majority of the changes are equally spread across the measurement indices and time.

6.3.3.1 Individual Auditory Measurement Sites

When comparing the structural positioning of the auditory cortex with the nearest location of the scalp electrodes, the auditory stimulation should show the greatest voltage change with electrodes located at positions 5, 6, 7, 13, 14, 15 with some changes expected on 21, 22, 24, 25.

The analysis of the individual normalised voltage measurements are shown in the plots show time-locked changes to the stimulus for experiments both with and without white noise in the outer headphones. For the case without white noise (figure 6.24) there are 5 time-locked changes on the left hand side measurements. As described previously there are no obvious time-locked changes over the right hand side auditory cortex (shown in figures 6.24 (b) and 6.25 (b)).

The largest of these voltage changes is with respect to the first stimulus at time 10.91 seconds peaking at 200 ms with amplitude of 63 μV. All of the individual changes peak between 200 ms and 300 ms post stimulus. For the example with white noise in the outer headphones there are 9 time-locked voltage changes to individual stimuli. The largest of these changes is also after the first stimulus at time 10.93 seconds peaking at 300 ms with amplitude of 63 μV. This trend is similar to the experiments without white noise. All the time-locked responses occur 200 ms to 300 ms post stimulus with habituation occurring after the first stimulus.

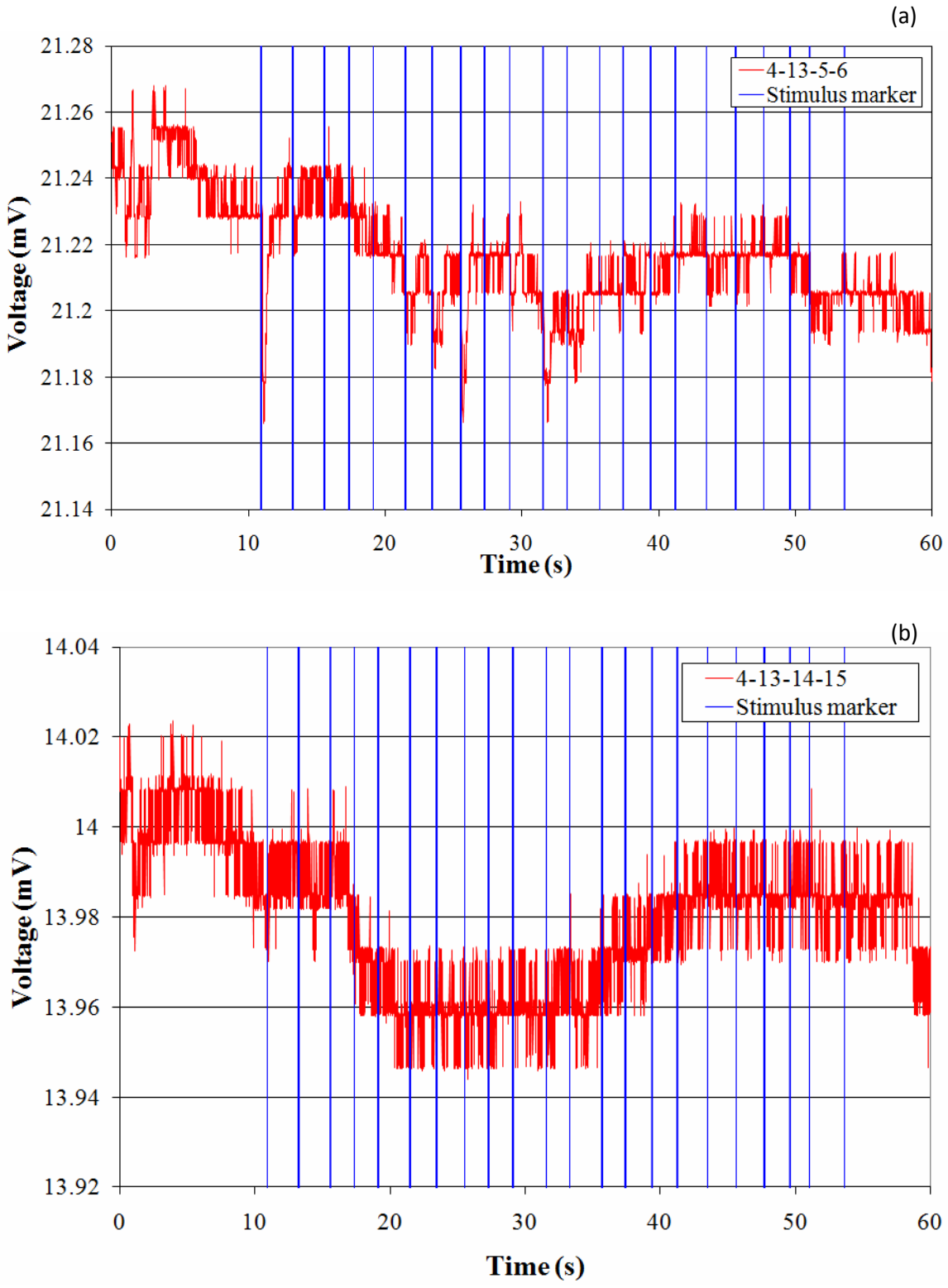


Figure 6.24 Normalised voltages for CP-MS, (a) 4-13 5-6 (LHS) and (b) 4-13 14-15 (RHS). White noise was not presented to the subject during these measurements.

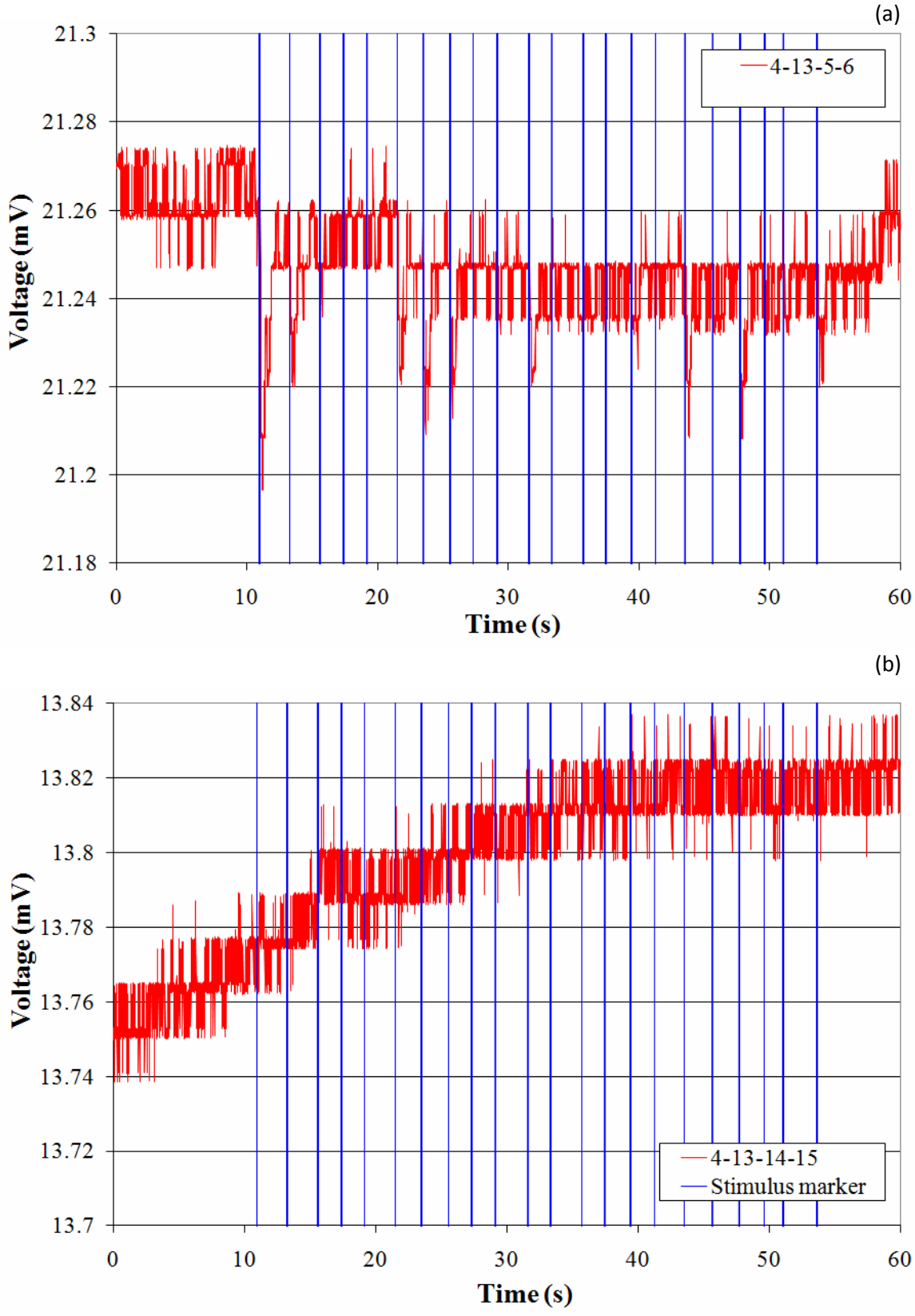
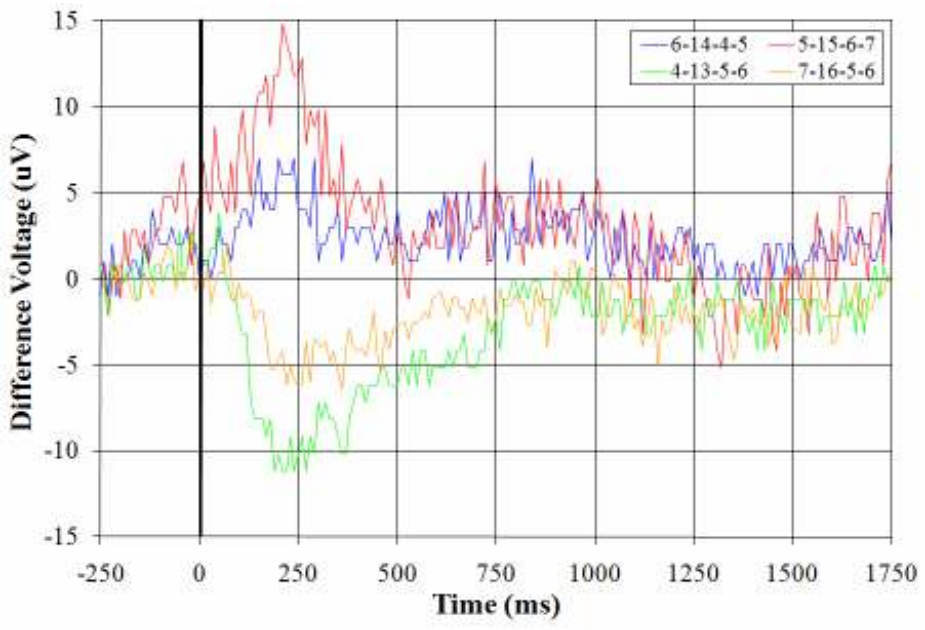


Figure 6.25 Normalised voltages for CP-MS, (a) 4-13 5-6 (LHS) and (b) 4-13 14-15 (RHS). White noise was presented to the subject during these measurements.

Since there were no obvious changes in the data in RHS measurements, data were averaged over the 22 stimuli for a sample of MS over the LHS and RHS auditory cortices. Figures 6.26 (no white noise) and 6.27 (white noise) show the averaged data for several measurements. The data was averaged around each stimulus; beginning 250 ms pre stimulus and finishing 1750 ms post stimulus (thus giving 2 seconds of averaged data). The stimulus marker is set at time 0 seconds. The plots show the difference voltage, $V_D(t)$, with respect to the averaged measurements from -250 ms to -210 ms.

(a)



(b)

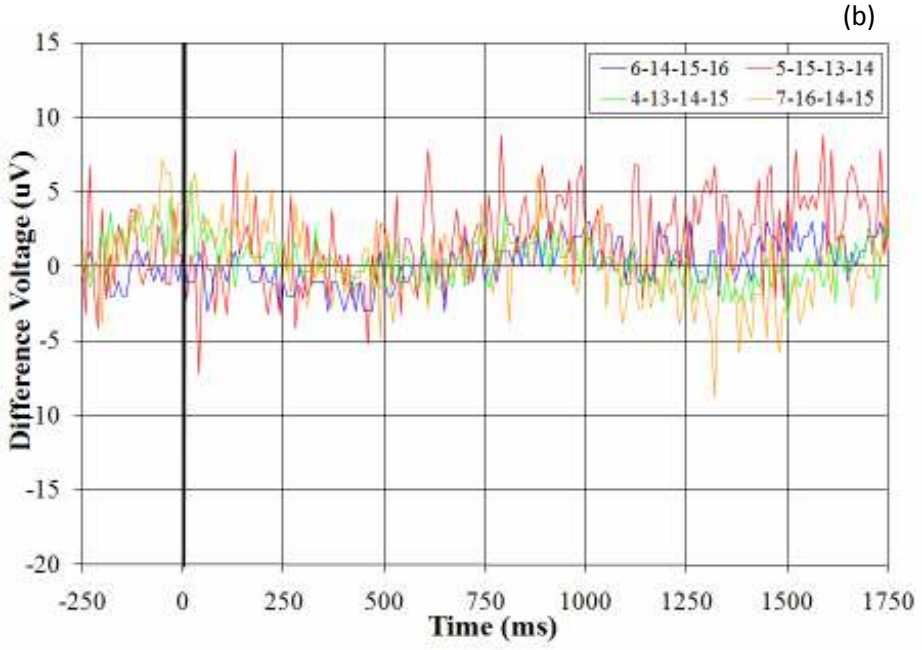


Figure 6.26 Difference voltages, $V_D(t)$, for 22 averaged stimuli over the (a) LHS auditory cortex and (b) RHS auditory cortex. (White noise was not presented during these measurements).

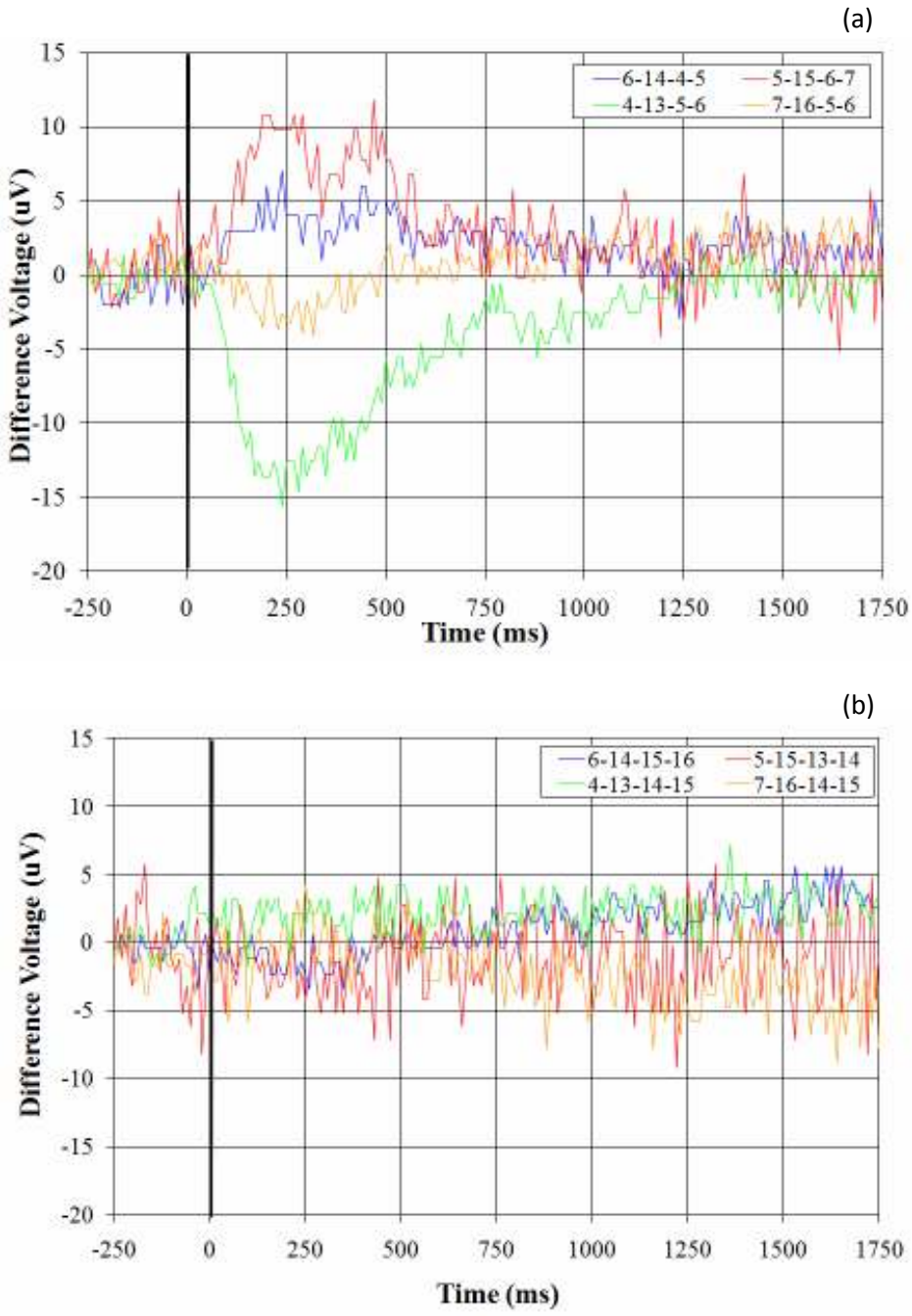


Figure 6.27 Difference voltages, $V_D(t)$, for 22 averaged stimuli over the (a) LHS auditory cortex and (b) RHS auditory cortex. (White noise was presented during these measurements).

The measurements for both experiments with white noise and without white noise show similar trends. After averaging the measured data from MS over the auditory cortices the LHS shows topographical differences. The largest of the voltage changes in the experiment without white noise are further towards the rear of the scalp, MS 6-7, with a voltage change of 15μV, whereas, the largest voltage change in the experiment with white noise is more

centralised, MS 5-6, having a voltage change of 15 μV. All of the changes peak at approximately 250 ms after the onset of stimulus. This is in contrast to the RHS data which does not show any changes over the averaged 22 stimuli.

The frontal and rear MS were also averaged over 22 stimuli, as shown in figures 6.28 and 6.29. The forehead measurements appear to have a 'saw tooth' trace, which is likely to be the remnants of the REG signal described in chapter 5 and not related to the auditory stimulus event. The rear sites do not show a response time-locked to the stimuli.

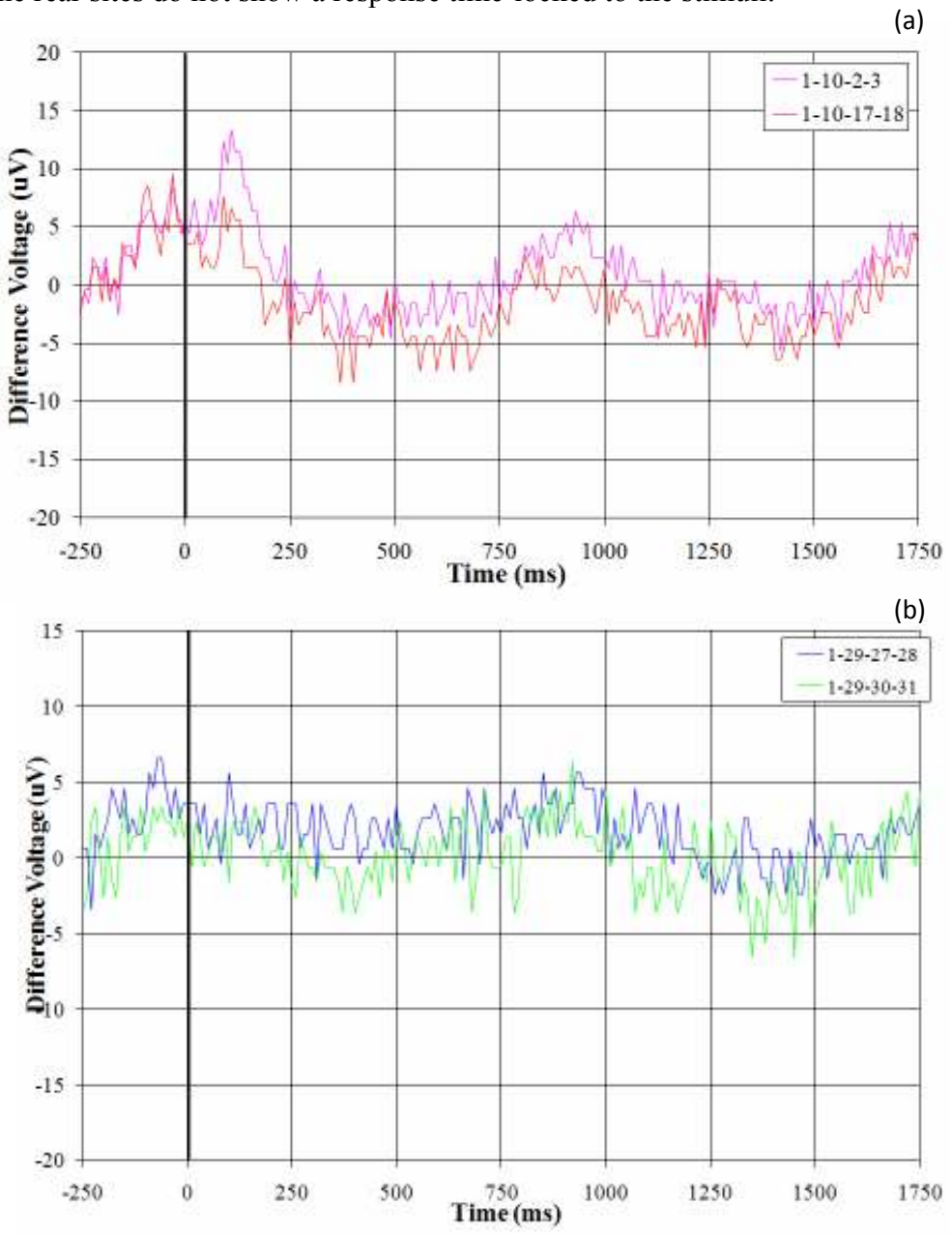


Figure 6.28 Difference voltages, $V_D(t)$, for (a) forehead and (b) rear sites. No white noise presented.

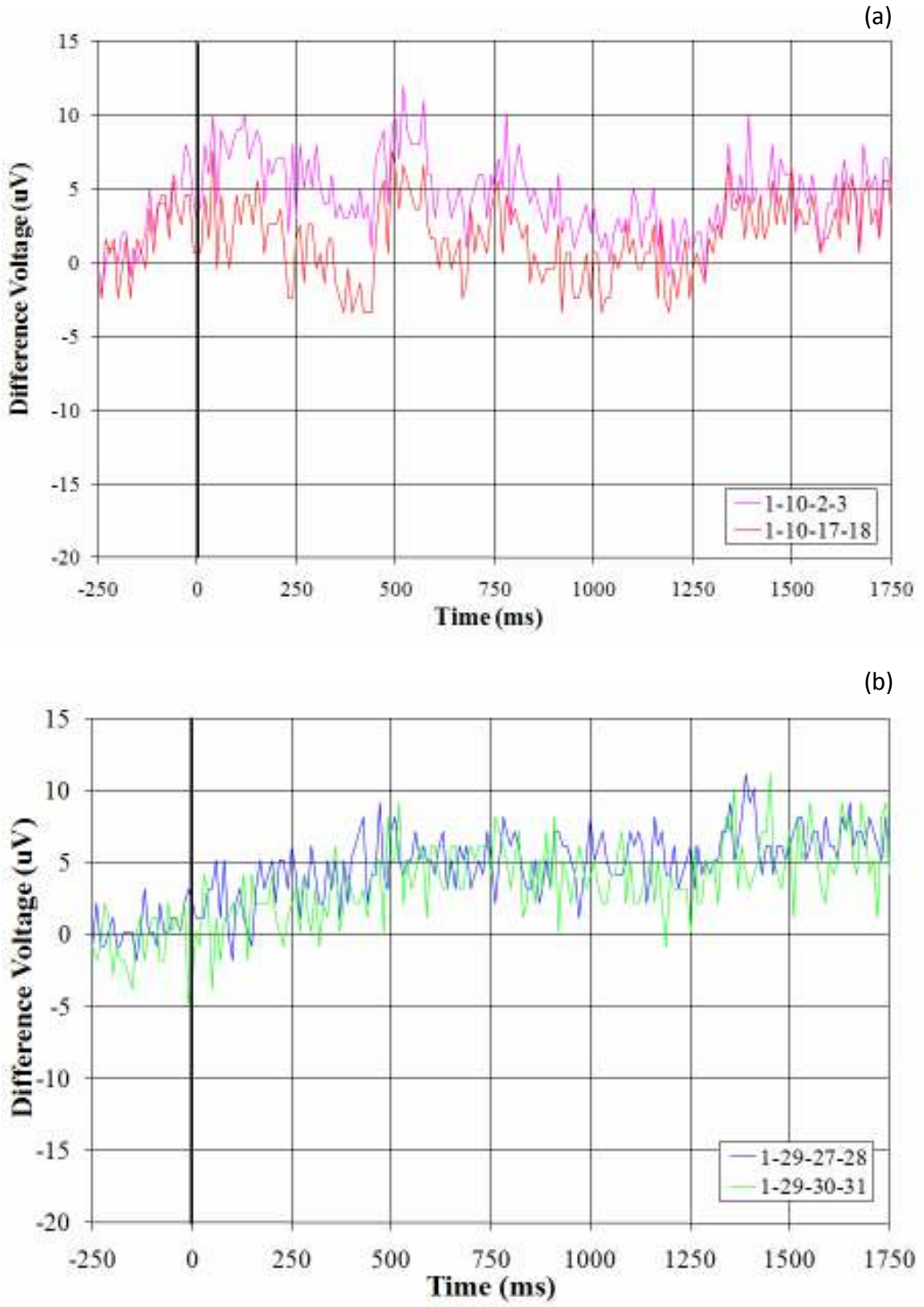


Figure 6.29 Difference voltages, $V_D(t)$, for (a) forehead and (b) rear sites. White noise presented.

6.4 Discussion

The auditory startle response shown in section 6.2, has large voltage changes across the whole of the measurement index which are time-locked to the onset of stimulus. The recovery to a baseline, seen in figure 6.8, takes between 4-7 seconds after the onset of stimulus. However, the signal is less stable than the data prior to the stimulus. Since this was an extreme stimulus (a broadband frequency, greater than 80dB SPL, lasting approximately 300 ms) the whole brain appears to become in an excited state. The lack of stability post stimulus may be due to general excitement (i.e. mass neurological activity) of the brain.

The voltage changes associated over the auditory cortices peak at two distinct times post startle stimulus (shown in figure 6.30). There is a fast voltage change peaking at approximately 200 ms and a slower change that peaks approximately 1.5 seconds post stimulus. The voltages remain at this level for approximately 3 seconds before returning to the original baseline.

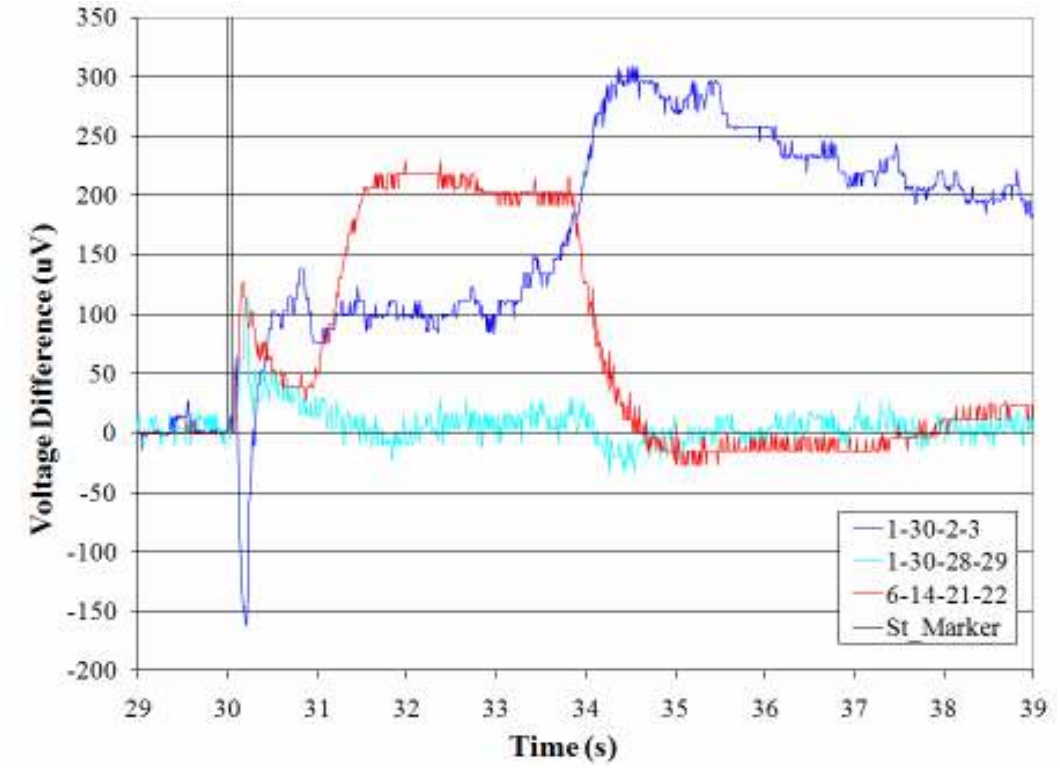


Figure 6.30 Voltage difference, $V_D(t)$, measurements of MS 2-3 (forehead), 28-29 (rear) and 21-22 (LHS) (subject B).

The rear measurements show an initial change in voltage but quickly return to baseline (within 200 ms). The frontal sites show three changes. The first is seen at 100 ms post

stimulus followed by a large voltage change at 200 ms post stimulus stabilising at a new voltage level for approximately 4 seconds. After this time the voltage changes again, to a higher value, before gradually returning to the original baseline.

The author suggests that these fast changes are due to the AEP and ASR fast neurological responses in the auditory cortex and the amygdale, respectively, and the slower changes are due to the haemodynamic response due to the change in oxygen demand by the increased neural activity.

Further evidence of neurological measurement comes from the P1-N1-P2 complex that was observed, shown in figures 6.31 and 6.32. The phase of the voltage changes are the opposite compared to figure 6.14, because the measurements are determined by electrode numbering (electrode 21 minus electrode 22). Therefore the phase of the plots does not mean an increase or decrease in conductance but merely represent a change. Figure 6.31 (from figure 6.14) has been flipped and it can be easily compared to figure 6.32. Figure 6.32 shows data from EEG measurements of the P1-N1-P2 complex. The EIT data times of the peaks and troughs post stimulus are similar to those found in AEP studies. The EIT data show a peak at 90 ms (P1), a peak at 140 ms (N1) and a peak at 200 ms (P2).

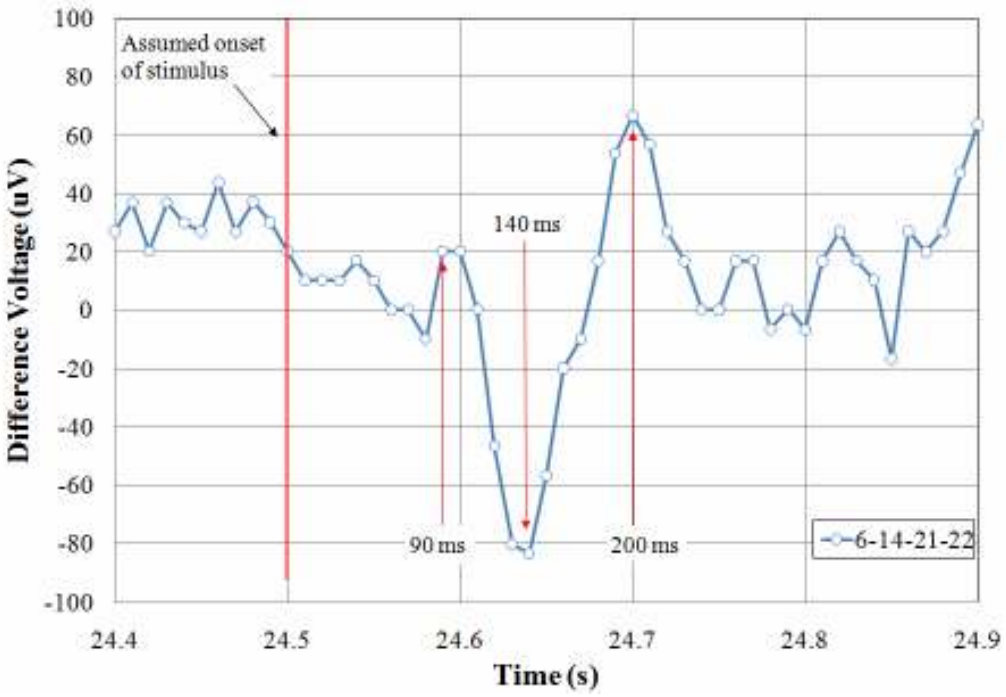


Figure 6.31 Measured data from MS over the auditory cortex, 21-22 (LHS). Subject A.

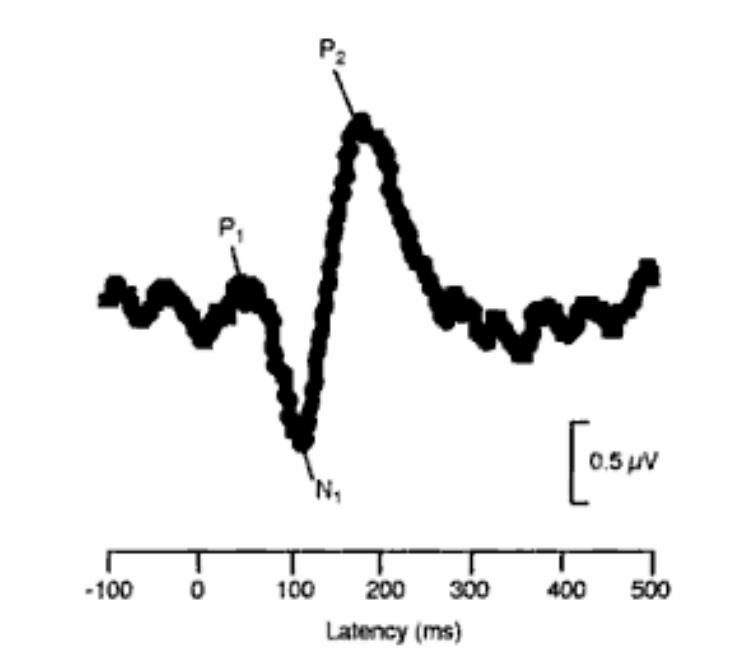


Figure 6.32 Typical data from a P1-N1-P2 study evoked by an auditory stimulus (Martin et al, 2007).

The slower changes of several seconds duration may be attributed to the haemodynamic demand by the neurons that were responding to the stimulus. This is supported by Holder *et al* (2009) when they obtained EIT measurements on the scalp. However, they used visual stimulus. This slower haemodynamic response is similar to those obtained when using BOLD fMRI as discussed in chapter 2. Recent new results using optical techniques are also relevant and supportive, e.g. they show start of increase of cerebral blood volume at approximately 800ms (Sirotin and Das, 2009).

The voltage changes measured for the auditory startle response are very large in comparison to the small changes that are usually seen in AEP studies, suggesting that most of the data are as a result of ASR. It is normal to average over several stimuli in AEP studies since the signals have significantly smaller amplitudes (typically a maximum of 10 μV peak to peak) compared to the data obtained in figure 6.31 (a maximum peak to peak of 140 μV) The EIT data presented here are based on single trials.

Auditory stimulus experiments on subject A show an asymmetry between the LHS and RHS MS, as shown in figure 6.11 and 6.12. The auditory stimulus was applied to ensure that the volunteers would receive the sound in each ear at approximately the same time. However, this volunteer has a severe hearing impairment in the left ear. Since plots show a significant contralateral difference in the data, it is suggested that the differences are mainly due to the volunteer's hearing loss. Furthermore the volunteer is right-handed. Therefore the left auditory cortex is the most dominant in processing auditory information (McKeever and Van Deventer, 1977). The known auditory cross-over in the brain usually results in 60% of the auditory cortex processing on the same side as the sensing ear and 40% on the opposite to the sensing ear (Martin *et al*, 2007). For this subject, this implies that the response to the ASR and AEP would be significantly greater on the LHS but not completely diminished on the RHS. Figure 6.12 supports this. It shows a large change in voltage, peaking at 350μV for the measurements on the LHS whilst the RHS voltage change occurs at the same time it has a peak amplitude of 160μV. Further experiments with subjects that have asymmetrical hearing could identify the spatial sensitivity of fEITER in the auditory cortices; perhaps aiding future treatments.

The data obtained from subject B showed voltage changes on both sides of the head, suggesting that the hearing of the subject was more symmetrical, figure 6.4. However, from the subject history it is known that they have a perforated left ear drum. It is possible that the effects of this are shown in figures 6.4 -6.6. The experiments were performed at 3 minute intervals, with a party popper released at 30 seconds into the EIT data (figures 6.4 and 6.5) and 10 seconds into the EIT data (figure 6.6). Large voltage changes can be seen across all measurements in figure 6.6. However, reduced voltage changes are shown in figures 6.5 and 6.6. The author suggests that this is similar to the known habituation of signals that occurs in EEG. Since subject B has a perforated ear drum, it is expected that the voltage change will be reduced on the RHS. Figures 6.5 and 6.6 do not show a voltage change time-locked to the stimulus on the RHS auditory cortices.

Following the startle response tests, a series of controlled auditory stimuli were applied. The control auditory tests began with developing an auditory sequence file that would produce the largest voltage changes. From the analysis in section 6.3, sequence file 2 was identified as the auditory sequence that produced stimulus time-locked voltage changes. Sequence 2 was at 2.5 kHz with tone burst duration of 50 ms, sequentially increasing in loudness from approximately 75 dB to 87 dB. The controlled data showed voltage changes over the areas involved in processing auditory information, Brodmann areas 41 and 42, as shown in figures 6.26 and 6.27.

The controlled data have very small changes compared to the ASR voltage changes, the largest being 58 μV at 150 ms post stimulus from the tests with white noise, whereas the largest startle voltage change at 150 ms post stimulus was 570 μV. However, on subject B both the startle and controlled auditory tests showed contralaterally differentiated results. This strongly suggests that the measured results are physiological in nature. Since the image reconstruction process is an ill-posed one it is only possible to create a conclusive image if there are large signals changes that are detectable on most, indeed preferably all, electrode measurement sites. The individual analysis on the control tests showed that not all measurement sites generated a response to the stimulus.

The small changes observed in the control tests did not show a significant difference between the experiments with white noise to those without white noise. However, all the experiments were carried out in a quiet darkened room. It may prove more valuable to use white noise in a more ‘realistic’ environment.

The results discussed in this chapter have been obtained using fEITER on two volunteers. For clarity the analysis of controlled auditory stimulus was only shown from subject A. As part of the MHRA submission (described in chapter 3), an expanded clinical trial to obtain data on 20 informed volunteers at the Manchester Royal Infirmary was continuing when this thesis was written. Based on the results discussed in this chapter, the auditory stimulus file sequence 2 was being applied to the informed volunteers in the hope of measuring AEP responses using fEITER.

Chapter 7 Conclusions & Further Work

7.1 Conclusions

Electrical impedance tomography (EIT) has been developed to be used in medical monitoring and imaging since the 1980s (Barber and Brown, 1984). Some of the ongoing advances are described in chapter 2, and cover the specifications for functional brain imaging. If the existing functional imaging modalities are compared in terms of temporal resolution, spatial resolution, depth sensitivity, cost and patient accessibility, each technique can be described as having some advantages and disadvantages. Unlike x-ray CT, EIT does not use ionising radiation; nor does it use large magnets like MRI and MEG devices, as such EIT does not require a specialised room. EIT is based on technology that does not require invasive techniques to obtain measurements. The combinations of these parameters mean that EIT is accessible to more patients, meaning it has the potential to benefit several areas of medical diagnostics and treatment.

fEITER has been designed to be compatible in operating theatres and intensive care units. It could be used as long-term bedside monitor or as a locally accessible imaging technique placed in ambulances or GP surgeries. The detailed specifications of fEITER are given in table 2.3, showing that it has excellent temporal resolution and has a greater depth sensitivity than other modalities (e.g. EEG). The research presented in this thesis has contributed to the development of the fEITER system.

There have been several areas within this thesis where the author has demonstrated original methodology and novelty. These are summarised here:

- The fEITER system and a proposed clinical trial were taken through local and national ethical and safety procedures. Currently, this is the only EIT device within the UK to have ‘notice of no objection’ from the MHRA, enabling fEITER to be used in a clinical trial. (As discussed in chapter 3).

- The measurement set-up for the composite impedance has been designed and implemented to measure the impedance that results from two electrodes, the electrolyte gel associated with each electrode and the bulk tissue. (As shown in chapter 4).

- The novel composite impedance measurements exhibit interesting characteristics, namely a minimum at 30-40 kHz. (As shown in chapter 4).

- The use of a bespoke EIT device, fEITER, to measure the blood flow/pressure within the brain. This type of recording is unique within EIT. (As shown in chapter 5).

- To the best of the author's knowledge a valsalva manoeuvre has never been recorded using an EIT device. (As discussed in chapter 5).

- EIT measurements were recorded whilst an auditory evoked stimulus was presented to a volunteer. This type of research is unique within EIT and the novel results suggest that the system is sensitive to fast (peaking at 100-200 ms) and slower (over a few seconds) impedance changes that are indicative of neural and haemodynamic responses respectively. (As discussed in chapter 6).

- Localised EIT measurements above the auditory cortex showed a P1-N1-P2 complex, which was recorded from a single stimulus. This is a unique measurement, as EEG measurements require several (up to 100) averaged data sets to extract this waveform. (As shown in chapter 6).

7.1.1 Composite Impedance

The composite impedance was measured on several subjects using three disposable electrodes; ZipPrep, Red Dot and ARBO electrodes. Understanding the composite impedance (i.e. the combined impedance of the electrode, the electrolyte/electrode barrier and the tissue) is important in EIT system design. The load impedance needs to be known to enable the appropriate design of the front end electronics (e.g. gain settings). The work carried out to understand the composite impedance is described in chapter 4.

A HP 4284A Impedance Analyser was used to measure the composite impedance on several sites, including the forearm, shin and scalp across the frequency range of 1 kHz to 100 kHz. Since the HP 4284A device was not a medical grade device it was necessary to introduce a

safety circuit between the equipment and the subject (as defined by the BS EN 60601-1:2006). The HP 4284A has a mechanism to null out the effects of additional impedances, meaning that impedances associated with the cables can be removed enabling specific component analysis. This nulling procedure was tested with the safety circuitry using RC networks and biological tissue (i.e. banana). The calibration procedure is described in chapter 4. The results from the calibration tests showed that the nulling procedure is successful at removing the impedances associated with the safety circuitry. Therefore, it was possible to conclude that the measurements from the HP 4284A were of the 'composite' system.

7.1.1.1 Forearm and Shin Measurements

Electrodes were fixed to the forearm and shin on several subjects. The forearm data was consistent between electrodes, showing a rapid decrease in composite impedance between 1 kHz and 10 kHz. All electrodes displayed a minimum impedance at approximately 30 kHz. The individual component analysis showed that the resistance decreased monotonically across the frequency range whereas the reactance became positive at approximately 30 kHz. The author suggests that the rise in impedance may be due to be hair follicles or it could be skin effect (i.e. cable skin effect), that change the behaviour at higher frequencies. However, further experiments and modelling are required to fully understand this.

The short and long term repeatability was analysed on the forearm and shin. Using ZipPrep and Red Dot electrodes on the forearm other aspects of variability were compared such as temporal changes, preparation techniques, separation distance between electrodes and muscular movement. The largest composite impedance change over time was measured when using the ZipPrep electrodes. At 1 kHz the ZipPrep electrode composite impedance decreased by 35% over 120 minutes, compared to the Red Dot (24% decrease) and ARBO (10.8% decrease). However, all electrodes were more stable over time at the higher frequencies (>10 kHz). Generally, the short-term repeatability (i.e. repeat measurements over a few seconds without replacing or removing the electrodes) on the shin was better with Red Dot electrodes compared to ZipPrep electrodes. For subject A, at 1 kHz the ZipPrep electrodes varied from 19.12 kΩ to 2.21 kΩ; compared to the Red Dot electrodes which varied from 17.56 kΩ to 10.95 kΩ. This was similar to the forearm measurements, the Red Dot electrodes (on subject A) has less variability over short term repeats (Red Dot electrodes varied from 11.2 kΩ to 9.1 kΩ. ZipPrep electrodes varied from 17.8 kΩ to 4.23 kΩ).

Two different preparation techniques were compared (abrasion and gentle removal using adhesive tape). The abrasion techniques described in section 4.5 showed a low frequency decrease in composite impedance between the unprepared and prepared conditions. Once the frequency was greater than 30 kHz there was little change in the composite impedance (few Ω). The gentle abrasion technique used adhesive tape to remove the upper layers of dead skin cells. At low frequencies (less than 10 kHz) the measured composite impedance decreased after the removal, there was a maximum decrease at 1 kHz of 1.98 kΩ.

The analysis from tests when the electrodes were separated showed a change in composite impedance for ZipPrep electrodes. Throughout the measurements the composite impedance changed with electrode separation. However these changes were not linear with distance. The maximum change for ZipPrep electrodes at 1 kHz was 9 kΩ, compared to a maximum change at the same frequency of 3.17 kΩ for Red Dot electrodes.

The composite impedance on the forearm was measured when the subject held their hand stationary and continually clenched and unclenched their fist. Analysis of this muscle movement did not show a significant difference below 70 kHz ($p<0.01$).

7.1.1.2 Scalp Measurements

Composite impedance measurements on the scalp were carried out using Red Dot and ZipPrep electrodes. As part of the standard practice the electrode site was unprepared (i.e. the skin was not cleaned or abraded). This resulted in the Red Dot electrodes having very high composite impedances throughout the frequency range. The table below shows the composite impedance measurements for the forehead using Red Dot and ZipPrep electrodes.

Table 7.1 Composite impedance measurements for Red Dot and ZipPrep electrodes on the forehead.

	1 kHz	10 kHz	100 kHz
Red Dot	31.7 kΩ	16.6 kΩ	10.4 kΩ
ZipPrep	5.02 kΩ	1.15 kΩ	1.79 kΩ

Table 7.2 shows a comparison of ZipPrep electrodes at different sites on the scalp. From this table a comparison between hirsute and non-hirsute sites can be analysed. At the lower frequencies the forehead has a lower composite impedance compared to hirsute sites. This is reflected in the slight increase in the composite impedance for the front to back measurements, which uses one non-hirsute site and one hirsute site. However, at the higher frequencies (greater than 10 kHz) the composite impedance is less affected by the site location. At 100 kHz the composite impedance varies from 1.5 to 1.9 kΩ.

Table 7.2 Mean composite impedances from all subjects using ZipPrep electrodes on the scalp.

Frequency (kHz)	Forehead (Fp1 and Fp2)	Rear (O1 and O2)	Side to Side (T7 and T8)	Front to back (Fp1 and O1)
1	3	6.9	6.1	4.6
10	1	2	1.5	1.7
100	1.5	1.5	1.7	1.9

For EIT on the scalp, ZipPrep electrodes show marked advantages in the comparisons presented in chapter 4. In general for all electrodes at frequencies in the range of 1 kHz to a few kHz a composite impedance is much larger than for frequencies greater than 10 kHz. The general results show that the composite impedance is at a minimum between 30-40 kHz for all electrodes types on all locations to ensure stable composite impedance the author suggests that EIT should be performed at a frequency greater than 10 kHz.

7.1.2 fEITER Tank Tests

The performance of the fEITER system on a realistic test tank is presented in chapter 5. The author built a realistic tank by drilling 33 circular holes (1cm^2) in a head shaped vessel. The holes were positioned in the same locations as the 10-20 montage, as shown in figure 2.4. The additional hole is for the reference electrode, which is positioned on the left mastoid. As described in section 2.1, MATLAB based code, known as EIDORS, was used to make predictions of the voltage measurements in the tank. The predicted and measured data showed good correlation (as shown in figure 5.4). Most of the discrepancies were due to the errors in the geometrical model and the modelled electrode size and positions. The

repeatability across frames was measured, showing a standard deviation of 11.2μV. The SNR was calculated across the measurement index resulting in a median SNR of 73.2dB.

The combination of fast temporal resolution and high SNR is unique to fEITER, compared with other EIT brain imaging devices. This is a clear indication of a system that has a low-noise performance offering the best opportunity for functional sub-second imaging.

The safety testing on fEITER was completed in accordance with the MHRA and BS EN 60601-1:2006. fEITER was independently reviewed by Dr A Taktak from the University of Liverpool, as described in chapter 3. The local ethics and national ethics (NRES) gave a 'notice of no objection' allowing the author to present the system to the MHRA. 'Notice of no objection' was received and the device was taken to clinical trial at the Manchester Royal Infirmary. The trial was underway as this thesis was written.

7.1.3 Non-Stimulus Data

The use of the fEITER system on human volunteers was reported in chapters 5 and 6. Initially measurement data sets were taken with no applied current (i.e. voltage measurement whilst fEITER is not applying a functional current). This was carried out as a method of understanding the passive voltage measurements at 10 kHz with and without stimulus. These passive measurements are similar to EEG measurements. EEG signals are composed of a wide spectrum of frequencies. However, evoked potential measurements in EEG are filtered to select the frequency band of interest. The results from fEITER with no applied current tests showed that the system is unable to detect EEG type signals at 10 kHz from evoked stimuli. The measurement sets with and without stimuli were compared and showed no significant difference ($p<0.01$).

The remaining fEITER tests were completed when the functional current was applied. A comparison between the EIDORS predicted measurements and fEITER measurements showed a good correlation. However, the fEITER data had reduced amplitude. The comparison of the peaks and troughs between the fEITER data and predicted data sets were temporally the same. This suggests that the discrepancies were due to further mismatching in the model (e.g. incorrect tissue conductivity values, electrode positions and size, and shape of the geometrical model).

Individual CP-MS analysis showed a 'saw tooth' wave with time. After simultaneously measuring the ECG and fEITER data it was thought that the saw-tooth pulses were related to the ECG. Further analysis showed that the latency between the peak of the ECG R wave and the peak of the EIT data was approximately 200 ms, as shown in figure 5.23. The QRS complex (which peaks with the R wave) represents the contraction of the ventricles within the heart. During this process the blood is pushed into the aorta, resulting in an increase in pressure (systole pressure). Since the blood from the aorta flows straight into the arch which leads to common carotid arteries, the transportation of blood to the brain is fast. From these observations the author suggests that the saw tooth wave in the EIT data are impedance changes due to the introduction of oxygenated blood into the head. Furthermore, subjects were asked to perform a valsalva manoeuvre to further confirm the saw tooth was linked to the ECG. Table 7.3 shows a comparison of pre-valsalva and post-valsalva voltage amplitudes.

Table 7.3 The voltage amplitude (peak-to-peak) for pre- and post-valsalva averaged over several cycles.

Location	Pre-Valsalva Voltage Amplitude (μV) (Mean of 7 pulses)	Post-Valsalva Voltage Amplitude (μV) (Mean of 5 pulses)
Forehead	53.9	92.8
Rear	22.0	22.8
Left Hand Side	34.0	56.0
Right Hand Side	29.1	47.5

As discussed in section 5.4, there is an increase in the amplitude of the EIT signal after the valsalva. There is also an increase in the number of pulses post-valsalva. These observations may be related to the physiological changes that are known to occur in the brain when a valsalva manoeuvre is performed. After a valsalva there is an increase in heart rate, which leads to an increase of systolic pressure. The increase in the EIT amplitude after the valsalva manoeuvre may be related to the increase in pressure. Whilst the increased number of pulses directly correlates with the increase in the number of heart beats, as shown by the ECG signal.

Discussion with other researchers and an extensive literature search into similar data captured on the head uncovered the technique of rheoencephalography (REG). REG is a method of measuring blood flow in the brain. It uses surface electrodes on the scalp to measure electrical impedance as an indirect measure of flow. There have been several reports in the

literature using REG on animals and humans (Bodo, 2010a) which have confirmed relationships between the measured REG and the cerebral blood flow (CBF), carotid flow (CF) and the intra-cranial pressure (ICP). The impedance changes can be measured on all parts of the body (shown in figure 5.29). The author suggests that these are the impedance changes that are being measured by fEITER, and can be seen as an indirect measure of CBF and CF.

7.1.4 Auditory Stimulus Data

The auditory cortices lay beneath the 10-20 montage electrode sites, T7, TP7, TP8 and T8 (shown in figure 2.4). fEITER was used to take measurements whilst the volunteer was subjected to auditory stimulus. Two types of auditory stimuli were delivered to the volunteers; a 'party popper' and a series of controlled tone bursts which were delivered through inner ear headphones.

The startling popper stimulus resulted in time-locked voltage changes occurring across the scalp, as shown in figure 6.5. Repeat measurements were taken 3 minutes apart. Habituation of the signal is seen after the 1st stimulus. If the amplitude of the stimulus-locked voltage change is compared between experiments it is possible to see habituation in the signals. Measurement sites (MS) on the rear of the head (9-10 and 10-11) at 11:09 (figure 6.5) show large changes of 50 μV and 70 μV; whilst at 11:12 (figure 6.6) and 11:15 (figure 6.7) there are no obvious changes on the rear. At time 11:09 the forehead MS, 1-2 and 17-18, show a voltage change of 100 μV and 150 μV respectively; however, 6 minutes later the changes are similar for MS 1-2 at 100 μV but reduced for MS 17-18 to 45 μV.

The MS above auditory cortices showed a peak at 230ms and 4 seconds, respectively (seen in figure 6.9). The author suggests that these are due to the AEP fast neurological responses in the auditory cortex and the amygdala. Further evidence of neurological measurement comes from the P1-N1-P2 complex that was observed, shown in figures 6.31. The EIT data times of the peaks and troughs post stimulus are similar to those found in AEP studies, the EIT data shows a peak at 90 ms (P1), a peak at 140 ms (N1) and a peak at 200 ms (P2).

The slow voltage changes, shown in figure 6.9, peaking at approximately 3 seconds post stimulus suggest a haemodynamic response. Due to the change in oxygen demand by the increased neural activity. This slower haemodynamic response is similar to those obtained when using BOLD fMRI as discussed in chapter 2. A more detailed view of the

topographical differences can be seen in figure 6.32, as an example of sites from across the head is compared against time.

During the auditory startle stimulus experiments an asymmetry between the LHS and RHS MS is observed, as shown in figure 6.12 and 6.13. The auditory stimulus was applied to ensure that the volunteers would receive the sound in each ear at approximately the same time. However, this volunteer (subject A) has a severe hearing impairment in the left ear. Since the measurements show a significant contralateral difference in the data. The author suggests that the differences are mainly due to the volunteer's hearing loss. Furthermore the volunteer is right-handed and hence the left auditory cortex is the most dominant in processing auditory information (McKeever and Van Deventer, 1977).

The controlled auditory data, carried out on subject A, have very small changes compared to the startle voltage changes. Voltage changes were not observed on measurements across all locations on the scalp. However, subjecting auditory sequence file 2 to the volunteers resulted in time-locked voltage changes above the auditory cortices. The largest AEP voltage changes was 58 μV at 100 ms post stimulus from the tests with white noise (as shown in figure 6.26), whereas the largest AEP voltage changes were 55 μV at 100 ms post stimulus for tests without white noise.

After averaging around the stimuli the measured data from MS over the auditory cortices show topographical differences on the LHS, as shown in figure 6.29. The largest of the average voltage changes in the experiment without white noise are further towards the rear of the scalp, MS 6-7, with a voltage change of 15μV, whereas, the largest average voltage change in the experiment with white noise is more centralised, MS 5-6, having a voltage change of 15 μV. All of the changes peak at approximately 250 ms after the onset of stimulus. This is in contrast to the RHS data which does not show any changes over the averaged 22 stimuli.

Based on the observations reported in this thesis both the startle and controlled auditory tests showed contralaterally weighted results, strongly suggesting that the measured results are physiological in nature. Since the image reconstruction process is an ill-posed one it is only possible to create a conclusive image if there are large signals changes that are detectable on most, indeed preferably all, electrode measurement sites. The individual analysis on the control tests showed that not all measurement sites generated a response to the stimulus.

7.2 Suggestions for Future Work

- With reference to the composite impedance study the author suggests expanding the frequency range to understand more about the composite impedance at higher frequencies. This may aid understanding of the increase in impedance at the higher frequencies (>50kHz). A robust model should be developed for the composite impedances at the higher frequencies.

- Based on the composite impedance study there is minimum at 30-40 kHz when using standard EEG electrodes. Future fEITER designs should consider increasing the frequency to have the lowest composite impedances and more scope for increased current amplitude. This would aid the sensitivity of the system by improving the SNR i.e. it would be more sensitive to smaller conductivity changes

- As discussed in chapter 6, the values of the voltage changes with respect to the stimuli are small (few μV). It is suggested that the amplitude of the functional current is increased the limit as set by BS EN 60601:1. This would mean an increase to 2.82 mA peak-to-peak at 10 kHz. This should result in larger voltage changes.

- Further reference measurements using fEITER need to be carried out to understand the REG signal. An anaesthetic changes the blood flow in the brain but does not change the blood pressure. Further experiments with patients under anaesthetic would change the mass neural activity enabling the verification that the fEITER signal is REG.

- This sensitivity to the change in impedance of blood flow and pressure in the brain may be useful in certain medical diagnosis. There are two types of stroke ischemic (a reduction of blood to an area) and haemorrhage (a bleed into an area). Both type of stroke cause a change in the haemodynamic concentration. The author suggests that this may be detectable using fEITER by analysing the REG signal. Further research into this area could provide valuable fast information on the type of stroke (for which there are distinctive different treatments).

- The saw tooth signal that is present in the data may be useful for haemodynamic analysis but needs to be removed to fully explore the effect of stimulus tests, as it would reduce the noise levels creating a greater sensitivity to changes in the data.

- The initial analysis using auditory stimulus has provided encouraging results. However this is based on a small number of volunteers. The author suggests expanding the auditory stimulus trial to a number that would provide statistically significant data.

- As described in chapter 2, the electrode montage is based on the 10-20 set-up with some additional electrodes to probe the visual cortex. A change in the montage to a more suitable auditory CP could increase the sensitivity to auditory stimulus.

- Further auditory stimuli tests on patients under anaesthetic should produce an initial response. However, this signal will reduce as the patient is put under a deeper sedative. Further research into this area may enable fEITER to be used as a depth of anaesthesia monitor.

- The author performed visual and pain response experiments that have not been reported in this thesis as the results from these were limited. However the author suggests carrying out further evoked response tests using fEITER. One of the largest EEG responses is to the pattern reversal stimulus. The author suggests using fEITER on a statistically significant number of volunteers for these tests.

- All of the stimuli tests described in this thesis and suggested future tests need to be compared to existing modalities. The author suggests carrying out interleaved EEG and fEITER tests whilst subjecting the volunteers to a set of stimuli. This will confirm the presence of neurological activity that can be directly compared to the fEITER measurements. An interleaved experiment comparing BOLD fMRI and fEITER would provide evidence of the presence of regional blood flow to the same set of stimuli, providing verification that fEITER is sensitive to both bulk neurological activity and the subsequent haemodynamic response to stimuli.

- Validation of the image reconstruction model must be completed before images of the conductivity changes can be shown for the reference and auditory data. This must

take into account the skin impedances as discussed in chapter 4, as well as the newly reported higher skull conductivity.

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Appendix I – Measurement Index

Measurement Index	Current Injection	Voltage Measurement
1-28	1-30	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 31-32
29-56	1-27	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 28-29, 29-30, 30-31, 31-32
57-83	22-26	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 23-24, 24-25, 27-28, 28-29, 29-30, 30-31, 31-32
84-110	9-18	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
111-137	7-16	1-2, 2-3, 3-4, 4-5, 5-6, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
138-134	3-12	1-2, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
165-192	1-28	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 29-30, 30-31, 31-32
193-220	8-12	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 9-10, 10-11, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
220-246	5-15	1-2, 2-3, 3-4, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
247-274	1-29	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 30-31, 31-32
275-301	4-13	1-2, 2-3, 5-6, 6-7,7-8, 8-9, 9-10, 10-11, 11-12, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
302-328	8-17	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
329-355	7-13	1-2, 2-3, 3-4, 4-5, 5-6, 8-9, 9-10, 10-11, 11-12, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
356-382	20-24	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 22-23, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32

383-409	6-14	1-2, 2-3, 3-4, 4-5, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32
410-437	1-31	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30
438-465	1-10	2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31
466-492	2-11	3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 20-21, 21-22, 22-23, 23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31
493-519	21-25	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 18-19, 19-20, 22-23, 23-24, 26-27, 27-28, 28-29, 29-30, 30-31
520-546	19-23	1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-16, 16-17, 17-18, 20-21, 21-22, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31

Appendix II – Local Ethical Applications

(A) Forearm and thigh study

UNIVERSITY OF MANCHESTER

COMMITTEE ON THE ETHICS OF RESEARCH

ON HUMAN BEINGS

Application form for approval of a research project

1 Title of project

Experiments to determine electrode-skin contact impedance at high frequency.

2 Details of applicant(s)

Ms Rebecca Robinson,

School of Electrical and Electronic Engineering,

Rebecca.Robinson@postgrad.manchester.ac.uk

The experiments are connected with a project funded by the Wellcome Trust ('functional Electrical Impedance Tomography of Evoked Responses'), in which the main investigators are Prof. Hugh McCann from the University of Manchester and Dr. Christopher Pomfrett of the University Department of Anaesthesia at Manchester Royal Infirmary.

3 Details of project

3.1 Context

A pilot study on functional electrical impedance tomography of evoked responses (fEITER) has been carried out at UMIST and VUM [1](see reference details at section 3.8). Extensive research using EIT for medical application has been carried out in many centres [2]. A major impediment to the use of this technique for medical diagnostic application is the difficulty in obtaining quantitative images. In turn, this requires accurate information on the electrical impedance of the contact between the subject's skin and the EIT electrodes. However, an extensive literature search and intensive interaction with industry have served only to demonstrate that there is very little (if any) reliable data on this topic. The present application is concerned only with the measurement of electrode-skin contact impedance.

As part of the Wellcome Trust fEITER project, novel forward calculations are being performed which have already shown the potential for exploitation of good impedance data at the electrode-skin contact. Among other things, this computational work has provided good analytical data (via calculations of current density) to support the empirical observations [1,2] that the fEITER technique is electrically very safe. A separate application will be submitted for the tests of the complete fEITER prototype instrument.

3.2 Purpose

More generally, very little is known about the electrophysiology of the fEITER technique. It is my aim to understand more about this area, beginning with the contact impedance topic.

Initial experiments have been performed using silicone analogues and biological materials, such as bananas. New electrode manufacturing techniques have been developed to improve the connection between the skin and the electrode, however the electrical properties of the skin-electrode contact have not been fully examined and the actual properties of this contact are largely unknown.

To understand the electrode properties of the skin in contact with the electrodes it is necessary to perform a set of experiments on the skin of a subject(s). Electrodes would be placed onto the forearm or thigh and the impedance would be measured over a frequency range of 1 kHz – 1 MHz. Risk analysis has been performed for the tests, and all plausible events have been assessed.

3.3 Similar research

There is a long history of electrodes being used within a medical environment and the use of them today is common practice. Limited research into the electrode properties and their effects has been investigated [3]. Closely related research areas include the development of the electrodes, and the importance of the electrode contact to the skin was recognised. New electrode manufacturing techniques were developed to improve this connection, however the electrical properties of the skin-electrode contact have not been fully examined and the actual properties of this contact are largely unknown.

3.4 Methods

Electrodes will be placed onto the forearm or thigh and the impedance would be measured over a frequency range of 1 kHz – 1 MHz. A HP 4284A precision LCR Impedance Analyzer will be used, allowing a large frequency range to be considered [4]. These experiments will be repeated several times with different locations, to determine the repeatability.

Risk analysis has been performed for the tests, and all plausible events have been assessed. As shown in Appendix 4.

3.5 Duration of the study

3 Month

3.6 Location of the study

Sensing, Imaging and Signal Processing Group (SISP)

Laboratory Area E45

Sackville St. Building

3.7 Staff involved

The principle investigators are Prof. Hugh McCann of the University department of Electrical and Electronics Engineering and Dr. Christopher Pomfrett of the University Department of Anaesthesia at Manchester Royal Infirmary.

3.8 Initiator/sponsor

The sponsor for this project is EPRSC. The results will be used in the Wellcome Trust functional Electrical Impedance Tomography for Evoked Responses (fEITER) project.

References:

[1] H, McCann et al., "Sub-second functional imaging by Electrical Impedance Tomography," IEEE EMBS Annual International Conference, 2006, pp. 4269 – 4272

[2] D. Holder (ed.), Electrical Impedance Tomograpy: Methods, History and Applications. Bristol, England: Institute of Physics Pub., 2005

[3] J. G. Webster., Medical Instrumentation: Application and Design: Third Edition: John Wiley & Sons, Inc., 1998

[4] Test Equipment Depot: Fotronic Corporation 1996-2006

4 Details of subjects

4.1 Total number

Maximum: 7

4.2 Sex and age range

Sex: M + F Ages : 24 - 52

4.3 Type

Staff, post doctorate researchers and students are to be used as subjects.

4.4 Inclusions and exclusions

Exclusions:

Any person with skin allergies, specifically latex allergies.

4.5 Method of recruitment

All subjects will be volunteers from the main fEITER team.

4.6 Payments to volunteers

No payments will be made to volunteers.

5 Details of risks

5.1 Drugs and other substances to be administered

N/A

5.2 Procedures to be undertaken

There will be no invasive procedures in the experiments. The experiments include electrodes being placed on the subject's skin. There is a possibility that this could cause skin irritation or an allergic reaction. A questionnaire will be supplied to the subject before the tests are carried out, therefore anticipating that it will eliminate these problems.

Once the electrodes are placed onto the subject's skin the HP impedance analyser will be attached and a series of impedance measurements taken.

A volunteer information sheet will be provided to the subject before the tests are carried out. As shown in Appendix 1.

5.3 Potential dangers, discomfort or inconvenience

It is possible that potential allergic reactions could occur due to the skin contact with the electrodes. This could be in the form of a skin rash/irritation or more serious as a latex allergy from the electrode pad. It may also be noted that there is a slight abrasion of the skin due to small in built tines in the ZipPrep electrodes, could cause irritation. As shown in Appendix 4.

Although allergies could potentially cause a adverse reaction, an extensive literature search has been carried out by Dr Christopher Pomfrett, his work concluded that no allergic reactions could been found in connection with the ZipPrep electrodes.

5.4 If a patient group is being studied:

N/A

5.4.1 Indicate whether (and if so, how) participation will affect their general treatment regime

5.4.2 Direct benefits

6 Safeguards

6.1 Precautions

Before the experiments are carried out a questionnaire will be completed by the subject giving all known allergies or other medical conditions that could cause an adverse reaction. As shown in Appendix 2.

6.2 GP's initial notification

As the use of electrodes in the medical environment is common practice, it is not deemed necessary to inform the subject's GP of the tests.

6.3 GP's notification of events/findings

See above.

6.4 Ethics Committee's notification

The Ethics Committee will be immediately notified (via the Secretary) of any adverse reactions or untoward events.

6.5 Informed consent

Please see Appendix 1 and 3.

6.6 Confidentiality

All of the data will remain confidential. Medical data that is obtained during the tests will be stored and processed using computers and, after the study is completed, these may be copied onto a permanent record which might be studied again at a later time.

6.7 Insurance

All of the subjects will be covered by The University of Manchester assuming the application is approved by the Committee.

7 Approval by another recognised ethics committee

Indicate whether this project has been considered by another recognised ethics committee.

YES/NO

Signatures of applicant(s)

....

Signed Date

....

Signed Date

(B) Scalp study

UNIVERSITY OF MANCHESTER

COMMITTEE ON THE ETHICS OF RESEARCH

ON HUMAN BEINGS

Application form for approval of a research project

1 Title of project

Experiments to determine electrode-skin contact impedance on the scalp at high frequency.

2 Details of applicant(s)

Ms Rebecca Robinson,

School of Electrical and Electronic Engineering,

Rebecca.Robinson@postgrad.manchester.ac.uk

3 Details of project

3.1 Context

The use of standard measurement electrodes is common practice in medical and research environments. However, very little is known about the electrophysiology of the contact impedance between electrodes and skin. It is my aim to understand more about this area. Previous impedance measurements have been carried out on the forearm and shin (University ethical approval granted ref: 06241). This work was very successful at determining the impedance contact on the forearm and shin. However, certain physiological measurements use electrodes that are attached to the scalp. Therefore it is important that the previous study is extended to include the impedance measurements on the scalp. Two electrodes will be used to make impedance measurements on the scalp.

Impedance measurements on the scalp will provide valuable information for the wider project, fEITER (Real-time functional brain imaging using electrical impedance tomography of evoked responses). fEITER is a Wellcome Trust project which has applied for and been provisionally granted a favourable NRES opinion (07/H1003/145) given by South Manchester REC pending a number of points, including an MHRA application being made. The pilot study for fEITER was carried out at The University of Manchester [1](see reference details at section 5.4). When the fEITER project is complete it will use electrodes on the scalp. Therefore the most

informative location at which to determine the contact impedance and its frequency-dependent properties would be on the scalp. Novel forward calculations are being performed which have already shown the potential for exploitation of good impedance data at the electrode-skin contact [2]. Among other things, this computational work has provided good analytical data (via calculations of current density) to support the empirical observations [1,3] that the fEITER technique is electrically very safe. A separate application has been submitted and NRES approved for the tests of the complete fEITER prototype instrument.

Extensive research using EIT for medical application has been carried out in many centres. Most notably, is the work of the UCL London group [4], where animals and human volunteers (including children) have been studied. Both presently and in the past, other university research groups such as Sheffield, Kyung Hee (Korea), and UPC (Barcelona, Spain) have also been active in the area of medical EIT. Additionally, EIT by Dartmouth College (Hanover, USA) has successfully been used in the area of breast cancer screening using a FDA approved commercial instrument [3]. A major impediment to the use of this technique for medical diagnostic application is the difficulty in obtaining quantitative images. In turn, this requires accurate information on the electrical impedance of the contact between the subject's skin and the EIT electrodes. However, an extensive literature search and intensive interaction with industry have served only to demonstrate that there is very little (if any) reliable data on this topic.

3.2 Purpose

Little is known about the electrophysiology of the contact impedance between electrodes and skin. The present application is concerned with the measurement of the electrode-skin contact impedance on the scalp. Having previously investigated the contact impedance on the arm and shin it is clear that the research into the electrode-skin contact impedance needs to be progressed. It is necessary to expand the study to include scalp measurements, the information gained will be unique as there is no published literature of the contact impedance using ZipPrep electrodes on the scalp. The measurements will also inform fEITER project.

3.3 Similar research

There is a long history of electrodes (including Aspect Medical Systems ZipPrep© and 3M Red Dot Electrodes©) being used within a medical environment and the use of them today is common practice in electroencephalography (EEG), electromyography (EMG) and electrocardiography (ECG) among other physiological measurement techniques. Limited research into the electrode properties and their effects has been published [5, 6]. Among other considerations artifacts created by movement, muscle action and other subject related conditions, have been identified as major influences on the electrode-skin contact properties. Closely related research areas include the

development of electrodes; hence the importance of the electrode physical contact to the skin was recognised. New electrode manufacturing techniques were developed to improve this connection [7]. However, the electrical properties of the skin-electrode contact have not been fully examined and are largely unknown.

Work has been carried out, by the applicant, in accordance with the previous ethical approval granted (ref: 06241). Experiments have been carried out on 12 subjects, and all tests were successful in providing the desired data. Each subject had impedance measurements taken from their forearm and shin using two types of standard electrodes (Aspect Medical Systems ZipPrep© and 3M Red Dot Electrodes©). The tests included assessment of the effects of subject movement, muscle contraction etc. Throughout these tests, no sensation was observed by any of the subjects. The high-frequency data (1 k – 100 kHz) obtained are of excellent quality and they appear to show important new phenomena that have not previously been reported in the literature. As a result conference and journal publications are now in preparation.
Comparing the recorded applied currents to the subjects, shown in Table 1, to the medical standards BS EN 60601-1-1[8] the levels of current applied to the subject are minimal and within the standards. As described in Table 1 none of the subjects have felt any sensation throughout the experiments on their forearm or leg.

Below table shows the current levels at 10kHz.

Date	Subject	Electrode Position	Current (mA)	Sensation
20/04/2007	A	F	0.920	NO
20/04/2007	B	F	0.593	NO
21/05/2007	A	S	0.604	NO
21/05/2007	B	S	0.530	NO
21/05/2007	C	F	0.486	NO
11/06/2007	D	F	0.486	NO
29/06/2007	E	S	0.827	NO
07/08/2007	F	F	0.642	NO
07/08/2007	F	S	0.569	NO
08/08/2007	G	F	0.618	NO
08/08/2007	G	S	0.431	NO
08/08/2007	H	F	0.495	NO
08/08/2007	H	S	0.379	NO
11/08/2007	I	F	0.483	NO
11/08/2007	I	S	0.415	NO
21/08/2007	C	S	0.646	NO
21/08/2007	J	F	0.998	NO
21/08/2007	J	S	0.797	NO
22/08/2007	E	S	0.914	NO
22/08/2007	K	F	0.395	NO

Key: F- Forearm, S - Shin ***Table 1***

3.4 Methods of scalp measurements

The experiments consist of attaching a single pair of standard medical electrodes (using either two Aspect Medical Systems ZipPreps© or two 3M Red Dot Electrodes©) to a subject's forehead and/or scalp. The electrodes are connected to the Impedance Analyser, along with advanced safety circuitry as previously used (see Figures 1(a) and 1(b)). The total impedance of the resulting circuit is measured at ac frequencies from 1kHz to 100 kHz. Risk analysis has been performed for the tests, and all cases have been assessed. A thorough risk assessment has been carried out and has been independently checked by Mr Frank Hogan, High Voltage Lab Manager, Senior Experimental Officer and Senior School Safety Officer, see Appendix 1.
It should be noted that, the proposed tests use the same safety equipment and setup as used in previous forearm and shin measurements (ref: 06241).
Throughout the proposed tests, the experimenter is always present along with a 3rd person. The subject is able to withdraw from the test at any time. This is done by him/her merely releasing their switch. Similarly the experimenter can stop the test at anytime by releasing their independent switch.
The impedance analyzer is calibrated at the beginning of each test sequence. Once calibrated it is connected to the controlling PC. The experimenter then sets out the operation parameters (described below) for the test. From this point onwards the settings on the impedance analyzer can ONLY be changed by going through series a of different screens on the PC control software.
The amount of data to be acquired is chosen, and the frequency range is set in two stages. Firstly a frequency sweep from 1kHz to 10kHz in 1kHz steps is performed and recorded. Secondly a frequency range from 10kHz – 100kHz is performed and recorded in 10kHz steps. The current that is applied to the subject to obtain each frequency sweep will take approximately 1 minute.

The subject will be asked to complete a range of tasks described in Table 2:

Tasks	***Time Required***
Remain still and quiet throughout the frequency sweeps	*Approx 3 mins*
Continuously raise and drop eyebrows throughout frequency sweeps	*Approx 3 mins*
Continuously blink throughout the frequency sweep	*Approx 3 mins*
To move head from side to side, i.e. looking left then right throughout frequency sweep	*Approx 3 mins*
Light will be flashed in the volunteer's eyes, 1 flash per 10s	*Approx 3 mins*

Table 2 *The experimental procedure including setup should last about 1 hour per subject.*
The last case in Table 2 is designed to test the effects of involuntary muscle/eye response to visual stimuli. The stimulus to be used is a standard form of visual stimulus used in neuroscience, neurological investigations and clinical practice.

3.5 Duration of the study

3 Months

3.6 Location of the study

Sensing, Imaging and Signal Processing Group (SISP)
Laboratory Area E45
Sackville St. Building

3.7 Staff involved

The experiments are connected with a project funded by the Wellcome Trust project 'Real-time functional brain imaging using electrical impedance tomography of evoked responses' (fEITER), which has applied for and been provisionally granted a favourable NRES opinion (07/H1003/145) given by South Manchester REC pending a number of points, including an MHRA application being made. The Principle Investigators of fEITER are Prof. Hugh McCann of the University of Manchester and Dr. Christopher Pomfrett of the Research School of Clinical & Laboratory Sciences, School of Medicine, University of Manchester. Other staff include Dr JL Davidson Postdoctoral Research Associate at The University of Manchester and Dr P Wright Senior Experimental Officer for Sensing, Imaging and Signal Processing at The University of Manchester.

3.8 Initiator/sponsor

The sponsor for this project is EPRSC. The results will be used in the Wellcome Trust functional Electrical Impedance Tomography for Evoked Responses (fEITER) project.

Figures:

Fig 1(a) *– experiment configuration*

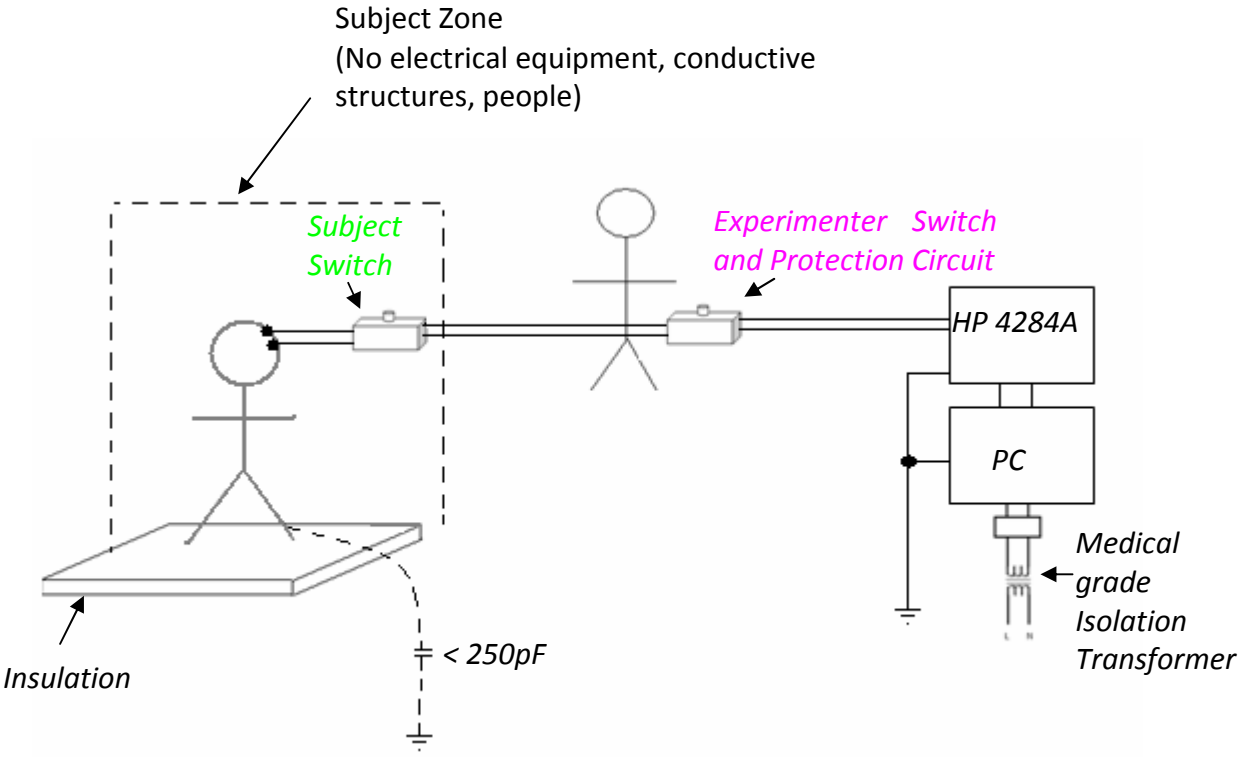
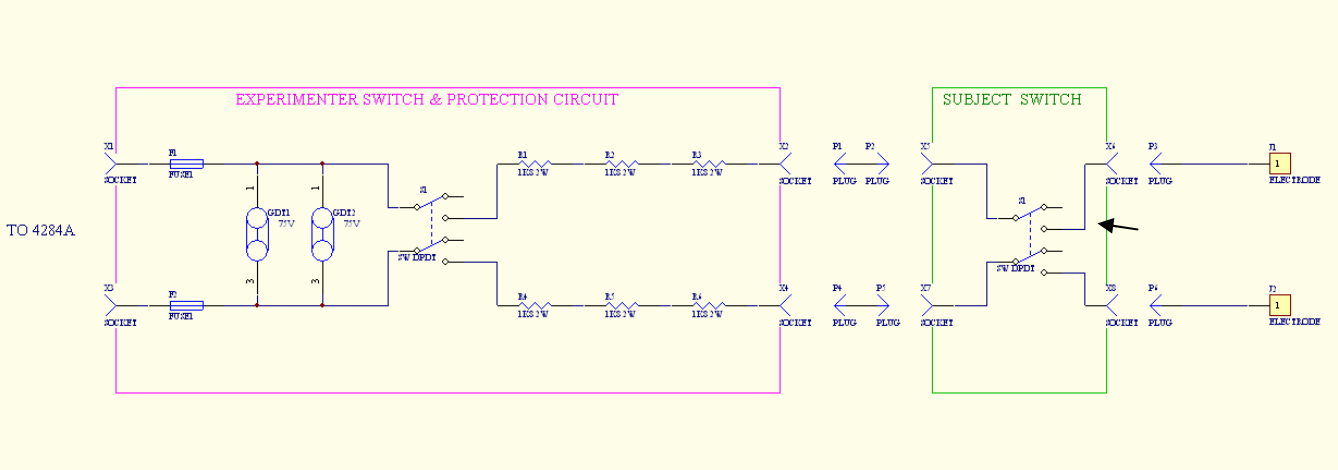


Figure 1(b) *– circuit diagram*



4 Details of subjects

4.1 Total number

Maximum: 12

4.2 Sex and age range

Sex: M + F Ages : 20-60

4.3 Type

Staff, post doctoral researchers and students.

4.4 Inclusions and exclusions

Exclusions:

Any person with skin allergies, specifically latex allergies or photosensitive epilepsy.

4.5 Method of recruitment

All subjects will be volunteers from the wider fEITER project team.

4.6 Payments to volunteers

No payments will be made to volunteers.

5 Details of risks

5.1 Drugs and other substances to be administered

N/A

5.2 Procedures to be undertaken

There will be no invasive procedures in the experiments. The experiments include electrodes being placed on the subject's scalp. There is a possibility that this could cause skin irritation or an allergic reaction. A questionnaire will be supplied to the subject before the tests are carried out, therefore anticipating that it will eliminate these problems.

Once the electrodes are placed onto the subject's skin the HP impedance analyser will be attached and a series of impedance measurements taken.

A series of tests will begin, as described in section 3.4. Due to visual stimuli being applied by flashing a light in the volunteer's eyes it is necessary to consider the risk of photosensitive epilepsy [9]. This risk is eliminated by using a rate of flash exposure of 1 flash every 10 seconds i.e. a frequency of 0.1Hz which is at least a factor of 50 slower than the frequencies associated with photosensitive epilepsy of 5-50Hz [10]. This risk will be further reduced by restricting volunteer tests to people without known forms of epilepsy. Volunteers will complete a questionnaire to identify and eliminate subjects who fall into any risk category.

A volunteer information sheet will be provided to the subject before the tests are carried out. As shown in Appendix 2.

5.3 Potential dangers, discomfort or inconvenience

It is possible that potential allergic reactions could occur due to the skin contact with the electrodes. This could be in the form of a skin rash/irritation or more serious as a latex allergy from the electrode pad. It may also be noted that there is a slight abrasion of the skin due to small in built tines in the ZipPrep electrodes, could cause irritation. As shown in Appendix 4.

Although allergies could potentially cause a adverse reaction, an extensive literature search has been carried out by Dr Christopher Pomfrett, his work concluded that no allergic reactions could been found in connection with the ZipPrep electrodes.

5.4 If a patient group is being studied:

N/A

5.4.1 Indicate whether (and if so, how) participation will affect their general treatment regime

5.4.2 Direct benefits

References:

[1] H. McCann et al., "Sub-second functional imaging by Electrical Impedance Tomography," IEEE EMBS Annual International Conference, 2006, pp. 4269 – 4272
[2] JL Davidson, C. J. D. Pomfrett and H. McCann, Predicted EIT current densities in the brain using a 3D anatomically realistic model of the head, In proc. ICEBI'07 (Graz, Austria, 2007).
[3] D. Holder (ed.), Electrical Impedance Tomograpy: Methods, History and Applications. Bristol, England: Institute of Physics Pub., 2005
*[4] R. Halter, A. Hartov and K.D. Paulsen, "Design and implementation of a high frequency electrical impedance tomography system," Physiol. Meas., **25**, 2004, pp. 379 – 390*
[5] J. G. Webster., Medical Instrumentation: Application and Design: Third Edition: John Wiley & Sons, Inc., 1998
[6] ET McAdams, J Jossinet, "Tissue impedance: a historical overview," Physiol. Meas., 1995
[7] http://www.aspectmedical.com
[8] BS EN 60601-1-1:2001 - Medical electrical equipment. General requirements for safety. Collateral standard. Safety requirements for medical electrical systems
[9] http://www.epilepsy.org.uk/downloads/pdf/epilepsyaction_photosensitive.pdf
[10] G.F.A. Harding, P.M. Jeavons, Photosensitive Epilepsy Clinics in Developmental Medicine No. 133, 1994

6 Safeguards

6.1 Precautions

Before the experiments are carried out a questionnaire will be completed by the subject giving all known allergies or other medical conditions that could cause an adverse reaction. As shown in Appendix 3.

6.2 GP's initial notification

As the use of electrodes in the medical environment is common practice, it is not deemed necessary to inform the subject's GP of the tests.

6.3 GP's notification of events/findings

See above.

6.4 Ethics Committee's notification

The Ethics Committee will be immediately notified (via the Secretary) of any adverse reactions or untoward events.

6.5 Informed consent

Please see Appendix 2 and 4.

6.6 Confidentiality

All of the data will remain confidential. Each volunteer will be assigned a number. The data that is obtained during the tests will be stored and processed using computers. After the study is completed, these may be copied onto a permanent record which might be studied again at a later time.

6.7 Insurance

All of the subjects will be covered by The University of Manchester assuming the application is approved by the Committee.

7 Approval by another recognised ethics committee

Indicate whether this project has been considered by another recognised ethics committee.

YES/NO

Signatures of applicant(s)

....

Signed Date

....

Signed Date

Appendix III – Consent forms and information sheets

nt Form

MANCHESTER 1824

The University of Manchester

VOLUNTEER CONSENT FORM

CONSENT FORM FOR HEALTHY VOLUNTEERS

Research Project

Experiments to determine electrode-skin contact impedance at high frequency

Principal Investigator

Rebecca Robinson

The nature of the research and what I would be asked to do as a volunteer has been fully explained to me.

I have read the Information Sheet that has been provided to me, and this Consent Form, and have been given the opportunity to ask questions about them. I am satisfied that I have all the information that I need to provide informed consent. [I acknowledge that the risks mentioned in the volunteer information sheets have been explained to me.]

As a volunteer, I understand that I am not being medically tested at the request of a Doctor for any specific medical condition.

I know of no reason why I should not undergo skin impedance analysing or take part in the study. I confirm that I do not have any skin allergies, principally I do not have a latex allergy. To the best of my knowledge I have never suffered from any form of epilepsy, principally photosensitive epilepsy.

I consent to take part as a volunteer, I know that I am under no obligation to take part in the study and I can withdraw at any time without giving any reason and without detriment to myself.

I agree that data obtained during my tests may be stored and processed using computers and, after the study is completed, that these may be copied onto a permanent record which might be studied again at a later time.

I agree to participate in the study and confirm that I have had fully explained to me the purpose and nature of the investigation and the risks involved.

Signature of volunteer

Name of volunteer (please print in block capitals)

Witnessed by (signature)

Name of witness (please print in block capitals)

Date

(B) Information Sheet - 1

MANCHESTER 1824 VOLUNTEER INFORMATION SHEET (1)

The University of Manchester

Experiments to determine electrode-skin contact impedance at high frequency

A pilot study on functional electrical impedance tomography of evoked responses (fEITER) has been carried out at The University of Manchester [1]. Extensive research using EIT for medical application has been carried out in many centres. Most notably, is the work of the UCL London group [2], where animals and human volunteers (including children) have been studied. Both presently and in the past, other university research groups such as Sheffield, Kyung Hee (Korea), and UPC (Barcelona, Spain) have also been active in the area of medical EIT. Additionally, EIT by Dartmouth College (Hanover, USA) has successfully been used in the area of breast cancer screening using a FDA approved commercial instrument [3].A major impediment to the use of this technique for medical diagnostic application is the difficulty in obtaining quantitative images. In turn, this requires accurate information on the electrical impedance of the contact between subject's skin and the EIT electrodes. However, an extensive literature search and intensive interaction with industry have served only to demonstrate that there is very little (if any) reliable data on this topic.

As part of the NRES approved Wellcome Trust fEITER project, novel forward calculations are being performed [4] which have already shown the potential for exploitation of good impedance data at the electrode-skin contact. Among other things, this computational work has provided good analytical data (via calculations of current density) to support the empirical observations [1,2] that the fEITER technique is electrically very safe.

More generally, very little is known about the electrophysiology of the fEITER technique. It is my aim to understand more about this area, beginning with the contact impedance topic.

To understand the interactions between skin and the electrodes it is necessary to perform a set of experiments on the scalp of a subject(s). Electrodes would be placed onto the scalp and the impedance would be measured over a frequency range of 1 kHz – 1 MHz. The frequency will not go below 1 kHz; this is significantly higher than the frequencies that could cause the skin to burn or interfere with normal brain functioning.

There is a long history of electrodes being used within a medical environment and the use of them today is still common practice. Although use of electrodes is common practice it is imperative that subjects with skin allergies, in particular latex allergies do not take part in this experiment. The tests will include a visual stimuli being applied at 10s intervals, if subject's have a history of any form of epilepsy they are unable to take part.

Research into the optimum electrode structure has been studied thoroughly [5]. During the development of the electrodes the importance of the electrode contact to the skin was

recognised. New techniques were developed to improve this connection, however the electrophysiology has not been fully examined and the actual properties of this contact are largely unknown.
The experimental process is completely non-invasive and safe. The experiment will take place in an isolated area, away from other electrical equipment. Two electrodes will be placed onto the scalp and the impedance would be measured over a large frequency range. A HP 4284A precision LCR Impedance Analyzer will be used to make measurements via safety circuitry, allowing a large frequency range to be considered. These experiments will be repeated several times with varying locations, to determine repeatability.

Tasks	***Time Required***
Remain still and quiet throughout the frequency sweeps	*Approx 3 mins*
Continuously raise and drop eyebrows throughout frequency sweeps	*Approx 3 mins*
Continuously blink throughout the frequency sweep	*Approx 3 mins*
To move head from side to side, i.e. looking left then right throughout frequency sweep	*Approx 3 mins*
Light will be flashed in the volunteer's eyes, 1 flash per 10s	*Approx 3 mins*

The tests will take approximately 1 hour per subject, including set-up.

The electrodes to be used are principally ZipPrep© electrodes (Aspect Medical Systems; Ag-AgCl electrodes printed on a polyester substrate with adhesive foam backing) and Red Dot© electrodes (3M; Ag-AgCl electrodes printed on a polyester substrate with adhesive foam backing). The ZipPrep© electrodes have small tines on the underneath. These are submerged in the conductive gel. Once the pad is positioned correctly the centre of the electrodes can be pressed into the skin. These tines part the outer layer of the dead skin cells and enter into the epidermis. This allows the impedance of the electrode-skin contact to be reduced and a higher quality signal can be monitored [6]. This type of technology can cause small lesions on the skin.

References:

[1] H, McCann et al., "*Sub-second functional imaging by Electrical Impedance Tomography,*" IEEE EMBS Annual International Conference, 2006, pp. 4269 – 4272
[2] D. Holder (ed.), Electrical Impedance Tomograpy: Methods, History and Applications. Bristol, England: Institute of Physics Pub., 2005
[3] JL Davidson, C. J. D. Pomfrett and H. McCann, "*Predicted EIT current densities in the brain using a 3D anatomically realistic model of the head*," In proc. ICEBI'07 (Graz, Austria, 2007).
[4] R. Halter, A. Hartov and K.D. Paulsen, "*Design and implementation of a high frequency electrical impedance tomography system,*" Physiol. Meas., **25**, 2004, pp. 379 – 390

[5] J. G. Webster., Medical Instrumentation: Application and Design: Third Edition: John Wiley & Sons, Inc., 1998, pp. 183 - 225
[6] http://www.aspectmedical.com

(B) Information Sheet - 2

MANCHESTER 1824

VOLUNTEER INFORMATION SHEET (2)

The University of Manchester

Experiments to determine electrode-skin contact impedance at high frequency

The experiments described are being carried out to discover accurate information on the electrical impedance of the contact between the subject's skin and the electrodes. Little is known about the electrophysiology of the interface between the electrodes and the skin. The aim is to understand more about this area, beginning with the skin contact impedance.

There is a long history of electrodes being used within a medical environment and the use of them today is still common practice. Although the use of electrodes is frequent it is imperative that subjects with skin allergies, in particular latex allergies do not take part in this experiment. The tests will include a visual stimuli being applied at 10s intervals, if subject's have a history of any form of epilepsy they are unable to take part.

The experiment will take place in an isolated area, away from other electrical equipment. Electrodes will be placed onto the forearm or thigh and the impedance would be measured over a frequency range of 1 kHz – 1 MHz. The frequency will not go below 1 kHz; this is set significantly higher than the frequencies that could cause the skin to burn or interfere with normal brain functioning.

The electrodes to be used are principally ZipPrep® and Red Dot© electrodes these are electrodes that are usually used for EEG (tests performed on the scalp) and are deemed very safe. Due to the small tines on the underneath of the ZipPrep© electrode pad this type of technology can cause small lesions on the skin.

The experiments will be repeated several times varying the location on the subject's skin, this is to determine repeatability. The following table describes the test procedure:

Tasks	***Time Required***
Remain still and quiet throughout the frequency sweeps	*Approx 3 mins*
Continuously raise and drop eyebrows throughout frequency sweeps	*Approx 3 mins*
Continuously blink throughout the frequency sweep	*Approx 3*

	mins
To move head from side to side, i.e. looking left then right throughout frequency sweep	*Approx 3 mins*
Light will be flashed in the volunteer's eyes, 1 flash per 10s	*Approx 3 mins*

The tests should take approximately 1 hour per subject, including set-up.

(C) Volunteer Questionnaire

MANCHESTER 1824

VOLUNTEER QUESTIONNAIRE

TO BE COMPLETED BEFORE EXAMINATION COMMENCES

The University of Manchester

Please answer the following confidential questions by circling YES or NO to each one.
If you do not understand any of the questions please ask someone to help you.

	Initials
1a. Do you/have you suffered from epileptic episodes?	
1b. Do you know of any medical reason you are unable to take part in tests that involve slow flashing lights?	
2a. Do you have any skin allergies?	
2b. If so, are you allergic to Latex?	
3. Are you prone to getting skin rashes/irritations?	
4a. Do you have severe scarring on your forehead?	
4b. If so, have you had a skin graft in that area?	

I confirm that I have read the above questions and that my answers are correct to the best of my knowledge and belief.

Signature of volunteer

Name of volunteer (please print in block capitals)

Witnessed by (signature)

Name of witness (please print in block capitals)

Date

Appendix IV – MHRA and NRES

(A) PCA1

COMPETENT AUTHORITY (UK)

MHRA

CLINICAL INVESTIGATION APPLICATION* FORM PCA 1

PART 1: *About the notification*

Complete this form in type face or block letters. Form PCA 2 must be used for all notifications.
PLEASE NOTE: The full fee should be sent to MHRA Corporate Finance, Market Towers, 1 Nine Elms Lane, London SW8 5NQ at the same time as the notification is made to the Competent Authority.

1. Enter the date documentation sent to the Competent Authority.

Day . Month . Year .

2. First or re-submission. Tick the appropriate box.

First ✓ | Re-submit

Original File Reference Number
CI / / /

COMPETENT AUTHORITY USE ONLY

File Reference Number
CI / / /

Date Received
. .

3. If this is part of multi-centre clinical investigation, enter details of other Countries that will be/ have been approached.

None

4. All notifications must be prefaced by this statement signed by the manufacturer's duly authorised signatory (where this is the manufacturer's authorised representative, please also complete 7 over page).

Failure to complete this declaration or to supply all necessary information could result in the notification being returned or cancelled.

*Regulation 16 and Regulation 29 of the Medical Devices Regulation 2002 (SI No 0618) refer.

For and on behalf of *(manufacturers name)*

The University of Manchester

I, *(please print full name)*

Professor Hugh McCann

1 certify that the device in question complies with the Essential Requirements apart from those aspects covered by the investigation and that with regard to these aspects, every precaution has been taken to protect the health and safety of the patient and/or user,

2 certify that the information and documentation submitted with this notification is correct in detail and all the information requested has been supplied,

3. undertake to keep available for the Competent Authority for a period of 5 years all the documentation referred to in Annex 6 Council Directive 90/385/EEC/Annex VIII Council Directive 93/42/EEC.

Signed: Date:

Authority *(print)* Principle Investigator

(State the capacity of the signatory who must be duly authorised to sign on behalf of the company or body)

I. (*print*) Professor Hugh McCann

confirm that the Clinical Investigation Application Form(s) has been faithfully reproduced with no changes

5. To be completed if a reproduced Clinical Application form is used.

Signed

PART 2: *Manufacturer Information*

6 Enter the full name and postal address of the manufacturer (including country of the site where the product is being manufactured).

Manufacturer's Name
The University of Manchester

Address
School of Electrical and Electronic Engineering
University of Manchester
Sackville Street Building
PO Box 88
Manchester
M13 9PL

Enter telephone and fax numbers including international codes.

Telephone Number 0161 306 4791

Fax number 0161 306 4789

COMPLETE 7 BELOW IF THE MANUFACTURER IS NOT ESTABLISHED IN THE EUROPEAN COMMUNITY, IF NOT APPLICABLE GO TO PART 3.

7 Enter the full name and postal address of the manufacturer's authorised representative responsible for this notification, if applicable.

Name

Address

Enter telephone and fax numbers including international codes.

Telephone Number

Fax number

PART 3: *Device Information*

8. Enter manufacturer's trade name (if different form 6 above) associated with the device.

Manufacturer's Trade Name

9. Enter details of Notified Body approval of quality system or process at the site referred to at 6 above relevant to the clinical investigation device.

Notified Body Ref. No. | Details of Certification

10. Enter the device identification name and/or number.

Device name and/or Device number

fEITER

11. Enter the generic name describing principal intended use.

Generic name

A real-time functional brain imaging system

12. Class of Device. Note this refers to the Classification of the device under investigation

Tick Device Classification

AIMD	III	IIb	IIa	I
			✓	

PART 4: *Clinical Trial Information*

13 Enter the number of devices in UK clinical trial and global number if part of a multi country trial.

Number of Devices in UK: One

Total Global number: One

14. Enter the proposed commencing and completion dates of clinical investigation in the UK.

Commencing Day Month Year | Completion Day Month Year

15. Enter details of who will be monitoring the clinical trial.

Trial monitor

Dr Chris J D Pomfrett

16 Enter the name and address of the person who should be directly contacted for information about this application including the post code (and country where appropriate) (UK contact

Title Professor Initials/Forename Hugh Surname McCann

Capacity Principle Investigator

Address

School of Electrical and Electronic Engineering
University of Manchester
Sackville Street Building
PO Box 88
Manchester, M13 9PL

16a Enter the contact's telephone and fax numbers including local and international codes (where appropriate).

Telephone number: 0161 306 4791

Fax number: 0161 306 4789

email: h.mccann@manchester.ac.uk

17 BELOW IS FOR USE AS A FINAL CHECK AND CONFIRMATION THAT THE INFORMATION IS ENCLOSED WITH THIS FORM

17 Complete the boxes by ticking and enclose the information with this form.

Copy of Local Research Ethics Committee opinion(s):

Enclosed ☑

To Follow ☐

Fee made payable to " MHRA No 2 A/C ", for the sum of £3000.00 ☑

Eight copies of the supporting documentation enclosed ☐

18 On occasions it may be helpful to MHRA to liaise with the National Research Ethics Service (or equivalent services in Scotland, Wales and Northern Ireland) and specifically the relevant Research Ethics Committee (REC). We would also like to send the REC a copy of our final decision on this application for their information. Please complete the information requested and sign below to allow us to discuss this case with the ethics committee if necessary and send them our final decision.

Ethics Committee address:
South Manchester Research Ethics Committee
Room 181
Gateway House
Piccadilly South
Manchester, M60 7LP

Ethics Committee Ref No: 07/H1003/145

I. (*print*) Professor Hugh McCann

confirm that the UK Competent Authority may discuss this application with the Research Ethics Service and the relevant Research Ethics Committee named above and provide the REC with a copy of their final decision.

Signed

19 Principal clinical investigator appointed to co-ordinate the work in a multi-centre clinical investigation (if relevant). Enter the full name and address including the post code.

Note. This must be an appropriately qualified practitioner to comply with EN ISO 14155.

Title	Initials/Forename	Surname

Academic Qualification

Institution (Hospital) Name

Address

19a Clinical investigator responsible for the conduct of the proposed clinical investigation. Enter the full name and address including the post code.

Title: Professor | Initials/Forename: Brian J | Surname: Pollard

Academic Qualification: BPharm, MB, ChB, MD, FRCA

Institution (Hospital) Name: The University of Manchester

Address:
School of Medicine
The University of Manchester
Anaesthesia
Manchester Royal Infirmary
Manchester
M13 9WL

19b Clinical investigator responsible for the conduct of the proposed clinical investigation. Enter the full name(s) and address including the post code.

Title: Dr | Initials/Forename: Chris J D | Surname: Pomfrett

Academic Qualification: BSc, PhD

Institution (Hospital) Name: The University of Manchester

Address:
School of Medicine
The University of Manchester
Anaesthesia
Manchester Royal Infirmary
Manchester
M13 9WL

PLEASE COPY IF ADDITIONAL PAGES ARE REQUIRED

18 - GENERAL INFORMATION

Edited by

Rebecca Robinson, Prof. Hugh McCann, Dr John Davidson, Dr Paul Wright

School of Electrical and Electronic Engineering

The University of Manchester

Dr Chris Pomfrett, Dr Angella Bryan

School of Medicine

The University of Manchester

Version 4 15th April 2009

18.1 Description of the intended purpose of device[±]

The device described in this document is given the acronym fEITER, which stands for "functional Electrical Impedance Tomography of Evoked Responses".

This document describes fEITER as a 'one-off' prototype device suitable for the clinical investigation described herein.

fEITER is intended to provide functional brain imaging, in a portable system with high-speed capability.

In the clinical investigation described here, fEITER will be assessed as a clinical tool for visualising brain function during anaesthesia and its sensitivity to known levels of reduction in general brain function (via anaesthesia) will be assessed.

The ultimate aim of the research programme is to evaluate fEITER as a portable, bedside brain function imaging monitor.

fEITER integrates existing Electrical Impedance Tomography (EIT) and Evoked Response techniques (ER), with the capability to yield continuous functional imaging of the brain at 100 frames per second.

The technology is based on a new concept which has been patented by the University of Manchester [1].

(References are listed at the end of each section of this document.)

[±] Please see NRES application, reference **07/H1003/145**, pages **6-8**.

18.2 A copy of the Research Ethics Committee opinion, if available

Please see Appendix I.

18.3 Copy of informed consent.

Please see Appendix II.

18.4 Reference to important relevant scientific literature (if any) with an analysis and bibliography

Background

Functional imaging of the whole brain is now an essential and well-established tool in medical and neuroscience research. It shows great promise for the assessment of brain trauma and dysfunction, e.g. due to stroke and degenerative diseases. However, functional brain scanners that are sensitive to activity in the deep regions of the brain are not available in every hospital due to their very high cost and need for dedicated accommodation suites. Several existing technologies can be used to present a clinician with images of the functioning of the brain. Electroencephalography (EEG) provides functional imaging capability, but only in regions that are within a few mm of the surface of the brain [2]. Established technologies that provide whole-brain functional imaging include positron emission tomography (PET) [3] and functional magnetic resonance imaging (fMRI) [4]. However, where they are available, they are large fixed installations that are not portable. The result is that there is usually a long waiting list for patients to be scanned, and functional scanning is not available to most patients in emergency situations. Moreover, the need for the patient to be taken to the scanner is a severe logistical limitation, e.g. continual functional imaging in the treatment or consulting location is not feasible.

Consequently, there is now a pressing need to develop a viable commercial technology for functional imaging of the whole brain that is portable and much cheaper than fMRI and PET systems. The clinical investigation described in this document is intended to evaluate fEITER, a new portable brain imaging technology.

EEG has been used for many years to study brain responses to standard stimuli, as a function of measurement position on the scalp. In particular, a range of visual and auditory stimuli (e.g. see [5] and [6] respectively) are known to evoke characteristic responses (or electrical potentials measured on the scalp), known respectively as Visual Evoked Response/Potentials (VEP) and Auditory Evoked Response/Potentials (AEP). These responses follow a complex signature in time, over a period of about 40 – 600ms after stimulus.

fEITER uses an EIT (electrical impedance tomography) sub-system to measure the electrical properties of the head tissues around which a set of electrodes are mounted on the scalp. From the measurement data, it is possible to infer the distribution of conductivity change within the brain on stimulus, which is attributed to functional brain activity. The reconstruction of conductivity

distributions from EIT measurements is well-established in process engineering [7, 8] and in biomedical applications [9, 10].

The fEITER system is highly portable. It is expected to be at least an order of magnitude cheaper than fMRI and PET systems. If successful, functional imaging using fEITER could be extended to many more bedside situations than is presently possible, such as stroke screening in emergency departments and early detection and subsequent monitoring of vCJD and Alzheimer's Disease in order to optimise therapies. However, there is a pressing need for any commercially viable technology to be demonstrated in a true clinical setting so that potential business partners can be recruited to fund the project through expensive development stages.

Biomedical Applications of EIT

EIT has been in clinical use for over twenty years in areas such as gastric function and lung function monitoring [10, 11]. It has been investigated by several university-based research groups, such as those at Sheffield, UCL (London), Gottingen, UPC Barcelona, Dartmouth College (USA) and Kyung Hee (Korea). Recently, EIT has successfully been used by Dartmouth College in the area of breast cancer screening using a FDA-approved commercial instrument [12, 13].

Most notable in the context of the fEITER project, is the work of the UCL group (e.g. [14]), where many human volunteers (including children) have been studied. The UCL group have principally investigated the situation where brain stimulus is maintained at high rates (several Hz) over long periods (several minutes), to produce each image from measurement data averaged over tens of seconds. They attribute their sensitivity to the brain's haemodynamic response, whereby increased blood flow and associated effects such as cell-swelling occur due to functional activity, over a period of many seconds. Related work on EIT spectroscopy of stroke patients has been carried out by a group at Harvard [15].

fEITER

From a patient safety and clinical protocol perspective, our work is no different from the other biomedical studies mentioned above when considering risk, safety and the nature of clinical investigation. Hence, our work can build on those earlier studies when considering risk and safety. In 2000 and 2001, we carried out a pilot study [16, 17] using a commercial EIT instrument, in conjunction with a standard ER system and a bespoke current limiter circuit, in order to monitor functional brain activity on experimenter volunteers within a laboratory environment. The pilot study

proved invaluable for demonstrating the technology at a basic level. Experience gained from the pilot study has informed the design of our new fEITER system specifically designed for brain function monitoring.

The principal difference between fEITER and the other medical EIT systems discussed above [10 - 15] is the encryption of the stimulus event markers with the EIT data. This is done in order to achieve functional imaging of the ER of the brain during the time-course of the expected ER, i.e. within a period less than 1 second after stimulus. By invasive measurement, Klivington and Galambos and co-workers observed such rapid Evoked Resistance Shifts (ERS) in the brains of cats in a variety of experiments [18 – 21]. The ERS had the same time-course as simultaneous VEP and AEP recordings, and it was demonstrated that the ERS is synaptic in origin, rather than haemodynamic. It is believed that this mechanism underlies our positive results in the pilot study [16, 17].

In the clinical trial discussed in Section 19, a range of visual and auditory stimuli will be tested on volunteers to identify which ones elicit the best responses in the fEITER system. The aim will be to evoke an EIT equivalent to the pattern responses typically seen in VEP and AEP techniques using EEG. We hope to distinguish between a visually evoked response using a flash and an auditory evoked response using a click.

In the clinical investigation, we propose a two-stage approach which will maintain patient and volunteer safety as a priority, and yet will realistically yield a sufficient number of results for clinical validation by statistical methods, where the reconstructed images can be tested to show whether the effects observed are truly indicative of active neural processes and not just random noise or other fluctuations.

After initial testing on project team volunteers in Stage A, fEITER will be tested on anaesthetised patient volunteers in Stage B. By simultaneously measuring brain function using a Bispectral Index monitor (BIS) in Stage B, we will be able to correlate the results obtained with those from functional imaging studies already performed by members of the team at the University of California. The BIS monitor is a licensed device which is available for use by the anaesthetist in surgical procedures to assess 'depth of anaesthesia'. In the Californian study, the performance of BIS was compared with 18 Fluorodeoxyglucose PET imaging [22].

References

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[9] Polydorides N, Lionheart W R B and McCann H, *Krylov subspace iterative techniques: On the detection of brain activity with Electrical Impedance Tomography,* IEEE Trans. on Medical Imaging, 2002; (21): 596-603

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(N.B. 4 intensive care patients imaged)

[12] Steven P. Poplack, Tor D. Tosteson, Wendy A. Wells, Brian W. Pogue, Paul M. Meaney, Alexander Hartov, Christine A. Kogel, Sandra K. Soho, Jennifer J. Gibson, Keith D. Paulsen, *Electromagnetic Breast Imaging: Results of a Pilot Study in Women with Abnormal Mammograms*, Radiology, 2007; (243):350-359

(N.B. 150 women imaged)

[13] Ryan J. Halter, Alex Hartov, and Keith D. Paulsen, *A Broadband High-Frequency Electrical Impedance Tomography System for Breast Imaging*, IEEE Trans. Biomed. Eng., 2008; (55): 650-659

(N.B. 96 women imaged)

[14] Tidswell AT, Gibson A, Bayford RH, and Holder DS, *Three-Dimensional Electrical Impedance Tomography of Human Brain Activity*, NeuroImage, 2001; (13) 283-294

(N.B. 39 human subjects imaged)

[15] Bonmassar G and Iwaki S, *The Shape of Electrical Impedance Spectroscopy (EIS) is altered in Stroke Patients*, Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA, USA, September 1-5, 2004: 3443-3446

(N.B. 6 human subjects measured, including 3 stroke patients)

[16] Murrieta-Lee JC, Pomfrett CJD, Beatty PCW, Polydorides N, Mussel CB, Waterfall RC and McCann H, *Sub-second observations of EIT voltage changes on the human scalp due to brain stimulus*, Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA, USA, September 1-5, 2004: 1317-1320.

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19 - INVESTIGATION PARAMETERS AND DESIGN

Edited by

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Dr Chris Pomfrett, Dr Angella Bryan

School of Medicine

The University of Manchester

Version 4 15th April 2009

19.1 Aims and objectives of clinical investigation (bearing in mind which essential requirements are being addressed by the clinical investigation in question)

Aims:

A. To evaluate the clinical utility of fEITER as a portable, bedside brain function imaging monitor;

B. To determine the sensitivity of fEITER as a clinical tool for visualising brain function during anaesthesia;

C. To compile a database of fEITER responses under various stimuli and various subject conditions.

Objectives:

Stage A: Project team volunteers.

1. To determine the ideal EIT response signature from fully awake and fully conscious subjects;
2. To determine the optimal visual and auditory stimulus sequences for Stage B;
3. To test if fEITER will permit identification of whether visual or auditory stimuli have been presented.

Stage B: Anaesthetised patient volunteers.

4. Determine the sensitivity of fEITER to known levels of reduction in brain metabolism with anaesthetic agents of known properties;
5. Calibrate the fEITER response against the depth of anaesthesia indicated by a medically validated, commercial technique (BIS monitor);
6. Correlate the above results with functional imaging studies already performed by members of the team at the University of California.

19.2 Type of investigation i.e. whether the use of a controlled group of patients is planned

The investigation will be conducted in two stages:

In Stage A, volunteers from the experimental project team will be subjects for fEITER data recordings using a variety of visual and auditory stimuli. Images of brain function will be reconstructed off-line, during the days after the recordings are made.

In Stage B, the subjects will be consenting patients; for these subjects fEITER data recordings will be made before, during and after they undergo anaesthesia. The stimuli used in this stage will be those that were found to be optimal in Stage A. Images of brain function will be reconstructed off-line, during the days after the recordings are made.

Number of patients, (with rationale)

Stage A: 10 subjects (i.e. n=10). From known features of visual neurophysiology, principally that a large fraction of the brain is involved in dealing with visual stimulus, and from the pilot study, it is expected that n=10 would be sufficient to allow an unequivocal demonstration of functional imaging. A smaller fraction of the brain is used in processing auditory stimuli. However, if sensitivity can be demonstrated, then fEITER should show function in different regions from those involved in visual processing. In this stage, it is feasible to ensure that good data records are obtained from all subjects.

Stage B: 10 subjects (i.e. n=10), all with good data records. 10 volunteer patients have been recognised as the variable response of patients to a given dose of anaesthetic and of the statistical nature of the SPM (statistical parametric mapping) analysis procedure [1]. Based on experience within the project team on the topic of making research measurements in the operating room (OR), it is proposed to study 35 anaesthetised patients, from which it is anticipated that fully satisfactory data records will be obtained on 10 patients (see further discussion below). Based on experience within the project team on using the BIS monitor with anaesthetised subjects, n=10 will provide a statistically robust sample for a definitive test of the correlation of BIS with fEITER, and thus to assess fEITER sensitivity to reduced levels of brain function due to anaesthesia.

It is anticipated that the various stages of volunteer patient recruitment will be less than 100% efficient. Experience within the team with previous lay volunteers for research tests with diagnostic-related instrumentation, suggests that:

- To get initial positive responses from 70 patient volunteers, it will be necessary to approach 140. These 70 will be identified in the weeks before they attend for surgical procedure.
- It is anticipated that half of the initial positive responders will withdraw consent after arriving in hospital.
- Allowance must be made for the impact of OR procedures on the setting up and running of the fEITER system; an efficiency of 30% is estimated, i.e. of the 35 patients who continue to give consent and who are fitted with electrodes, subsequently to attempt the fEITER process in the OR, it is anticipated that good data records will be obtained for only 10 patients.

Reference

[1] Friston KJ, *Statistical Parametric Mapping : The Analysis for functional Brain Images,* Elsevier/Academic Press, 2007

19.4 Duration of study with start dates and finish dates and proposed follow-up period, (with rationale)

Stage		Start Date	End Date
A	Commence trial (n=4)	01/06/2009*	11/07/2009
A	Analysis of first data from Stage A	01/07/2009	01/08/2009
A	Complete Stage A data acquisition (n=6)	03/08/2009	16/08/2009
A	Analysis of data from whole of Stage A	17/08/2009	30/08/2009
B	Commence patient trial (n'=35, to obtain n=10)	31/08/2009	28/02/2010
B	Analysis of data from patients	31/08/2009	28/03/2010

Initial commissioning of the fEITER system for human tests and refinement of experimental procedures, will be carried out in tests with four volunteers. This is expected to take 1 month.

The quality of the data from the initial experiments will be assessed and image reconstruction algorithms will be refined, using these initial data. This data analysis period will take 1 month.

The majority of the team volunteer data will be recorded after the above off-line data quality checks. Data analysis will be carried out immediately after each volunteer test. This will take 2 weeks.

Overall assessment of data and its significance will take 2 weeks after the data collection has finished.

With all procedural details ironed out, with a body of data from volunteers already analysed, and optimal stimuli identified, Stage B will then commence.

It is expected to take 6 months to carry out Stage B tests on the required number of patients (n') to ensure that an adequate number (n) have good data records.

Significant data analysis will be carried out off-line for each patient after the equipment is disconnected, and before the next patient is tested. It will be necessary, e.g. to assess the overall quality of the patient's data record, and to apply the image reconstruction algorithms as refined in Stage A.

During Stage B, Professor Brian Pollard FRCA will be consulted on each case.

* This is the anticipated start of the trial, it is dependant on a (i) letter of no objection from the MHRA, (ii) the legalities finalised by the clinical governance at Manchester Royal Infirmary.

19.5 Criteria for patient selection. Inclusion and exclusion criteria. Criteria for withdrawal.

Selection Criteria - Stage A:

Healthy volunteers will be recruited from the project team, and comprise staff of the University of Manchester who are not paid from the grant. The grant-holding investigators and inventors (Professor McCann and Dr Pomfrett) will act as subjects for fEITER before others are recruited. Healthy volunteers will be recruited by poster advertisement placed in the two University research groups involved in this project (Engineering and Anaesthesia). Potential volunteers will be invited to collect the information sheet from secretarial and technical support staff not involved in this project.

Selection Criteria - Stage B:

The patient volunteers for this trial will be ASA I or II, i.e. fit and well, or with minor systemic disease processes which do not limit their everyday activities.

All patient volunteers will be under the continuous care of Professor Brian Pollard FRCA throughout the research procedure and anaesthesia, who will halt the procedure if there are any concerns for the welfare of the patient. They will in addition receive all normal routine care and monitoring.

For patient volunteers, there will be a requirement for the study protocol to be scheduled at the same time as the patient's surgery and to fit in with the order of the surgical list.

Patients scheduled for general anaesthesia during elective surgery will be identified by Professor Pollard from his normal operating theatre lists. Potential patient volunteers will be identified on the basis of the research protocol not delaying the normal schedule for the operating room, i.e. tolerating the inclusion of a fifteen-minute awake-measurement step.

For each patient volunteer, fEITER recordings will be made whilst awake, as a tolerance test before subsequent study during anaesthesia. Although the patient will be unconscious (anaesthetised) for part of the monitoring period, consent will have been taken before anaesthesia and before the 'awake' test, i.e. the patient will be able to give fully informed consent in advance.

Recruitment Process

Each potential volunteer will be approached at least 24 hours before the proposed tests by Dr Angella Bryan, a clinical scientist dedicated to this project, who is not a member of the normal care team for any of the patients or staff to be recruited. Dr Bryan is employed by Christie Hospital NHS Trust and is independently supervised. Dr Bryan will explain the fEITER project and the procedures that will be conducted. Potential volunteers will be given an information sheet and told what the project will entail.

Records of consent or refusal to consent will be kept confidential so that there is no chance for coercion of staff or patients to participate in the trial.

All volunteers will be requested to read an information sheet and sign a consent form at least 24 hours before the procedure. In the case of the patient volunteers this will very likely be given to them at the

routine preoperative visit 2−3 weeks before the scheduled operation date. An additional consent form will be presented to the volunteer subjects before the procedure, and, in the case of patients, before the administration of any preoperative medication.

Criteria for Exclusion

Patients who are unable to communicate rapidly with the researchers will be excluded from this study because of the need for rapid intervention in the event that fEITER becomes uncomfortable during the trial on awake subjects.

Rapid communication will be tested at the recruitment interview by asking the candidate to release a spring−loaded hand−held trigger in response to visual (flash), auditory (click) and shoulder-tap cues. Any delay in response of over 1 second, or no response, will exclude the candidate from the trial, as will lack of comprehension of the instructions.

Criteria for Withdrawal

All volunteers are free to withdraw from the trial at any time. They will be fully informed on their right to withdraw when completing the consent forms (see Section 18.3).

After the fEITER system is mounted and operating on an awake volunteer, he/she can stop the current injection at any time by pressing a hand-held button switch that is connected to the headbox. (See system details in Section 21.1 and in the Technical File). Similarly, the experimenter operating the system can stop the current injection at any time by pressing another hand-held button switch that is connected to the headbox. The system then remains in an idle state until the experimenter presses and holds the switch for 5 seconds. The experimenter and clinical team will assess the volunteer/patient, and will determine whether his/her consent is continued, before progressing.

19.6 Description of the generally recognised methods of diagnosis or treatment of the medical condition for which the investigational testing is being proposed

N/A

This investigation will not be used for diagnosis or treatment.

The image reconstruction of all the fEITER data will be carried out ‘off-line’, in the days after the data are recorded. It is anticipated that the system will produce data that will enable imaging of the change of electrical conductivity within the brain, due to visual/auditory stimuli being applied. Until this can be achieved routinely, it will not be possible to consider the use of fEITER for treatment or diagnosis.

19 - DATA COLLECTION/ ANALYSIS/STATISTICS

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20.1 Description of end points and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation

Stage A:

End-point for each subject:

Completion of fEITER data recording at a satisfactory level of data quality.

Data recorded:

1. fEITER measurements in response to several variants of visual stimuli and several variants of auditory stimuli;
2. Before, during and after each fEITER recording, heart-rate, blood pressure, VEP or AEP, and comments by the subject will be logged;
3. In each fEITER measurement session, a video record will be made of the subject and of the measurement equipment;
4. Manual notes will be logged in the event of an end-point being forced by either the subject or the experimenter, or in the event of any equipment malfunction;
5. Further comments by each subject will be gathered at intervals during the 72 hours after the end of each fEITER recording session.

Patient follow-up:

If any adverse event should occur during fEITER recording, the clinical members of the project team will ensure comprehensive care is provided.

Assessment and monitoring during the investigation:

The clinical trial will take place in clinical high-dependency environments at Manchester Royal Infirmary in the presence of resuscitation-trained anaesthetists with full backup, including defibrillation. The data identified above will be monitored during the fEITER recording sessions by the clinical team members, and the subject's general condition will be monitored.

Stage B:

End-point for each subject:

Completion of fEITER data recording before, during and after anaesthesia.

Data recorded:

1. fEITER measurements in response to optimal visual and/or auditory stimuli;
2. Before, during and after each fEITER recording, heart-rate, blood pressure, VEP or AEP, and comments by the subject will be logged (the last of these will not be available during anaesthesia);
3. During anaesthesia, BIS monitor recordings will be made and patients will be subject to normal clinical monitoring including the electrocardiogram, electroencephalogram, blood oxygen saturation, and non-invasive blood pressure, which will be logged to a standard automated electronic patient record system;
4. In each fEITER measurement session, a video record will be made of the subject and of the measurement equipment;
5. Manual notes will be logged in the event of an end-point being forced by the subject, the experimenter, or the anaesthetist, or in the event of any equipment malfunction;
6. Further comments by each subject will be gathered at intervals during the 72 hours after the end of surgery.

Patient follow-up:

If any adverse event should occur during fEITER recording, the clinical members of the project team will ensure comprehensive care is provided.

Assessment and monitoring during the investigation:

Throughout the research procedure and anaesthesia, all patient volunteers will be under the continuous care of Professor Brian Pollard FRCA, who will halt the procedure if there are any concerns for the welfare of the patient.

The clinical trial will take place in clinical high-dependency environments at Manchester Royal Infirmary in the presence of resuscitation-trained anaesthetists with full backup, including defibrillation.

20.2 Description of procedures to record and report serious adverse events and adverse device related events

A Risk Assessment is included as Appendix IV.

A Risk Management Plan is included in the Technical File.

Should an adverse event or device-related event happen it will be reported by letter to the South Manchester Local Ethics Committee, the University of Manchester Research Ethics Committee, the Central Manchester University Hospitals Foundation Trust research governance manager, and the MHRA within seven days of the event. Events will be fully documented in the master record file in accordance with Good Clinical Practice in Research.

No potential adverse effects, risks or hazards have been reported for the injection of high-frequency, low-amplitude electrical currents into the brain, other than inadvertent activation of the trigeminal nerve due to misplaced electrodes.

The magnitude of EIT currents used will not exceed those defined by the BS EN 60601-1:2006 limits prescribed for auxiliary currents. These magnitudes are much lower than those used repeatedly in electroconvulsive therapy, and are similar to commercially available, active electrode impedance testing systems (e.g. Aspect Medical Systems BIS monitor) used to check the integrity of EEG electrodes.

20.3 Description and justification of statistical design, method and analytical procedures (if relevant)

Stimuli:

Within a 1-minute block of fEITER data recording, stimuli will be delivered to the subject in bursts of several seconds (typically 12 seconds), with non-stimulus periods of approximately 15 seconds between bursts. Within a burst, the stimuli will be introduced in a time-randomised sequence at intervals of 1-15 seconds.

The stimuli will be flashes or auditory stimuli.

Randomisation of the stimulus presentation will primarily ensure that the central nervous system does not become adapted to a predictable, repetitive stimulus. Secondarily, randomisation will facilitate blinding of the study; the engineering team responsible for data reconstruction and later analysis of the images do not know the nature of the stimuli presented to the volunteer.

The visual stimuli will be bright flashes which will be introduced to the subjects to produce fEITER images of elicited responses from the visual cortex of the brain and associated areas. Flashes of 50ms duration will be produced from red LEDs [1]. The flashes will be presented through modified safety goggles placed over closed eyes. Similarly, auditory stimuli administered through standard headphones will also be investigated where responses from areas such as the cochlear nuclei and primary auditory cortices in the brain will be tracked. The auditory stimuli will be within normal ranges of hearing volume and frequency for the adult ear. The stimuli will include 75dB SPL (sound pressure level) clicks presented at rates of 5Hz to both ears simultaneously; these have been used extensively under clinical conditions as described by Thornton and Newton and are harmless [2]. In addition the so-called "oddball" paradigm where different tones are presented at random, will also be presented (more detail can be found in Section 21.1).

The fEITER measurement process and the electrodes used are similar to EEG monitoring, but unlike EEG, fEITER involves the passing of small currents between electrodes to actively determine the electrical nature of the tissues. The currents and voltages involved are small; subjects will normally be unaware of the electrical activity during the measurement. In fact, any sensation would be evidence of an unintended stimulus and would invalidate the functional aspect of the experiment. Similarly, in all tests the subject's field of view of all other contents in the experiment location will be blocked, and the subject's hearing of all sounds in the experiment location will be muffled, to prevent the administration of competing stimuli.

EIT:

Up to 32 disposable electrodes will be attached to the head of each subject using selected locations within the standard 10-20 EEG system.

A series of geometrically varying ac current patterns will be injected through the subject. The two current injection electrodes are diametrically opposed to each other, or as nearly so as possible, in

order to maximise current flow through the deepest regions of the brain and thus maximise measurement sensitivity. fEITER will use 20 different current patterns per frame of EIT data.

As described in Section 21.1 the amplitude of the injected current will always be kept within the prescribed safety limits. In the fEITER system, current frequencies of 10kHz – 100kHz are used, with preference for the lower end of the range, based on the measurements by Klivington, Galambos and co-workers discussed in section 18.4. Initial measurements will be taken at 10kHz. In all cases, fEITER voltage measurement data will be recorded at 100 frames per second (fps), in order to allow the time-course of the brain's response to be resolved.

For each current pattern, the recorded voltages are the amplitudes of ac voltage differences (synchronous with the injected ac current) between each electrode and a reference electrode. (In off-line analysis, the voltage data will be considered in terms of voltage difference between pairs of nearest-neighbour electrodes.) The complete set of raw measurement data for all current injections is termed a "frame" of data, approximately 400-600 measurements per frame in our case (dependent on the number of current patterns). On the basis of previous experience, this number will allow adequate spatial resolution in the subsequent off-line image reconstruction process; in the pilot study discussed in section 18.4, up to 96 measurements per frame were gathered and provided approximately 2.5% spatial resolution by area in the brain cross-section.

In common with previous biomedical applications of EIT, the measurement method used will be the so-called "dynamic" method, whereby:

(a) EIT data are recorded whilst the subject is in one defined condition,
(b) EIT data are recorded again whilst the subject is in another defined condition,
(c) the difference vector of the EIT voltage measurements is made between the two conditions, and
(d) the distribution of the change in conductivity between the two conditions is reconstructed.

In the fEITER case, the first condition is that when no stimulus is applied (variously called the "no-stimulus" or the "reference" condition), and the second condition is that when the stimulus is applied. In the clinical investigation described here, data processing and image reconstruction corresponding to steps (c) and (d) above will take place off-line, during the days after the fEITER measurement data (a) and (b) are recorded.

Steps (a) – (d) above translate into the following operational steps:

(e) Ready the subject for a particular type of stimulus and fEITER data recording;
(f) With no stimulus applied to the subject, record a number of frames of EIT data in continuous EIT operation mode. Provision is made in the fEITER operation process to gather periods of 1 minute of no-stimulus data. (In off-line processing, either a single selected one of these frames, or an average of several of them, will provide a "reference frame" of voltage data. The number of frames to be averaged is a research question to be addressed in the study; however, the pilot study suggests that about 20-50 frames may suffice.)
(g) During a 1-minute period of EIT data recording in continuous mode, apply a stimulus or a sequence of stimuli to the subject. The time of each stimulus generation is marked in the fEITER data record. After each application of a stimulus, continue recording EIT data for up

to 15 s. (The interval between application of stimuli will be up to 15s, in order to allow the decay of the haemodynamic response, in some presentations, to the preceding stimulus before the next one is applied.)

(h) Repeat (f) and (g) above for a period in the order of several minutes until a sufficient body of data are gathered.

(i) If all stimulus types have been tested, stop the experiment; otherwise return to (e) and change the stimulus type.

(j) Off-line (i.e. after disconnecting the equipment from the subject), create the appropriate voltage differences and reference frames and subtract as appropriate from each post-stimulus frame, to input data into reconstruction of the distribution of conductivity change relative to the pre-stimulus condition, at 100 fps. These images will be able to be displayed both in a project-specific software environment and via the standard SPM software package used for clinical imaging.

Specific issues re Stage A:

In Stage A, a large database of "reference" frames will be built for the purpose of off-line statistical analysis of raw voltage measurements. The effects of possible drift in the reference frames will be analysed by taking at least three 1-minute blocks reference data (6,000 frames per block) on each subject during each experimental period, one at the beginning of the measurement period, one after 10 minutes, and one at the end of the measurement period. In addition, the data frames recorded long after stimulus (e.g. 10 – 15s) but before the next stimulus, will be analysed as if they were reference frames in order to monitor reference drift effects on a finer timescale.

Suitable non-parametric tests (including the Mann-Whitney test) will be performed off-line to compare, for each electrode pair, the difference in behaviour between reference measurements and post-stimulus measurements. This comparison may be carried out for every time-point in the post-stimulus sequence. Therefore, for each stimulus condition and each frame time after stimulus, the fEITER database from Stage A needs to be built to allow sufficient statistical discrimination. On the basis of our experience with the pilot study, about 200 fEITER recordings of stimuli responses will be adequate. This implies that, in Stage A, each subject will be measured under each stimulus condition for up to 40 minutes.

Ideally, fEITER will permit identification of whether visual or auditory stimuli have been presented.

The questions in off-line data analysis will be *"Does the sequence of post-stimulus EIT voltages and images differ from the no-stimulus period, and can the method of stimulus be identified purely from the reconstructed EIT image?"*

This stage is a milestone for further development.

The optimal visual and auditory sequences will be chosen for Stage B.

Specific issues re Stage B:

Thirty-five patients undergoing elective surgical procedures will be recruited to perform fEITER imaging before, during and after general anaesthesia with standard agents (e.g. propofol and sevoflurane).

The BIS monitor uses a sensor incorporating 4 electrodes which are similar to standard EEG electrodes but specifically designed to be used with this monitor. The sensor is placed on the subject's forehead to measure brain activity and the monitor incorporates software that translates this into a number between 100 (wide awake) and zero (absence of brain electrical activity).

A reduced range of fEITER operating parameters is envisaged, having been informed by the Stage A analysis.

The fEITER electrodes will be mounted on the patient's scalp in the anaesthetic room prior to induction of anaesthesia. A BIS sensor will also be attached to the patient's forehead in preparation for monitoring during the surgical procedure. After the electrode touch-proof leads are connected to the fEITER headbox, the base unit will begin a period of initial data acquisition to record EIT data without any stimulus applied, for at least 1 minute, to establish a baseline and a "reference frame" of EIT voltage data. The optimal stimuli will be applied, as found in Stage A. These data will provide, for each patient, a record of his/her fEITER responses before the induction of anaesthesia.

Following induction of anaesthesia and transfer to the operating room, a further series of fEITER data will be collected along with corresponding BIS data during maintenance of anaesthesia. Reference frames and many repeated post-stimulus recordings will be acquired in 1-minute blocks; after each 1-minute block, experimenter intervention is required to initiate the next block. The surgical procedures targeted will last less than 20 minutes and this will limit the number of data blocks recorded.

Further fEITER data will be recorded on recovery at the end of surgery.

Data Assessment:

In addition to the analysis discussed above, fEITER images will be made available and statistically analysed using SPM, a standard software package for display of conventional medical images.

At the end of the proposed study all researchers, both experimental and clinical will meet to interpret and analyse the final images produced and discuss the practical implications before designing further studies for the next stage of system development. At the end of the clinical testing as described here we expect to have a strong statistical basis of evidence for the efficacy of fEITER, including an image database from patients.

References

[1] Chi Oz & Field, *Effects of enflurane on visual evoked potentials in human,*. British Journal of Anaesthesia 1990; 64:163−6

[2] Thornton C, Newton DEF. *The Auditory Evoked Response: A Measure of Depth of Anaesthesia.* Balliere's Clinical Anesthesiology 1989; 3(3):559−585

21 - DEVICE DETAILS

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21.1 *Brief description of device and other devices designed to be used in combination with it. It is helpful if the information includes a drawing/photograph of the device.

Introduction

The ultimate aim of this clinical trial is to evaluate a portable instrument which integrates Electrical Impedance Tomography (EIT) with standard Evoked Response (ER) techniques in order to investigate functional brain behaviour. The instrument is called fEITER (functional Electrical Impedance Tomography of Evoked Responses) and, essentially, involves the measurement of scalp voltages on adult volunteers and patients undergoing surgical procedures during the application of visual or auditory stimulus. The measurement process and electrodes are very similar to EEG (electroencephalography) recording but EIT is able to provide more information due to the passing of small electrical currents between electrodes to actively probe tissue properties. The voltages and currents involved are small and the subjects will normally be unaware of the electrical activity during the measurement.

The intention of this section is to give a brief description of the design of the complete fEITER system. Initially, in this section, fEITER is presented at the conceptual level. Further description is given at a schematic level alongside photographs and high-level drawings where appropriate. Information at a more detailed level, e.g. engineering drawings and electronic circuits, are given in the appendices and the Technical File.

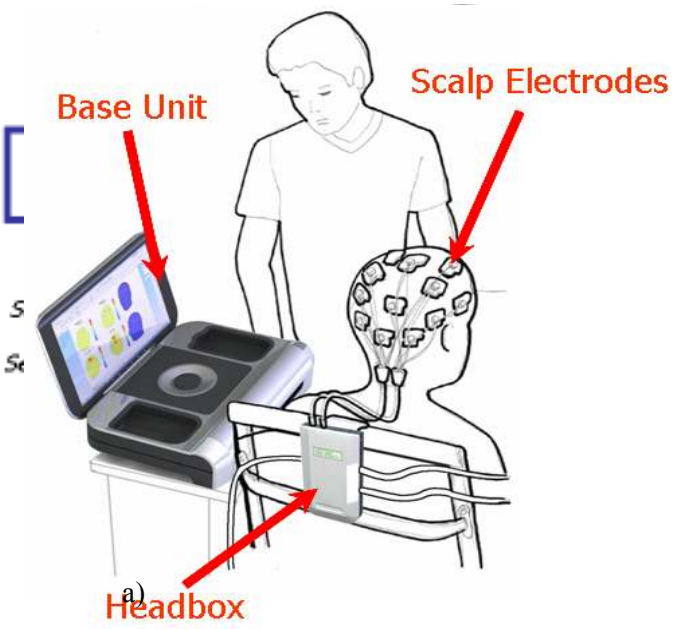
Concept of the fEITER Device

The key concept of fEITER is to integrate a fast 32-electrode Electrical Impedance Tomography sub-system together with an evoked response system. This will provide a facility to investigate functional brain activity as a consequence of stimulating the brain using visual and auditory stimuli. The stimuli are produced in a standard manner as is routinely performed in neuroscience research and clinical neurological practice.

The concept of the fEITER system is shown in figure 21.1.1(a-b). The stimulus generator is a Cambridge Electronic Design (CED) Micro 1401 [1] and is used to provide randomised stimulus trains to evoke a neurological response using a flash of light and/or audible clicks. The sequencing of CED 1401 for providing sensory stimuli will be drawn from extensive psychophysical literature and controlled using CED Signal v3.09 software, which is used routinely in evoked response studies. The LED goggles are based on modified lightweight wraparound safety spectacles (conforming to EN166) and the headphones are of the TDH type commonly used in the area of audiology.

EIT data acquisition is provided by an EIT sub-system from The University of Manchester designed and constructed in accordance with relevant safety standards. The EIT sub-system is a Class II medical device and has been designed to withstand the processes of electrosurgery and defibrillation, in order to allow the use of the device in the operating room. The device also provides galvanic separation interfaces thereby allowing connection to both the CED 1401 and a data collection laptop without the need for external separation devices. The EIT sub-system comprises of two parts; a headbox unit and a base unit which are shown at the conceptual level in figure 21.1.1(b).The headbox unit is a fully floating device measuring approximately 186 mm in width, a total of 313 mm in length and a depth approaching 40 mm. The headbox provides the small tomographic sinusoidal currents and digitizes the measured scalp voltages which are transferred to the base unit of the EIT sub-system. The headbox unit is designed to meet the standard associated with a Type II BF part in accordance with BS EN 60601-1:2006.

The base unit of the EIT sub-system provides interfacing to the headbox unit, data acquisition laptop and the CED1401. Interfacing to the laptop and CED1401 are both galvanically separated from the connection of the base unit to the headbox unit. The galvanic isolation complies with BS EN 60601-1:2006. The electronics of the EIT sub-system base unit is enclosed within a 2U 19" rack mount case with a depth of 363 mm. Both the EIT sub-system base unit and CED1401 are housed in a single commercial 19" case measuring 3U in height and 500 mm in depth (Schroff, Comptec desk top case). Internal communication wiring between the CED 1401 and the EIT sub-system base unit is routed within the rear of the instrument case. The instrument case also houses a medical grade power supply for the EIT sub-system base unit, the CED1401 power supply and the NI DAQ card with power supply.



a)

b)

Figure 21.1.1 The concept of the fEITER instrument showing; (a) schematic of fEITER and (b) illustrative drawing of the device in use.

Description of the fEITER Device

Figure 21.1.2 shows a schematic of the complete fEITER system comprising of the 5 major hardware blocks of the system; the selected stimulus device, scalp electrodes, headbox unit, base unit (incorporating CED 1401 unit), data capture laptop. This section describes each of the major hardware blocks as shown in figure 21.1.2.

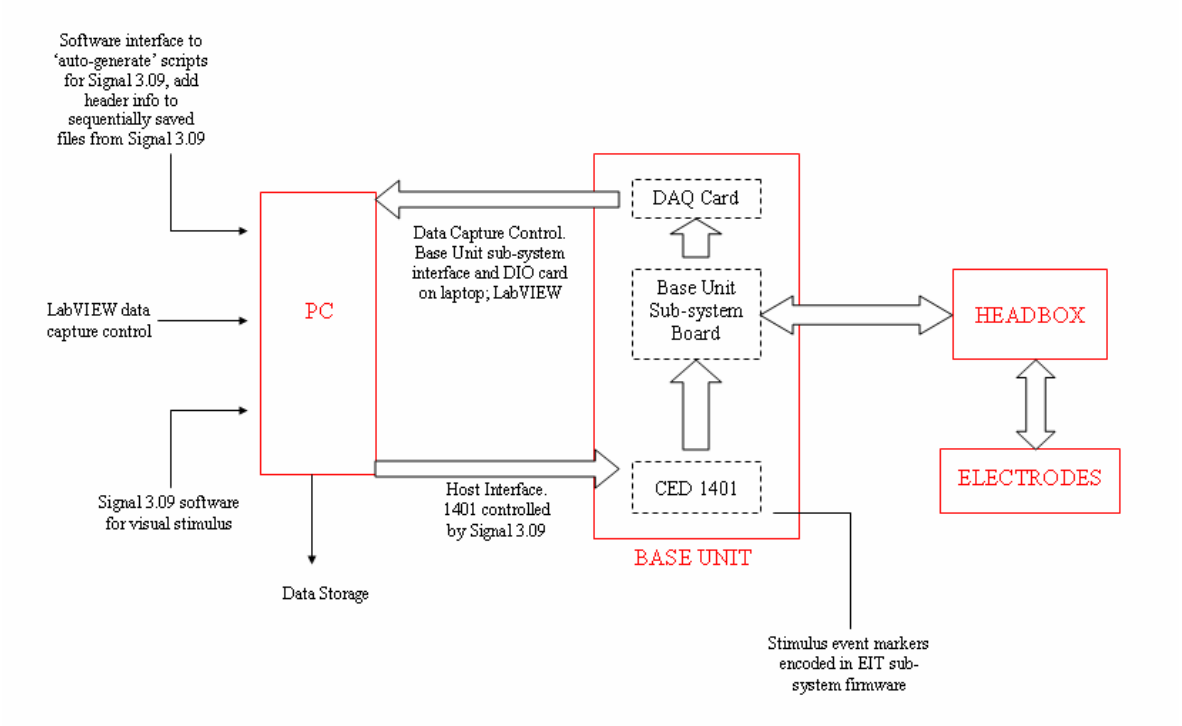


Figure 21.1.2 Schematic of the fEITER system showing the hardware components and controlling software.

Stimulus Devices

LED-based goggles provide a visual sensory stimulus, controlled via the CED Micro 1401. The goggles are based on a pair of modified lightweight wraparound safety spectacles and use four 5 mm super-bright red LEDs (RS 228-5578) mounted in standard PCB LED holders. The goggles feature adjustable side-arms in order to accommodate the differences in head size and thereby provide a comfortable fit for the subject. The lenses of safety spectacles have been spray painted with plastic primer followed by matt black paint to reduce ambient light levels presented to the subject. Each eye is presented with two LEDs which are spaced approximately 12 mm apart in order to provide the facility of separately stimulating both the left and right hemi-field areas of vision. The LEDs are connected to the BNC digital outputs of the front panel of the CED micro 1401 via a total cable length of approximately 2.5m. The cable is divided into two parts. Firstly, a bright yellow UTP cable of length 2.3m, which enables connection of all four LEDs at the front of the safety spectacles and provides a single flexible cable giving a clear visual indication of cable placement within the clinical

environment. Secondly, the UTP cable divides into two short lengths (approx. 10cm and 20cm) of BNC (commercially terminated) cables which enable control of the two hemi-field stimulating areas. The ends of the BNC are clearly marked LH-0 and RH-1 for left hemi-field and right hemi-field control and plug into the "0" and "1" digital outputs of the micro 1401. Standard techniques of strain relief and cable marking have been used throughout the assemblage.

Figure 21.1.3 Photograph of the visual stimulus goggles for fEITER clinical trials.

For auditory stimulus headphones are used to produce a click. The headphones used are Telephonics TDH-49P, which are used in most standard practices within audiometry research. The headphones are connected to the BNC DAC outputs of the front panel of the CED micro 1401 via a total cable length of approximately 2.5 metres. Each ear can be stimulated independently.

CED 1401

The fEITER system uses a standard Cambridge Electronic Design (CED) Micro 1401 [1] for stimulus generation. Visual stimulus is sequenced in a pseudo-random manner using Signal v3.09 software (CED) which controls the CED1401 via the USB interface. The visual stimuli signals are routed via the two front panel digital outputs (TTL) of the CED 1401 to the LED goggles. In a similar manner, for auditory investigations, binaural and oddball auditory stimuli are provided using the two front panel DAC outputs of the CED1401. The CED1401 is housed within the fEITER base unit 19" instrument case. To enable fEITER imaging of the brain's processing of individual stimulus events, the spacing between stimulus events is at least 1 second and can be as high as 10 seconds. This also ensures that there is no risk of adverse patient reaction to stimuli, e.g. photo-sensitive epilepsy.

Electrodes

For clinical trials, fEITER will use disposable commercial ZipPrep electrodes. These electrodes are widely used in medicine, including EEG monitoring. The electrodes are CE marked and manufactured by Aspect Medical Systems Inc. For our trials, up to 32 Zipprep electrodes (plus an addition electrode for local potential reference) will be in contact with the scalp of the subject. For further details, the reader is referred to section 21.6.

Headbox Unit

The EIT current injection and voltage measurement sub-system are built around the use of a FPGA (Field Programmable Gate Array, XILINX VIRTEX-4 SX35). The firmware is described in the section Final System Documents of the Technical File. The FPGA digitally synthesises a sinusoidal waveform which is used both for current generation and as a reference for lock-in voltage measurement. The injected current is set at frequency 10 kHz within firmware and its amplitude is monitored via an active current safety monitoring module which sets the current to 1mA pk-pk, this is approximately one third of the permitted level set by BS EN 60601-1:2006 for auxiliary currents at this frequency. The current is injected between pairs of (typically) diametrically opposite electrodes. Voltages are measured on each non-current injecting electrode. Then the current injection is switched to a new pair of electrodes. This sequence continues until the predefined current injection is competed. The voltage measurement circuit recovers both the in-phase electrode voltage (due to resistive impedance) and the 90 degrees out-of-phase electrode voltage (due to reactive impedance relative to the reference electrode). Differential voltage measurements are acquired using parallel ADCs capable of providing 100 tomographic frames per second.

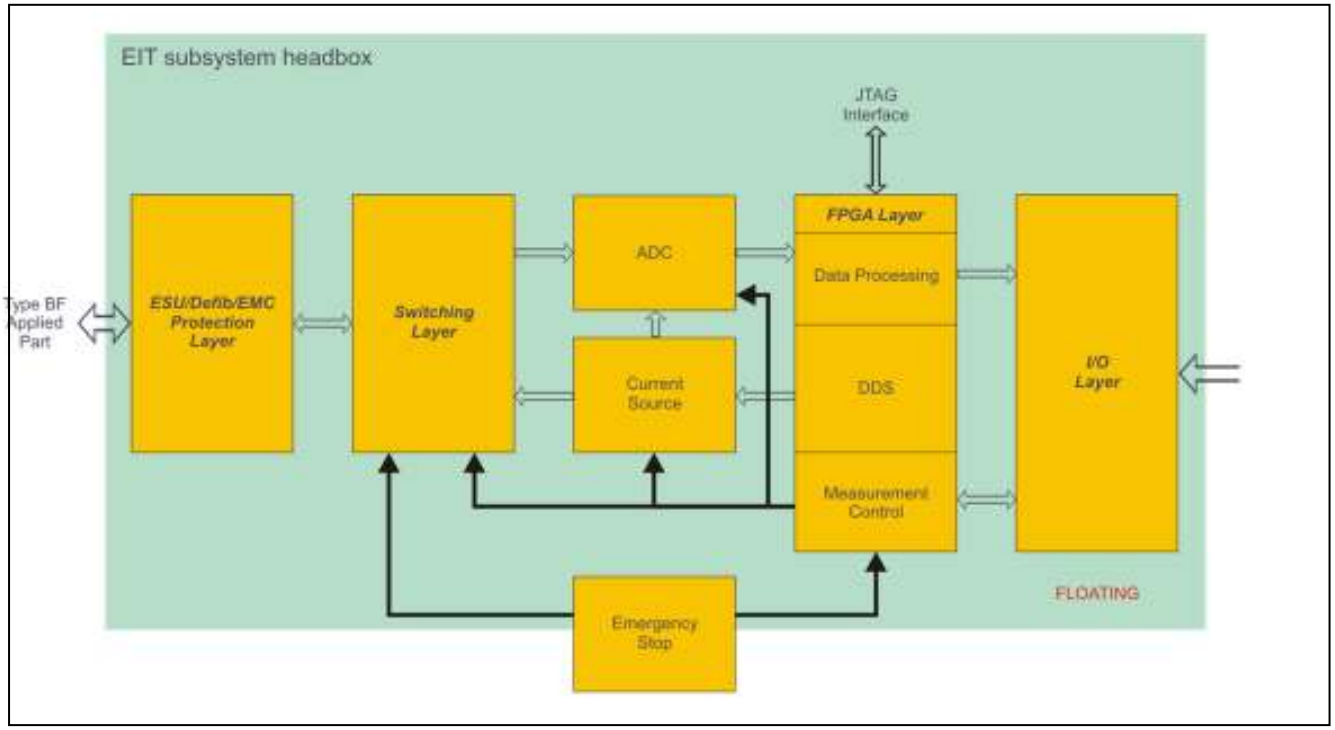


Figure 21.1.5 Hardware schematic of the headbox unit.

Figure 21.1.5 shows a schematic block hardware diagram of the headbox unit. For clarity, the diagram shows only one ADC, however, in reality *each* measurement channel (maximum 32) uses one ADC. The front end electronics uses a combination of miniature gas discharge tubes, clamping diodes and other components to provide a protection layer against the high currents and voltages that may be present during electrosurgery (ESU). This layer also provides EMC protection. The protection is designed not only to protect the front end measurement electronics but also to ensure protection of the patient against possible fault conditions potentially giving rise to alternate burn sites during ESU. The headbox unit monitors the current being driven to the electrodes using firmware within the FPGA. This provides an auto shut-off of the applied current should the current exceed 99% of 1m pk-pk. The speed of the shut-off has been tested and results show that the current is shut-off within 4μs. Additionally, an emergency stop which is independent of firmware, disables the applied current, and this can be enabled by either the intervention of the clinical team or (in the case of awake subjects) by the volunteer/patient. For the case of intervention by the clinical team, there are two emergency stops via red push button switches that are clearly visible on the front of the headbox unit and base unit. The headbox emergency switch is firmware controlled and stops the current injection through the 32 electrodes, resulting in the headbox going into in a 'fault' state, which continues until the switch is pressed and held for 5 seconds, thus restarting the headbox allowing measurements to be taken. The base unit emergency switch stops all power from mains, cutting power to the EIT system, including the headbox, base unit and 1401 stimulus generator. For the case of intervention by the subject, the emergency stop feature is controlled directly by using a hand-held push-button switch. This is firmware controlled and stops the current injection to the headbox and switches the headbox into a 'fault' state.

Photographs of the populated PCB of the headbox are shown in figure 21.1.6. The PCB is a 8-layer type and figure 21.1.6(a) shows the side populated with the FPGA (marked "Virtex 4"). This side of the board clearly shows the parallel measurement front ends (32 tomographic channels plus 2 reference channels) which are structured on the periphery of the board; the 33 gas discharge tubes occupy the outermost edge of the PCB. The opposite side of the PCB is shown in figure 21.1.6(b).

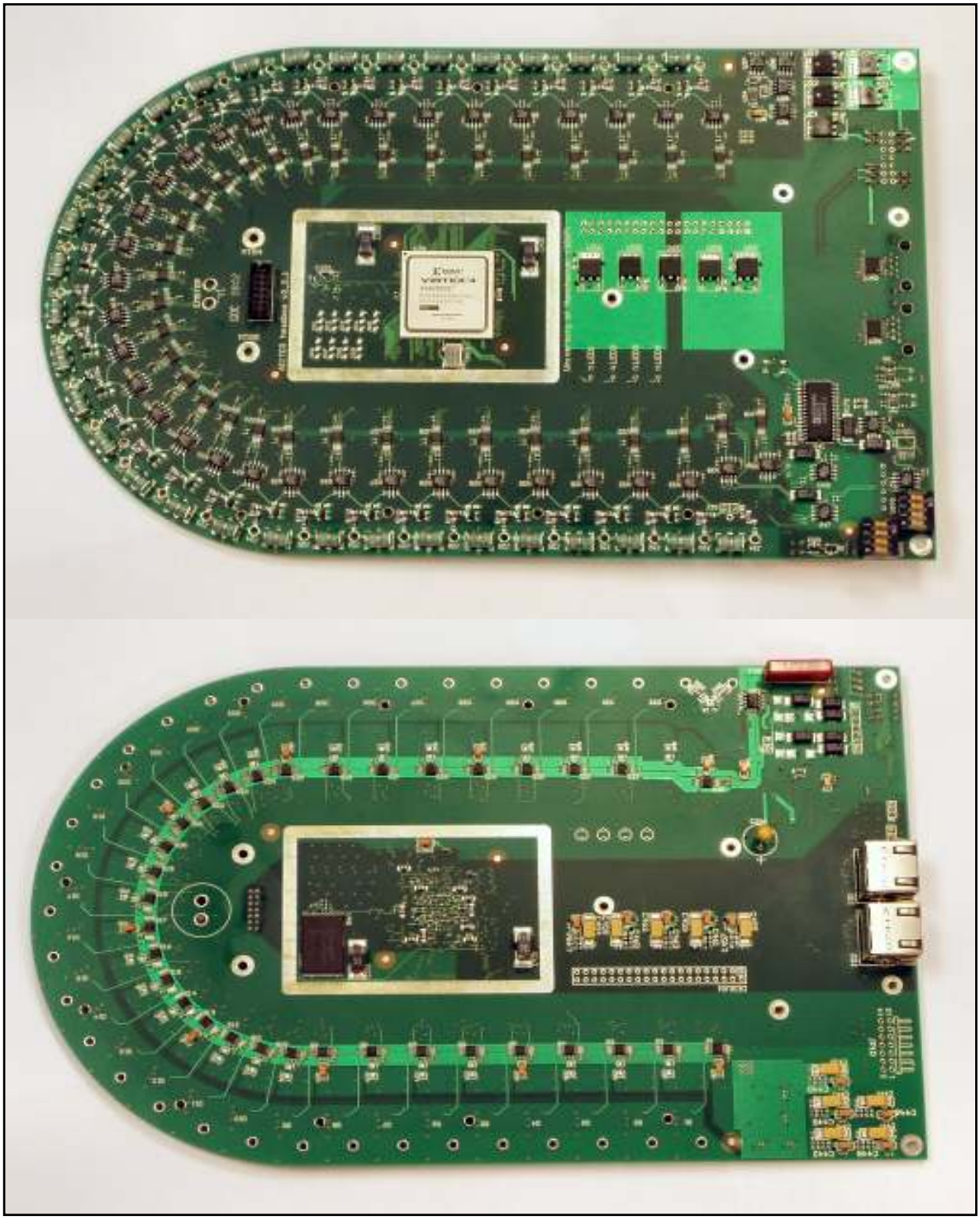
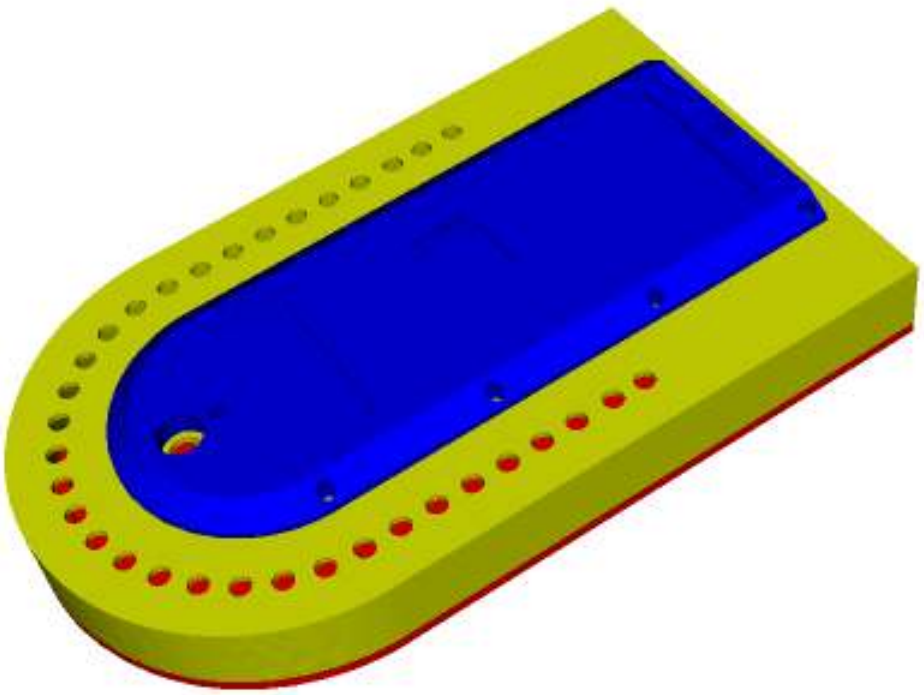


Figure 21.1.6 Populated multi-layer PCB of the EIT subsystem headbox showing; (a) side with Virtex 4 FPGA and, showing discharge tubes, differential amplifiers and ADCs and (b) reverse side of board.

a)



b)

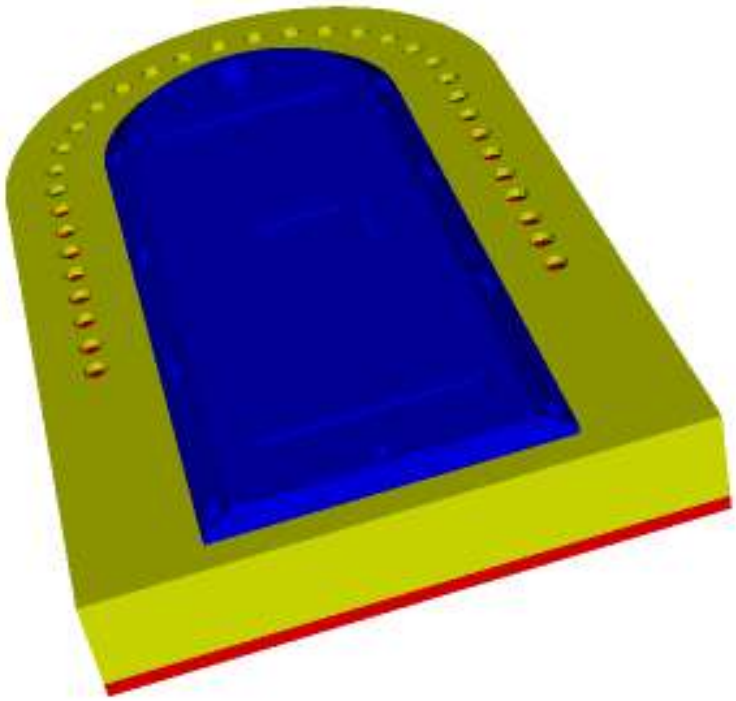


Figure 21.1.7 General views of 3-component housing showing: main body in yellow/green, top lid in blue and larger bottom plate in red.

The enclosure for the headbox electronics is a bespoke unit manufactured in-house from Acetal copolymer. A basic CAD drawing of the enclosure is shown in figure 21.1.7. The enclosure is a three-part unit, comprising of a main body, bottom plate and top lid. The main body provides the structural fixing of the headbox PCB. The two access lids are sealed to the main body via nitrile rubber gaskets to protect against liquid ingress. Two strain relief cable glands (M12 size) provide cable exits for power and data transfer lines. Two medical type panel receptacle sockets are used for connection to hand-held triggers via 1.8 metres of cable. The first trigger switch is used to control the mode of operation of the device, and the second trigger is for the subject-activated emergency stop. (Scale engineering drawings and measurements of the enclosure can be found in Appendix III.)
The top surface of the enclosure contains the 34 panel receptacles (32 tomographic channels plus 2 reference channels) for providing connection to the scalp electrodes via touch-proof leads. The panel receptacles are 1.5 mm medical grade touch-proof sockets and are colour coded in a repetitive sequence of red, black, white and yellow for all 32 tomographic channels and green for the reference channels. The connection leads to the electrodes (Integral Process, ECG patient cable, CEI 601-1) are also colour coded and cable marked in the same sequence as used by the headbox unit. The enclosure (including connection receptacles) has been designed and constructed for cleaning using sterile alcohol wipes (e.g. Sterets, Alcowipes). Figure 21.1.8 shows the completed headbox unit.

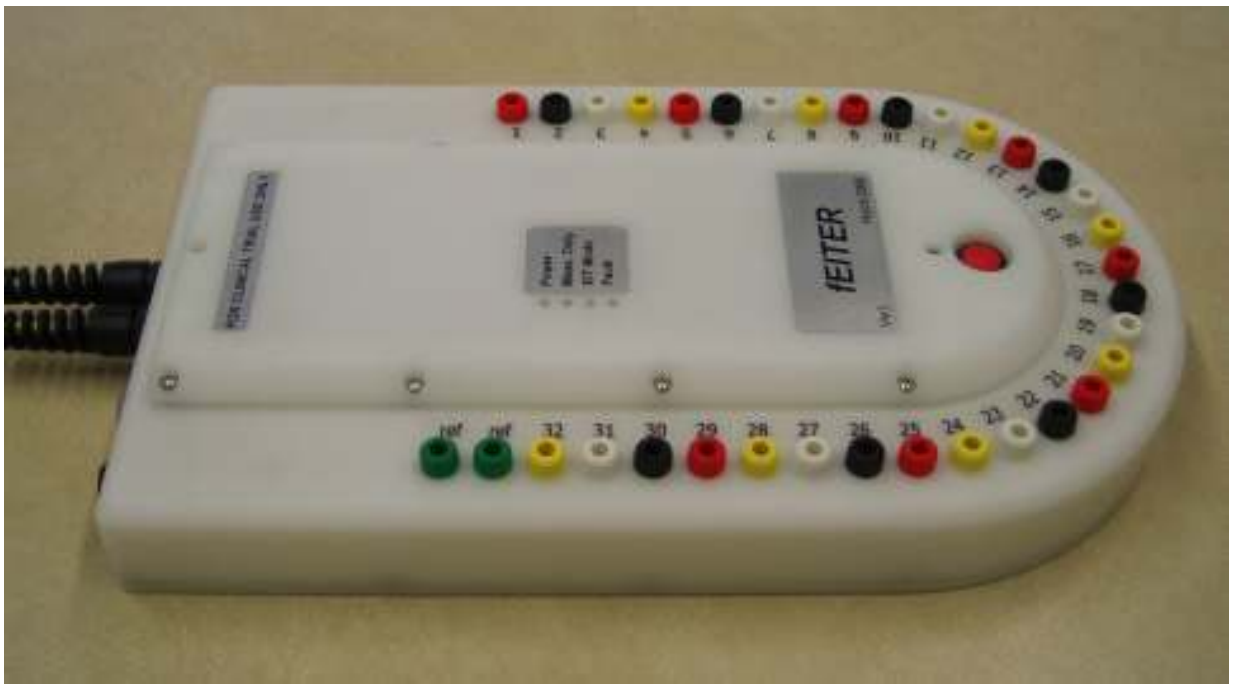


Figure 21.1.8 General view of the completed headbox unit.

Base Unit

A schematic of the base unit is shown in figure 21.1.9, and figure 21.1.10 shows the final PCB of the base unit. The base unit enables the interfacing of the CED 1401 and controlling laptop via a galvanic separation in accordance with BS EN 60601-1:2006. The base unit receives the data and transfers it

through USB DAQ card onto a laptop, for offline image reconstruction. The full firmware is described in the Technical File.

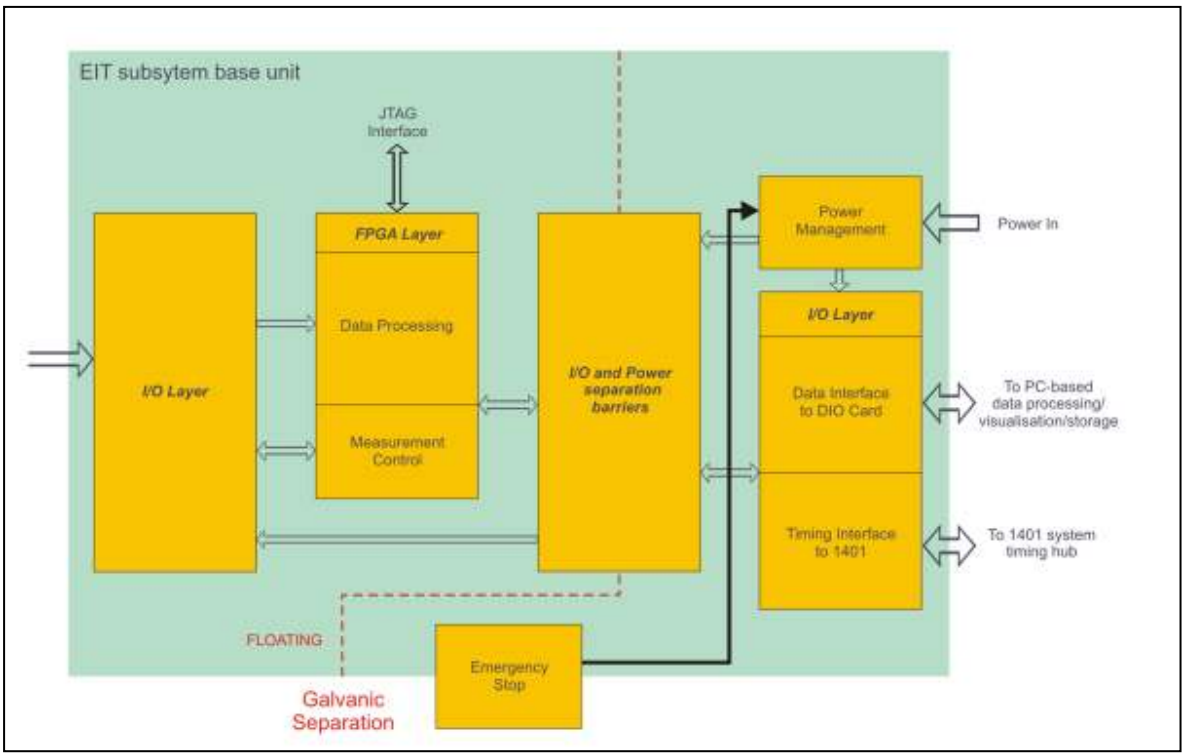


Figure 21.1.9 Hardware schematic of the EIT sub-system base unit.

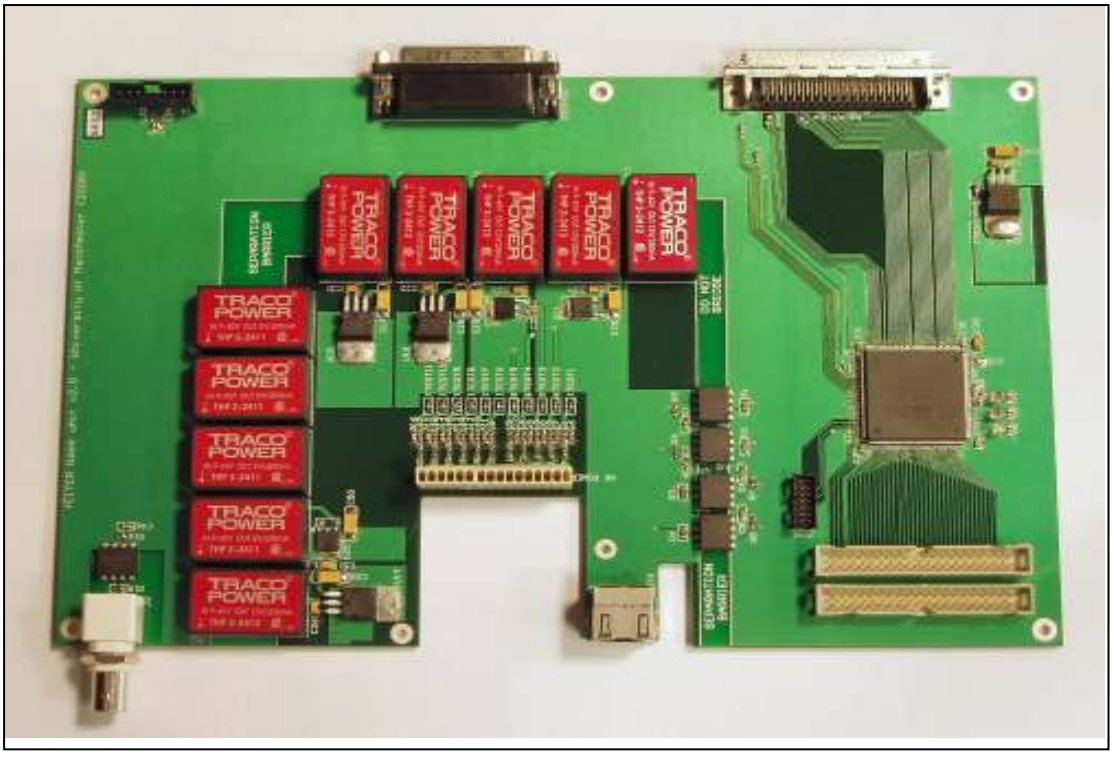


Figure 21.1.10 Populated multi-layer PCB of the EIT subsystem base unit showing the galvanic isolation

Figure 21.1.11 Photograph of the external view of the inner base unit casing, showing the 32 LED monitor channels, the data input and headbox power sources.

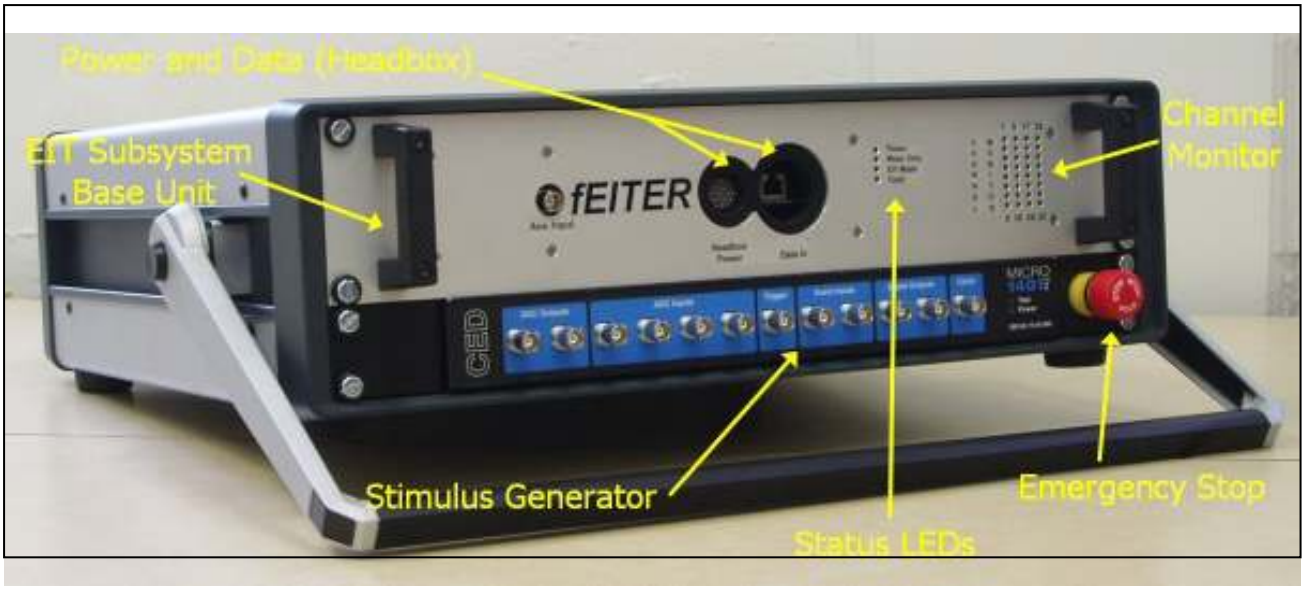


Figure 21.1.12 Photograph of the base unit, labels showing the features.

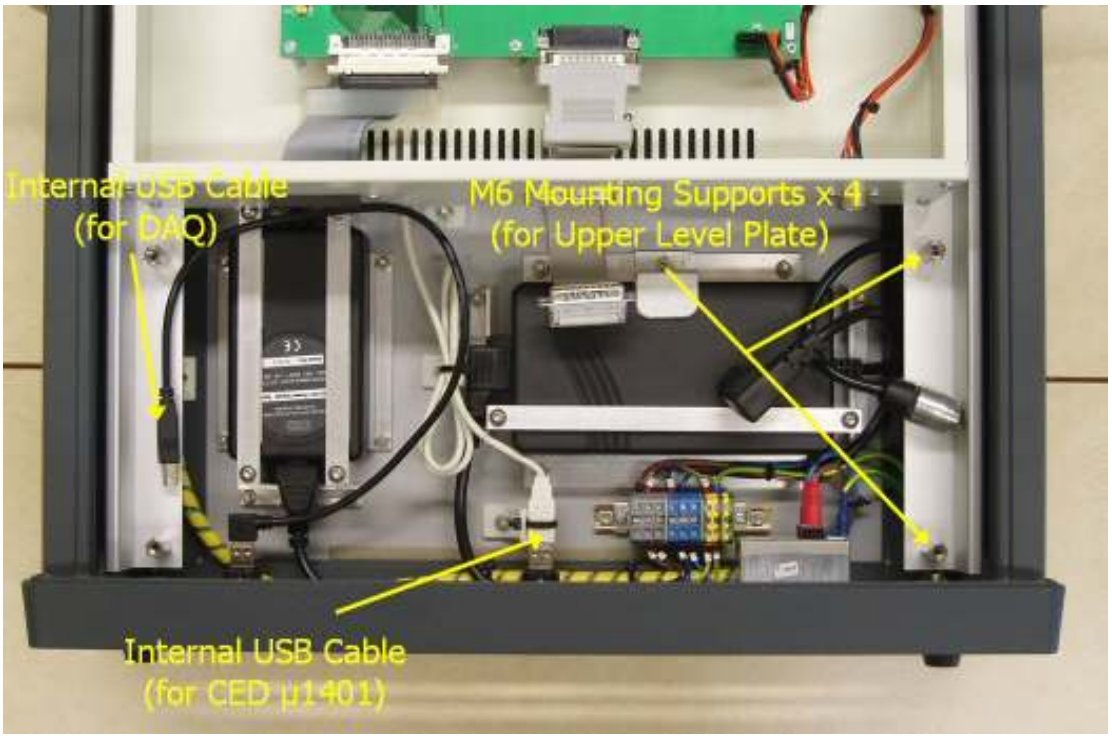


Figure 21.1.13 Photograph of the internal view of the casing - lower level, labels showing the features.

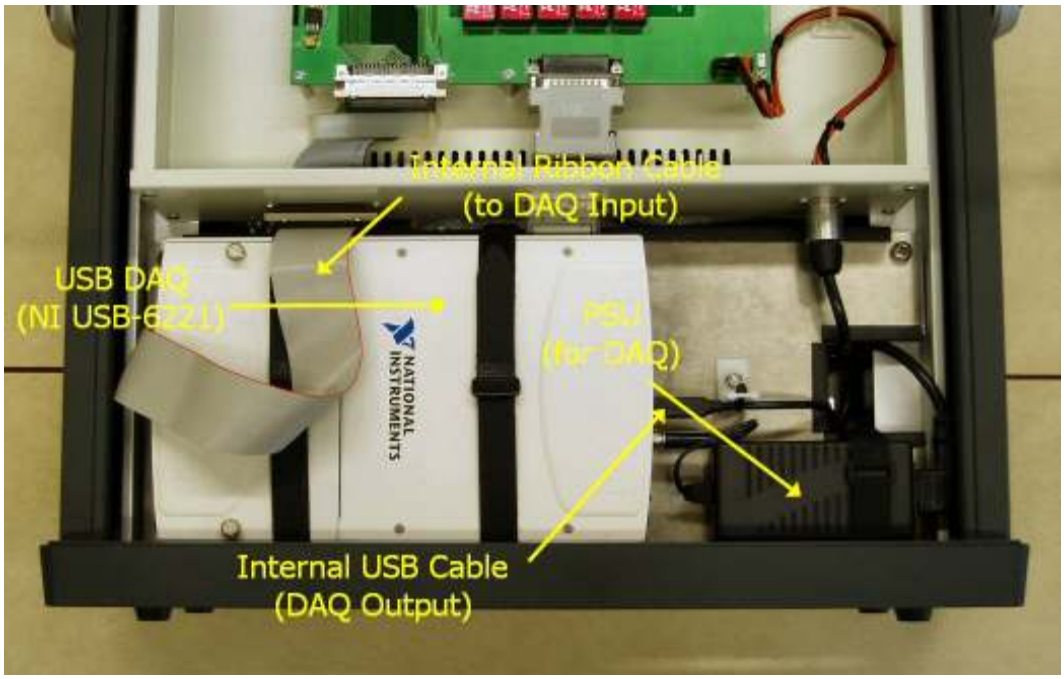


Figure 21.1.14 Photograph of the internal view of the casing – upper level showing the USB DAQ, labels showing the features

PC and Data Acquisition

A Toshiba Tecra M9-136 laptop is used for control of the stimulus generator and EIT data capture. The laptop hosts the CED Signal software for control of the micro 1401. Data capture is via a National Instruments DAQCard-6221 M-series (USB version, product No. 779808-06) [2] and controlled using LabVIEW software. Tomographic data is captured in 1-minute data blocks stored on the laptop (or external firewire/USB HDD powered directly from the laptop) using a user-inputted filename and sequential file numbering system. Data records are transferred to optical storage media at the end of each volunteer/clinical session, and outside the clinical environment. The laptop will be battery powered during the clinical trials.

21.2 Identification of any features of design that are different from similar previously marketed product (if relevant).

Not Applicable.

This is a ***one-off device***, for research purposes. The fEITER system described in this application has been designed from first principles in order to achieve an integrated EIT and ER system with the encryption of the stimulus event marker in the EIT data measurements. Nevertheless, every constituent part of the fEITER system described here has been applied, in different embodiments, to human EIT and ER measurements, including EIT measurements on the human head, as described in section 18.4. Therefore, all of the principles of the operation have been previously tested.

21.3 Details of any new or previously untested features of design including, where applicable, functions and principles of operation.

The integration of EIT and ER and the specific electronic and mechanical form of the instrument are new.

The integration of EIT and ER, in the protocol described in section 20.3, introduces no additional hazards.

The mechanical form of fEITER, as a Base Unit and Headbox, is novel. It exceeds the standards of all the previous EIT systems in terms of general robustness to handling, transport, and potential liquid impacts. The design standards used meet those required for use in the OR and ICU.

The Base Unit ensures a high degree of patient electrical isolation, as discussed in detail in section 21.1. It also ensures robust temporal marking between the EIT and ER sub-systems, and provides a coherent data structure to the Data Acquisition Computer.

21.4 Summary of any experience with any similar devices manufactured by the company including length of time on the market and a review of performance related complaints.

No system equivalent to fEITER has previously been manufactured for sale. In the present project, fEITER is being developed as a ***one-off prototype*** instrument for the purpose of the clinical investigation proposed here.

Members of the team undertaking the presently proposed clinical investigation have very long previous experience that covers all of the constituent technologies of fEITER and the proposed investigation programme, namely EIT, ER and anaesthesia, and of clinical trials involving human subjects in those areas.

Two members of the team (HMcC, CJDP) were the leaders of the pilot study conducted in 2000-2001 that preceded the fEITER project.

In terms of measurement performance, the system used in the pilot study exceeded all expectations in terms of sensitivity to the relevant neural phenomena [3, 4]. This is now understood in the light of definitive data [5] published since the time of the pilot study, that shows the conductivity of human skull in vivo to be many times larger than was thought in the 1990s (e.g. see [6]). In addition, the current injection frequency used in the pilot study, 9.6 kHz, was highly optimal for sensitivity to the relevant phenomena, as shown by the work of Klivington, Galambos and Velluti [7 – 10], when viewed in the light of the (leakage) current limits set by BS EN 60601-1:2006. Hence, the new system described in section 21.1 exploits the same frequency.

In terms of measurement integrity, one of the failings of the system used in the pilot study was the lack of any operator warning of electrode disconnect from the scalp, or diagnostic data content relating to it. The system is engineered to provide operator warning via the base unit front panel indicator lights, and by the inclusion of a firmware measurement protocol to provide diagnostic content in the recorded data, presently this is not implemented within the LED panel but future models could have this activated.

Another failing of the system used in the pilot study was the sporadic occurrence of corrupted voltage measurements (which had a clear signature) [11]. This effect was never fully understood, but its occurrence was seen to be reduced to a near-negligible level by running the EIT system in continuous mode, rather than triggering its operation after each stimulus; continuous mode is used in the new system described in section 21.1. Furthermore, efforts to understand that effect in the pilot study data were hampered by the fact that the system used there could only operate in a mode whereby internal

analogue processing was used to deliver the voltage differences between nearest-neighbour electrodes, and only the voltage differences were recorded. The new system records voltage measurements for all electrodes relative to a common reference location, and voltage-difference data are then calculated off-line. This allows a much deeper analysis of any irregularities that may occur in recorded data.

During the EIT tests, all volunteers reported that they observed no effects, with the following two exceptions:

- One volunteer experienced severe trigeminal neuralgia as a result of the combination of (a) placing electrodes too close to the trigeminal nerve on the forehead, and (b) the use of a non-standard protocol for switching between current injection patterns. *In the new clinical investigation proposed here, the potential risk of such a re-occurrence is reduced by the use of a fixed electrode placement grid (selected locations within the standard 10-20 EEG arrangement), and by the use of a firmware fixed sequence of current patterns that cannot be altered by the system operator. Furthermore, the sequence of current patterns is arranged to prevent the electrical stimulation of the trigeminal nerve. This issue is discussed further in the Risk Assessment.*

- Another volunteer experienced discomfort when the mains power supply to the equipment was abruptly interrupted. The discomfort arose due to the discharge of the stored energy of the EIT system through the reference electrode, and the fact that the EIT system power supply stored a relatively large amount of energy. *In the new system described in section 21.1, this type of incident is protected against by two measures: the use of a medical-grade power supply for the EIT sub-system, and the use of hardware circuitry in the EIT headbox to limit the current flow between any two voltage-measuring electrodes to 400 □A rms. This issue is discussed further in the Risk Assessment.*

21.5 Identification of hazards and estimated risks associated with the manufacture and use of the device (ISO14971) together with a description of the actions that have been taken to minimise or eliminate the identified risks.

See the Risk Assessment Plan in Appendix IV and the Risk Management Plan in Appendix V.

21.6 Description of materials coming into contact with the body; why such materials have been chosen; standards with which they comply (if relevant).

The only point of contact to the patient is through the CE-marked ZipPrep EEG electrodes, supplied by Aspect Medical Systems, Inc. ZipPrep means zero preparation, in that they are directly applied to the skin without prior preparation of the skin, describing its main advantage over other electrodes. ZipPrep electrodes have small 'tines' on the underneath of the electrode plate, shown in Figure 21.6.1, providing a less resistive passage for the current without the need for abrasion.

The ZipPrep electrode was given FDA clearance in June, 1994. The clearance allowed them to be used as a single patient use, disposable pre-gelled electrode that is applied directly to the patient's head to record electro-physiological signals.

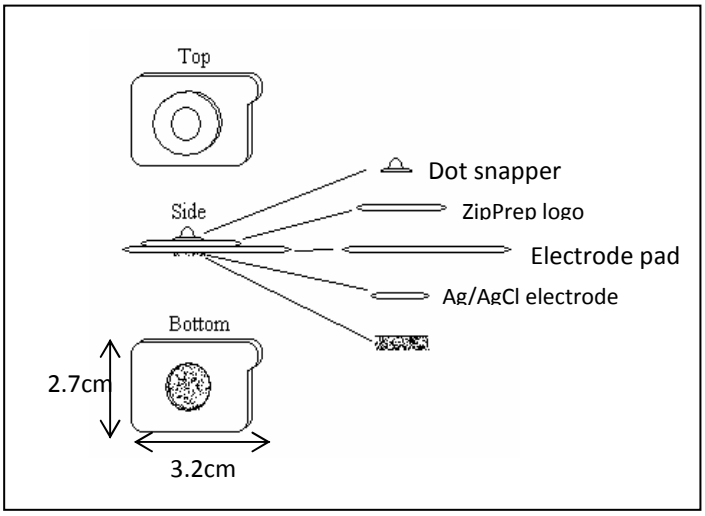


Figure 21.6.1 Diagram shows the structure of a ZipPrep electrode

This type of electrode structure has been found to be a good electrode sensor reducing capacitive effects between the electrode plate and the electrolyte gel [12]. Aspect Medical Systems have further developed the structure of the electrodes to reduce the electrode impedance by creating small tines [13]. These tines penetrate the dead skin cells at the surface of the epidermis allowing the chloride gel to flow into a better constant connection, thus reducing the impedance of the contact.

21.7 Identification of any pharmacological components of device.

Not Applicable.

The device does not contain any pharmacological components.

21.8 Identification of any tissue of animal origin.

Not Applicable.

The device does not contain any tissues of animal origin.

21.9 Identification of any special manufacturing conditions required and if so how such requirements have been used.

Not Applicable.

There are no special manufacturing conditions required for the build of this device.

21.10 Description of packaging used for sterilisation of device.

The only component of the fEITER system coming into contact with the subject is the electrodes. For clinical trials, fEITER will use disposable commercial ZipPrep electrodes manufactured by Aspect Medical Systems Inc., as described in Section 21.6. These are self-prepping, pre-gelled, single use electrodes which carry a CE mark. The electrodes are supplied sterilised in sealed, foil-lined paper packs of five individual electrodes contained on a plastic backing strip. Once used, the electrodes will be disposed of in accordance with the standard clinical waste disposal procedures of Manchester Royal Infirmary, involving placement in approved yellow bags for later incineration.

If necessary, the EIT system headbox and base unit can be cleaned using sterile alcohol wipes for the cleansing of medical devices (e.g. Sterets Alcowipes). Such alcohol based wipes are packaged in small foil-lined paper pack sterile sachets. Alcowipes will also be used, when appropriate, for cleaning the visual stimulus goggles and the ear-pads of the stimulus headphones. However the headbox has been designed to IP65, and therefore if required could withstand more rigorous medical sterilisation.

21.11 A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the Essential Requirements.

Throughout the development of fEITER it has been necessary to refer to relevant recommended standards BS EN 60601-1:2006. As fEITER is a 'one-off' prototype it would be impossible to fully comply with all the requirements of the standards. The areas of compliance have been listed in the Technical File.

NB As part of the BS EN 60601-1:2006 protocol fEITER has undergone a two-part independent validation;

(i) functional operation – Dr Steve Carey, Research Fellow, Electrical and Electronics Engineering, The University of Manchester

(ii) compliance with BS EN 60601-1:2006 – Dr Azzam Taktak, Consultant Clinical Scientist, The University of Liverpool

Details of tests carried out and both validation reports can be found in the Technical File.

21.12 Instruction for use, and where relevant, installation of the device. Alternatively enclose a copy of the manufacturer's instructions for use that will accompany the device and be issued to the user.

Please see Appendix VI

References

[1] Cambridge Electronic Design (for Micro 1401 and Signal Software) at: http://www.ced.co.uk

[2] National Instruments Corporation (for DAQ and LabVIEW software) at: http://www.ni.com/products

[3] Chi Oz & Field, *Effects of enflurane on visual evoked potentials in human,*. British Journal of Anaesthesia 1990; 64:163−6

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[15] Kelley. S., 'BIS *Information and the Patient "At Risk",*' 2001

(C) NRES Application

Date: 13/09/2007 Reference: 07/H1003/145 Online Form

APPLICANT'S CHECKLIST

All studies except clinical trials of investigational medicinal products

REC Ref:	07/H1003/145
Short Title of Study:	fEITER real−time functional brain imaging v8.0
CI Name:	Dr Christopher J.D Pomfrett The University of Manchester

Please complete this checklist and send it with your application

- ◆ Send ONE copy of each document (except where stated)
- ◆ ALL accompanying documents must bear version numbers and dates (except where stated)
- ◆ When collating please do NOT staple documents as they will need to be photocopied.

Document	Enclosed?	Date	Version	Office use
Covering letter on headed paper	◉ Yes ○ No	10/08/2007		
NHS REC Application Form, Parts A&B	Mandatory	10/08/2007	7	
Site−Specific Information Form (for SSA)	◉ Yes ○ No	10/08/2007	7	
Research protocol or project proposal (6 copies)	Mandatory	07/08/2007	1	
Summary C.V. for Chief Investigator (CI)	Mandatory	10/08/2007		
Summary C.V. for supervisor (student research)	○ Yes ◉ No			
Research participant information sheet (PIS)	◉ Yes ○ No	07/08/2007	1.1	
Research participant consent form	◉ Yes ○ No	07/08/2007	1.1	
Letters of invitation to participants	○ Yes ◉ No			
GP/Consultant information sheets or letters ◉	◉ Yes ○ No	07/08/2007	1.1	
Statement of indemnity arrangements	◉ Yes ○ No	10/08/2007		
Letter from sponsor	○ Yes ◉ No			
Letter from statistician	○ Yes ◉ No			
Letter from funder	○ Yes ◉ No			
Referees' or other scientific critique report	○ Yes ◉ No			
Summary, synopsis or diagram (flowchart) of protocol in non−technical language	Yes No			
Interview schedules or topic guides for participants	Yes No			
Validated questionnaire	○ Yes ◉ No			

Non−validated questionnaire	○ Yes ◉ No			
Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	Yes No			

WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

○ Yes ◉ No

2. Select one research category from the list below:

- ○ Clinical trials of investigational medicinal products
- ◉ Clinical investigations or other studies of medical devices
- ○ Other clinical trial or clinical investigation
- ○ Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ○ Research involving qualitative methods only
- ○ Research limited to working with human tissue samples and/or data
- ○ Research tissue bank

If your work does not fit any of these categories, select the option below:

○ Other Research

2a. Select one category from the list below:

- ◉ Is this a clinical investigation of a medical device?
- ○ Is this a performance evaluation of an in vitro diagnostic device?
- ○ Is this a drug/device combination of both an investigational medical device and an investigational medicinal product?
- ○ Is this a post−market surveillance study of a CE Marked product?

2b . Please answer the following questions:

a) Does the study involve the use of any ionising radiation?	○ Yes ◉ No
b) Will you be taking new human tissue samples?	○ Yes ◉ No
c) Will you be using existing human tissue samples?	○ Yes ◉ No

3. Is your research confined to one site?

◉ Yes ○ No

4. Does your research involve work with prisoners?

○ Yes ◉ No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

○ Yes ◉ No

6. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ◉ No

NHS Research Ethics Committee NHS
Application form for a clinical investigation of a medical device

This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.

Short title and version number: (maximum 70 characters − this will be inserted as header on all forms)
fEITER real−time functional brain imaging v8.0

Name of NHS Research Ethics Committee to which application for ethical review is being made:
South Manchester Research Ethics Committee

Project reference number from above REC: 07/H1003/145
Submission date: 13/09/2007

PART A: Introduction

A1. Title of the research

Full title: Real−time functional brain imaging using electrical impedance tomography of evoked responses (fEITER)
Key words: Imaging, Brain, Anaesthesia

A2. Chief Investigator

Title:	Dr Forename/Initials: Christopher J.D Surname: Pomfrett
Post:	Lecturer in Neurophysiology applied to Anaesthesia
Qualifications:	B.Sc.,Ph.D.
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E−mail:	chris.pomfrett@manchester.ac.uk
Telephone:	0161 276 8582
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Mobile:	07885 202017

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application

A3. Proposed study dates and duration

Start date: 02/06/2008
End date: 31/03/2008
Duration: Years: 0 ; Months: 10

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

Question(s) 5 disabled.

A6. Does this research require site−specific assessment (SSA)? (Advice can be found in the guidance notes on this topic.)

◉ Yes ○ No

If No, please justify:

If Yes, an application for SSA should be made for each research site on the Site−Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main application has been booked for review and validated by the main Research Ethics Committee.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site−Specific Information Form.

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

The project is intended to evaluate the clinical utility of a new portable brain imaging technology called fEITER (functional Electrical Impedance Tomography by Evoked Response). We wish to compare healthy volunteers and patients undergoing anaesthesia in order to determine the sensitivity of fEITER as a clinical tool for visualising brain function during anaesthesia.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance?*(Must be in language comprehensible to a lay person.)*

Brain function monitors are used extensively in the assessment of brain dysfunction, such as stroke and degenerative diseases. There are several existing technologies that allow brain function to be presented to a clinician as an image. These include positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). PET and fMRI scanners are fixed, room−sized installations requiring the use of either radioactive isotopes injected into the patient (PET), or powerful magnets (fMRI) that prevent the use of other clinical equipment near to the monitor. fEITER is fundamentally different in that fEITER is portable and will be taken to the patient. This will allow functional brain imaging in scenarios where it has not been possible
before, such as the operating room, bedside and in an out−patient environment. Anaesthesia is a standardised clinical intervention affecting brain function, with which we can calibrate the performance of fEITER.

A10−1. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order.

This section must be completed in language comprehensible to the lay person. It must also be self−standing as it will be replicated in any applications for site−specific assessment on the Site−Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

The ultimate aim of this research project is to evaluate a portable, bedside brain imaging monitor called fEITER. fEITER is a patented, prototype system that integrates existing Electrical Impedance Tomography (EIT) and Evoked Response techniques (ER), with the capability to yield continuous functional imaging of the brain at 100 frames per second.
This project will involve the application of electrical impedance tomography using scalp electrodes to the heads of human, adult volunteers and patients undergoing surgical procedures. EIT has been in clinical use for some 20 years and has been investigated extensively by other research groups. Perhaps most notable is the work of the UCl London group, where rabbits and human volunteers have been studied and brain images have been performed including recordings from children (Holder D (Ed. Electrical Impedance Tomography,
2005. Institute of Physics Publishing).
EIT involves the measurement of the electrical properties of the tissue beneath a set of electrodes applied to the skin in the region of interest, in this case the brain. The measurement process and electrodes are very similar to an EEG (electroencephalography) recording but EIT is able to provide more information as it

passes small electrical currents between electrodes to actively probe the properties of the tissue. The currents and voltages involved are exceedingly small; subjects will normally be unaware of the electrical activity during the measurement. In fact, any sensation would provide an alternative stimulus and invalidate the functional aspect of the experiment.

The principal difference between fEITER and other EIT systems is the simultaneous application of a stimulus to achieve functional imaging. The fEITER system will in addition be highly portable. It will also be at least an order of magnitude cheaper than functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) systems. If successful, functional imaging (using fEITER) could be extended to many more bedside situations than is presently possible, such as stroke screening in emergency departments and early detection and subsequent monitoring of vCJD and Alzheimer's Disease sufferers to optimise therapies.

Apart from temporal presentation of stimuli and the presence of evoking sensory stimuli, our work is no different and can build from earlier studies in this field when considering risk and safety. However, there is a pressing need for any commercially viable technology to be demonstrated in a true clinical setting so that potential partners can be recruited to fund the project through expensive stages leading to formal validation and type approval under the medical devices directive and other international regulations.

We propose to evaluate in a range of trials visual and auditory stimulation of volunteers within the research team and patients receiving anaesthesia. Where possible, results obtained with fEITER will be compared to those obtained from the same subjects with fMRI and PET technologies.

The visual stimuli will be of bright flashes which will be introduced to the subjects while the fEITER system is in place in order to produce images of elicited responses from the visual cortex of the brain and associated areas. The bright flashes of 50ms duration will be produced from red LEDs (Chi Oz & Field. Effects of enflurane on visual evoked potentials in humans. British Journal of Anaesthesia 1990; 64:163−6). The flashes will be presented through goggles. Similarly, auditory stimuli through headphones will also be investigated where responses from areas such as the cochlear nuclei and primary auditory cortices in the

brain will be tracked. The auditory stimuli will be within normal hearing volume and frequency of the adult ear. They will include 75dB SPL (sound pressure level)clicks presented at rates of 5Hz to both ears simultaneously, these have been used extensively under clinical conditions as described by Thornton and Newton and are harmless (Thornton C, Newton DEF. The Auditory Evoked Response: A Measure of Depth of Anaesthesia. Balliere's Clinical Anesthesiology 1989; 3(3):559−585). In addition the so−called "oddball" paradigm where different tones are presented at random, will also be presented.

Functional responses will be expected at different time intervals after the application of a stimulus denoted by different areas of the brain being visualised on successive frames of the image. A wide range of stimuli will

be tested on normal volunteers to identify which elicit the best responses in the fEITER system. The aim will be to evoke an EIT equivalent to the pattern responses typically seen in Visual Evoked Response (VEP) and Auditory Evoked Response (AEP) techniques which use EEG recordings. We hope to distinguish between a VEP using a flash and an AEP using a click.

We propose a two stage approach which will maintain patient and volunteer safety as a priority, and yet will realistically yield useful numbers of results for clinical validation. Such results need large enough numbers to apply statistics to the reconstructed images to show that the effects observed are truly indicative of active neuronal processes and not just random noise.

Clinical work will take place in clinical high dependency environments at Manchester Royal Infirmary in the presence of resuscitation−trained anaesthetists with full backup, including defibrillation.

Part 1. Experimenter volunteers.

The clinical team will commence a series of randomized, controlled trials on volunteers from the experimental team.

Up to 32 disposable electrodes will be attached to the head of the subject who will be

lying comfortably with eyes open. After attachment of the head stage of the fEITER monitor a series of images will be recorded over
1min to establish a baseline. Sensory stimuli will then be introduced in randomised sequence and 1min recordings will continue after each stimulus. The stimuli will be flash images introduced through a pair of goggles and auditory stimuli presented through isolated, infrared headphones. The ideal EIT response times will be determined from part 1.

Ideally, fEITER will permit identification of whether visual and auditory stimuli have been presented. Randomisation of the stimulus presentation will ensure that the engineering team responsible for data reconstruction and later analysis of the images do not know the nature of the stimuli presented to the volunteer. The question will be "can the method of stimulus be identified purely from the reconstructed EIT image?" Until this can be performed reliably in such healthy volunteers, there is no point moving on to obtaining informed consent from patients, so this phase is a milestone for further development.

Part 2. Anaesthetised patient volunteers.
fEITER was originally envisaged as a tool for the anaesthetist, providing functional, real−time brain imaging in an environment where none currently exists. Twenty patients undergoing elective surgical procedures will
be recruited to undergo fEITER imaging before, during and after general anaesthesia with standard agents
(e.g. propofol and sevoflurane).
By simultaneously measuring brain function using a Bispectral Index monitor (BIS), we will be able to correlate these results with functional imaging studies already performed by the team at the University of California. The BIS monitor is a licensed monitor which is available for use by the anaesthetist in surgical procedures to assess 'depth of anaesthesia. In the Californian study, the performance of BIS was compared with 18 Fluorodeoxyglucose PET imaging (Alkire M T,Pomfrett C J D. Toward the fundamental unit of anesthetic depth: positron emission tomography suggests that bispectral index (BIS) monitors an important component of anesthetic depth. Anesthesiology 1996 85, A174). The BIS monitor uses a sensor incorporating 4 electrodes which are similar to standard ECG electrodes but specifically designed to be used with this monitor. It is placed on the subject's forehead and measures brain activity translating this into a number between 100 (wide awake) and zero (absence of brain electrical activity).
Up to 32 disposable electrodes will be placed on the patient's head in the anaesthetic room prior to induction of anaesthesia. A BIS sensor wilL also be attached to the patient's forehead in preparation for monitoring during the surgical procedure. After connection to the fEITER monitor, simple patterns of auditory and visual stimuli made up of 75dB SPL clicks and red LED flashes will be presented in turn through earphones and goggles placed over closed eyes. Following induction of anaesthesia and transfer to the operating room a series of images will be collected along with corresponding values of BIS during maintenance of anaesthesia and then on recovery at the end of surgery.
At the end of the proposed study all researchers, both experimental and clinical will meet to interpret and analyse the final images produced and discuss the practical implicatons before designing further studies for the next stage of product development. At the end of the clinical testing as described here we expect to have a strong statistical basis of evidence for the efficacy of fEITER, including an image database from patients.

A10−2. In which parts of the research have patients, members of the public or service users been involved?

- [x] As user−researchers
- [ ] As members of a research project group
- [x] As advisor to a project
- [ ] As members of a departmental or other wider research strategy group
- [ ] None of the above

Please provide brief details if applicable:

Potential service and user researchers i.e. clinicians and scientists, have been consulted regarding the footprint and potential utility of fEITER in a clinical setting.

A10−3. Could the research lead to the development of a new product/process or the generation of intellectual property?

◉ Yes ○ No ○ Not sure

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care.*(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*

Additional Intervention	**Average number per participant**		**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have**
	Routine Care	Research		
Imaging Investigations (not radiation)	0	1	15 mins	Evaluation of fEITER novel imaging technology in volunteers. 32 disposable EEG electrodes will be attached to the scalp by a Clinical Scientist. Visual or auditory stimuli will be presented at intervals of 1min. This will be limited to flashes or clicks for patient volunteers. We will allow 5mins for the setting up of the electrode montage & equipment and 10min for the testing protocol to give a total of 15min.

A13. Give details of any non−clinical research−related intervention(s) or procedure(s).*(These include interviews, non−clinical observations and use of questionnaires.)*

Additional Intervention	**Average number per participant**	**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

○ Yes ◉ No

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

The subjects will be studied by fEITER for fifteen minutes at each recording session. This will be a one−off event for patient volunteers, and a repeated event for the volunteers drawn from the investigator team.

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non−clinical)?

There are no potential adverse effects, risks or hazards reported for the injection of low current, high frequency electricity into the brain other than inadvertent activation of the trigeminal or facial nerves due to misplaced electrodes, see A17.

The currents used (up to 1mA) are much lower than those used repeatedly in electroconvulsive therapy, and are of a similar amplitude to commercial, active electrode impedence testing systems (e.g, Aspect Medical Systems BIS monitor) used to check the integrity of electroencephalograph electrodes.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

There is a potential uncomfortable effect from the accidental injection of current in sequence across facial nerves; inadvertant activation of the trigeminal or facial nerves may induce neuralgia which may last for the duration of the electrical stimulation. During a separate, University based, volunteer trial with a previous generation of the device, this was observed due to erroneous electrode placement in one volunteer from the investigator team, and was painful. Care with placement of electrodes and a current injection sequence chosen to randomly "break step" avoids sequential stimulation along facial nerves and has successfully avoided this effect in pilot studies. All those applying electrodes will receive prior training and practice.

A18. What is the potential for benefit to research participants?

There is no anticipated benefit for research participants.

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

The initial volunteers are going to be drawn from the researchers. As volunteers the potential for inadvertant neuralgia caused by electrical stimulation of facial nerves could lead to transient pain and discomfort.

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

i) Volunteers identified.

Healthy controls will be drawn from the experimenter team, and comprise staff of the University of Manchester who are not paid from the grant. The inventors (Dr Pomfrett and Professor McCann) will evaluate the use of fEITER on themselves before others are recruited. Healthy volunteers will be recruited by poster advertisement placed in the two University research groups involved in this study (Engineering and Anaesthesia). Potential volunteers will be invited to collect the information sheet from secretarial and technical support staff not involved in this study.

Patients scheduled for general anaesthesia during elective surgery will be identified by Professor Brian Pollard FRCA from his normal operating theatre lists. Patients will be identified on the basis of the research protocol not delaying the normal schedule for the operating room i.e. tolerating the inclusion of a fifteen minute awake measurement step. All patients will be under the continuous care of Professor Pollard throughout the reserch procedure and anaesthesia. They will in addition receive all normal routine care and monitoring.

ii) Volunteers approached.

Volunteers will be approached at least 24 hours before the proposed study by Dr Angella Bryan, a clinical scientist dedicated to this project, who is not a member of the normal care team for any of the patients or staff to be recruited. Dr Bryan is employed by Christie Hospital NHS Trust and is independently supervised. Dr Bryan will explain the fEITER project and the procedures that will be conducted. Potential volunteers will be given an information sheet and told what the project will entail. Records of consent or refusal to consent will
be kept confidential so that there is no chance for coercion of staff or volunteers to

participate in the trial. iii) Volunteers recruited.

Patients and volunteers will be requested to read an information sheet and sign a consent form at least 24 hours before the procedure. In the case of the patients this will very likely be given to them at the routine preoperative visit 2−3 weeks before the scheduled operation date. An additional consent form will be presented to the subjects before the procedure, and, in the case of patients, before the administration of any preoperative medication.

A21. Where research participants will be recruited via advertisement, give specific details.

☑ Not Applicable

If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).

A22. What are the principal inclusion criteria?*(Please justify)*

All patients and volunteers will be considered.
For the patient group there will be a requirement for the study protocol to be scheduled at the same time as the patient's surgery and to fit in with the order of the surgical list.

A23. What are the principal exclusion criteria?*(Please justify)*

Patients who are unable to rapidly communicate with the researchers will be excluded from this study because of the need for rapid intervention in the event that fEITER becomes uncomfortable during the trial on awake volunteers and patients whilst awake. Rapid communication will be tested at the recruitment interview by asking the candidate to release a spring−loaded hand−held trigger in response to visual (flash), auditory (click) and shoulder tap cues. Any response of over 1−second delay, or no response, will exclude the candidate from the trial, as will lack of comprehension of the instructions.

A24. Will the participants be from any of the following groups?*(Tick as appropriate)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☑ Adults who are unconscious or very severely ill
- ☐ Adults who have a terminal illness
- ☐ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
- ☐ Adults with dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☐ Adults in Scotland who are unable to consent for themselves
- ☑ Healthy Volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☐ Other vulnerable groups

Justify their inclusion.

One of the tests for efficacy of fEITER in measuring brain function, will be to test it on patients undergoing anaesthesia. These patients will be ASA I or II i.e. fit and well or with minor systemic disease processes which do not limit their everyday activities. In each subject, fEITER will be evaluated on them whilst awake as a tolerance test before subsequent study during anaesthesia.
Although the patients will be unconscious (anaesthetised) for part of the monitoring, consent will have been taken before anaesthesia and before the 'awake' test i.e. they will be able to give fully informed consent in advance.
All subjects will be under the continuous care of Professor Pollard during the anaesthesia who will halt the study if there are any concerns for the welfare of the patient. None of the experimenter volunteers will be paid through the research rant for the study.

- ☐ No participants from any of the above groups

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

○ Yes ◉ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information
(in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

Dr Angella Bryan will ensure that an information pack is distributed to the volunteer at least 24 hours before trials commence. Dr Bryan will obtain written, informed consent in person, and will ensure that the volunteer understands the protocol. Any persons identified as not completely understanding the protocol will be thanked but not included in the recruitment process.

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

The participant will have at least 24 hours to consider whether to take part in the research.

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

If the volunteers or patients do not speak English an interpreter will be engaged to explain the nature of the project. As it is essential that the subjects are able to rapidly communicate their feelings regarding fEITER in English so that the researchers can assess whether there are any problems, interpreters will also be required to be on hand during the procedure.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Progress on the trial will be made available on the University of Manchester web site. The lead researcher will contact all participants by phone or letter should any information become available during the course of the research that may be relevant to their continued participation.

A30−1. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

○ The participant would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained. Any identifiable data or tissue would be anonymised or disposed of.

◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study.

○ The participant would continue to be included in the study.

○ Not applicable – informed consent will not be sought from any participants in this research.

Further details:

Participants should be informed when seeking initial consent if it is planned to retain and make further use of identifiable data/tissue in the event of loss of capacity.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit? *(see the guidance notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) be informed that they are taking part in the study?

◉ Yes ○ No

If Yes, enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A32b. Will permission be sought from the research participants to inform their GP or other health professional before this is done?

◉ Yes ○ No

If No to either question, explain why not

It should be made clear in the patient information sheet if the research participant's GP/health professional will be informed.

A33. Will individual research participants receive any payments for taking part in this research?

○ Yes ◉ No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

○ Yes ◉ No

A35. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35−1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s)* for harm to participants arising from the *management of the research*?

Note: Where a NHS organisation has agreed to act as the sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, describe the arrangements and provide evidence.

○ NHS indemnity scheme will apply
◉ Other insurance or indemnity arrangements will apply (give details below)

The University of Manchester will provide indemnity insurance.

Please enclose a copy of relevant documents.

A35−2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s) or employer(s)* for harm to participants arising from the *design of the research*?

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), describe the arrangements and provide evidence.

○ NHS indemnity scheme will apply to all protocol authors
◉ Other insurance or indemnity arrangements will apply (give details below)

The University of Manchester will provide indemnity insurance.

Please enclose a copy of relevant documents.

A35−3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of *investigators/collaborators* and, where applicable, *Site Management Organisations*, arising from harm to participants in the *conduct of the research*?

Note: Where the participants are NHS patients, indemnity is provided through NHS schemes or through professional indemnity. Indicate if this applies to the whole of the study (there is no need to provide documentary evidence). Where non−NHS sites are to be included in the research, including private practices, describe the arrangements which will be made at these sites and provide evidence.

○ All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
◉ Research includes non−NHS sites (give details of insurance/indemnity arrangements for these sites below)

The University of Manchester will provide indemnity insurance.

Please enclose a copy of relevant documents.

A36. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

◉ Yes ○ No

If Yes, give details of the compensation policy:

The project will be covered by the No Fault Compensation Policy held by the University of Manchester.

Please enclose a copy of relevant documents.

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

☑ Peer reviewed scientific journals
☐ Internal report
☑ Conference presentation
☑ Other publication
☑ Submission to regulatory authorities

☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

☐ Written feedback to research participants

☐ Presentation to participants or relevant community groups

☑ Other/none e.g. Cochrane Review, University Library

If other/none of the above, give details and justify:

A38. How will the results of research be made available to research participants and communities from which they are drawn?

Information will be posted on the University of Manchester web site.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

☐ Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access

☐ Electronic transfer by magnetic or optical media, e−mail or computer networks

☐ Sharing of data with other organisations

☐ Export of data outside the European Union

☐ Use of personal addresses, postcodes, faxes, e−mails or telephone numbers

☐ Publication of direct quotations from respondents

☐ Publication of data that might allow identification of individuals

☐ Use of audio/visual recording devices

☐ Storage of personal data on

any of the following: ☑

Manual files including

X−rays

☐ NHS computers

☐ Home or other personal computers

☑ University computers

☐ Private company computers

☐ Laptop computers

Further details:

These documents relate to signed consent forms for this study and any MRI or PET scans which are done on volunteers for comparison purposes with the fEITER images.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

Dr Angella Bryan will be the sole member of staff with access to details capable of identifying the volunteer or patient. All such information will be encrypted using Windows XP Pro/Windows Vista Ultimate and kept on optical disk archives locked within the Department of Anaesthesia, Manchester Royal Infirmary. All consent forms will be stored in locked filing cabinets in the above department

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Anonymised outputs from the fEITER system will be studied at the University of Manchester by members of the project team.

A42. Who will have control of and act as the custodian for the data generated by the study?

Dr Angella Bryan will control access to, and act as custodian for, the data generated by this study.

A43. Who will have access to research participants' or potential research participants' health records or other personal information? *Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.*

Only Dr Angella Bryan (Clinical Scientist in Anaesthesia) and Professor Brian Pollard (Professor of Anaesthesia) will have access to health records.

A44. For how long will data from the study be stored?

15 Years **0** Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:

It is envisaged that the clinical data obtained during trials of fEITER will be used for regulatory approval by competant bodies e.g. the FDA and MHRA, in the event that fEITER becomes a commercial product. All data will be preserved by Dr Angella Bryan.

A45−1. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

☑ Independent external review
☐ Review within a company
☐ Review within a multi−centre research group
☐ Review within the Chief Investigator's institution or host organisation
☐ Review within the research team ☐ Review by educational supervisor ☐
Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The project has been awarded funding by the Wellcome Trust under the University Translation Award (UTA)
scheme.

A45−2. How have the statistical aspects of the research been reviewed? *(Tick as appropriate)*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☑ Other review by individual with relevant statistical expertise

In all cases give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title:	Forename/Initials:	Surname:
Dr	Christopher J	Pomfrett

Department: Research School of Clinical & Laboratory Sciences, School of Medicine
Institution: The University of Manchester
Work Address: Manchester Royal Infirmary
Oxford Road, Manchester

Postcode: M13 9WL Telephone: 0161 276 8582
Fax: 0161 273 5685
Mobile: 07885 202017
E−mail: chris.pomfrett@manchester.ac.uk

Please enclose a copy of any available comments or reports from a statistician. Question(s) 46−47 disabled.

A48. What is the primary outcome measure for the study?

fEITER is a novel brain imaging device. The primary outcome will be an evaluation of the clinical utility of fEITER i.e. does fEITER offer any useful insight into brain function.

A49. What are the secondary outcome measures?*(if any)*

A50. How many participants will be recruited?
If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.

The two principal applicants for this study will be the first volunteers (phase I). Ongoing trials will then proceed with healthy volunteers recruited from Manchester University staff (n=20). From the results obtained with volunteers, with which the efficacy of imaging will be evaluated, a decision will then be made on the number of anaesthetised patients studied. It is proposed to study 20 anaesthetised patients.

A51. How was the number of participants decided upon?

Healthy volunteer trial numbers derived from available staff considering a 50% recruitment rate. There is no available information available for fEITER with which to perform a sample size calculation.
I*f a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

A52. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, give details of the intended method of randomisation:

Randomisation will be at the level of order for sequential stimulus presentations and directed by a computer−generated random number generator.

A53. Describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Imaging data from fEITER will be imported into Statistical Parametric Mapping (SPM99) software for comparison with estabished neuroanatomical and physiological landmarks.

A54. Where will the research take place?*(Tick as appropriate)*

☑ UK
☐ Other states in European Union
☐ Other countries in European Economic Area
☐ Other

If Other, give details:

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

○ Yes ◉ No

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
☑ Acute teaching NHS Trusts	1
☐ Acute NHS Trusts	

☐ NHS Primary Care Trusts or Local Health Boards in Wales
☐ NHS Trusts providing mental healthcare
☐ NHS Health Boards in Scotland ☐
HPSS Trusts in Northern Ireland ☐ GP Practices
☐ NHS Care Trusts
☐ Social care organisations
☐ Prisons
☐ Independent hospitals
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

NHS clinical governance regulations will cover this trial. NHS Trust and University research monitoring and audit procedures willl also apply.

A57a. Will a data monitoring committee be convened?

○ Yes ◉ No

If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.

What are the criteria for electively stopping the trial or other research prematurely?

In the event that adverse reactions to the use of fEITER are suspected, the experimenters will stop all use of the fEITER technology until the cause is identified.

A58. Has external funding for the research been secured?

◉ Yes ○ No

If Yes, give details of funding organisation(s) and amount secured and duration:

Organisation:

The Wellcome Trust

Address: 215 Euston Road
London

Post Code:	NW1 2BE
UK contact:	Dr Glenn Wells
Telephone:	020 7611 7356
Fax:	020 7611 8857
Mobile:	
E−mail:	g.wells@wellcome.ac.uk
Amount (£):	287,000
Duration: 60 Months	

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

○ Yes ◉ No

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

◉ Yes ○ No

Lead sponsor *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor

for the research: The University of Manchester

Status:

NHS or HPSS care organisation | Academic | Pharmaceutical industry | Medical device industry | Other

If Other, please specify:

Address:	Oxford Road Manchester
Post Code:	M13 9PL Telephone:
F a x :	

Sponsor's UK contact point for correspondence with the main REC *(must be completed in all cases)*

Title: Dr Forename/Initials: Karen Surname: Shaw

Work Address: Head of the University Research Office, The University of Manchester
Oxford Rd, Manchester

Post Code: M13 9PL Telephone: 0161 275 8795

Fax: Mobile:

E−mail: research−governance@manchester.ac.uk

Co−sponsors

Are there any co−sponsors for this research?

Yes No

Give details of all co−sponsors:

Organisation: Central Manchester & Manchester Children's Hospital NHS Trust

Address: Manchester Royal Infirmary
Oxford Road

Manchester Post Code: M139WL Telephone:

Fax: Mobile:

E−mail:

Describe how the responsibilities of sponsorship will be allocated between the co−sponsors:

The University of Manchester and Central Manchester NHS Trust have a pan−Manchester collaborative agreement with regard to clinical academic research. All trials of fEITER will be conducted on NHS premises, and ongoing technical development with software design with be conducted on University premises.
The University is responsible for authorisations and ethical approval. The Trust is responsible for good clinical practice.

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

○ Yes ◉ No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share−holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

A65. Research reference numbers: *(give any relevant references for your study):*

Applicant's/organisation's own reference number, e.g. R&D (if available): R012106
Sponsor's/protocol number: Funder's reference number:
International Standard Randomised Controlled Trial Number (ISRCTN):
Project website:

A66. Other key investigators/collaborators *(all grant co−applicants or protocol co−authors should be listed)*

Title: Professor Forename/Initials: H Surname: McCann

Post: Professor of Industrial Tomography Qualifications: BSc,PhD,CPhys,MInstP,FIEE,CEng Organisation: University of Manchester
Work Address: Electronic & Electrical Engineering D48b Sackville St Building University of Manchester
Postcode: M60 1QD Telephone: 0161 306 4791
Fax: 0161 306 4789
Mobile:
E−mail: Hugh.McCann@manchester.ac.uk

Title: Professor Forename/Initials: Brian J Surname: Pollard

Post: Professor
of Anaesthesia Qualifications: BPharm,
MB, ChB, MD, FRCA Organisation:
University
of Manchester
Work Address: Department of
Anaesthesia,
Manchester Royal
Infirmary, Oxford
Rd Manchester
Postcode: M13 9WL Telephone: 0161 276 8651
Fax: 0161 273 5685
Mobile:
E−mail: Brian.Pollard@manchester.ac.uk

Title: Dr Forename/Initials: Angella Surname: Bryan

Post: Clinical
Scientist in Anaesthesia Qualifications:
BSc, MSc,
PhD, CSci Organisation: Christie
Hospital NHS Trust Work Address:
Department
of Anaesthesia
Manchester Royal
Infirmary, Oxford
Rd
M
anchester Postcode: M13 9WL Telephone: 0161 276 4537
Fax: 0161 273 5685
Mobile:
E−mail: Angella.Bryan@manchester.ac.uk

A67. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Such arrangements are not appropriate for this study.

PART A: Summary of Ethical Issues

A68. What are the main ethical issues with the research?

Summarise the main issues from the participant's point of view, and say how you propose to address them.

fEITER is a new brain imaging modality. There are a number of potential ethical issues:
1) Participants may experience unexpected side−effects relating to current injection through the head. The only side−effect envisaged is the very slight possibility of neuralgia caused by electrical stimulation of nerves underlying electrode sites on the scalp e.g the trigeminal nerve. We propose to avoid placing electrodes over cranial nerves, and to use a current injection pattern that avoids stimulation of cranial nerves.

2) It is possible that investigation with fEITER may reveal a functional abnormality in the brain of a participant that had not been previously identified. We propose to notify the GP of all participants regarding participation in this trial, and Professor Brian Pollard will write a letter to the patient's GP in the event that an abnormal response were detected, with advice that further follow−up should be undertaken.

Indicate any issues on which you would welcome advice from the ethics committee.

Question(s) 69−71 disabled.

PART B: Section 1 − List of proposed research sites

List below all research sites you plan to include in this study. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or a consortium – see the guidance notes.

Principal Investigators at other sites should apply to the relevant local Research Ethics Committee for site−specific assessment (SSA) using the Site−Specific Information Form. Applications for SSA may be made in parallel with the main application for ethical review (once the main REC has validated the application), or following issue of a favourable ethical opinion. Approval for each site will be issued to you by the main REC following SSA.

1. Name of the research site:

Central Manchester & Manchester Children's University Hospital NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Chris J.D. Surname: Pomfrett

Post: Lecturer in Neurophysiology applied to Anaesthesia
Work Address: Dept.Anaesthesia Manchester Royal Infirmary Oxford Road, Manchester
Postcode: M13 9WL

PART B: Section 2 − Investigation of medical devices

1. Give details of the medical device(s) to be used in the study

Device description:	fEITER (functional Electrical Impedance Tomography by Evoked Response)	
Manufacturer:	The University of Manchester	
Use:	Brain Function Imaging	
Length of time since device came into use:	New device	* Does the device have a CE mark? ○ Yes ◉ No

** For all products with CE mark please attach instructions for use.*

2. Does the study involve the use of a *new* medical device or *new* implantable material or the use of an existing product outside the terms of its CE market intended purpose?

◉ Yes ○ No

In addition to the instructions for use, the following details should be provided where applicable:

− Description of new device, materials, method of use or operation and a summary of the intended purpose
− Composition of any new implantable materials, including summary of biocompatibility findings from studies to date
− If already CE marked, a summary of any proposed changes to the CE marked intended purpose

Description of New Device:

The fEITER system will integrate evoked response (ER) stimulation and electroencephalograph (EEG) recording hardware within the same assemblage as the EIT system. Trigger pulses will operate both the ER and EIT systems to study different sensory modalities (e.g. flashes of light), within a highly flexible set−up. This will facilitate the use of randomised stimulus trains in order to eliminate all effects of habituation and adaptation to
the sensory stimuli, as well any possible effects of repetitive presentation of EIT current injection through the brain. All stimuli will be presented using established ER software and standard hardware integrated within the assemblage comprising the fEITER system.

The fEITER image display software will be interfaced with the Statistical Parametric Mapping (SPM) technique, in order to enable easy use and interpretation of fEITER images by clinicians, and to enable comparison of fEITER images with PET and fMRI. SPM is an open source, Matlab based software package which is widely accepted as the standard tool for analysing neuroimaging data. Consequently, we have developed software which enables the fEITER images to be configured in a compatible form for SPM. This novel software has been extensively tested and is the subject of a paper at an internationally renowned conference on Medical EIT (ICEBI'07, Graz, Austria). In the clinical evaluation phase, we anticipate that there will be a need to reconstruct a large volume of tomographic data.

A primary requirement of the design and build phases will be to ensure patient safety. In particular, it is necessary to protect actively against injection of currents in excess of the European Medical Device Directive (in compliance with BSEN 60601−1−1). Unlike the pilot study equipment, current limiting circuitry will be integrated into the fEITER prototype, rather than being added as a separate unit. The internal circuitry used in the pilot study will serve as a good starting point for the new prototype. Further steps will be taken in both hardware and software to ensure that the system will be failsafe. Experience in the pilot study shows that it is also necessary
to integrate an electrode contact impedance monitoring system into the fEITER unit.

The current injection and voltage measurement system will be built around the use of field programmable gate array (FPGA) technology for lock−in measurement techniques, building on our own in−house experience and on that of recent medical EIT system developers. An FPGA will digitally synthesise a sinusoidal waveform that is used both for current generation and as a reference for lock−in voltage measurement. Various steps will be necessary to generate the analogue current with the lowest possible content of harmonics, such as use of relatively long (18−bit) digital words, digital switching as far as possible, etc. We will develop a voltage measurement circuit that recovers both the in−phase scalp voltages (i.e. due to resistive impedance) and the
90degrees out−of−phase scalp voltage (i.e. due to reactive impedance). Subsequent analysis of these components will shed light on the nature of the impedance variations in the brain. Our aim is to achieve 2−component voltage measurement in 10 cycles of current injection, with SNR of 80dB over 250Hz bandwidth.

In order to achieve the necessary frame rates, the multi−channel system is being built on the principle of using a dedicated front−end for each electrode, consisting of pre−amplifier, filter(s) and fast ADC. Development work includes the overall design architecture (e.g. optimal division of software and hardware functions) and a consideration of how many voltage measurement channels can be handled by an FPGA of a given type. Although early development is be facilitated by in−house fabrication of circuits on 2−layer Printed Circuit Boards (PCBs), subsequent production and population of multi−layer PCBs will be contracted out to known suppliers.

The ER sub−system will be defined prior to the final design of the fEITER system. In−house development will include making provision for flexible stimulus delivery and EIT triggering, and for the driving of a visual display unit for flexible delivery of a variety of visual stimuli, as advised by Prof. Foster. The hardware integration of the whole system will be carried out in−house. The fEITER prototype will be highly flexible under computer control, in view of the wide range of tests that are foreseen. It is an essential part of the programme that the finished fEITER system will be subjected to safety acceptance tests by the Medical Engineering & Maintenance Department (MEAM) at Central Manchester & Manchester Children's University Hospitals NHS Trust.

The system will include several elements, including a PC for data processing, display and storage, a Cambridge Electronic Design 1401 for experiment timing control, and various subsystems to provide the EIT and stimulus functions (Fig. 1). The system as a whole will be constructed to meet BS EN 60601−1−1. Depending upon their specific function, individual subsystems may or may not need to be medical devices. The EIT subsystem will be a medical device (Class II, Type BF applied part), as will any stimulus subsystems that require an applied part. The EIT subsystem will be proof against electrosurgery and defibrillation, to allow its use in the operating room.
It will also provide galvanically separated interfaces to allow connection to both the 1401 and the PC without the need for external separation devices.

Although 60601−1 does not impose limits on functional currents in medical devices, it does define the permissible auxiliary leakage (i.e. unintentional) current, that may flow between applied parts of a medical device. In the case of Type BF applied parts (isolated but unsuitable for direct cardiac application) this current must not exceed 100 microamps for AC signals at frequencies up to 1 kHz, rising to 10 mA at 100 kHz (upper limit of fEITER operating frequency range) under normal operation. Under a single fault condition these levels are increased five−fold. The measurement currents used by the fEITER system will not exceed the permissible normal condition auxiliary leakage current limits and are therefore considered not to present any risk. The applied current is continuously monitored as part of the measurement process. The detection of excessive current flow will cause the EIT subsystem to cease normal operation and electrically disconnect itself from the patient electrodes until a manual reset is applied.

See attached Fig. 1

Summary of intended purpose:

EIT involves the measurement of the electrical properties of the tissue beneath a set of electrodes applied to the skin in the region of interest. The currents and voltages involved are exceedingly small; subjects will be unaware of the electrical activity during the measurement.
fEITER is a portable, bedside brain imaging monitor that is a patented, prototype system that integrates existing Electrical Impedance Tomography (EIT) and Evoked Response techniques (ER), with the capability to yield continuous functional imaging of the brain at 100 frames per second. It involves the application of EIT using scalp electrodes to the heads of human, adult volunteers and patients undergoing surgical procedures.

Materials:

The intention of this section is to more fully describe the design of the complete fEITER system. Emphasis is placed on the hardware design. For clarity, many of the diagrams are at the schematic level, although at the time of writing, the hardware design exists at the PCB level.

Figures 2,(The operation of fEITER and the patient environment) and Figure 3. (Division of electrical safety in accordance with medical standard: BS EN 60601−1−1)are attached separately to this form. They show the fEITER instrument in the context of the medical standard, BS EN 60601−1−1. The bespoke electronics for fEITER comprises of a main EIT subsystem (or 'base unit') along with a separate head box unit. The head box provides the small tomographic sinusoidal currents as described in the previous section and digitizes the measured scalp voltages which are transferred to the base unit subsystem. The head box will meet the standard associated with a Class II, type BF part. The principle of adopting this type of subsystem approach has been independently scrutinized by a consultant in the area of electromedical safety.

Figure 4 (Circuit block description of the fEITER headbox unit) shows at the schematic block level the hardware design of the head box. For clarity, the diagram shows only one analogue−to−digital converter, ADC, however, due to the high frame rates of fEITER, we will be using parallel measurements on all measurement channels i.e. one ADC per channel. The front end electronics uses a combination of miniature gas discharge tubes,
clamping diodes and other components to provide a protection layer against the high currents and voltages present during electrosurgery (ESU) and defibrillation. This layer also provides EMC (electromagnetic compliance) protection. The protection is designed not only to protect the front end measurement electronics but also (and more importantly) to ensure protection of the patient against possible fault conditions potentially giving rise to alternate burn sites during ESU. The head box unit will continuously monitor the current being driven to the electrodes using firmware within the FPGA layer. This will be used to provide an auto shut−off of the applied current should the current exceed the limits described in the previous section (for a given injection frequency). Additionally, an emergency stop which is independent of software, will shutdown the current source by either the intervention of the clinical team or (in the case of awake patients) by the volunteer/patient. The division of the galvanic separation can be seen in the schematic of the base unit shown in figure 5 (Circuit block description of the fEITER EIT base unit sub−system). The base unit is considerably less complex than the head box being predominately digital. The base unit interfaces with the CED 1401 as shown previously in figure 1 along with a laptop used for driving the fEITER system and providing data storage. A further description of the interaction between subsystems is given in figure 6 (Main communication channels of fEITER showing software control and data capture methods).
As can be seen, much of the control will be provided by commercially available software such as CED Signal, Vision EGG and NI Labview. It is our intention to also provide a bespoke user interface which will operate at the highest software level.

Early prototyping of the main EIT fEITER subsystem has involved the development of a high quality single channel current excitation and voltage measurement circuit board. Figure 7 shows a schematic of the design. This prototype has undergone extensive testing and provides SNR better than 80dB for the current excitation. The single channel system has enabled many of the critical EIT design issues to be explored prior to incorporation into the full channel system. Many of the components and electronic methods used in the single channel system are to be used in the full fEITER design.

The hardware assemblage of the fEITER EIT base unit subsytem and CED1401 will utilize a commercial 19" instrument case giving full compliance with EMC regulations and be suitable for use in the operating room. The case will also house medical grade power supplies in accordance with BSEN60601. Figure 8 shows a schematic side elevation of the proposed design. Internal communication wiring between the CED 1401 and the EIT base unit will be routed within the rear of the case. The hardware will be powered via an external medical grade isolation transformer. The front elevation of the hardware assemblage is given in figure 9. As can be seen, the front panel of the case will incorporate an emergency stop (independent of all software) available for use by the operator of fEITER. Additionally, activity lights for each channel will give a positive indication of suitable electrode contact.

Instructions for use:

1. The volunteer or patient should be lying comfortably in a semi−recumbent or a supine position.
2. The electrodes (self−adhesive surface−type) are attached to the head in the positions indicated on the attached figure. Hair should simply be parted and no attempt made to shave local areas of scalp. The electrodes will function quite well if they are just pressed firmly in place.
3. The electrically isolated head−stage is placed beside the head on the pillow and the individual leads connected one by one to the electrodes. The order of connection is not important as the equipment will not be switched on at this point.(See Figure 10).
4. The head−stage should then be connected to the main processing module taking care not to exert any traction on the cable or the electrodes on the head.
5. The CE marked clear plastic safety goggles will be placed over the subject's eyes. The electrically isolated infrared headphones will be placed over the ears. In the case of anaesthetised subjects the BIS monitor will be attached to the patient's forehead according to the manufacturers' instructions.
6. The equipment may then be switched on by the member of the research team.
7. The member of the research team will conduct the initiation procedure and prepare for data collection. During the stage of development and testing of the equipment a suitably qualified individual from the development team will be present to operate the equipment and so no specific instructions for use for this stage are possible. Furthermore the actual order of processes may change with time as the equipment use develops.
8. Data collection will then commence according to the protocol of the study.
9. Once the study is complete, the technician will disconnect the head stage cable from the main processing unit. Archiving of the data will then be completed and the hard copy (CD or DVD) of data will be given to the custodian of the data. All data stored within the processing unit will then be erased.
10. The cables will be disconnected from the electrodes. The electrodes will be carefully removed from thehead of the patient or volunteer taking care not to remove any hair with the electrodes. All figures are attached in Appendix of Protocol (version 1.1 7 Aug 07)

3. For electrical devices give summarised details of acceptance and safety testing

The fEITER assemblage system will be subjected to safety and acceptance tests by the Medical Engineering
& Maintenance Department (MEAM) at Central Manchester & Manchester Children's University Hospitals
NHS Trust.

4. Is a medical device or other commercial company arranging this trial?

○ Yes ◉ No

a) Is this trial a clinical investigation requiring notification to the MHRA?	◉ Yes	○ No
b) Does the company have a Notice of No Objection from the MHRA?	○ Yes	◉ No
c) Has MHRA approval been applied for but not yet received?	○ Yes	◉ No

Note: An application can be made prior to receipt of a valid Notice of No Objection from MHRA. The Notice will be issued subject to the sponsor subsequently receiving a favourable opinion. There is no requirement for a valid Notice of No Objection to be provided to relevant ethics committee before the research can be given a favourable opinion.

5. Have any of the medical devices been transferred from one organisation (legal entity) to another for the purpose of this trial?

◉ Yes ○ No

Give details:

The University of Manchester will manufacturer fEITER for evaluation on NHS premises.

6. In cases of equipment or medical devices, what arrangements have been made with the manufacturer to provide indemnity?

The University of Manchester is the manufacturer of fEITER, and will provide indemnity insurance.

Enclose a copy of the relevant correspondence, with a version number and date.

PART B: Section 8 − Declarations

Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.

4. I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.

5. I undertake to submit annual progress reports setting out the progress of the research.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.

7. I understand that research records/data may be subject to inspection for audit purposes if required in future.

8. I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:

   − Will be held by the main REC until at least 3 years after the end of the study.

   − May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.

   − May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.

   − Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature:

Print Name:

Date: (dd/mm/yyyy)

Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the sponsor nominated to take the lead for the REC application.

I confirm that: *(tick as appropriate)*

☐ This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

☐ An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

☐ Any necessary indemnity or insurance arrangements, as described in question A35, will be in place before this research starts.

☐ Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

☐ Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

☐ The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Signature:

Print Name:

Post: Organisation:

Date: (dd/mm/yyyy)

Site−Specific Information Form

Does this application relate to a research site for which the NHS (or HPSS in Northern Ireland) is responsible or to a non−NHS research site?

- (●) NHS site
- ( ) Non−NHS site

For HPSS sites in Northern Ireland, separate arrangements are in place for R&D applications. There is no need to complete questions marked "R&D only" on this form.

This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.

In which country is the research site located?

- ( ) England
- ( ) Wales
- ( ) Scotland
- ( ) Northern Ireland

The data in this box is populated from Part A:

Short title and version number:
fEITER real−time functional brain imaging v8.0

Name of NHS Research Ethics Committee to which application for ethical review is being made: South Manchester Research Ethics Committee

Project reference number from above REC: 07/H1003/145

Name of NHS REC responsible for SSA: SSA reference (for REC office use only)

Name of NHS care organisation to which application is being made for permission to conduct the research:

NHS organisation reference (for R&D office use only):

1. Title of the research *(populated from A1)*

Full title: Real−time functional brain imaging using electrical impedance tomography of evoked responses (fEITER)

Key words: Imaging, Brain, Anaesthesia

2. Name of Chief Investigator *(populated from A2)*

Title: Dr
Forename/Initials: Christopher J.D
Surname: Pomfrett

3. Name of organisation acting as lead sponsor for the study *(populated from A59)*

The University of Manchester

4. Research reference numbers if known *(populated from A65)*

Applicant's/organisation's own reference number, e.g. R&D: R012106

Sponsor's/protocol number:

Funder's reference number:

International Standard Randomized Controlled Trial Number (ISRCTN):

Project website:

6. Give the name of the NHS site within or through which the research will take place under the responsibility of the PI or Local Collaborator. *Please give the name only. Further details of locations should be given in question 8. The name of the site is normally the name of the relevant NHS organisation. Each NHS general or dental practice is a separate site unless a formal consortium/network is in place.*

Central Manchester & Manchester Children's Hospital NHS Trust

Is this a primary care site? ○ Yes ◉ No

If Yes, give the name of the primary care organisation responsible for the site below:

8. Specify all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

List all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Include details of any centres at other NHS organisations where potential participants may be seen or referred for inclusion in the research at this site. Give details of any research procedures to be carried out off site, for example in participants' homes.

	Location	Activity/facilities
1	Department of Anaesthesia laboratory	Volunteer testing with resuscitation
2	Operating Theatre Suites, Manchester Royal Infirmary	Patient testing

12. Who is the Principal Investigator or Local Collaborator for this research at this site?

Title:	Forename/Initials:	Surname:
Dr	Chris J.D.	Pomfrett

Post: Lecturer in Neurophysiology applied to Anaesthesia
Qualifications: Organisation:
Work Address: Dept.Anaesthesia

Manchester Royal Infirmary

Oxford Road, Manchester

Postcode: M13 9WL
Telephone: Fax:Mobile:

E−mail:

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? ○ Yes ◉ No

b) Does this person hold a current substantive or honorary contract with the NHSorganisation or accepted by the NHS organisation? ◉ Yes ○ No

Please provide a copy of the c.v. for the PI.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

15. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share−holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

If Yes, give further details:

16. What is the proposed local start and end date for the research at this site?

Start date:	02/06/2008 *(dd/mm/yyyy)*
Duration (Months):	10
End date:	31/03/2009 *(dd/mm/yyyy)*

17. Summary of the research *(populated from A10−1)*

The ultimate aim of this research project is to evaluate a portable, bedside brain imaging monitor called fEITER. fEITER is a patented, prototype system that integrates existing Electrical Impedance Tomography (EIT) and Evoked Response techniques (ER), with the capability to yield continuous functional imaging of the brain at 100 frames per second.

This project will involve the application of electrical impedance tomography using scalp electrodes to the heads of human, adult volunteers and patients undergoing surgical procedures. EIT has been in clinical use for some 20 years and has been investigated extensively by other research groups. Perhaps most notable is the work of the UCI London group, where rabbits and human volunteers have been studied and brain images have been performed including recordings from children (Holder D (Ed. Electrical Impedance Tomography, 2005. Institute of Physics Publishing).

EIT involves the measurement of the electrical properties of the tissue beneath a set of electrodes applied to the skin in the region of interest, in this case the brain. The measurement process and electrodes are very similar to an EEG (electroencephalography) recording but EIT is able to provide more information as it passes small electrical currents between electrodes to actively probe the properties of the tissue. The currents and voltages involved are exceedingly small; subjects will normally be unaware of the electrical activity during the measurement. In fact, any sensation would provide an alternative stimulus and invalidate the functional aspect of the experiment.

The principal difference between fEITER and other EIT systems is the simultaneous application of a stimulus to achieve functional imaging. The fEITER system will in addition be highly portable. It will also be at least an order of magnitude cheaper than functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) systems. If successful, functional imaging (using fEITER) could be extended to many more bedside situations than is presently possible, such as stroke screening in emergency departments and early detection and subsequent monitoring of vCJD and Alzheimer's Disease sufferers to optimise therapies.

Apart from temporal presentation of stimuli and the presence of evoking sensory stimuli, our work is no different and can build from earlier studies in this field when considering risk and safety. However, there is a pressing need for any commercially viable technology to be demonstrated in a true clinical setting so that potential partners can be recruited to fund the project through expensive stages leading to formal validation and type approval under the medical devices directive and other international regulations. We propose to evaluate in a range of trials visual and auditory stimulation of volunteers within the research team and patients receiving anaesthesia. Where possible, results

obtained with fEITER will be compared to those obtained from the same subjects with fMRI and PET technologies.

The visual stimuli will be of bright flashes which will be introduced to the subjects while the fEITER system is in place in order to produce images of elicited responses from the visual cortex of the brain and associated areas. The bright flashes of 50ms duration will be produced from red LEDs (Chi Oz & Field. Effects of enflurane on visual evoked potentials in humans. British Journal of Anaesthesia 1990; 64:163−6). The flashes will be presented through goggles. Similarly, auditory stimuli through headphones will also be investigated where responses from areas such as the cochlear nuclei and primary auditory cortices in the brain will be tracked. The auditory stimuli will be within normal hearing volume and frequency of the adult ear. They will include 75dB SPL (sound pressure level)clicks presented at rates of 5Hz to both ears simultaneously, these have been used extensively under clinical conditions as described by Thornton and Newton and are harmless (Thornton C, Newton DEF. The Auditory Evoked Response: A Measure of Depth of Anaesthesia. Balliere's Clinical Anesthesiology 1989; 3(3):559−585). In addition the so−called "oddball" paradigm where different tones are presented at random, will also be presented.

Functional responses will be expected at different time intervals after the application of a stimulus denoted by different areas of the brain being visualised on successive frames of the image. A wide range of stimuli will be tested on normal volunteers to identify which elicit the best responses in the fEITER system.

The aim will be to evoke an EIT equivalent to the pattern responses typically seen in Visual Evoked Response (VEP)
and Auditory Evoked Response (AEP) techniques which use EEG recordings. We hope to distinguish between a
VEP using a flash and an AEP using a click.

We propose a two stage approach which will maintain patient and volunteer safety as a priority, and yet will realistically yield useful numbers of results for clinical validation. Such results need large enough numbers to apply statistics to the reconstructed images to show that the effects observed are truly indicative of active neuronal processes and not just random noise.

Clinical work will take place in clinical high dependency environments at Manchester Royal Infirmary in the presence of resuscitation−trained anaesthetists with full backup, including defibrillation.

Part 1. Experimenter volunteers.

The clinical team will commence a series of randomized, controlled trials on volunteers from the experimental team. Up to 32 disposable electrodes will be attached to the head of the subject who will be lying comfortably with eyes open. After attachment of the head stage of the fEITER monitor a series of images will be recorded over 1min to establish a baseline. Sensory stimuli will then be introduced in randomised sequence and 1min recordings will continue after each stimulus. The stimuli will be flash images introduced through a pair of goggles and auditory stimuli presented through isolated, infrared headphones. The ideal EIT response times will be determined from part 1.

Ideally, fEITER will permit identification of whether visual and auditory stimuli have been presented. Randomisation of the stimulus presentation will ensure that the engineering team responsible for data reconstruction and later analysis of the images do not know the nature of the stimuli presented to the volunteer. The question will be “can the method of stimulus be identified purely from the reconstructed EIT image?” Until this can be performed reliably in such healthy volunteers, there is no point moving on to obtaining informed consent from patients, so this phase is a milestone for further development.

Part 2. Anaesthetised patient volunteers.

fEITER was originally envisaged as a tool for the anaesthetist, providing functional, real−time brain imaging in an environment where none currently exists. Twenty patients undergoing elective surgical procedures will be recruited to undergo fEITER imaging before, during and after general anaesthesia with standard agents (e.g. propofol and sevoflurane).

By simultaneously measuring brain function using a Bispectral Index monitor (BIS), we will be able to correlate these results with functional imaging studies already performed by the team at the University of California. The BIS monitor is a licensed monitor which is available for use by the anaesthetist in surgical procedures to assess 'depth of anaesthesia. In the Californian study, the performance of BIS was compared with 18 Fluorodeoxyglucose PET imaging (Alkire M T,Pomfrett C J D. Toward the fundamental unit of anesthetic depth: positron emission tomography suggests that bispectral index (BIS) monitors an important component of anesthetic depth. Anesthesiology 1996 85, A174). The BIS monitor uses a sensor incorporating 4 electrodes which are similar to standard ECG electrodes but specifically designed to be used with this monitor. It is placed on the subject's forehead and measures brain activity translating this into a number between 100 (wide awake) and zero (absence of brain electrical activity).

Up to 32 disposable electrodes will be placed on the patient's head in the anaesthetic room prior to induction of anaesthesia. A BIS sensor wilL also be attached to the patient's forehead in preparation for monitoring during the surgical procedure. After connection to the fEITER monitor, simple patterns of auditory and visual stimuli made up of 75dB SPL clicks and red LED flashes will be presented in turn through earphones and goggles placed over closed eyes. Following induction of anaesthesia and transfer to the operating room a series of images will be collected along with corresponding values of BIS during maintenance of anaesthesia and then on recovery at the end of surgery.

At the end of the proposed study all researchers, both experimental and clinical will meet to interpret and analyse the final images produced and discuss the practical implicatons before designing further studies for the next stage of product development. At the end of the clinical testing as described here we expect to have a strong statistical basis of evidence for the efficacy of fEITER, including an image database from patients.

18. Details of clinical interventions *(populated from A12 where enabled)*

Additional Intervention	Average number per participant		Average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Imaging Investigations (not radiation)	0	1	15 mins	Evaluation of fEITER novel imaging technology in volunteers. 32 disposable EEG electrodes will be attached to the scalp by a Clinical Scientist. Visual or auditory stimuli will be presented at intervals of 1min. This will be limited to flashes or clicks for patient volunteers. We will allow 5mins for the setting up of the electrode montage & equipment and 10min for the testing protocol to give a total of 15min.

19. Details of non−clinical interventions *(populated from A13 where enabled)*

Additional Intervention	Average number per participant	Anticipated average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.

20. Will any aspects of the research at this site be conducted in a different way to that described in Parts A and B or the study protocol?

○ Yes ◉ No

If Yes, explain and give reasons.

21. How many research participants/samples is it expected will be recruited/obtained from this site?

20 volunteers. 20 surgical patients.

22. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study?

Healthy controls will be drawn from the experimenter team, and comprise staff of the University of Manchester. The inventors (Dr Pomfrett and Professor McCann) will evaluate the use of fEITER on themselves before others are recruited. Others healthy volunteers will be recruited by poster advertisement.

Volunteers will be approached at least 24 hours before the proposed study by Dr Angella Bryan, a clinical scientist dedicated to this project. Dr Bryan will explain the fEITER project and the procedures that will be conducted. Potential volunteers will be given an information sheet and told what the project will entail. Records of consent or refusal to consent will be kept confidential so that there is no chance for coercion of staff or volunteers to participate in the trial.

Patients and volunteers will be requested to read an information sheet and sign a consent form at least 24 hours before the procedure. An additional consent form will be presented to the subjects before the procedure, and, in the case of patients, before the administration of any preoperative medication.

Patients scheduled for general anaesthesia during elective surgery will be identified by Professor Brian Pollard FRCA from his normal operating theatre lists. Patients will be identified on the basis of the research protocol not delaying the normal schedule for the operating room i.e. tolerating the inclusion of a fifteen minute awake measurement step.

23. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

1 ☑	Dr Chris J.D. Pomfrett	Clinical Scientist & Honorary Researcher CMMC NHS Trust.
2 ☑	Professor Brian J Pollard	Professor of Anaesthesia & Consultant Anaesthetist

3 ☑	Dr Angella Bryan	Clinical Scientist & Honorary Researcher CMMC NHS Trust

27. Is there a contact point where potential participants can seek independent advice about participating in the study?

The local NHS Patient Advisory Liaison Service (PALS) and the local NHS R&D office

R&D Only

28. Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. *This must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).*

If you consider that changes should be made to the generic content of the information sheet to reflect site−specific issues in the conduct of the study (see 20), give details below. A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.

29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.) (Populated from A29)*

If the volunteers or patients do not speak English an interpreter will be engaged to explain the nature of the project. As it is essential that the subjects are able to rapidly communicate their feelings regarding fEITER in English so that the researchers can assess whether there are any problems, interpreters will also be required to be on hand during the procedure.
What local arrangements have been made to meet these requirements (where applicable)?As above.

30. What arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

Professor Brian Pollard will inform the volunteer's or patient's GP of their inclusion in the study by letter also informing them of any observations arising from the use of fEITER.
In the case of the anaesthetised participants, the surgeon responsible for the care of the patient will be informed in advance and sent this ethical application and NRES opinion.
Professor Pollard will be the responsible for the anaesthesia care of all participants.

33. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

Volunteer studies will take place in the laboratory area of the Department of Anaesthesia with Advanced Life Support trained personnel present and full backup of resuscitation equipment.

Patient studies will be performed in clinical high dependency environments (operating theatres) at Manchester Royal
Infirmary in the presence of resuscitation−trained anaesthetists.

37. Will any external funding be provided for the research at this site?

(•) Yes ( ) No

If Yes, indicate the source and details of the funding:

38. Which organisation will receive and manage this funding?

University of Manchester

39. Authorisations required prior to R&D approval

This section deals with authorisations by managers within the NHS organisation. It should be signed in accordance with the guidance provided by the NHS organisation. This may include authorisation by line managers, service managers, support department managers, pharmacy, data protection officers or finance managers, depending on the nature of the research. Managers completing this section should confirm in the text what the authorisation means, in accordance with the guidance provided by the NHS organisation. This section may also be used by university employers or research staff to provide authorisation to NHS organisations, in accordance with guidance from the university.

Declarations

Declaration by Principal Investigator or Local Collaborator

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.
4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.
5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.
6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.
7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.
8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.
9. I undertake to complete any interim and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.
10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.
11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.
12. I understand that information relating to this research, and about me as a researcher, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
13. I understand that information relating to this research, and about me as a researcher, will be held by RECs undertaking site−specific assessment and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
14. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

Signature of Principal Investigator or Local Collaborator:

Print Name:

Date:

Appendix V – Local Ethical Application fEITER

Ethical Application using fEITER

The University of Manchester

UNIVERSITY OF MANCHESTER

COMMITTEE ON THE ETHICS OF RESEARCH

ON HUMAN BEINGS

Application form for approval of a research project

1 Title of project

Experiments to determine skull impedance using fEITER (functional electrical impedance tomography of evoked responses) at 10 kHz.

2 Details of applicant(s)

Ms Rebecca Robinson,

School of Electrical and Electronic Engineering,

Rebecca.Robinson@postgrad.manchester.ac.uk

The experiments are connected with a project funded by the Wellcome Trust ('functional Electrical Impedance Tomography of Evoked Responses'), in which the main investigators are Prof. Hugh McCann from the University of Manchester and Dr. Christopher Pomfrett of the University Department of Anaesthesia at Manchester Royal Infirmary.

3 Details of project

3.1 Context

A pilot study on functional electrical impedance tomography of evoked responses (fEITER) has been carried out at The University of Manchester [1]. fEITER is a Wellcome Trust project which has applied for and been provisionally granted a favourable NRES opinion (07/H1003/145) given by South Manchester REC pending a notice of no objection by the MHRA submitted June 2009. fEITER is a patented, prototype system that integrates existing Electrical Impedance Tomography (EIT) and Evoked Response techniques (ER), with the capability to yield continuous functional imaging of the brain at 100 frames per second.

Work has been carried out, by the applicant, in accordance with the previous ethical approval granted (ref: 06241and ref: 07185). Experiments have been carried out on 12 subjects, and all tests were successful in providing the desired data. Each subject had impedance measurements taken from their forearm, shin and scalp using three types of standard electrodes (Aspect Medical Systems ZipPrep©, 3M Red Dot Electrodes© and Kendall Arbo Electrodes ©). The tests included assessment of the effects of subject movement, muscle contraction etc. Throughout these tests, no sensation was observed by any of the subjects. The high-frequency data (1 k – 100 kHz) obtained are of excellent quality and they appear to show important new phenomena that have not previously been reported in the literature [2,3].

I have carried out previous impedance measurements on the forearm, shin and head (university ethical approval granted ref: 06241 and ref: 07185). These experiments were carried out using a commercial LCR meter and specifically designed safety circuitry. This work was very successful at determining the composite impedance on the forearm, shin and scalp.

3.2 Purpose

The ultimate aim of this proposed study will use the fEITER device to collect data on two subjects, Prof. Hugh McCann and Dr Chris Pomfrett, to investigate the skull conductivity and perfect the application of electrode attachment before the project progresses to group participants and patient volunteers (subject to notice of no objection from the MHRA).

The accurate measurements of the skull conductivity will provide valuable information for fEITER. Novel forward calculations have been performed which have already shown the potential for exploitation of good impedance data at the skull [4]. This new set of data would enable the fEITER team to improve the data inversion methods for the image reconstruction.

3.3 Similar research

Extensive research using electrical impedance tomography (EIT) for medical application has been carried out in many centres. Most notably, is the work of the UCL London group [5], where animals and human volunteers (including children) have been studied. Both presently and in the past, other university research groups such as Sheffield, Kyung Hee (Korea), and UPC (Barcelona, Spain) have also been active in the area of medical EIT. Additionally, EIT by Dartmouth College (Hanover, USA) has successfully been used in the area of breast cancer screening using a FDA approved commercial instrument [6].A major impediment to the use of this technique for medical diagnostic application on the head is the difficulty in obtaining quantitative images. This requires accurate information on the electrical impedance of the skull. An extensive literature search has revealed that there is very little accurate published data on this topic, the most relevant being from Hoekema et al [7].

3.4 Methods

This proposed study will involve the application of EIT using 32 scalp electrodes to two volunteers, Prof. Hugh McCann and Dr Chris Pomfrett.

fEITER is a new prototype device that delivers a small current of 1mA (p-p) at 10kHz, this is only a third of the permitted current set by the British Safety Standard 60601-1:2006 [8]. fEITER has the capability of continuous functional imaging at 100 frames per second. The HeadBox provides these small tomographic sinusoidal currents and digitizes the measured scalp voltages which are transferred to the base unit of the EIT sub-system. The HeadBox unit is designed to meet the standard associated with a Type II BF part in accordance with BS

EN 60601-1:2006 [8]. The base unit of the EIT sub-system provides interfacing to the HeadBox unit, data acquisition laptop. fEITER will be connected to each volunteer via touch-proof leads and the chosen electrodes. fEITER consists of a Head Box Unit and a Base Unit, seen in Figure 1 and 2 respectively. EIT involves the measurement of the electrical properties of the tissue beneath a set of electrodes applied to the skin in the region of interest, in this case the head. The measurement process and electrodes are very similar to an EEG (electroencephalography) recording but EIT is able to provide more information as it passes small electrical currents between electrodes to actively probe the properties of the tissue. As currents and voltages involved are exceedingly small; subjects will be unaware of the electrical activity during the measurement.

Throughout the proposed tests, the experimenter is always present along with a 3rd person. The volunteer is able to withdraw from the test at any time. This is done by merely pressing their switch. Similarly the experimenter can stop the test at anytime by pressing the independent switches on the HeadBox and Base Unit.

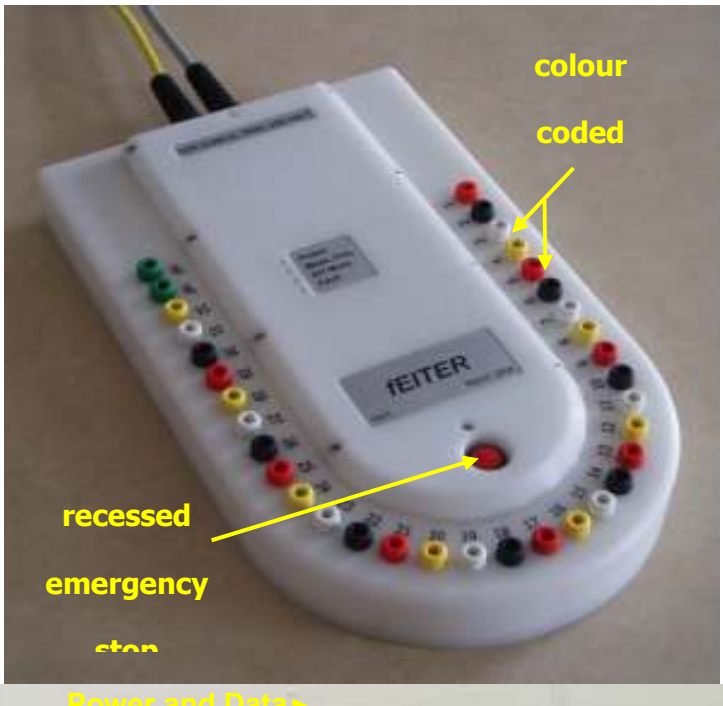

Figure 1. *HeadBox and* ***Figure 2***. *Base Unit*

3.5 Duration of the study

3 Months

3.6 Location of the study

Sensing, Imaging and Signal Processing Group (SISP)

Laboratory Area E45

Sackville St. Building

3.7 Staff involved

The Principle Investigators of fEITER are Prof. Hugh McCann of the University of Manchester and Dr. Christopher Pomfrett of the Research School of Clinical & Laboratory Sciences, School of Medicine, University of Manchester.

Other staffs include Dr JL Davidson Postdoctoral Research Associate and Dr P Wright Senior Experimental Officer for Sensing, Imaging and Signal Processing at The University of Manchester.

3.8 Initiator/sponsor

The sponsor for this project is EPRSC. The results will be used in the Wellcome Trust functional Electrical Impedance Tomography for Evoked Responses (fEITER) project.

4 Details of subjects

4.1 Total number

Maximum: 2

4.2 Sex and age range

Sex: M Ages :

4.3 Type

Principle Investigators on fEITER project; Prof McCann and Dr Pomfrett

4.4 Inclusions and exclusions

N/A

4.5 Method of recruitment

Both subjects are named in this document, they are the principle investigators. No one else will be recruited for these experiments.

4.6 Payments to volunteers

No payments will be made to volunteers.

5 Details of risks

5.1 Drugs and other substances to be administered

N/A

5.2 Procedures to be undertaken

There are no invasive procedures in the proposed study. The experiments include surface electrodes being placed on the scalp. Both subjects have previously taken part in an experiments which used the same type of electrodes that will be used in this experiment (ethics approval ref: 06241 and ref: 01785), neither subject had any skin irritation or allergic reaction.

5.3 Potential dangers, discomfort or inconvenience

N/A

5.4 If a patient group is being studied:

N/A

5.4.1 Indicate whether (and if so, how) participation will affect their general treatment regime

N/A

5.4.2 Direct benefits

N/A

6 Safeguards

6.1 Precautions

Previous studies have used the same electrodes (ref: 06241and ref: 07185), both volunteers have completed a questionnaire to determine if they would be allergic to any of the materials used in the manufacture of the electrodes. Neither volunteer had an adverse reaction to any of the previous tests.

If there was an adverse event the volunteer has a pendant switch which automatically stops the current flow. The experimenter has access to two emergency switches; (a) the Head Box switch, this stops the current flow and sets the Head Box into a fault state meaning it cannot accidentally be turned back on again. To resume experiments the experimenter must hold the experimenter pendant switch for a continuous 5 seconds and (b) the emergency stop button on the base unit, this turns off all power to the fEITER system and requires a full start up again to turn back on.

6.2 GP's initial notification

N/A

6.3 GP's notification of events/findings

N/A

6.4 Ethics Committee's notification

The Ethics Committee will be immediately notified (via the Secretary) of any adverse reactions or untoward events.

6.5 Informed consent

There are only going to be two volunteers, the principal investigators on the fEITER project.

6.6 Confidentiality

The data obtained during the tests will be stored and processed using computers. After the study is completed, these may be copied onto a permanent record which might be studied again at a later time.

6.7 Insurance

Both subjects will be covered by the University of Manchester assuming the application is approved by the Committee.

7 Approval by another recognised ethics committee

Indicate whether this project has been considered by another recognised ethics committee.

YES/NO

Signatures of applicant(s)

....

Signed Date

....

Signed Date

References

[1] H. McCann et al., 'Sub-second functional imaging by Electrical Impedance Tomography,' IEEE EMBS Annual International Conf. (New York City, USA, 2006)
[2] R Robinson, CJD Pomfrett and H McCann, 'Composite Electrode-Tissue Impedance for EIT System Design,' In proc. Biomedical Electrical Impedance Tomography Conference (Dartmouth, USA, 2008)
[3] R Robinson et al., 'A Study of Composite Electrode-Tissue Impedance,' IEEE EMBS Annual International Conf. (Vancouver, Canada, 2008)
[4] JL Davidson, C. J. D. Pomfrett and H. McCann, 'Predicted EIT current densities in the brain using a 3D anatomically realistic model of the head,' In proc. ICEBI'07 (Graz, Austria, 2007).
[5] D. Holder (ed.), Electrical Impedance Tomograpy: Methods, History and Applications. Bristol, England: Institute of Physics Pub., 2005
[6] R. Halter, A. Hartov and K.D. Paulsen, 'Design and implementation of a high frequency electrical impedance tomography system,' Physiol. Meas., 25, 2004, pp. 379 – 390
[7] R. Hoekema et al., 'Measurement of the Conductivity of Skull, Temporarily Removed During Epilepsy Surgery,' Brain Topography, 16, 2003, pp. 29-38
[8] BS EN 60601-6:2006 Medical electrical equipment. General requirements for basic safety and essential performance.