

Electrical Impedance Tomography of brain function

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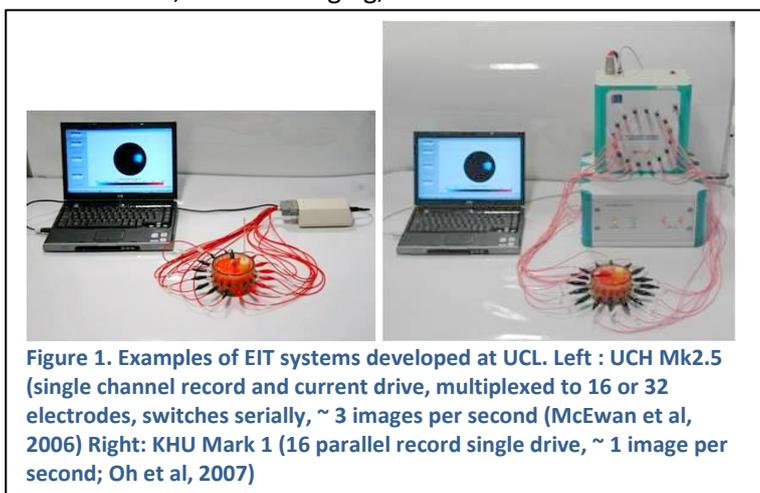
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Abstract— Electrical Impedance Tomography is a recently developed imaging technique, with which images of the internal impedance of the subject can be rapidly collected with rings of external ECG-type electrodes. It is fast, inexpensive, portable and sensitive to physiological changes which affect electrical impedance properties. For about two decades, satisfactory images have been obtained of changes over time related to gastric emptying and ventilation and cardiac output in the thorax. The main work of our group at UCL has been to adapt existing EIT designs for the demanding application of imaging changes in the brain due to conditions like stroke, epilepsy or normal physiological brain activity. Its portability and low cost would give it unique practical advantages over existing methods such as fMRI. Innovations in hardware and image reconstruction algorithms developed in our group enable accurate images in tanks resembling the human head, and in experimental animals with electrodes on the brain. Advanced signal processing, improved numerical models for image reconstruction, the use of frequency difference imaging and an automated self-abrading helmet have been developed to allow the final step of successful imaging in the clinic with scalp electrodes. It also has the potential for providing images of fast neural activity in the brain over milliseconds. Recently, we have been able to record fast neural activity in rat cerebral cortex during evoked responses or epilepsy with a resolution of $<200\mu\text{m}$ and 1 msec which provides a unique new method for imaging functional activity in the brain.

I. INTRODUCTION TO ELECTRICAL IMPEDANCE TOMOGRAPHY (EIT)

Electrical Impedance Tomography (EIT) is a relatively new medical imaging method, which has the potential to provide novel images of brain function. It is fast, portable, safe and inexpensive, but currently has a relatively poor spatial resolution. It produces images of the internal electrical impedance of a subject using rings of ECG like electrodes on the skin. (See Holder, 2005 for a review).

Historically, most EIT measurements were of differences over time at a single frequency; these relied on changes in resistance such as air entering the lungs during breathing, or ingestion of a salty drink to image gastric emptying. More recently, systems have been constructed which measure over a range of frequencies at once – “multi-frequency” EIT (MFEIT), which enables tissue characterization in single images. These usually record from about 1kHz to 1 MHz. About twenty different designs have been constructed and reported since 1984. They may employ injection through adjacent pair or multiple electrodes, 2 or 3D imaging, or measurements based on two electrode measurement.



These series of measurements of the transfer impedance of the subject may be transformed into a tomographic image using similar methods to back projection in X-ray CT. Most systems now employ a more powerful method, based on a “sensitivity matrix”. This is based on a matrix, or table, which relates the resistivity of each voxel in the subject, and hence, images, to the recorded voltage measurements. The method requires a mathematical model of the body part of interest such as the Finite Element Model of the head shown in Fig. 2.

To produce an image, it is necessary to invert this “forward” solution so that values of the impedance properties of its voxels are calculated from measured boundary voltages. Initially, reconstruction was always performed with the assumption that the subject was a two dimensional circle. For simplicity, many

continuing clinical studies still use this approach. The sensitivity matrix approach described above requires an assumption that there is a direct unvarying, or “linear” relationship between the resistance of a voxel and its effect on recorded voltage. In practice, this is almost true for small changes in impedance below about 20%. However, it is not true for larger changes. This can be overcome by using more accurate “non-linear” approaches. In practice, accurate images can be produced, typically with a spatial resolution of about 10% of the subject diameter (Fig. 2).

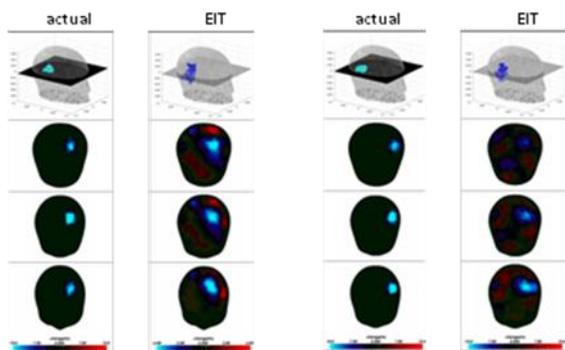
II. ELECTRICAL IMPEDANCE TOMOGRAPHY OF BRAIN FUNCTION

EIT has the potential for imaging brain function or pathological conditions. It also has the potential to provide a novel neuroimaging technology capable of addressing important questions in clinical or cognitive

neuroscience by imaging fast neuronal depolarization. Unfortunately, this presents unique technical difficulties, as the impedance changes are small, and the skull has a high resistance and so provides a barrier to current injection. Our group at University College London has been addressing these problems over the past two decades. We have developed EIT hardware for imaging of brain function, and algorithms which can produce good quality images in realistic saline filled tanks. It has been developed to the stage where it can be used for imaging brain function in animal studies with electrode mats on the brain. It is not yet at a stage where it can be used routinely for clinical or psychophysiological imaging, but this may become possible with technical advances in the near future. The following is a review of the work of our group at UCL in developing its use for imaging brain function



Fig. 2. Left : Finite element of the head used to produce images. Right: Example of EIT images produced in a saline filled tank



A. Physiological rationale

Impedance changes in the brain in two main ways – 1) “Slow” changes analogous to the changes seen in diffusion weighted MRI or fMRI : These occur over tens of seconds. The mechanisms of these impedance changes are : 1) During ischaemia or energy supply failure, water moves from the extracellular space into cells; as current at the frequencies used passes almost entirely in the extracellular space; this causes impedance increases of many tens of per cent. Blood flow, volume and temperature changes during activity also cause impedance decreases of a few per cent. 2) Impedance also changes during neuronal depolarization in the brain because the opening of ion channels decreases the bulk resistance of the brain; these changes occur over milliseconds.

B. Potential applications

a) Slow metabolic activity related changes. 1) Evoked responses. EIT could be used to image changes in blood flow and volume known to occur during evoked activity in the brain, in a similar fashion to fMRI. It could be used as a low cost portable imaging system for studies in cognitive neuroscience at the bedside or in psychological laboratories. 2) Epileptic seizures. Impedance changes in the brain due to increased blood flow or cell swelling during epilepsy. In pre-surgical assessment for intractable epilepsy, EIT images could be acquired continuously over days and so be recorded during seizures. This could permit imaging of the ictal onset zone and so avoid the need for intracranial electrodes and their associated morbidity and complexity. It could also be used in epilepsy diagnosis, where fMRI like images could be obtained by triggering from spikes on the EEG. Unlike the EEG, EIT can image deep into the head, so this would permit much more accurate diagnosis of epilepsy syndromes in an out-patient setting. EIT could soon provide a routine bedside method for continual production of images, which can be used retrospectively to identify

the seizure onset site in patients awaiting surgery to remove the epileptic trigger zone. 3) EIT of acute stroke. In the past few years, there has been a dramatic development in treatment for acute stroke, with the acceptance that thrombolytic agents, such as tissue plasminogen activator (tPA), can cause a significant reduction in morbidity if administered within a few hours of onset. However, there are severe practical limitations in its applicability. It is essential that neuroimaging is performed before administration, as tPA is only safe if given to stroke due to infarction; if a haemorrhage exists the thrombolytic effect can extend the damage. Unfortunately, there is a scarcity of suitable and rapidly available neuroimaging devices, which can be pressed into service whenever needed. EIT could be used to provide rapid and practicable neuroimaging for this purpose. It is inexpensive, small, portable and safe, and could be made available in casualty departments or small hospitals, to allow screening before tPA is administered.

b) Fast neuronal depolarization. EIT could also be used to image the fast changes over milliseconds which occur during electrical activity in the brain. This is technically demanding, as the changes are fast and at the limits of detectability. However, such imaging is not presently possible by any other method; if this were possible, EIT could be used to produce images during repeated evoked responses with a temporal resolution of milliseconds and a spatial resolution of perhaps a few cubic millimetres and permit the quantitative analysis and mathematical modelling of evoked activity in neuroanatomical circuits. If possible, this would be a revolutionary advance in neuroscience technology.

C. Developments in hardware and reconstruction algorithms

EIT systems developed elsewhere were designed for imaging the chest or abdomen, and were unsuitable for imaging cerebral activity with scalp electrodes, because the high resistance of the skull does not permit sufficient current to enter the brain, and certain assumptions of the reconstruction algorithm were violated. As a result, our group has now developed and built EIT systems optimized for use in imaging brain function with the use of scalp electrodes. The first dedicated system was the "UCLH Mark 1b" which could apply low frequencies, had a miniaturized headbox on a 10m lead, and was suitable for use on the ward for ambulatory monitoring (Yerworth et al, 2002). Many early EIT studies were performed using a current applied at a single frequency of about 50 kHz. EIT may also be performed at multiple frequencies at a time (MFEIT). This has the advantage that tissue may be characterized much better, because different tissues have different spectral properties. It also has the important practical advantage that single images in time may be produced. With MFEIT, the image is of one frequency referenced to another; both may be collected at the same time to give a "one-off" image. The UCH 2.5 MFEIT system (Yerworth et al, 2003; McEwan et al, 2006) can record over multiple frequencies. In collaboration with Prof. E. Woo of Kyung Hee University, Seoul, South Korea, we have also developed the KHU Mk 1 which records at multiple frequencies in the range 20Hz – 1 MHz but has parallel data recording (Oh et al, 2007) (Fig. 2). The systems can record from 32 electrodes over the range 20 Hz – 1 Mhz and can produce up to 4 images per second. We have recently developed a single frequency system optimized for recording fast neural activity up to 3kHz with 128 electrodes, based on a commercial EEG recording system.

In order to reconstruct images of the head, a model of the head is needed to calculate the sensitivity matrix. We developed a method for producing images using an accurate FEM of the head, initially with a prototype FEM and then with individual subject meshes derived from their MRI or CT (Bagshaw et al, 2003; Tizzard et al, 2005; Vonach et al, 2012); see Fig 2). Other improvements to the image reconstruction software include the use of statistical analysis, as used in other neuroimaging methods like fMRI (Yerworth et al, 2007), use of principal component analysis (PCA) to improve data quality, incorporation of anisotropy into the forward model and solution (Abascal et al, 2007), optimised methods for regularization of the inversion of the sensitivity matrix (Horesh, et al, 2006b), linkage of reconstruction to the GRID academic computing network (Fritschy et al, 2005) and use of a fast parallel computing forward solver (Jehl et al, 2014).

D. Tank studies

With these methods, it has been possible to produce reproducible time and EITS frequency difference images in fluid filled tanks, both for the simpler cases of a 2D cylinder, and with a head shaped tank

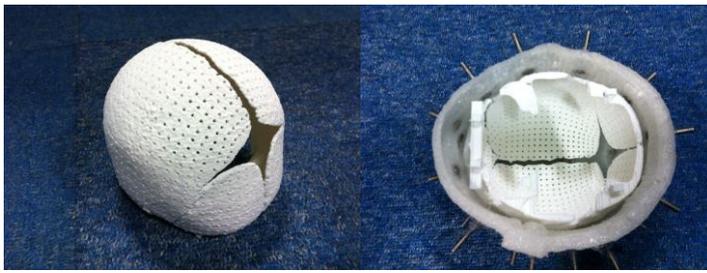


Fig. 3. 3D printed tank to resemble neonatal head and skull; skull perforated to yield electrical properties of real skull.

containing a skull, for test objects such as a sponge or banana with impedance contrasts similar to those encountered in the proposed neuroimaging applications (Tidswell et al, 2001; Romsauerova et al, 2007, Fig. 2). With these, there is blurring of the test object compared to CT or MRI, but it can be clearly visualized. All new hardware and imaging software developments are tested in such tanks. Recently, we have developed anatomically correct tanks with simulated skulls, using 3D printing of perforated plastic (Fig. 3).

E. Physiological and preliminary clinical studies

In the 1990's, studies were undertaken to demonstrate the proof of principle that EIT could be used to image brain function. These were all undertaken with the Sheffield Mk 1 system, which recorded time difference images in 2D at 50 kHz with 16 electrodes. These were undertaken in anaesthetized rats or rabbits, with a ring of electrodes placed directly on the exposed brain. Reproducible images were obtained during stroke (Holder, 1992), cortical spreading depression (Boone et al, 1994), evoked responses (Holder et al, 1996; Fig. 3), and epilepsy (Rao et al, 1997). Recent studies in the rat with cortical electrodes during fast neural activity are presented below.

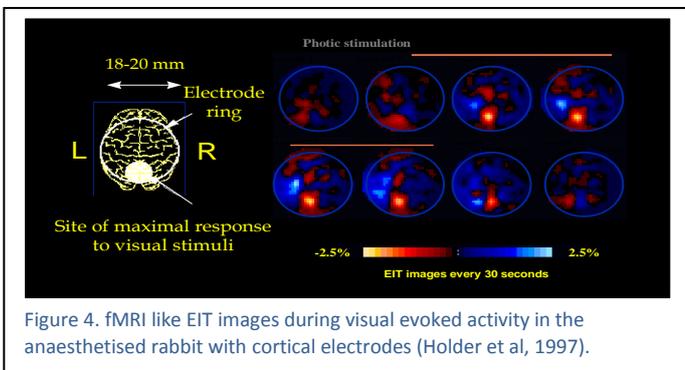


Figure 4. fMRI like EIT images during visual evoked activity in the anaesthetised rabbit with cortical electrodes (Holder et al, 1997).

After development of the algorithm for imaging in the head and the Mark 1 and 2 UCH systems, a series of the first non-invasive human recordings with scalp electrodes were undertaken from 2001 – 5. During evoked responses recorded with a block paradigm over 30 second intervals, reproducible raw resistance changes of about 0.5% were recorded (Tidswell et al, 2001), but images, produced with the currently available simplified spherical head model, were too noisy for clinical use.

Unfortunately, images produced during other studies in the fields of interest were encouraging although too noisy for reliable clinical use – conditions simulating stroke (Romsauerova et al, 2006), epileptic seizures (Fabrizi et al, 2006), and also neuronal depolarization during evoked potentials (Gilad et al, 2009).

In summary, at the end of these studies, electronic hardware and reconstruction algorithms had been developed which were optimized for the demanding application of imaging brain function through the skull. Reliable images could be obtained in fluid filled tanks and in animal studies with electrodes on the brain but the final hurdle of image production in human subjects has not yet been surmounted. This could be attributed to a lower signal to noise ratio in such studies, due to dilution of the signal by diversion of current applied to the skull, movement artefact in awake subjects, and uncertainty in factors such as electrode position and the impedance properties used in the head models.

III. WORK IN PROGRESS

A. Slow metabolic activity related changes.

In order to maximize the chances of producing accurate images in stroke, epilepsy and evoked responses, the recording systems and reconstruction algorithms have been re-engineered. With respect to imaging in acute stroke, specifications for accuracy were produced by computer modeling using an anatomically accurate Finite Element Model of the head. This indicated that large impedance contrasts of up to 100% translate into scalp voltage changes of up to 7% and that uncertainties in factors such as electrode position and head model shape and conductivity, can produce errors of this magnitude (Horesh et al, 2005). In

addition, the accuracy of impedance measurement across frequency may vary with the measured load, which varies from 5 – 70 Ohm in different leads. This may introduce substantial errors of up to 5% but these have been reduced by careful engineering to 0.2% (McEwan et al, 2006). Errors in electrode position may be reduced by the use of a digital camera and a photogrammetric registration approach, and that of the head model by use of individual patient specific meshes (Vonach et al, 2012).

For imaging in epilepsy, a similar modelling study indicated that increases of about 10% in resistance in the brain translated into peak changes of 0.3 – 1.0% on the scalp (Fabrizi et al, 2006), compared to noise of about 0.1% (Fabrizi et al, 2007). With averaging over the 1 second needed to resolve seizures, the modelling suggested that it should be possible to produce reliable images for larger and more superficial seizures, at 50 kHz (as electrical safety standards permit more current application at this higher frequency) and with the KHU 16 channel EIT system, as its parallel design allows more averaging. A further important consideration is to minimize movement artefact. A self-abrading electrode helmet has been designed which automatically optimizes electrode contact with the scalp (Avery et al, 2013; Fig. 5). Recording at multiple frequencies, although still over time, may also allow reduction of movement artefact by subtraction.

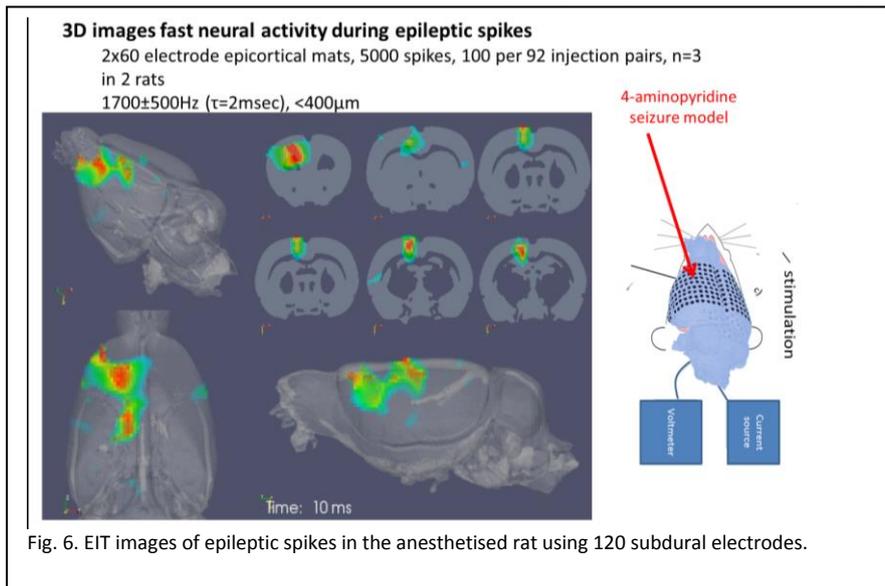


Fig 5. The servo-electrode helmet automatically optimises electrode contact throughout recording period

With these innovations, which will produce more accurate data less prone to movement artifact, and a more accurate model of the head with accurate electrode positions, more clinical studies are planned.

B. Fast neuronal depolarization

Modelling indicates that resistance changes of about 1% in the cerebral cortex (Liston et al, 2012) during neuronal depolarization may be predicted to translate into changes of about 0.005% on the scalp, which is at the limit of detectability. Using electrodes specially designed to permit optimal current application (Gilad 2007), changes of this magnitude were detected in human studies using detection either of voltage with scalp electrodes or the magnetic field with a Magnetoencephalography (MEG) system (Gilad 2009). Unfortunately, these were not sufficiently large to permit reliable imaging.



The prediction of expected changes relies on modelling studies which calculated a resistance change of 1% locally in the brain. This has been examined in a study in the anesthetized rat, with electrodes placed directly on exposed cortex. It was possible to record reproducible impedance changes during sensory and visual evoked responses, or epileptic spikes, with a temporal and spatial resolution of 1 msec and 200 μm in the cerebral cortex

with 30 -120 electrodes placed on the cortical surface (Oh et al, 2011; Aristovich et al, 2014; Figs. 6, 7). These occurred at the same time as the physiological activity. It is possible to track the trajectory of the volley of evoked activity (Fig. 7). This enters at 1 mm deep in the cortex, which corresponds to Layer IV, the layer at which the largest changes are expected on physiological grounds (Fig. 4). These are the first such validated unique tomographic images of fast neural activity.

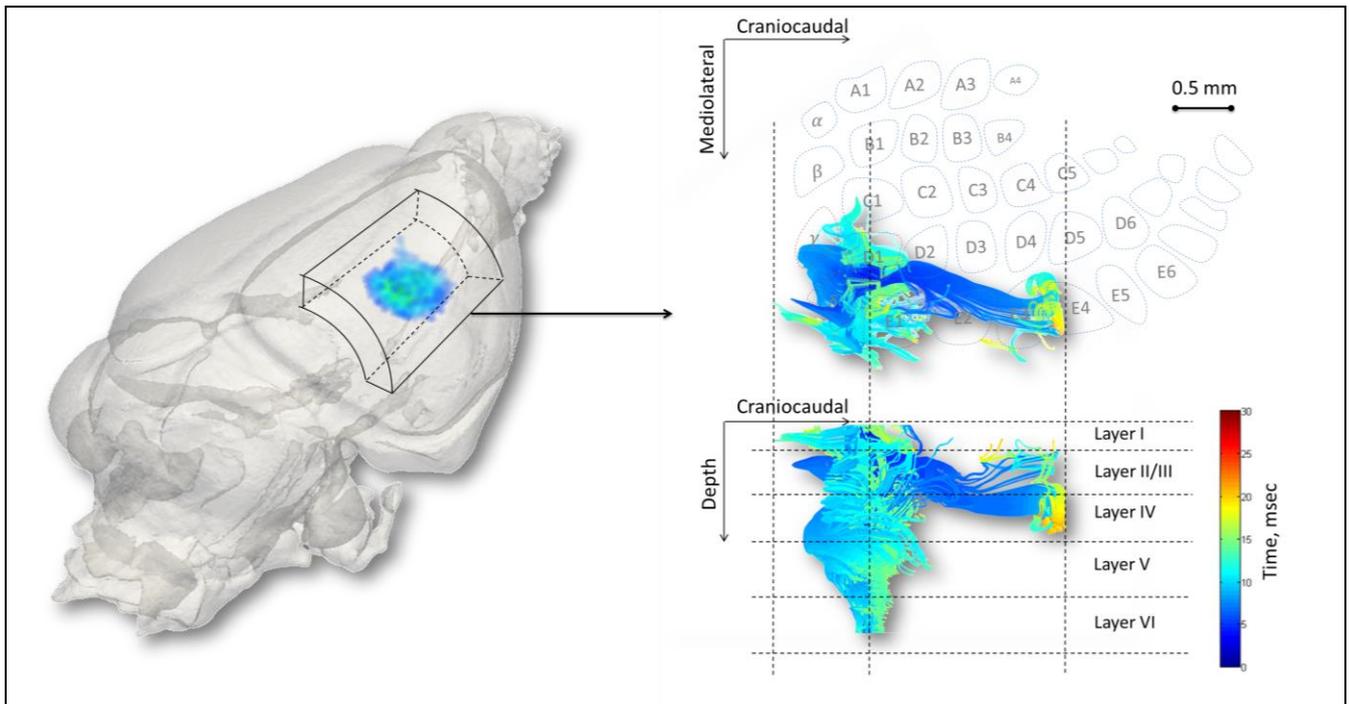


Fig. 7. Left – 3D image of peak fast neural activity occurring at 10ms after stimulating the rat whisker. Right – Functional connectivity in the somatosensory cortex of the rat in response to mechanical stimulation of whiskers. The timing of activation over milliseconds is colour-coded.

IV. CONCLUSION

EIT holds promise to provide a new medical imaging modality which is safe, portable and inexpensive and has the possibility of yielding a revolutionary new method for imaging fast electrical activity in the brain, as well as slower changes during stroke and epilepsy. It requires interdisciplinary collaboration from biomedical scientists, electronic engineers and mathematicians, and holds great interest for those interested in interdisciplinary work in these fields. We currently have a validated system suitable for imaging fast neural activity in the brain using subdural electrodes. This is ready for use in cognitive neuroscience as a complementary technique to optical methods such as 2-photon calcium imaging. It is ready for extension to recording in human subjects undergoing presurgical evaluation for epilepsy surgery, who have electrode mats surgically implanted on the brain. Robust pilot evidence exists that it will also be possible to use EIT for imaging in epilepsy and stroke with scalp electrodes. Recent technical innovations include advanced electronic hardware, image reconstruction methods and a self-adjusting electrode helmet. Whether these can be translated into clinically reliable images is the subject of continuing research.

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