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Intracranial neuronal ensemble recordings and analysis in epilepsy

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ABSTRACT

Pathological neuronal firing was demonstrated 50 years ago as the hallmark of epileptically transformed cortex with the use of implanted microelectrodes. Since then, microelectrodes remained only experimental tools in humans to detect unitary neuronal activity to reveal physiological and pathological brain functions. This recording technique has evolved substantially in the past few decades; however, based on recent human data implying their usefulness as diagnostic tools, we expect a substantial increase in the development of microelectrodes in the near future.

Here, we review the technological background and history of microelectrode array development for human examinations in epilepsy, including discussions on of wire-based and microelectrode arrays fabricated using micro-electro-mechanical system (MEMS) techniques and novel future techniques to record neuronal ensemble. We give an overview of clinical and surgical considerations, and try to provide a list of probes on the market with their availability for human recording.

Then finally, we briefly review the literature on modulation of single neuron for the treatment of epilepsy, and highlight the current topics under examination that can be background for the future development.

Contents

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1. Introduction

The demonstration of aberrant neuronal firing was the first experimental evidence of the neuronal theory of epilepsies set by Hughlings Jackson in 1873 (Jackson, 1873; Reynolds, 2001). According to him the origin of seizure disorder is the "occasional, sudden, excessive, rapid, and local discharges of grey matter". The neuronal phenomenon provoked by focal application of penicillin on cat neocortex was named paroxysmal depolarizing shift (PDS), which is thought to be analogous to the human interictal discharge (Matsumoto and Ajmone-Marsan, 1964).

The excessive neuronal discharge is considered as the holy grail of epileptology, providing a common ground for both basic and clinical research with the goal of an ultimate resolution of the nature of the epileptic cortex and a perfect marker to detect it.

2. Sensors recording neuronal activity

There are two fundamental approaches to detect neuronal activity. The intracellular approach enables the recording intracellular postsynaptic and action potentials (AP). Based on the diameter of the glass microelectrode, this approach also allows the modulation of the selected neuron by clamping the intracellular voltage at a specific level. This technique allows examination of cellular properties including input/output relationships, ion channel content, and synaptic behavior. Among several electrode configurations, the patch-clamp technique provides the strongest control on the recorded neuron (Sakmann and Neher, 1984).

The extracellular approach, on the other hand, utilizes electrodes that do not penetrate the neuron and instead are situated in the extracellular matrix in close proximity to the neuron. Based on the size and impedance of the recording contacts we can distinguish sensors suitable for field potential and for neuronal recording. Lower impedance intracerebral macroelectrodes like deep-brain electrodes are capable to record field potentials while higher impedance microelectrodes can record single neuronal potentials. Neurons situated close to the recording electrode will generate action potentials with large enough amplitude to be identified as originating from one neuron. Often an extracellular recording site captures the APs of more than one neuron. In this situation, based on the spatial arrangement of the recording contacts, one neuron can be observed in more than one electrode. To avoid the confusion coming from the uncertain source of one AP train, the series that is supposed to come from one neuron is referred to as "unit" activity. If many units are firing simultaneously such that it is impossible to discriminate them, this phenomenon is termed *multiple-unit* or *multi-unit activity* (MUA) (Gray et al., 1995).

The signal quality, topologic relationship of the electrode to the neuron, and the electrode's ability to reliably record unit activity determine the accuracy of the recording. The amplitude and waveform of the action potential change as a function of the distance from the recording electrode, the shape of the neuron and its ion-channel configuration. The relationship of distance and cell density on the quality and number of recorded units is shown in Fig. 1 of Henze (Fig. 6 in Henze et al., 2000).

Another detailed analysis of extracellular waveform variance suggested that the potassium channel configuration has higher impact than the shape of the neuron on the recorded waveform (Gold et al., 2006). Both papers demonstrated that the extracellular AP amplitude drops in an exponential manner with a half amplitude distance of about 40–50 μm. This distance contains 100–150 neurons in an average cortical area that can theoretically be separated from each other. Typically, MUA is gathered from an average radius area of 150 μm encompassing more than 1000 neurons.

Mathematical approaches are used to solve the spatial problem of separating multiple units recorded from the same microelectrode. These algorithms are constantly evolving, highlighting the importance of the problem, the need for accurate detection automats, and the complexity in identifying neurons recorded from the extracellular space (Azami et al., 2015; Franke et al., 2015; Kaneko et al., 2007; Paraskevopoulou et al., 2014; Rall, 1962).

While MUA can be recorded with a wider range of electrodes, even at far distances including the cortical surface (Fedele et al., 2012), specific considerations are for electrode type are necessary to detect single unit activity (SUA). The main factors influencing SUA recordings are the diameter and the impedance of the electrode. The relationship between the size of the electrode surface and the impedance is inversely proportional, with electrodes with larger area exhibiting lower impedance (Butson et al., 2006; Ludwig et al., 2006). Prasad et al. found that the ideal resistance for SUA detection is between 40 and 150 kΩ (Prasad and Sanchez, 2012).

3. Stability of unit recordings

Several factors influence the ability to obtain high quality unit recordings. The implanted material should avoid tissue damage, remain intact, and be resistant to corrosion during implantation and recording in order to provide good signal to noise ratio (SNR) (Merrill, 2014). Even if the electrode has the ideal biocompatibility and impedance characteristics, the tissue reacts to the foreign body and reorganization occurs in close proximity to the electrode (He et al., 2006; Polikov et al., 2006; Zhong and Bellamkonda, 2005). Microglia and astrocytes grow slowly around the electrode, regardless of the electrode material or shape and pushes the neurons away from the electrode. This leads to decreasing neuronal signal quality and SNR (Ludwig et al., 2006; Plenk, 2011; Wang et al., 2005). The microelectrode impedance fluctuates (Ward et al., 2009) and increases over time after contacting the biological tissue (Prasad and Sanchez, 2012). There are studies however, demonstrating long term biocompatibility of microelectrodes. Suner et al. reported no evidence of SNR change and a poor relationship between impedance and SNR during long term microelectrode recordings (Suner et al., 2005). The carrier, or insulating agents encapsulating the wire electrodes can be important in this process.

4. Materials considerations in human unit recordings

Since the 1940s glass micropipettes filled with solution analogous to the extracellular matrix was employed to record neural cell function. Unfortunately, using this technique allowed a maximum of one or two electrodes to be simultaneously inserted into the immobilized brain (Renshaw et al., 1940). In the 1950s, simpler metal wire electrodes insulated with platinum, iridium, stainless