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Accurate resistivity mouse brain mapping using microelectrode arrays

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ABSTRACT

Electrical impedance spectroscopy measurements were performed in post-mortem mice brains using a flexible probe with an embedded micrometric electrode array. Combined with a peak resistance frequency method this allowed obtaining intrinsic resistivity values of brain tissues and structures with submillimetric resolution. Reproducible resistivity measurements are reported, which allows the resistivity in the cortex, ventricle, fiber tracts, thalamus and basal ganglia to be differentiated. Measurements of brain slices revealed resistivity profiles correlated with the local density of cell bodies hence allowing to discriminate between the different cortical layers. Finally, impedance measurements were performed on a model of cauterized mouse brain evidencing the possibility to measure the spatial extent and the degree of the tissue denaturation due to the cauterization.

1. Introduction

Neurosurgery can be considered as a high-tech speciality which is strongly dependent on technological innovations aiming at improving patient treatment and clinical outcome. During the last decades neurosurgery has improved substantially, thanks to the introduction of applied imaging technologies such as computed tomography and magnetic resonance tomography, and new surgical modalities like brain navigation (Kikinis et al., 1994; Mohri et al., 2012). In particular, accuracy of targeting is critical for the success of numerous brain surgery techniques because brain damage has a very negative impact on the patient's quality of life. For example, in Parkinson disease, precise placement of electrodes for deep brain stimulation (DBS) is an essential determinant of outcome: electrodes have to be placed accurately in the hypothalamus in order to stimulate the appropriate neurons and reduce side effects to a minimum. Similarly, proper electrode placement is essential for the correct interpretation of stereoelectroencephalography recordings used to identify the area of the brain where epileptic seizures originate. In operations involving resective surgery such as radiofrequency ablation, thermal ablation or cryoablation for medically refractory epilepsy (Gigante and Goodman, 2012), hypothalamic hamartoma (Mittal et al., 2013) or metastatic brain tumors (Li et al., 2010), precise localization but also precise information about the extent of the ablated tissue is absolutely essential in order to minimize the damage caused to the brain. Recently, it has been estimated that around 10% of patients who had resective epilepsy surgery have to undergo a second intervention (Surges and Elger, 2013). Causes of failure in the first epilepsy surgery vary but they include incorrect localization and incomplete resection of the seizure focus. Finally, information about the extent and development of local tissues abnormalities such as tumors and lesions are also valuable for the medical diagnosis before and during surgery.

Standard magnetic resonance imaging and X-ray computed tomography are typically used for imaging the brain and taking landmarks for the later surgical operation before opening the skull of the patient. As such, these techniques take into account neither brain release at the moment of skull opening nor possible accidental movements during the surgery. Techniques such as intraoperative magnetic resonance imaging (iMRI) and intraoperative computed tomography (iCT) are used for brain imaging and needle guidance during surgical operations, for example for deep brain stimulation needle placement (Burchiel et al., 2013; Lim et al., 2013) and recently also for tumor ablation with high-intensity focused ultrasounds (Ellis et al., 2013). However these techniques imply complex surgical conditions and organization and also require complex data treatment and expensive equipment. Further, iCT implies irradiation of the patient or use of radioactive contrast agents, putting the patient's health at risk when used too frequently.

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In addition, image quality in magnetic resonance imaging (MRI) is degraded by the metallic objects such as the implanted electrodes.

In order to overcome these difficulties, the neurosurgical procedure would benefit from new simple instruments or techniques enabling localizing directly and precisely brain structures or distinguishing different types of tissues, such as for example healthy and tumor tissues for proper resection of the latter with minimal damage to the former. Furthermore, an “in situ” and “real time” technique allowing obtaining information on the properties of tissues could open wide possibilities for the research of the direct effects of drug delivery and local stimulation on the long term evolution of diseased tissue.

The imaging of conductivity distributions gives valuable information on physiological and pathological parameters, which are not obtained by anatomical imaging. For example, conductivity measurements can be used to classify different tissue types (Mayer et al., 2006), and to detect edema (Merwa et al., 2004). Electrical impedance tomography (EIT), in which surface potentials are measured during application of currents via surface electrodes, has been applied to obtain conductivity distributions in living bodies (Metherall et al., 1996; Saulnier et al., 2001). However, EIT has relatively low spatial resolution when using a limited number of surface electrodes. Moreover, conductivity distributions of the brain are difficult to obtain with EIT because most of the current does not penetrate the skull due to its low conductivity (Sekino and Ueno, 2002). Recently, Wang et al. (2008) proposed another method to estimate conductivity from diffusion tensor MRI, though the application of this method is limited to white matter tissues. An alternative to EIT is electrical impedance spectroscopy (EIS), which has already been used for detecting both local pathologies such as brain tumors in rats (Jahnke et al., 2013) and global abnormalities such as hypoxic ischemic encephalopathy of neonates (Seoane et al., 2012). It has also been proven useful to monitor temporal changes such as the evolution of the tissue reaction to neuroprostheses (Mercanzini et al., 2009). Recently, impedance-based tissue discrimination for needle guidance has been proposed (Kalvøy et al., 2009; Trebbels et al., 2012). However, impedance measurements with very high resolution enabling discrimination of submillimetric structures are still missing.

In this report, we propose the usage of electrical impedance spectroscopy (EIS) for a fine discrimination in brain tissue structures. By taking advantage of the latest advances in both microelectrode fabrication and EIS analysis, we demonstrate that impedance spectroscopy can be performed in a minimally invasive fashion and that it allows distinguishing fine brain structures such as the cortical layers of a mouse brain. The peak resistance frequency (PRF) analysis method allowed obtaining intrinsic “tissue resistivity” values that depend neither on the electrode size nor on the measurement frequency, as soon as tissue structures of interest are larger than electrode diameter. In this work, the term “resistivity” does not refer to the classical configuration in which homogeneous materials with defined dimensions are investigated but reports values for sub-millimetric volumes of the brain surrounding measurement electrodes. Measurements were performed first on post-mortem mice brains and then on brain slices for a better understanding of the mechanisms at play. We demonstrate the distinction of brain structures such as different cortical layers, fiber tracts, ventricles, thalamus and basal ganglia and evidence the impact of cell density on impedance measurements. In an application perspective, we further demonstrate that our method can be used to discriminate healthy and cauterized tissue in the brain and quantify the graduated cauterization effects. The developed flexible microelectrodes can be easily integrated on existing electrodes already used for DBS or epilepsy issues. The integration of local impedance measurements in real time during probe implantation or tissue stimulation would also raise knowledge on tissue integrity and on the propagation of electrical stimulation, i.e. lead to a better knowledge of the passive electrical properties of the brain tissues.

2. Materials and methods

2.1. Probe microfabrication

Neural probes were fabricated using standard clean room procedures. Fig. 1a and b shows the resulting microfabricated neural probe. The fabrication process has been presentedin detail elsewhere (Cheung et al., 2007; Mercanzini et al., 2008; Metz et al., 2004).

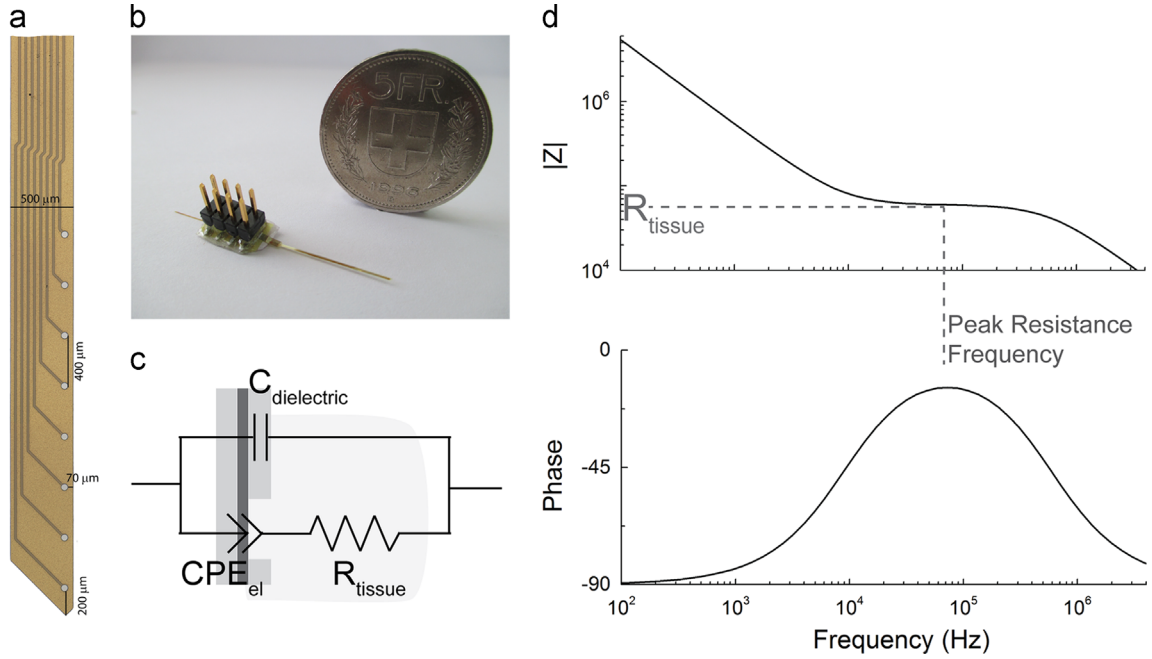

Fig. 1. Impedance measurement device and configuration. a. Microscope image of the polyimide probe used for measurements consisting of an array of eight 50 µm diameter platinum electrodes. b. Photograph image of the probe with glued connector and capillary. c. Electrical circuit model for the electrode/tissue/counter-electrode system. d. Corresponding impedance modulus, phase spectra and peak resistance frequency measurement method.