NON-INVASIVE IMAGING OF SYNCHRONIZED NEURONAL ACTIVITY USING LOW FREQUENCY ELECTRICAL IMPEDANCE TOMOGRAPHY

O. Gilad*, L. Horesh* and D.S. Holder*

* University College London, Department of Medical Physics & Bioengineering, London, UK

o.gilad@ucl.ac.uk

Abstract: Electrical impedance Tomography (EIT) has the potential to achieve non-invasive functional imaging of fast neuronal activity in the human brain. During evoked responses, fast (~1ms) local impedance changes of ~1% below 100Hz, were estimated to occur in our group using cable theory modelling and animal studies. The purpose of this work was to quantify the expected voltage changes in EIT potentials over the scalp during visual stimulation and to estimate the SNR that could be expected in real human measurements. Modelling was performed using an anatomically realistic mesh of the head. Recordings were made in a saline filled tank and human experiments during visual stimulation. Numerical simulations predicted that resistivity changes of 1% in the primary visual cortex translated into scalp voltage changes of 0.001%. In human scalp recordings, a sensitivity limit of 0.003% was reached. Low SNR conditions obscured resistivity changes in most subjects but possible changes were observed in 29% of the experiments with the highest change of 0.01% (SNR=4). SNR is mainly limited by the background electroencephalography (EEG) signal. These experimental results are in broad agreement with the predictions but indicate that the measurement of fast impedance changes related to neuronal depolarization is not yet possible.

Introduction

EIT is a new non-invasive functional imaging technique potentially capable of measuring fast (~1 ms) neuronal activity in the human brain, which is yet to be reliably achieved by any other method [1], or slow (~1 sec) impedance changes related to hemodynamic processes [2]. Arrays of EEG type surface electrodes are applied on the scalp, a low level of current is applied through pairs of electrodes and voltages are measured through other pairs. Recordings from multiple current pairs allow reconstruction of the internal impedance properties.

Our aim is to develop a non-invasive method for measuring resistivity changes related to neuronal activity. Studies into imaging of brain function require active and synchronised neuronal activity at a known brain region. This can be achieved by visual stimulation, such as a bright flash or pattern reversal checkerboard screen, which causes activity in the visual cortex. The brain activity generates potentials on the scalp at the back of the head known as Visual Evoked Potential (VEP).

There are two main mechanisms for bioimpedance changes during normal functional brain activity:

Slow changes: Active brain tissue draws more blood to compensate for the increased metabolic activity. The increase in blood volume causes local impedance changes of the order of 10% over tens of seconds and was demonstrated in our group during human VEP [2].

Fast changes: The change of resistive properties in individual neurones underlies all neural activity. When an action potential propagates along a nerve, ion channels in the cell membrane open to allow ions flow. The electrical resistivity of the cell membrane decreases during neuronal depolarisation, thus allowing external current to flow more freely through the cell [3]. These changes last tens of milliseconds and are maximal at frequencies below 100Hz. Membrane capacitance limits current from flowing into the cell at low frequencies whereas at high frequencies the current can flow through the membrane regardless of the state of ion channels. When the activity of a population of neurones displays spatial and temporal coherence such as in visual evoked response, it will be accompanied with resistivity change of the active tissue as a whole.

The magnitude of such fast changes has been investigated by modelling and animal studies in our group (Table 1). Mathematical modelling, based on cable theory, estimated local resistivity changes near DC to be 3.7% for peripheral nerve bundles and 0.06-1.7% for the cortex during Evoked Potentials (EP) [4,5]. These predictions agree with measurements done on crab peripheral nerve which showed a change of 0.5-1.0% change [5-7] and measurement on the surface of rabbit cortex during median nerve evoked response which showed a change of 0.01-0.03% [5,8].

In order to predict how such local changes are translated when measured on the surface of the scalp, Liston [4] initially estimated the boundary changes to drop to 0.006-0.17%. Ahadzi [9] then used realistic Finite Element Method (FEM) of the head and solution of the forward problem to quantitatively estimate the changes on the scalp when a 1% local resistivity changes occurred at the visual cortex during the VEP. Boundary voltage changes were estimated to be 0.02-0.04% for optimal four terminal resistivity measurements. These numeric predictions are further refined in the present study (see below). A desirable

ISSN: 1727-1983

sensitivity for measuring those small resistivity changes on the scalp appears to be 0.01-0.001%.

Table 1: Summary of predicted and measured fast resistivity changes [%].

	Cable Theory	FEM	Measured
Crab peripheral nerve	~ 3.7 [4,5]	-	0.5-1.0 [5-7]
Rabbit cortex, EP	0.06-1.7 [4,5]	-	0.01-0.03 [5,8]
Human scalp, EP	0.006-0.17 [4]	0.02-0.04 [9]	-

The purpose of this study was to quantify the expected voltage changes recorded on the scalp during visual stimulation producing Visual Evoked Responses (VER) recorded with Low Frequency EIT (LFEIT) measurement. In order to achieve this, we estimated the Signal to Noise Ratio (SNR) that could be expected in human measurements. We set out to quantify the signal and noise level when the measurement was performed with scalp electrodes during VEPs. Unfortunately, the EIT signal is contaminated and obscured by the VEP and background EEG signals within the same frequency band. Therefore, the need to separate the different components of the recorded signal and to maximize the signal to noise ratio (SNR) poses a substantial signal processing challenge.

We refined the FEM simulations done by Ahadzi [9] for the prediction of voltage changes, implemented a prototype LFEIT and performed phantom and human experiments to validate the predictions. We induced brain activity using VEP and applied a 1Hz square wave current synchronized to the visual stimuli. Resistivity changes were extracted by calculating the sum and difference between the two polarities and compared with a reference recording of current without VEP. Resistivity changes were expected to occur when the VEP showed a peak activity 100ms after stimulation (P100).

Materials and Methods

FEM Simulations: we predicted the voltage changes using a four layer (brain, cerebrospinal fluid, skull and scalp) realistic head Finite Element Method (FEM) mesh (136,000 elements), for solution of the forward problem [10]. The primary visual cortex (V1 area) was also modelled (Figure 1). The refinements of the simulations described in [9] included 1) an array of 21 electrodes placed on the back of the head instead of 31 electrodes all over the head, 2) taking into account all possible current injection and voltage measurement pairs, and 3) using the true electrodes positions as placed on individual subjects. The boundary voltage predictions for the standing voltage and the voltage changes resulting from local resistivity change were compared to measurements done on a spherical saline tank and human subjects (see below). The FEM simulations also suggested the optimal placement of electrodes for the prototype system measurements.

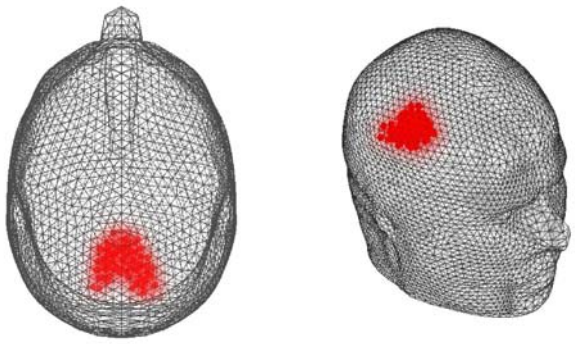

Figure 1: Realistic head mesh and the visual cortex (red).

Prototype system: Data acquisition for the human subjects was done using 21 standard Ag/AgCl EEG electrodes placed on the back of the head centred above the visual cortex (5cm above the inion of the occipital bone). The reference and ground electrodes for all channels were the standard EEG positions Fz (forehead) and Cz (vertex) respectively. In a typical recording session, 19 electrodes were used to record the voltage signals and 2 electrodes were used to inject current (Figure 2). Signals were recorded with a SD128 EEG acquisition system (Micromed, Italy) with 16bit resolution, ±12.8mV extended dynamic range, 1024Hz sampling rate, high pass input filter of 0.15Hz (40 dB/decade), common mode rejection ratio > 105 dB @ 50 Hz and input impedance > 1000GΩ. 2Hz trigger pulses were produced by the same machine and recorded on a separate channel for later analysis. These pulses were used to trigger the visual stimulation and the square wave current source.

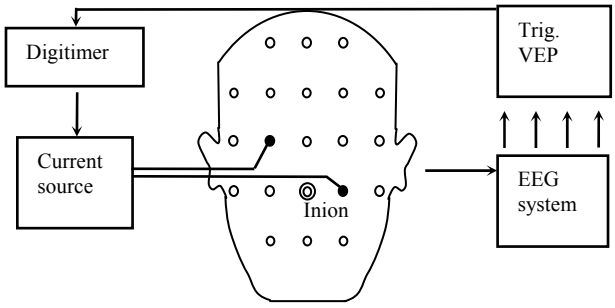

Figure 2: The experimental setup.

A current level of a 100-200μA bipolar square wave was injected at several pairs out of the 21 channels. The custom made constant current source was calibrated for baseline offset <1% prior to each experiment to prevent DC components. The current source was triggered by a DDU-315 unit (Digitimer, UK), which was set to 150ms delay between the current source and visual stimulation triggers.

Visual stimulation was triggered from the EEG system at a rate of 2 reversals per sec. A full field

ISSN: 1727-1983

pattern reversal black/white checkerboard (Pattern 10, Micromed, Italy) was applied to the subject while seated 70cm from the stimulating screen in a dark room. The subject was requested to focus on a centred fixation yellow point on the screen. The check size was 41.7' (60 minutes = 1º), field size 22ºx17º (32x24 checks) and 100% contrast. Each stimulation session lasted 60sec to prevent the effect of accommodation to the stimulus.

At every 60sec session, 39-41 out of 60 square wave cycles were averaged after rejecting 30% of outliers ascribed to eye blinking, muscular and movement artefacts and discontinuous eye focus on the screen marker. Resistivity changes from the resulting signal were calculated by subtraction of the two polarity segments of the square wave.

Six normal subjects (1 male, 5 females) age 25-42 years participated in this study. Control recordings were done before and after the resistivity change measurements including a) background EEG, b) visual stimulation without current and c) current without visuals stimulation. Two different current injection pairs were used consecutively in four subjects and one current pair of these was used in two subjects. One subject was repeated to confirm reproducibility of the results. Each injection pair session was repeated 10 times with and without visual stimulation to construct a grand average to reduce noise levels. The total number of grand average sessions across subjects which could be regarded as different experiments was 14.

The tank experiment was done with the same recording setup on a spherical tank (19 cm diameter) filled with 0.2% saline and 31 Ag/AgCl 2 mm diameter ball electrodes. Local resistivity changes of 19% in the visual cortex area were simulated using a sponge ellipsoid of volume 18.5 cm3.

First order linear regression was used to compare the measured and predicted standing voltages and voltage changes for both tank and human measurements. Statistical values given below are the slope mean, standard deviation (SD) and correlation coefficient R.

Results

The numerical simulation predicted that resistivity changes of 1% in the primary visual cortex translate into a maximal voltage change of 0.001% on the scalp. There was a significant correlation between predicted and recorded standing voltages for the tank with a slope of 1.02 ± 0.05 (Mean ± SD; R = 0.98) and for the human measurements with a slope of 1.1 ± 0.4 (Mean ± SD, R = 0.95) (Figure 3).

Voltage changes due to local resistivity changes were confirmed in the tank with a slope of 0.87 ± 0.40 (Mean ± SD; R = 0.86). However, such comparison was limited by poor SNR for the human measurements. The main source of noise was the background EEG signal caused by spontaneous brain activity (~10μV), which coexisted within the same band of the LFEIT measurements. The sensitivity limit was 0.003% after averaging n = 1000 stimuli (~10 min for 2 stim./s) for 10 minutes with another 10 minutes recording as reference.

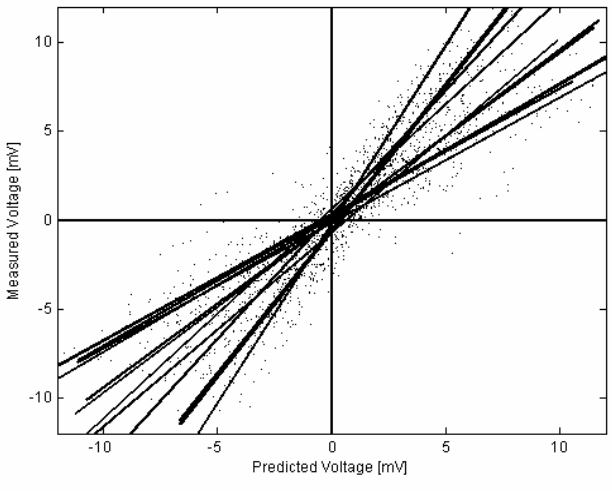

Figure 3: Measured vs. predicted standing voltages for all human subjects.

A significant resistivity change was observed in 4 out of 14 grand averaged sessions (29%). These 4 sessions were recorded from 3 different subjects and the best case had a maximal change of 0.01% and SNR of 4 (Figure 4a). Reproducibility could not be confirmed from a repeated recording for the same subject. A normal VEP, containing the expected P100, was extracted during current injection (Figure 4b).

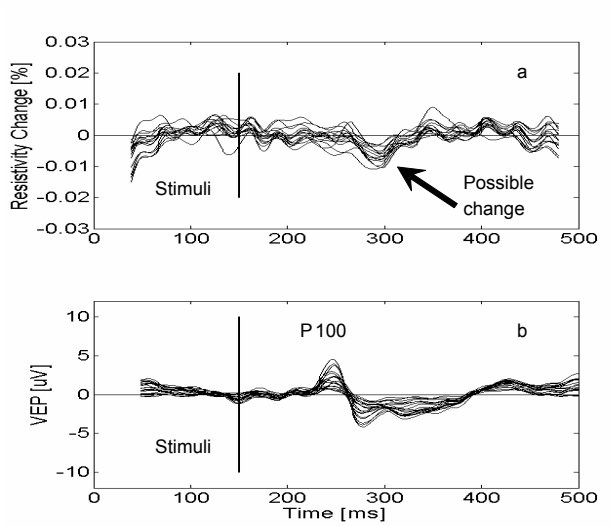

Figure 4: Grand averaged a) resistivity changes for 15 measurement pairs and b) VEP for 19 channels.

Discussion

The FEM simulations were validated by comparing the predicted standing voltages with measurements from both tank and humans. The dispersion around a unity slope in a linear fit (Figure 3) is most probably related to inaccurate registration of conductivities in the four layers of the mesh, and usage of single standard head geometry in the mesh which did not take account of individual differences in anatomy, and no allowance for

ISSN: 1727-1983

tissue anisotropy. Predictions for changes in boundary voltages are of the order of 0.001%, an order of magnitude less than the value reported previously [9]. This is related to the refinements we incorporated into our modelling study as described in the methods section. The sensitivity of the prototype system with our experimental protocol was 0.003% which is an order of magnitude better than the sensitivity of 0.03-0.06% we have reported previously [11]. Signal levels are proportionate to the level of current used. However, it is limited by safety issues and the possible effect of the current on changing the brain activity. The low SNR conditions obscured resistivity changes in most subjects. Yet, possible changes were observed in 28.5% of the experiments with the highest change of 0.01% with SNR of 4. These changes are delayed by 50ms from the P100 peak. The low SNR prevented statistical validations of significance and reproducibility.

Conclusions

No reproducible fast impedance changes related to neuronal activity could be detected. It is just possible that some were at the border of detectability using this new approach. However, the long acquisition protocol limits the feasibility of designing an imaging system at this stage. Work in progress is to examine the possibility of using Magnetoencephalography (MEG) methods to increase the sensitivity of the measurement side as the skull is transparent to magnetic fields.

Acknowledgements

This study was funded by the Biotechnology and Biological Sciences Research Council (UK) and the Epilepsy Research Foundation (UK).

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ISSN: 1727-1983