A first pilot study of Electrical Impedance Tomography with scalp electrodes during epileptic seizures in humans

L Fabrizi¹, M. Sparkes³, L Horesh¹, J F Perez-Juste Abascal¹, A McEwan¹, R H Bayford², R. Elwes³, C.D. Binnie³ and D S Holder¹

¹ Department of Medical Physics and Bioengineering, Malet Place Engineering Building, Gower Street, University College London, London WC1E 6BT, UK
² School of Health, Environmental and Biological Sciences, Middlesex University, Archway Campus, London N19 5ND, UK
³ Department of Clinical Neurophysiology, King’s College Hospital, London SE5 9RS, UK

E-mail: l.fabrizi@ucl.ac.uk

Abstract. Electrical Impedance Tomography (EIT) has the potential to produce images during epileptic seizures. This would improve the accuracy of the localization of epileptic foci in patients undergoing presurgical assessment for curative neurosurgery. It has already been shown that impedance increases by up to 22% during induced epileptic seizures in animal models, using cortical or implanted electrodes in controlled experiments. The purpose of this study was to determine if reproducible raw impedance changes and EIT images could be collected during epileptic seizures in patients who were undergoing observation with video-ElectroEncephalography (EEG) telemetry as part of evaluation prior to neurosurgery to resect the region of brain causing the epilepsy. A secondary purpose was to develop an objective method for processing and evaluating data, as seizures arose at unpredictable times from a noisy baseline. Four-terminal impedance measurements from 258 combinations were collected continuously using 32 EEG scalp electrodes in 22 seizure episodes from 7 patients during their presurgical assessment together with the standard EEG recordings. A reliable method for defining the pre-seizure baseline and recording impedance data and EIT images was developed, in which EIT and EEG could be acquired simultaneously after filtering of EIT artefact from the EEG signal. Baseline fluctuations of several per cent over minutes were observed in the baseline between seizures. During seizures, boundary voltages diverged with a standard deviation of 1-54%, but no reproducible changes with the expected time course of some tens of seconds and magnitude of c. 0.1% could be reliably measured. This demonstrates that it is feasible to acquire EIT images in parallel with standard EEG during pre-surgical assessment but, unfortunately, expected EIT changes on the scalp of about 0.1% are swamped by much larger movement and systematic artefact. Nevertheless, EIT has the unique potential to provide invaluable neuroimaging data for this purpose and may still become possible with improvements in electrode design and instrumentation.

Keywords: EIT, Epilepsy, Human Measurements, Telemetry

1. Introduction

Epilepsy is the most common neurological disorder after stroke and 60 million individuals are affected by this disease world-wide. Seizures can be arrested or reduced in 75% of the cases by administration of the appropriate anticonvulsant drug and 7-8% may benefit from neurosurgery, in which the part of the brain that is considered to be the origin of the seizure is surgically removed (Engel, Jr. 1993). This operation can only be performed if the epileptic activity arises from a discrete focus and its success is strictly linked with the accuracy with
which this source is localized. Nevertheless surgery fails to relieve the seizures in almost a fourth of cases, and this could be due to an inaccurate identification of the focus or to the presence of multiple or diffuse foci (Polkey 1988).

Our group at University College London has been developing the use of EIT for imaging brain function. One of our major goals has been to use EIT to provide images of the source of epileptic seizures in patients with epilepsy. We have demonstrated in animal models that seizures can be imaged by EIT (Rao et al. 1997) and have specifically designed an EIT system for this purpose with a small headbox on a lead 10m long so that EIT can be recorded continuously over days while a patient is observed with EEG and video on the ward (Cusick et al. 1994; Yerworth et al. 2002). We have also developed reconstruction algorithms which can image small impedance changes in the brain by using a sensitivity matrix approach and detailed anatomically realistic Finite Element Meshes of the head (Tidswell et al. 2001; Bagshaw et al. 2003). In principle, EIT could image in much the same way as if a patient were to have a seizure while in a functional Magnetic Resonance Imaging or Positron Emission Tomography scanner, as impedance changes due to changes in blood flow and cell swelling. However, seizures arise unpredictably – usually about once or so each day, so it is not practicable to perform this in one of these large immobile scanners. EIT with the UCLH Mark 1 system can be collected continuously over several days and so, uniquely, be analyzed retrospectively at the time of a seizure, when these are identified by the use of video or changes on EEG. The limited success of resective surgery is due in part to an inability to image the seizure source directly. If successful, EIT would provide a vital additional method for presurgical evaluation in intractable epilepsy.

This study was the first attempt to build on the previous development work and collect EIT data and images under the challenging conditions of recording over days in epileptic patients observed on the ward.

1.1. Presurgical assessment in epilepsy
At present, epileptic presurgical assessment is performed using techniques intended to identify the epileptogenic lesion and seizure onset zones of the cerebral cortex (Rosenow and Luders 2001). The epileptogenic lesions were identified in the past with Computer Tomography (CT), but today structural Magnetic Resonance Imaging (MRI) is more commonly used (Rosenow and Luders 2001; Kuzniecky and Knowlton 2002). The onset zone, which is the area of the brain from which the clinical seizures are generated, is routinely evaluated with prolonged EEG (scalp or invasive) and video-EEG (Porter and Sato 1993; Rosenow and Luders 2001). Epileptic patients are admitted to a Telemetry ward, which is a specialized monitoring unit equipped with instrumentation for automatic measurement and transmission of 24 hour video-EEG for several days, and video-EEG recordings are made until several seizures are detected. The integration of EEG and seizure semiology, recorded by the video, helps the doctors to elaborate a hypothesis on the location of the epileptic onset zone. Sometimes the information given by the scalp EEG is inconclusive, since the signal is attenuated and distorted by the conductive volume between the signal source and the scalp, especially in deep epileptic sources. In this case an invasive implantation of subdural or depth electrodes may be needed (Jayakar 1999), which is an expensive and hazardous procedure. The use of an additional, non-invasive, imaging technique capable of monitoring the raise of the epileptic activity would reduce the need for this practice. Established functional imaging techniques, such as fMRI and PET require the use of scanners, which is evidently impractical for continuous monitoring. Ictal SPECT is a method in which a radioisotope is injected manually as soon as a seizure commences (Van Paesschen 2004). However, it carries various technical difficulties: the radioisotope has to be available for immediate injection at the seizure onset, the personnel of the telemetry ward have to be trained to use radioactive substances, and it only detects blood flow changes some tens of seconds after true seizure onset.

EIT could be suitable for a bedside continuous non-invasive monitoring of the conductivity changes associated with epilepsy. Therefore it could be a valid method to
integrate EEG information with a 3-Dimensional functional imaging technique during seizures, which would increase accuracy in localization of deep epileptic foci.

1.2. Impedance changes in epilepsy
The localization of epileptiform foci has been addressed as a possible application of EIT (Boone et al. 1994; Rao A. 2000). During the 1960s, impedance changes related to induced epileptic activity were measured in various animal experiments with cortical and implanted electrodes (VAN HARREVELD and Shade 1962; Shalit M.N. 1965; Elazar et al. 1966). The impedance increased by 3-12%, at a recording frequency of 1 kHz. Fox et al. (Fox et al. 2004) measured impedance increases of 22±3% in a low-Ca\(^2+\) hippocampal slice preparation using 5-10 nA current at 50 Hz. These changes were attributed to movement of sodium and chloride ions from the extra- to intracellular compartment of the brain and to neuronal cell swelling. During intense neuronal activity, the cell membrane becomes more permeable to sodium, which creates an osmotic gradient that leads to a movement of water inside the cells. The extracellular space shrinks and impedance at relatively low frequencies is correspondingly increased. The movement of sodium and calcium inside the cell prevent them from free participation in the transport of the measuring current, since they are surrounded by the highly resistive cell membrane.

In our group, Rao (Rao A. 2000) reconstructed images of impedance increases of 5.5-7.1% related to focal and generalized epileptic activity using cortical electrodes and a current of 5 mA at 51 kHz. Although direct impedance measurement showed only impedance increases of 9.5-14.3% (current of 1 mA at 47 kHz), impedance decreases of similar magnitude appeared in some areas adjacent to the stimulation site in the reconstructed images, and were then attributed to a shadowing effect of the reconstruction software.

The impedance change locally in the cerebral cortex during seizures is therefore well established, and is about 10% when recorded with applied current of some tens of kHz. For the purposes of this study, it is important to have an estimate of the expected magnitude when this is recorded with scalp electrodes. This is not exactly known but may be expected to be attenuated, due to partial volume effects, the shunting of current by the cerebrospinal fluid and scalp, and resistance of the skull. This has been modelled in our group for the specific case of visual evoked potentials recorded near DC, when local changes were attenuated by three orders of magnitude (Gilad et al. 2005). In epilepsy, it may be expected that larger volumes of cortex would be activated and, at least at some stages, would be in superficial cortex. A reasonable estimate, therefore, would be that an upper bound for the expected impedance changes in this study would be 0.1%.

1.3. Purpose
The purpose of the present study was to assess, for the first time, if large-scale changes in conductivity due to epileptic activity could reproducibly be measured with EIT from scalp electrodes in human subjects. These would be measured in form of boundary voltage variation and localised in reconstructed tomographic images. Measuring impedance changes related to spontaneous seizures from scalp electrodes may be predicted to suffer from several technical problems. First, using scalp electrodes, the current that will flow through the brain will be considerably reduced with respect to that in the scalp, owing to the high skull resistivity, and the voltage changes at the boundary due to impedance changes in the brain will be small. Secondly, seizures are an unpredictable event, which prevent the possibility of controlled experiment and often involves dramatic movement of the subject, which were inhibited in animal studies with anesthetization or brain stem transection. In addition, the EIT procedure injects a large artefact into the EEG signal, which must be recorded simultaneously for clinical purposes. A secondary purpose of this work was to develop a reliable method for simultaneous collection of EIT and EEG and objective analysis of the impedance changes at the time of the seizure.
1.4. Experimental design

EIT was set to run continuously together with the EEG on 7 patients undergoing pre-surgical assessment for Neurosurgery at King’s College Hospital London. EIT was recorded using the UCLH-EIT Mark 1b (Yerworth et al. 2002) which utilized a single impedance 4 terminal measuring circuit multiplexed up to 31 electrodes. Segments of the two recordings close to seizures were considered together. The boundary voltage measurements were normalized to a period preceding the epilepsy onset chosen as baseline, which represented their value during normal brain activity. The conductivity changes characteristic of a seizure would then translate in a significant deviation of the boundary voltages from the baseline of some fractions of percent in the period immediately before the seizure onset (pre-onset period; figure 1). A delay between the impedance change and the scalp EEG onset could be expected due to the time the epileptic activity takes to build up and propagate from the deep focus to the brain surface. After being normalized and filtered, measurement combinations, which were likely to be corrupted, were eliminated and the significance and size of the remaining voltage changes were assessed. A set of other EIT segments not related to any seizure was analysed with the same method to determine whether these changes occurred in concurrence with epilepsy. Image reconstruction of the data obtained at the seizure onset was done using a linear algorithm based on truncated singular value decomposition (tSVD), with the sensitivity matrix constrained to the brain. The results were then visually inspected and compared to the EEG, video and MRI findings.

Figure 1. Example of a boundary voltage measurement. In most of the cases in this study, seizure onset was in the deep mesial temporal lobe. Activity would commence here and then only spread to the surface cortex after several seconds. The scalp EEG only detects activity in superficial cortex so, in the ideal case, EIT would detect impedance changes due to the deep onset several seconds before the scalp EEG changed or clinical activity could be seen. The period between the end of the baseline (black bar) and therefore deep seizure onset, and the scalp EEG onset, is termed the pre-onset period (grey bar) and is the period during which we expect to see the boundary voltage changes.

In the study, impedance was recorded using the UCLH Mark 1b system, in which constant current was injected, and the in-phase component of the resulting voltages were recorded and used to calculate the transfer impedance. The terms “impedance” or “voltage” below are used interchangeably and refer to this in-phase component which strictly is the real component of the transfer impedance.

2. Methods

2.1. Trial set-up

Seven patients undergoing pre-surgical assessment for Neurosurgery at the King’s College Hospital, London were voluntarily recruited for this study (table 1). Each subject gave informed consent for the study, which was approved by the local committee on the Ethics of Human Research. EIT and video-EEG ran continuously with two separated sets of electrodes for periods of 2 to 10 days in order to collect data during spontaneous epileptic seizures.

Table 1. Patients characteristics, including MRI and EEG findings and doctor diagnosis. (MTS = mesio-temporal sclerosis; DNET = dysembryoblastic neuroepithelial tumour; CPS = complex partial seizure).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>MRI</th>
<th>EEG</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>20</td>
<td>No definite abnormalities</td>
<td>Rt posterior temporal/ mid-</td>
<td>CPS, Rt temporal onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>-------------------------------------</td>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>37</td>
<td>Rt MTS</td>
<td>temporal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rt fronto-temporal, some Lt</td>
<td>CPS, Rt superior frontal/ pre-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>involvement. Not conclusive</td>
<td>frontal on-set with gradual</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>spreading</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>30</td>
<td>Lt DNET at parahippocampal gyrus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rt fronto-temporal onset, some Lt</td>
<td>CPS, onset on the Lt</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>temporal involvement</td>
<td>parahippocampal gyrus with</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rapid spread to the Rt</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>32</td>
<td>No definite abnormalities</td>
<td>No clear lateralization</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lt MTS and abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in inferior part</td>
<td>Lt occipital onset</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>26</td>
<td>Lt MS and abnormalities</td>
<td>No clear lateralization,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in inferior part</td>
<td>possibly Rt predominance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inferior Lt temporal onset</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>male</td>
<td>39</td>
<td>Lt frontal convexity cavernous</td>
<td>No clear lateralization,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>haemangioma</td>
<td>possibly Lt onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lt fronto-temporal onset</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>20</td>
<td>Lt hippocampal atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CPS, Lt temporal onset</td>
<td></td>
</tr>
</tbody>
</table>

The EEG was recorded with 21 electrodes in a modified Maudsley electrode placement system (Binnie et al. 1982) and 32 similar additional EIT electrodes were applied in a modified 10-20 electrode placement system (figure 2). Standard 10 mm diameter silver/silver-chloride EEG cup electrodes were used for both systems and electrode paste was applied every morning to enhance the contact impedance.

A high pass filter (1 kHz) was required on the voltage measurements lines of the EIT system to reduce the low-frequency artifacts due to the switching of the measurement current injecting electrode pair and a low pass filter (43 Hz) on the EEG line to prevent the high-frequency EIT signal from interfering with the EEG trace. An additional software filter based on an fMRI artifact subtraction method (Allen et al. 1998) was applied on the EEG signal to eliminate the residual of the low-frequency switching artifacts. The EIT measuring current injected was of 2.2 mA at 38.4 kHz from diametrically opposed electrodes. Time difference images of conductivity were reconstructed from boundary voltages variations with respect to a period preceding the seizures (baseline), using a linear algorithm based on truncated singular value decomposition. Each image was obtained starting from sets of 258 boundary voltage measurements collected with a sampling rate of 2-2.5 Hz (one full image data set collection every 0.4-0.5 seconds).

Figure 2. EIT electrodes positions. Electrode positions 12-18-28-31 were added to the International 10-20 system and the electrodes of the mid-line (Fz, Cz and Pz) were placed 1 cm behind the normal positions (modified from Tidswell et al. 2001).

2.2. Raw data processing
EIT impedance measurement segments of 50-190 seconds were analyzed in relation to the onset of the EEG (EEG onset) and the one observed on the video (Clinical onset).

Preliminary impedance measurement elimination. Each segment included measurements from 258 different electrode combinations (EC), which were median filtered with a window 5
data samples long. EC have been discarded if the absolute value of the impedance measured was exceeding 4.8 V or going below 0.2 V for more than 70% of the length of the segment.

**Baseline selection.** The baseline was chosen, after visual inspection of all the remaining EC (ECR), as a reference period of 20 seconds common to all the ECR preceding the seizure onset for no more than 90 seconds, according to the following criteria. (i) Less than 10% of ECR had to have a standard deviation during the baseline period that exceeded 2% of the mean value of the baseline, after linear baseline correction (see below). (ii) Without considering this additional ECR subset, the absolute slope of the linear fit to the 20 seconds following the baseline had to be larger than the absolute slope of the linear fit to the baseline in more than 50% of the recording combinations.

**Baseline correction and outlier elimination.** ECR were low-pass filtered (35th order FIR filter, -6dB point at 0.2 Hz) and for each ECR a least-squares procedure was employed to find the best linear fit to the baseline period (Boone et al. 1994). The slope and intercept of this line were then used to correct all the traces, which were expressed as a percentage change respect to the mean value of the baseline. If the standard deviation during the baseline period was exceeding 2% or changes larger than +/- 10% were seen for more than 50% of the period between the end of the baseline and the seizure onset, the ECR was discarded. For clarity we will refer to the remaining normalized boundary voltage as NBV.

**Pre-onset period.** The pre-onset period was defined as the period between the end of the baseline and the first evident movement artefact, defined as a sudden change within 3 data points of more than 1% occurring in the trace obtained as the average of the absolute value of the NBV, or the EEG or Clinical seizure onset if they occurred earlier. An evident movement artifact is.

‘Dummy’ seizures. An identical analysis was conducted for comparison in 7 EIT segments (1 for each patient) recorded in periods not related with any seizure, when no impedance change was expected. They were 120 seconds long and the EEG and Clinical onset were both defined at 90 seconds.

2.3. Image reconstruction

A linear reconstruction was performed using truncated singular value decomposition (TSVD), which has been previously used as linear reconstruction algorithm for EIT of brain function (Bagshaw et al. 2003), with a fixed truncation level of $10^3$ the magnitude of the largest singular value. The forward problem was solved using a UCL group modified version of EIDORS-3D Toolkit (Polydorides N and Lionheart W.R.B. 2002) and a realistic head shaped 4 layer model (scalp, skull, CSF, brain) of 136000 elements generated with I-DEAS software (Tizzard et al. 2005). The conductivity values given to each compartment were: 0.15 S/m for the scalp, 0.015 S/m for the skull, 1.79 S/m for the CSF, 0.37 S/m for the brain. The sensitivity matrix was calculated for the whole head and then constrained to the brain region. This was done only once since the used head mesh and measuring protocol were standard for all the patients. The rows of the sensitivity matrix corresponding to the measurement combinations discarded in the raw data processing were removed before the pseudo-inversion. The data used to reconstruct the images were the average of 3 individual data sets. This was done to reduce the high frequency noise in the data and to look for significant changes occurring over a time-scale of a few seconds (Fox et al. 2004).

This approach alters the scaling between the reconstructed change within the image and the boundary voltages. In order to correct for this, the conductivity value of each voxel of the reconstructed image was multiplied by a scaling factor of 3.5, according to an empiric calibration based on simulations of spherical conductivity increases of 5%, 10% and 15% of 20mm radius in 3 different position of the brain.

3. Results

A total of 22 seizures in 7 patients were collected with simultaneous EIT and EEG, ranging from 1 seizure to 6 seizures per subject. In 3 seizures, it was not possible to find a baseline period that satisfied the criteria described above and were not considered.
3.1. Technical issues
All the necessary electrodes (31+1 for the EIT and 19+1 for the EEG) were successfully positioned on the patients' head. The level of current was insensible in all subjects and they were all willing in carry on with the experiments. The EEG was recovered accurately with the filtering and allowed the clinical diagnosis of the epileptic conditions.

3.2. Raw voltage changes
No reproducible changes were observed during seizures and the changes were substantially larger than the estimated magnitude of 0.1%. The baseline periods ended between 80 to 5 seconds before the EEG onset and the absolute trend of the linear fit after the baseline was larger than that of the baseline in 55.3% and 97.8% of the electrode combinations considered in each seizure. The total amount of electrode combinations eliminated per seizure according to the criteria described in section 2.2 ranged from 3.5 to 43.4%. In 15 seizures, the normalized boundary voltage (NBV) diverged at the EEG onset, or at the clinical onset if it occurred earlier, with a standard deviation between 1.1 and 7.6%; the remaining 4 seizures had a standard deviation exceeding 13% (table 2). The boundary voltages of seizure 1 and 6 of patient 1 after the analysis are presented in figure 3. Measurements from similar seizure episodes from the same patient did not have a repeatable time course or magnitude.

Similar results were obtained for the EIT segments not related with any seizure (table 3). The absolute trend of the linear fit after the baseline was larger than that of the baseline in 64%-92% of the electrode combinations. The total amount of electrode combinations eliminated ranged from 3.5% to 18.2% and the NBV had a standard deviation at the ‘EEG onset’ between 1 and 5.4%.

Table 2. Parameters calculated for each seizure: percentage of electrode combinations with an increase of the trend of the linear fit after the baseline (I.T.); total amount of electrodes combinations eliminated (E.C.E.); standard deviation of the voltage changes at the first onset (EEG or Clinical) (S.C.).

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>I.T.</td>
<td>66.9</td>
<td>95.4</td>
<td>96.5</td>
<td>82.7</td>
<td>88.9</td>
<td>75.6</td>
<td>57.7</td>
</tr>
<tr>
<td>EC.E.</td>
<td>7.4</td>
<td>20.5</td>
<td>34.9</td>
<td>21.3</td>
<td>43.4</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>S.C.</td>
<td>2.1</td>
<td>4.8</td>
<td>15</td>
<td>4.1</td>
<td>53</td>
<td>1.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 3. Parameter calculated for each ‘dummy’ seizure.

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.T.</td>
<td>92.1</td>
<td>83.7</td>
<td>70.7</td>
<td>67.6</td>
<td>78.4</td>
<td>79.9</td>
<td>64.5</td>
</tr>
<tr>
<td>EC.E.</td>
<td>12.4</td>
<td>10.8</td>
<td>18.2</td>
<td>8.9</td>
<td>4.6</td>
<td>3.5</td>
<td>4.6</td>
</tr>
<tr>
<td>S.C.</td>
<td>3.7</td>
<td>5.4</td>
<td>4.4</td>
<td>3</td>
<td>1</td>
<td>1.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Figure 3. Boundary voltages linearly corrected and normalized to the mean baseline value (expressed in % changes) from 2 seizures of patient 1. The black horizontal line marks the baseline period while the red line marks the pre-onset. The time is referred to the EEG onset.

3.3. Image reconstruction

Similarly, no consistent changes between or within subjects could be recognised in reconstructed images. In 6 out of 19 seizures, localized conductivity decreases could be recognised together with other broader changes before seizure onset and only two seizures of subject 1 had similar location and time course (figure 4). All the localized conductivity changes reconstructed were 60% up to 450% in regions of the brain not concordant with the EEG and MRI findings.
4. Discussion

4.1. Summary of results
Experiments were performed to develop for the first time a method to record and analyse EIT during natural epileptic activity in concurrence with video-EEG from standard scalp electrodes in humans. Seizures are unpredictable events, preventing the possibility of conducing controlled experiments, so we proposed long term EIT during presurgical video-EEG monitoring in a Telemetry ward as a feasiblesolution. Hours of EIT were available at the end of the experiments and only relevant segments were considered in a similar method to that of standard EEG analysis. There were significant boundary voltage changes in the majority of the electrode combinations after the baselines, before seizure onset, and led to voltages that diverged at seizure onset with standard deviations between 1.1% and 53% after elimination of the noisiest combinations (3.5-43.4% of the 258 combinations used). This exceeded the feasibility study predictions by about two orders of magnitude. Similar results were obtained in EIT segments not related with any seizure occurrence. The conductivity reconstructions did not display consistent reproducible changes and showed decreases far larger than that measured locally with cortical and implanted electrodes during induced epilepsy in animals.

4.2. Robustness of the data collection and analysis method
We have shown that simultaneous measurement can be done using two separated sets of electrodes for EIT and EEG and that EEG can be recovered for clinical diagnosis through hardware and software filtration. The EIT electrodes can easily be positioned by a technician of the ward in between the EEG electrodes and the signals can be successfully synchronized by using the EIT artifact in the EEG recordings as reference.

4.3. Explanation of observed changes
The raw impedance changes are therefore unlikely to be related to seizure activity; these were probably artifact caused by unstable electrode contact, as similar changes were measured during periods not seizure related.

The major sources of error were possibly random, as predicted by Boone et al. (Boone et al. 1994), the signal-to-noise ratio being inadequate for the following reasons. (i) The amount of current passing through the brain was probably too small compared to that shunted by the scalp and then the sensitivity to impedance changes in the brain insufficient; (ii) the boundary voltage measurements were probably corrupted by subject movements, which changed the
electrodes contact with the scalp, giving rise to apparent voltage variations; (iii) the baseline itself was difficult to identify and its variability was often larger than the signal we intended to measure.

The artifacts in the boundary voltage probably hid any genuine change due to impedance variation inside the brain, and then the reconstructed images did not display reproducible features. In two seizures similar conductivity alterations were reconstructed, but they were far too large to be genuine.

Systematic errors due to various simplifications of the reconstruction algorithm could be present. Factors that might be expected to influence the precision of the forward problem solution include the following: (i) assuming a standard geometry for the head shape and the electrodes position for all the patients; (ii) assuming anisotropic tissues (neuronal tissue and skull for example) isotropic; (iii) using a fixed truncation level for the tSVD, disregarding the noise level of the data. Furthermore the calibration of the reconstructed conductivity did not take into account some factor on which it depends such as: the number of singular values used for the decomposition or the number of electrodes combinations eliminated.

4.4. Is the method we used optimal?
The trial set up has integrated well with standard EEG practice and has shown that it does not interfere with patient clinical evaluation. On the EIT side, considering that conductivity changes are likely to be due to cell swelling, a lower frequency for the measuring current might be expected to produce larger changes and less errors due to stray capacitance. Most in vivo impedance measurements inevitably include baseline fluctuation (Boone et al. 1994) and can be corrupted by subject movement or electrode misplacement. These issues might be ameliorated by the baseline linear correction and voltage measurement outlier elimination we employed: (i) The linear drift correction of the baseline would compensate for slow baseline fluctuation. (ii) The threshold on the baseline noise would eliminate electrode combinations with unstable electrode contact. (iii) The threshold on the changes occurring before the EEG onset would eliminate electrode combinations most influenced by movement. (iv) The low pass filtering would allow detection of voltage changes occurring in a physiological time scale. Ideally the threshold settings should be stricter than those used in our study to detect changes of the order of 0.1%.

4.5. Future work
The principal source of error appears to be movement artefact. The design of conventional EEG electrodes – a cup which contains a semi-liquid gel – is already well designed to reduce movement artefact, but hydro-gel electrodes may be superior. We have examined different electrode designs for scalp EIT recording (Tidswell et al. 2003) and future work will include a re-examination of these in relation to recording under epilepsy telemetry conditions. Signal processing tools already implemented in EEG analysis could be used to separate the feature of interest from major noise in our boundary voltage measurements.

Improvements to the forward and inverse problem may also help, if data quality can be improved. Individual head shape geometry could be obtained from patient MRI (Tizzard et al. 2005) and accurate electrodes positions could be detected using 3-dimensional electrode localization methods, such as photogrammetry (Russell et al. 2005). The forward model could be also improved and include the anisotropy of the head tissues. Finally, a truncation level prediction method could be implemented to take into account the noise level of the data and to optimize the solution to the inverse problem (Handersen 1992; Perez-Juste Abascal et al. 2005).

Overall, this pilot study has been disappointing in that it was not possible to record reproducible and physiologically realistic changes in EIT images. Nevertheless, it has allowed us to recognise the bottleneck and so give a sound basis for future studies. We have successfully developed a method for simultaneous recording of EEG and EIT data. Building on this, it still seems plausible that baseline variability can be reduced to about 0.1%, as this has been possible in animal studies. Together with planned improvements in reconstruction
algorithms for EIT of the head, it still may be possible to refine the method to the point where EIT could provide a valuable new method for Neuroimaging in epilepsy.

5. References

Bagshaw A P et al. 2003 Electrical impedance tomography of human brain function using reconstruction algorithms based on the finite element method Neuroimage. 20 752-64


Elazar Z, Kado R T and Adey W R 1966 Impedance changes during epileptic seizures Epilepsia 7 291-307


Gilad O, Horesh L, Ahadzi G M, Bayford R H, and Holder D S 2005 Could synchronized neuronal activity be imaged using Low Frequency Electrical Impedance Tomography (LFEIT)? XI Conf. on Biomedical application of EIT (London, UK)

Handersen P C 1992 Numerical tools for analysis and solution of fredholm integral equations of the first kind Inv. Problems 8 849-72


Perez-Juste Abascal J F, Arridge S, Bayford R, and Holder D S 2005 Selecting the regularization parameter for linear Electrical Impedance Tomography of brain function XI Conf. on Biomedical application of EIT (London, UK)


Rao A 2000 Electrical Impedance Tomography of brain activity: studies into its accuracy and physiological mechanisms (London: University College London)


Rosenow F and Luders H 2001 Presurgical evaluation of epilepsy Brain 124 1683-700


Tidswell A T, Gibson A, Bayford R H and Holder D S 2001 Validation of a 3D reconstruction algorithm for EIT of human brain function in a realistic head-shaped tank Physiol Meas. 22 177-85

Tizzard A, Horesh L, Yerworth R J, Holder D S and Bayford R H 2005 Generating accurate finite element meshes for the forward model of the human head in EIT Physiol Meas. 26 S251-S261

Van Harreveld A and Shade J P 1962 Changes in the electrical conductivity of cerebral cortex during seizure activity Exp. Neurol. 5 383-400

Van Paesschen W 2004 Ictal SPECT Epilepsia 45 Suppl 4 35-40

Yerworth R J, Bayford R H, Cusick G, Conway M and Holder D S 2002 Design and performance of the UCLH mark 1b 64 channel electrical impedance tomography (EIT) system, optimized for imaging brain function Physiol Meas. 23 149-58